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Commentary

Brain Oscillations, Medium Spiny Neurons, and Dopamine

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SUMMARY

1. The striatum is part of a multisynaptic loop involved in translating higher order cognitive activity into action. The main striatal computational unit is the medium spiny neuron, which integrates inputs arriving from widely distributed cortical neurons and provides the sole striatal output.

2. The membrane potential of medium spiny neurons' displays shifts between a very negative resting state (down state) and depolarizing plateaus (up states) which are driven by the excitatory cortical inputs.

3. Because striatal spiny neurons fire action potentials only during the up state, these plateau depolarizations are perceived as enabling events that allow information processing through cerebral cortex – basal ganglia circuits. In vivo intracellular recording techniques allow to investigate simultaneously the subthreshold behavior of the medium spiny neuron membrane potential (which is a "reading" of distributed patterns of cortical activity) and medium spiny neuron firing (which is an index of striatal output).

4. Recent studies combining intracellular recordings of striatal neurons with field potential recordings of the cerebral cortex illustrate how the analysis of the input–output transformations performed by medium spiny neurons may help to unveil some aspects of information processing in cerebral cortex – basal ganglia circuits, and to understand the origin of the clinical manifestations of Parkinson's disease and other neurologic and neuropsychiatric disorders that result from alterations in dopamine-dependent information processing in the cerebral cortex – basal ganglia circuits.

KEY WORDS: striatal medium spiny neuron; cerebral cortex; in vivo intracellular recording; Parkinson's disease; EEG.

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The computations performed by the basal ganglia on cortical input, which are strongly dependent on the action of dopamine (DA), are required for sensorimotor competence, cognitive operation, and motivational processes. Neurons located in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) provide DA input to the dorsal striatum (DSt) and nucleus accumbens (NAcc), which are key components of parallel cerebral cortex – basal ganglia circuits. The *dorsal circuit*, which involves the DSt, is implicated in sensorimotor and cognitive function (Fig. 1), while the *ventral circuit* concerns the NAcc and is involved in cognition and motivation. The cerebral cortex provides an orderly projection to the DSt and NAcc, which in turn provide feedback to the frontal cortex via multisynaptic pathways involving the remaining basal ganglia nuclei and the thalamus (Albin *et al.*, 1989; Alexander *et al.*, 1986; Joel and Weiner, 1994; Kalivas and Nakamura, 1999; Pennartz *et al.*, 1994; Smith *et al.*, 1998).

The main striatal computational unit is the medium spiny neuron (MSN). A typical MSN receives a rich DA innervation and thousands of synaptic contacts proceeding from neurons distributed across several cortical areas. MSNs account for more than 90% of all striatal neurons, and constitute the only significant output of the striatum (Bolam *et al.*, 2000). Given that the MSNs are essential components of the cerebral cortex – basal ganglia multisynaptic loops, altered processing of cortical input at MSNs may affect higher brain functions. It is currently believed that abnormal processing of cortical input in the striatum, linked to deficient or enhanced DA neurotransmission, is involved in the genesis of Parkinson's disease, schizophrenia, Tourette's syndrome, obsessive–compulsive disorder, attention-deficit hyperactivity disorder, drug-addiction, and other widespread disorders (for reviews see Albin *et al.*, 1989; Brown *et al.*, 1997; Graybiel and Rauch, 2000; Nestler, 2001; O'Donnell, 1999; Wichmann and DeLong, 1996).

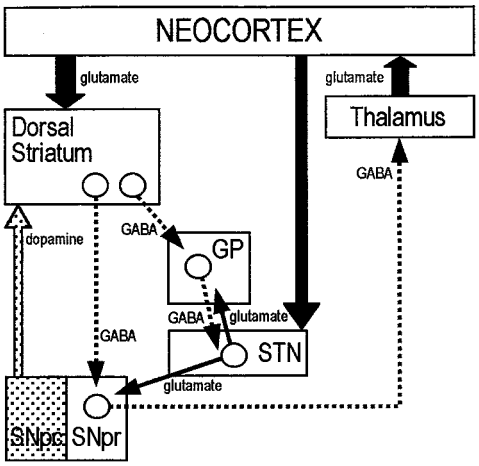

Fig. 1.

I. STRIATAL MEDIUM SPINY NEURONS DISPLAY A ROBUST SUBTHRESHOLD MEMBRANE POTENTIAL FLUCTUATION WHICH IS DRIVEN BY SYNCHRONOUS EXCITATORY SYNAPTIC INPUT

In intact anesthetized animals, striatal MSNs display a very polarized resting potential (*down state*) that is interrupted by robust depolarizing events known as *up states* (DSt: Calabresi *et al.*, 1990; Hull *et al.*, 1970; Wilson and Groves, 1981; NAcc: O'Donnell and Grace, 1995; Yim and Mogenson, 1988) (Fig. 2). Because striatal MSNs fire action potentials only during the up state, these plateau depolarizations have been perceived as "enabling events" that allow information processing through cerebral cortex – basal ganglia circuits (O'Donnell and Grace, 1995; Stern *et al.*, 1998).

In acute in vitro preparations, where active synaptic input is greatly reduced, potassium inwardly rectifying (Kir) currents hold the V_m of MSNs continuously in the down state (Nicola *et al.*, 2000; Surmeier and Kitai, 1993; Wilson, 1993). Therefore, up states are believed to be driven by excitatory input. In vivo studies revealed that DSt MSNs do not display up states in adult decorticated animals (Wilson, 1993; Wilson *et al.*, 1983). Furthermore, transitions between up and down states become evident in rat DSt neurons only 1 month after birth (Tepper *et al.*, 1998), corresponding to the time at which synapses between cortical axons and MSNs attain adult morphological features (Sharpe and Tepper, 1998). In NAcc neurons, up states are probably induced by hippocampal input, because fornix stimulation induces up states in NAcc neurons, while fornix lesions force NAcc neurons into a continuos down state (O'Donnell and Grace, 1995).

The view that the cerebral cortex is the main source of the "enabling input" is strongly supported by studies performed in organotypic cultures. As stated above, MSNs do not exhibit up states in acute brain slices, but they display plateau depolarizations having all the basic features of up states in chronic organotypic cultures constituted exclusively by neocortical and DSt tissue (Plenz and Aertsen, 1996). The fact that the glutamate receptor antagonist CNQX blocked the plateau depolarizations of MSNs suggest that in these cultures up states were induced by glutamate released

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Fig. 1. The cerebral cortex and basal ganglia are related via parallel multisynaptic loops. The main basal ganglia structure in the *dorsal circuit* is the dorsal striatum (DSt), which receives projections from almost all the neocortex and has a powerful direct inhibitory influence on the activity of the basal ganglia output nuclei (substantia nigra pars reticulata—SNpr—and entopeduncular nucleus—not shown). The output nuclei are further controlled by two strongly interconnected structures, the globus pallidus (GP) and subthalamic nucleus (STN). The activity of the GP–STN network is under the influence of the DSt (via an inhibitory DSt → GP connection) and the cerebral cortex (via an excitatory cerebral cortex → STN projection). Inhibitory projections from the output nuclei to the thalamus close the loop. This anatomical organization is often interpreted as to suggest that information flows from the DSt to the output nuclei through a *direct pathway* (DSt → output nuclei) and an *indirect pathway* (DSt → GP → STN → output nuclei). Activation of the MSNs that give rise to the direct pathway results in positive feedback to the cerebral cortex via the thalamus. Most basal ganglia structures receive dopamine from neurons located in the substantia nigra pars compacta (SNpc), but the DSt receives the bulk of the SNpc output. The entopeduncular nucleus and GP are the rodent homologues of the primate internal and external segments of the GP respectively.

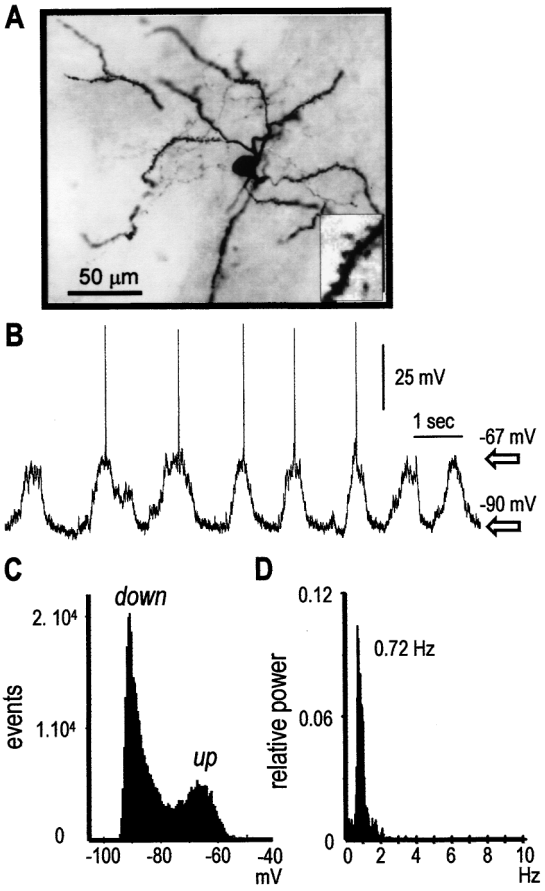

Fig. 2. A typical MSN of the dorsal striatum (A). Note the dendrites densely covered with spines. In anesthetized rats, the V_m of MSNs alternates rhythmically between a very polarized resting potential (*down state*) and plateau depolarizations lasting several hundred milliseconds (*up states*) (B). The histogram depicting the amount of time spent at any given potential illustrates the two-state behavior of the MSN V_m (C), and the power spectrum unveils the oscillatory nature of the MSN subthreshold fluctuation (D).

by corticostriatal axons (Plenz and Kitai, 1998). Interestingly, up states were separated by down states lasting several seconds in the chronic organotypic cultures. In contrast, down states typically last a few hundred milliseconds in intact anesthetized rats (Stern *et al.*, 1997). This difference led Plenz and Kitai (1998) to suggest that the pattern of cortical activity in the cultures differed from that observed in vivo, probably because of the lack of sculpturing thalamic activity in the cultures.

The above summarized facts stimulated in vivo studies aimed at disclosing the relationship between cortical activity and striatal MSN activity. Stern *et al.* (1997) found that corticostriatal neurons (CSNs) exhibited a robust two-state V_m fluctuation

that closely resembled that of DSt MSNs, in anesthetized rats. Given that CSNs fired action potentials only during the plateau depolarizations and that several thousand CSNs contact each MSN, the authors proposed that up states of CSNs should be nearly synchronous; otherwise the up states should be longer in MSNs than in CSNs. Taken together with the fact that the V_m fluctuation of both CSNs and MSNs exhibited a periodic behavior (~1 Hz), these findings suggested that CSNs and MSNs were oscillating synchronously.

In order to provide unequivocal evidence of oscillatory synchronization in a neuronal network several individual neurons must be recorded simultaneously. Alternatively, field potential recordings, like the electroencephalogram (EEG), provide information regarding synchronous activity of neuronal populations (McCormick and Bal, 1997; Steriade *et al.*, 2001; Varela *et al.*, 2001). A few laboratories have recently recorded the cortical field potential and the V_m of MSNs simultaneously, with an aim at understanding how cortical activity impacts on MSN function. Mahon *et al.* (2001) found that up states in both DSt MSNs and CSNs were tightly coupled to negative EEG waves that reflect a synchronous depolarization of cortical neurons, with CSN firing preceding MSN firing by ~20 ms. Similarly, Goto and O'Donnell (2001a) reported that up states in NAcc MSNs were tightly correlated to negative waves in the hippocampal field potential (~1 Hz) in chloral hydrate-anesthetized rats. Finally, we found (Kasanetz *et al.*, 2002; Tseng *et al.*, 2001a) that the two-state V_m of DSt MSNs and the slow rhythm that dominates the frontal cortex field potential of urethane-anesthetized rats exhibit a strong coherence at a frequency of ~1 Hz, with the cortical rhythm leading the MSN V_m fluctuation by ~20 ms (Fig. 3). Coherence attains a maximum value at a given frequency when the phase shift and ratio between the amplitudes of two waveforms remains constant (i.e., is a measure of the linear association between two signals), and is a very strong index of synchronous oscillation (Lopes da Silva *et al.*, 1989).

There is also evidence that up states occur synchronously in striatal MSNs. Stern *et al.* (1998) recorded pairs of DSt MSNs, and found that transitions between up and down states were tightly correlated among neurons. Furthermore, up states in NAcc neurons are synchronous with negative shifts in the NAcc local field potential (Goto and O'Donnell, 2001b; Leung and Yim, 1993), suggesting that these field potential variations reflect synchronous transition to the up state in a population of NAcc neurons.

II. CHRONIC NIGROSTRIATAL LESIONS PROMOTE SPREADING OF SLOW CORTICAL RHYTHMS THROUGH THE STRIATAL MEDIUM SPINY NEURONS TO THE BASAL GANGLIA OUTPUT NUCLEI

Taken together, the above revised findings indicate that the slow synchronous rhythm that dominates the cortex of anesthetized animals is encoded by striatal MSNs as a subthreshold V_m oscillation, i.e., the MSN V_m fluctuation is a "reading" of the pattern of incoming cortical input. This reading is likely to be influenced by several factors, including intrinsic membrane currents of MSNs (Nicola *et al.*, 2000; Surmeier and Kitai, 1993; Wilson, 1993), the actions of striatal interneurons (Kaneko *et al.*, 2000;

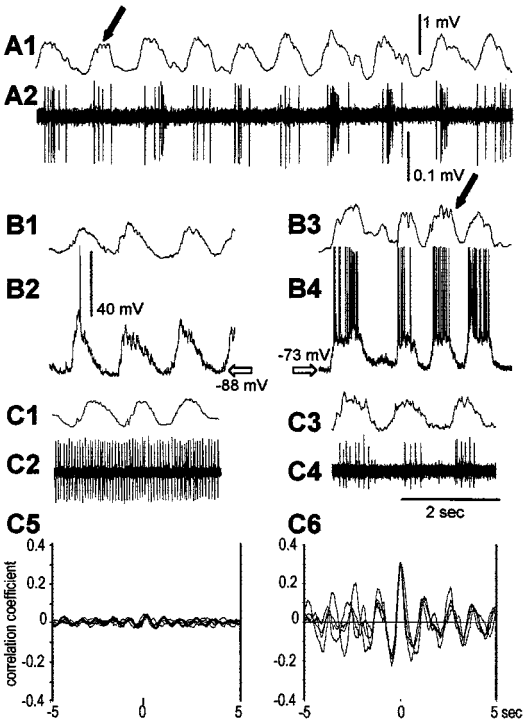

Fig. 3. In urethane-anesthetized rats the local field potential recorded through a macroelectrode placed in the frontal cortex displays a high-amplitude ~1 Hz rhythm (A1), which is known as "the slow oscillation" (Steriade, 2000). This slow oscillation reflects widespread synchronous activity of neurons in the thalamo-cortical network. Neurons in the deep layers of the frontal cortex exhibit action potential bursts (A2) that, in our recording conditions (differential recording through macroelectrodes placed in the frontal cortex), coincide with the positive wave of the field potential oscillation. The "active phase" of the wave can also be identified by the presence of spindles (*black arrows*). Simultaneous recordings of the frontal cortex field potential (B1) and the V_m of DSt MSNs (B2) revealed that the two-state behavior of the MSN V_m reflects the slow neocortical oscillation. The strength of this correlation is similar in control (B1, B2) and 6-OHDA-lesioned rats (B3, B4). But the cortical slow oscillation is well reflected only in the spike trains of MSNs from rats with nigrostriatal lesions, because the MSNs from control rats have a very low firing probability during the up states (Tseng *et al.*, 2001a). The SNpr units of control rats (C2) do not reflect the cortical slow oscillation (C1). In contrast, the rhythmic bursts (C4) of units from the SNpr of a rat with a severe nigrostriatal lesion are strongly coupled to the cortical slow oscillation (C3) (Belluscio *et al.*, manuscript in preparation). (C5, C6) Cross-correlograms of the simultaneous EEG-SNpr recordings displayed above. Results from several disjoined epochs were superimposed to demonstrate the stability of the correlation.

Kawaguchi *et al.*, 1995; Koos and Tepper, 1999, 2002; Saka *et al.*, 2002), the local network of axon collaterals of MSNs (Bar-Gad and Bergman, 2001; Groves, 1983; Plenz and Kitai, 2000; Wickens, 1993), and the short- and long-term plasticity phenomena that take place at corticostriatal synapses (Arbuthnott *et al.*, 2000; Centonze *et al.*, 2001; Cepeda and Levine, 1998; Lovinger and Tyler, 1996). DA modulates all these cellular and network features (see references above). Therefore, the MSN V_m waveform seems a good starting point to analyze the impact of changes in DA-mediated transmission on the representation of cortical activity in the basal ganglia.

During some years we have been interested in the electrophysiological changes that take place in the basal ganglia in experimental parkinsonism. In idiopathic Parkinson's disease, clinical signs become evident when ~80% of striatal DA content and more than 50% of SNpc neurons are lost (Bernheimer *et al.*, 1973; Fearnley and Lees, 1991). Degeneration of SNpc neurons begins several years before the clinical signs of Parkinson's disease become unambiguous. The signs of the disease are believed to result from changes in the activity of neurons in the denervated striatum, the globus pallidus – subthalamic nucleus (GP–STN) network, and the basal ganglia output nuclei (Bergman *et al.*, 1990; Davis *et al.*, 1997; Filion *et al.*, 1991; Levy *et al.*, 2001; Limousin *et al.*, 1995).

It has been repeatedly demonstrated that the temporal pattern of activity of neurons in the GP and Substantia nigra pars reticulata SNpr (which are the main targets of DSt MSNs; Fig. 1) is altered in animal models of Parkinson's disease. Specifically, (SNpr) and GP neurons display rhythmic bursting activity in animals with chronic severe lesions of the nigrostriatal pathway (MacLeod *et al.*, 1990; Murer *et al.*, 1997; Ni *et al.*, 2000; Pan and Walters, 1988). In the 6-hydroxydopamine-(6-OHDA) lesioned rat (a widespread experimental model of parkinsonism), we found that 30–40% of the units recorded from the SNpr exhibited *periodic* bursts at a frequency of ~1 Hz (Fig. 3) (Tseng *et al.*, 2001b). The fact that this rhythmic burst firing was reduced to a regular firing pattern (resembling activity in control rats) after intrastriatal administration of DA receptor agonists suggested the involvement of the DSt in the genesis of oscillatory bursting in the parkinsonian SNpr (Murer *et al.*, 1997; Tseng *et al.*, 2000, 2002).

Then, a substantial part of the SNpr units recorded from urethane-anesthetized 6-OHDA rats exhibit oscillatory bursting at the same frequency at which the V_m of DSt MSNs oscillates synchronously with the frontal cortex field potential in the healthy urethane-anesthetized rat. Given that, we performed in vivo intracellular recordings of DSt neurons in 6-OHDA-lesioned rats, and noticed that their MSNs exhibited short duration and more depolarized down states, and were more likely to fire action potentials during the up states than were MSNs of control rats. As a result, the ~1 Hz neocortical rhythm was well reflected in the spike trains of MSNs from rats with nigrostriatal lesions, but not in those of control rats, the MSNs of which displayed a very low firing probability (Fig. 3) (Tseng *et al.*, 2001a). By recording the frontal field potential together with unit activity in the SNpr we have been able to demonstrate a strong correlation between the slow rhythm that dominates the neocortex of anesthetized animals and oscillatory bursting in the 6-OHDA rat SNpr (Fig. 3) (Belluscio *et al.*, manuscript in preparation; Tseng *et al.*, 2002).

Our results support that the increased firing probability of DSt MSNs allows spreading of slow cortical rhythms to the GP and the basal ganglia output nuclei in experimental parkinsonism. But this is probably not the only mechanism contributing to the appearance of oscillatory bursting in parkinsonism. The fact that MSNs of rats with nigrostriatal lesions display increased coupling via gap junctions may contribute to synchronize neuronal activity in the DSt (Cepeda *et al.*, 1989; Onn and Grace, 1999; Tseng *et al.*, 2001a). There is also evidence that the corticosubthalamic pathway contributes to the propagation of slow cortical rhythms to the GP in rats with chronic nigrostriatal lesions (Magill *et al.*, 2001) (Fig. 4). In addition, the GP–STN network can behave as a pacemaker oscillating at 0.4–2 Hz in chronic organotypic cultures lacking DA neurons (Plenz and Kitai, 1999). It seems likely that in vivo the spreading of slow cortical rhythms through the DSt → GP and the cerebral cortex → STN pathways would bolster the intrinsic oscillatory capacity of the GP–STN network and contribute to the generation of rhythmic bursting activity in the basal ganglia output nuclei in experimental parkinsonism. Indeed, STN lesions reduce the proportion of units showing rhythmic bursts in the SNpr of 6-OHDA-lesioned rats (Tseng *et al.*, 2001b).

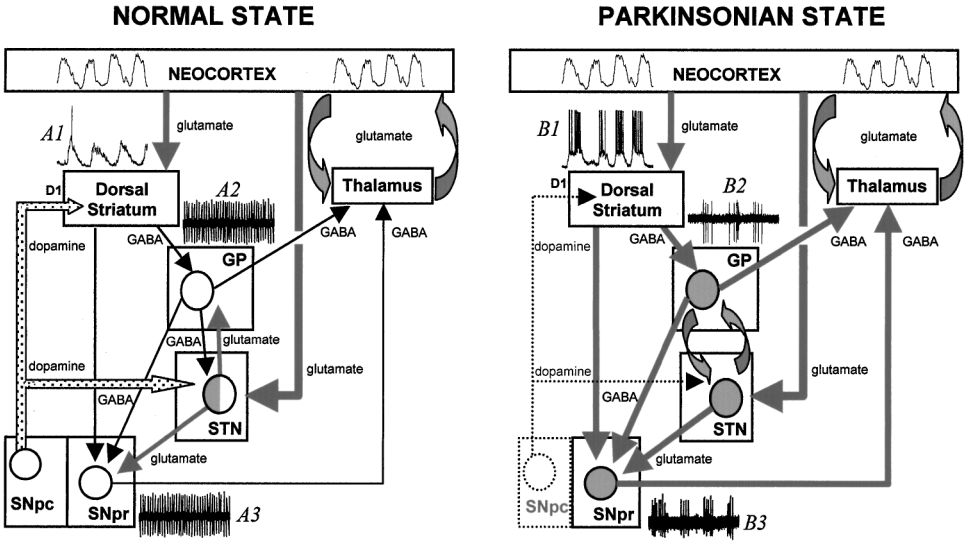

Fig. 4. Possible mechanisms involved in the generation of low-frequency oscillatory bursting of basal ganglia neurons in 6-OHDA-lesioned rats. In normal conditions (*left*), slow oscillations in the thalamo-cortical network do not have a strong impact on the firing pattern of units in the SNpr and GP. Even though the thalamo-cortical slow rhythm is reflected in the subthreshold oscillation of MSNs (A1), the firing probability of MSNs is too low to encode the rhythm and drive the activity of GP (A2) and SNpr (A3) units. Severe nigrostriatal lesions (*right*) liberate MSNs of the continuous restraining action exerted by D1-class dopamine receptors, allowing the transfer of cortical slow rhythms through MSNs (B1) to the GP (B2) and SNpr (B3) (Tseng *et al.*, 2001a). The cortical slow rhythm is also transferred more efficiently via the corticosubthalamic pathway to the GP and SNpr after nigrostriatal lesions (Magill *et al.*, 2001). It seems likely that the influence of these combined oscillatory inputs, together with the lack of dopamine, should unmask the intrinsic oscillatory potential of the GP–STN network (Plenz and Kitai, 1999). Taken together, these observations suggest that nigrostriatal lesions propitiate a reinforcing interaction between the thalamo-cortical and GP–STN networks that promotes oscillatory synchronization of large populations of forebrain neurons at low frequencies.

Interestingly, oscillatory activity in the parkinsonian basal ganglia should be expected to have a strong impact on thalamic activity. In the parkinsonian state, not only the output nuclei projection directed to ventral and anterior thalamic nuclei, but also the GP projection directed to the thalamic reticular nucleus (Smith *et al.*, 1998), probably encode as rhythmic burst firing the low frequency signal emanating from the neocortex. In turn, this rhythmic basal ganglia activity may reinforce oscillatory synchronization at low frequencies in the thalamo-cortical network (Steriade, 2000). This mutually reinforcing interaction may promote resonance of large populations of thalamo-cortical and basal ganglia neurons at low frequencies and corrupt the computations underlying behavioral activity (Brown and Marsden, 1998; see below).

III. D1-CLASS DOPAMINE RECEPTORS CONTROL THE FLOW OF CORTICAL SLOW RHYTHMS THROUGH STRIATAL MEDIUM SPINY NEURONS IN EXPERIMENTAL PARKINSONISM

Our observations indicating that rhythmic burst firing in the SNpr can be reduced to a regular firing pattern (resembling activity in control rats) after intrastriatal administration of D1-class DA receptor agonists (Tseng *et al.*, 2000, 2002) suggested that striatal D1-class receptors control the flow of cortical slow rhythms through the DSt in the parkinsonian state. Given that the change that propitiates spreading of ~1 Hz cortical synchronous activity to striatal projection targets is apparent in the attributes of the V_m of MSNs, we assessed the effect of D1-class agonists on MSNs in anesthetized 6-OHDA rats (Tseng *et al.*, manuscript submitted for publication).

The MSNs recorded from 6-OHDA rats displayed a more depolarized membrane potential (resulting in increased firing probability), and spent less time in the down state (Tseng *et al.*, 2001a). After systemic administration of D1-class agonists (but not vehicle) the V_m in both the down and up states was significantly more polarized, the down states lasted longer, and most MSNs became silent. Activation of D1-class DA receptors did not have strong effects on the monosynaptic response of MSNs to frontal cortex stimulation. In contrast, the changes induced by 6-OHDA lesions in the long-lasting hyperpolarization–depolarization sequence evoked by cortical stimulation, which reflects interactions at multiple levels along the cerebral cortex – basal ganglia network, were normalized by systemic administration of D1-class agonists (Fig. 5), but not by vehicle. These observations suggest that the D1-class agonists had an impact on network dynamics that probably results from subtle actions at multiple pre- and postsynaptic sites.

Despite the large body of in vitro data on DA actions at the cellular and synaptic level, it has been difficult to characterize the impact of DA at the "systems level," largely because it is difficult to preserve functional connectivity in acute in vitro preparations. The picture emerging from in vitro studies stresses that D1-class receptors increase "signal-to-noise ratio" in MSNs (reviewed by Nicola *et al.*, 2000), by increasing the Kir currents that hold them in the down state (Pacheco-Cano *et al.*, 1996) while enhancing calcium L-type currents that can sustain up states and promote firing (Hernández-López *et al.*, 1997; Surmeier *et al.*, 1995) as well as NMDA receptor-mediated synaptic excitation (Cepeda and Levine, 1998). Indeed, Hernández-López

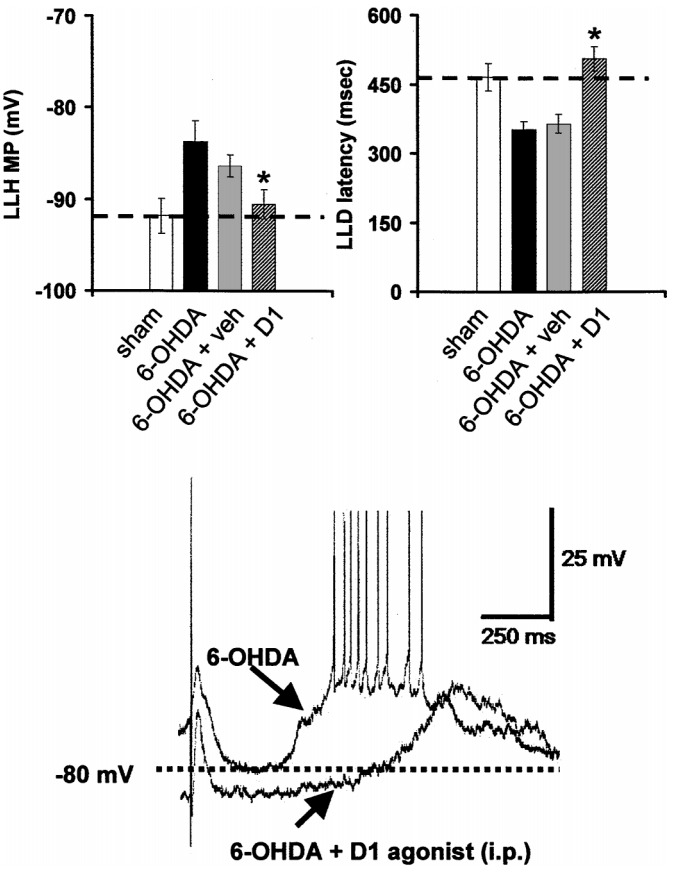

Fig. 5. The response of DSt MSNs to frontal cortex stimulation comprises a monosynaptic EPSP followed by a long-lasting hyperpolarization (LLH) and a long-lasting depolarization (LLD). The EPSP is produced by activation of a small volume of cortical tissue around the electrode tip. Instead, the LLH–LLD sequence is probably driven by a hypersynchronous cortical activity cycle that indicates resumption of the endogenously generated rhythm. Then, the LLH–LLD sequence closely resembles a down-to-up state transition (Wilson, 1993; Tseng *et al.*, 2001a). The latency, amplitude, and duration of the EPSP are not affected by 6-OHDA lesions or D1-class agonists. In contrast, the changes induced by 6-OHDA lesions in the LLH–LLD sequence (more depolarized LLH and reduced latency of the LLD) were reduced to normal values by systemic administration of D1-class agonists. *significantly different from 6-OHDA + vehicle.

et al. (1997) found that firing evoked by a current step was decreased by D1-class agonists when the resting MSN V_m was close to the potassium equilibrium potential, but if the resting V_m was held at a depolarized value (around −55 mV) D1-class agonists increased the firing response to further current injection. These findings suggest that the action of DA through D1-class receptors is opposite to the effect of cortical input when MSNs are at the down state, but promote firing once MSNs have reached the up

state (Hernández-López *et al.*, 1997). Even though a comprehensive analysis of DA actions on striatal neurons is beyond the scope of the present paper (see Calabresi *et al.*, 2000, Cepeda and Levine, 1998; Nicola *et al.*, 2000, for recent reviews), we will briefly discuss our findings in the context of current understanding of D1-class receptor function in vivo, because at first glance our data seem to indicate that D1-class receptors largely inhibit striatal neuron activity in the parkinsonian state.

It has been proposed that there are two modes of DA release by mesencephalic DA neurons. A tonic release mode contributes to sustain a stable low level of extracellular fluid (ECF) DA in the forebrain, while a phasic release mode steeply increases DA at synaptic clefts when mesencephalic DA neurons are activated by behaviorally meaningful stimuli (Grace, 1991). A study by Kiyatkin and Rebec (1999) provided evidence suggesting that the steady low level of ECF DA contributes to restrain striatal neuron responsiveness to excitatory input via an action on D1-class receptors. Specifically, systemic administration of a D1-class antagonist strongly elevated spontaneous activity in the striatum of awake unrestrained rats, attenuated the inhibitory effect of iontophoretically applied DA on basal firing rates, and increased striatal neuron responsiveness to iontophoretically applied glutamate. In contrast, studies aimed at examining the effect of phasic DA release suggested an excitatory action of D1-class receptors. Gonon (1997) reported that DA released in the DSt by burst stimulation of the medial forebrain bundle had an excitatory effect on a subpopulation of striatal neurons, which was mediated by D1-class receptors. Furthermore, DA released by burst stimulation of the VTA contributes to sustain plateau depolarizations in prefrontal cortex neurons via stimulation of D1-class receptors (Lewis and O'Donnell, 2000). It is tempting to speculate that continuous stimulation of D1-class receptors by ECF DA contributes to hold MSNs in the down state, but when the excitatory input becomes strong enough as to overcome the restraining effect of the ECF DA tone, concomitant phasic DA release helps to sustain the up state and promotes firing by activating a subset of D1-class receptors that are close to the DA release sites.

In this context, the increased impact of cortical input on DSt MSNs from 6-OHDA rats may primarily reflect the reduction of the D1-class receptor-mediated restraining effect of ECF DA tone. Consistent with this interpretation, 6-OHDA administration does not give rise to behavioral deficits unless the damage to the nigrostriatal system was severe enough as to produce a significant decrease of ECF DA concentration (Abercrombie *et al.*, 1990; Robinson *et al.*, 1994; Robinson and Whishaw, 1988).

IV. COUPLING BETWEEN EEG RHYTHMS AND OSCILLATORY ACTIVITY IN THE HUMAN PARKINSONIAN BASAL GANGLIA DEPENDS ON THE AVAILABILITY OF DOPAMINE

The above summarized conception regarding the propagation of slow cortical rhythms through the basal ganglia in experimental parkinsonism and its dependence on the lack of stimulation of D1-class DA receptors is based on data from anesthetized rats. It is clear that population activity of the thalamo-cortical network is

strongly influenced by anesthesia. Rhythmic high-amplitude slow waves synchronized over widespread areas of the neocortex dominate the EEG of animals and humans during anesthesia and natural slow-wave sleep (SWS). The most powerful spectral component of this "synchronized EEG" has a frequency of 0.5–1 Hz and is called "slow oscillation." The EEG slow oscillation reflects synchronous shifts in the V_m of large populations of cortical neurons (Steriade *et al.*, 2001). During the depolarizing phase of the V_m oscillation, cortical neurons (including CSNs; Mahon *et al.*, 2001) fire action potential bursts (reviewed by Steriade, 2000).

If the ~1 Hz neocortical oscillation is typical of SWS and anesthesia, what is the meaning of the spreading of this rhythm through the basal ganglia in experimental parkinsonism? Rhythmic bursting activity is increased in the striatum, GPe, STN, and basal ganglia output nuclei of awake monkeys after methyl-phenyl-tetrahydropyridine- (MPTP) induced lesions of the nigrostriatal system (Bergman *et al.*, 1994; Filion and Tremblay, 1991; Goldberg *et al.*, 2002; Nini *et al.*, 1995; Raz *et al.*, 1996, 2000, 2001), and there is strong evidence supporting the synchronization of abnormal burst discharges within the basal ganglia in this model (Goldberg *et al.*, 2002; Nini *et al.*, 1995; Raz *et al.*, 1996, 2000, 2001). Furthermore, the STN and GPi exhibit synchronous oscillatory activity in awake individuals with Parkinson's disease (Brown *et al.*, 2001; Cassidy *et al.*, 2002; Hurtado *et al.*, 1999; Levy *et al.*, 2000, 2002a,b). Both in the MPTP monkey and in idiopathic Parkinson's disease, synchronous oscillations occur in a broad frequency band (from <5 Hz to ~40 Hz). We have proposed that the different frequencies of oscillations recorded from the basal ganglia of anesthetized 6-OHDA rats and awake parkinsonian primates may reflect the distinct patterns of cortical activity that characterize particular behavioral states (Tseng *et al.*, 2001a).

During quiet resting the animal and human EEG displays synchronous oscillations, but these oscillations have higher frequency (theta and alpha rhythms) than do the "slow oscillation." An EEG pattern characterized by low-amplitude high-frequency modulations (beta and gamma activity) becomes prevalent when a subject performs demanding sensorimotor or cognitive tasks. This EEG pattern has traditionally been referred to as "desynchronized EEG," because the underlying cortical neuronal activity is poorly correlated across the neocortex when compared to that giving rise to slow waves. However, the term "desynchronized EEG" is somehow misleading, because a close examination of neocortical activity during behavioral operation reveals that functionally related spatially distributed cortical foci become transiently synchronized in the gamma band range. These brief episodes of high-frequency synchronization are believed to encode information related to expectancy, action planning, perceptual grouping, and other sensorimotor and cognitive processes (reviewed by Engel *et al.*, 2001; Pulvermuller *et al.*, 1997; Rodriguez *et al.*, 1999; Varela *et al.*, 2001).

Recent studies by Brown and colleagues provide compelling evidence supporting that synchronous oscillatory activity in the human parkinsonian basal ganglia is coupled to neocortical rhythms, and that this coupling depends on the availability of brain DA. In awake patients "off medication" the field potential activity recorded from the STN and GPi was coherent with EEG activity picked up from electrodes placed over the sensorimotor cortex in two major frequency bands, <10 Hz and

15–30 Hz, with the EEG leading both the STN and GPi field potential by 20–30 ms (Marsden *et al.*, 2001; Williams *et al.*, 2002). The fact that conduction time between the cerebral cortex and STN in humans is probably less than 10 ms (Ashby *et al.*, 2001; Nambu *et al.*, 2000) favors the view that the striatum routes these cortical rhythms to the STN and GPi in the parkinsonian state (Williams *et al.* 2002). Levodopa administration reduced the degree of coupling between STN and GPi activity at low frequencies (<30 Hz) and resulted in a new coherence peak at ~70 Hz (Brown *et al.*, 2001). Interestingly, activity in the STN led that in the EEG at 70–85 Hz by ~20 ms (Williams *et al.*, 2002).

V. THE PREVALENT CORTICAL ACTIVITY STATE SETTLES THE TEMPORAL FEATURES OF MEDIUM SPINY NEURON ENABLING EVENTS

It is clear that the subthreshold V_m oscillation exhibited by MSNs in anesthetized animals reflects synchronous rhythmic activity of large populations of cortical neurons. But, how do MSNs behave under the influence of a "desynchronized EEG"? What is the functional meaning of up states? Do MSNs encode high-frequency cortical rhythms?

We have recently examined the effect of desynchronizing the EEG on the V_m of DSt MSNs. In anesthetized animals, EEG desynchronization may occur spontaneously or can be induced by sensory stimulation or electrical stimulation of the mesopontine tegmentum (Herculano-Houzel *et al.*, 1999; Moruzzi and Magoun, 1949; Steriade *et al.*, 1991). Instead of showing robust two-state V_m fluctuations, MSNs displayed a "persistent up state" during episodes of EEG desynchronization, which lasted until the frontal cortex resumed the ~1 Hz synchronous activity that is prevalent under urethane anesthesia (Fig. 6) (Kasanetz *et al.*, 2002). During EEG desynchronization, most cortical neurons exhibit irregular firing at high rates (Steriade *et al.*, 2001), suggesting that continuous impinging of excitatory input may have contributed to maintain MSNs in these persistent up states. The fact that each CSN provides synaptic input to hundreds to thousands of MSNs and each MSN receives contacts from thousands of CSNs (Cowan and Wilson, 1994) makes the corticostriatal projection a suitable anatomical substrate to provide the kind of sustained synaptic barrage required to hold a distributed set of MSNs in a persistent up state. In good agreement with this view, Mahon *et al.* (2001) reported that most CSNs are tonically active and DSt MSNs exhibit a steadily depolarized V_m in rats under neurolept analgesia, which is a pharmacologically induced state characterized by a "disorganized EEG" lacking slow rhythmic activity. Mahon *et al.* (2001) further showed that the ~5 Hz cortical rhythm induced by barbiturate anesthesia drives a robust ~5 Hz V_m fluctuation in MSNs. These observations strongly support the view that the V_m of MSNs is shaped by the activity states of the thalamo-cortical network.

Two-state transitions have been observed in MSNs of locally anesthetized paralyzed rats, in which up states can last several seconds (Wilson, 1993; Wilson and Groves, 1981). Indeed, Hull and coworkers reported in 1970 that the resting V_m of caudate nucleus neurons exhibits depolarizing shifts lasting "several seconds to

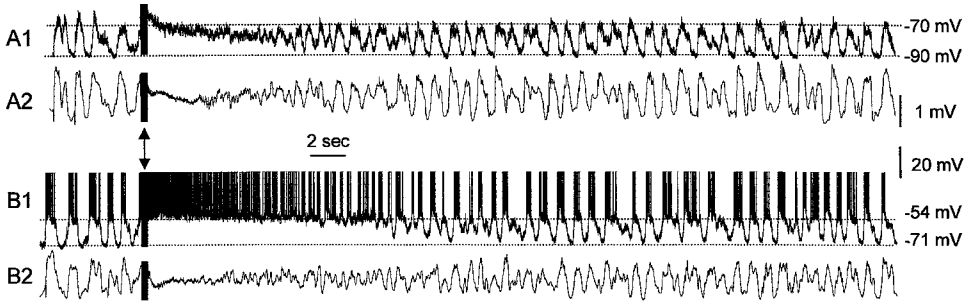

Fig. 6. Episodes of EEG desynchronization (A1, B1) evoked by electrical stimulation of the mesopontine tegmentum (*arrow*) in control (A) and 6-OHDA-lesioned rats (B). These episodes of desynchronization have been extensively used as models for the study of cortical activated states (Herculano-Houzel *et al.*, 1999; Moruzzi and Magoun, 1949; Steriade *et al.*, 1991). The two-state behavior of the MSN V_m (A2, B2) is disrupted during EEG desynchronization. Instead, the MSNs displayed "persistent up states" during EEG desynchronization (Kasanetz *et al.*, in press).

minutes" during which the neurons become spontaneously active, in nonanesthetized paralyzed cats. Thus, up states were less stereotyped and had more variable lengths in nonanesthetized preparations, the cortical activity states of which should have fluctuated dynamically (Wilson, 1993). This observation is also consistent with the idea that the cortical activity state settles the shape of the MSN V_m, and indicates that up states are not a peculiarity of anesthetized preparations, but a natural process that must have a deep impact on MSN computational capabilities.

VI. ENABLING EVENTS OF DIFFERENT LENGTH MIGHT UNDERLIE THE PROCESSING OF DIFFERENT KINDS OF CORTICAL INFORMATION

The conceptual framework underlying current theoretical analysis of the functional meaning of up states has been elegantly put forward by O'Donnell and Grace in 1995. In the NAcc the input producing up states comes from the hippocampus (see Section I). Because NAcc MSNs fire action potentials only in response to prefrontal cortex stimulation during the hippocampal driven plateau depolarizations, O'Donnell and Grace (1995) postulated that by impelling ensembles of NAcc neurons into the up state, the hippocampus selects subcortical channels for processing the neocortical inputs that underlie cognitive operations. The fact that the hippocampus and other limbic structures display a synchronous field potential oscillation (theta rhythm) during exploratory activity and bar pressing in rats (Feder and Ranck, 1973; Leung and Yim, 1993; reviewed by Lopes da Silva *et al.*, 1990), together with the finding that synchronous hippocampal activity drives up states in the NAcc (Goto and O'Donnell, 2001a), advocates for a role of two-state alternation of NAcc neurons in information processing. Indeed, pairs of simultaneously recorded NAcc and hippocampal units exhibit synchronous rhythmic firing (theta band frequency) in behaving rats (Tabuchi *et al.*, 2000). Thus, synchronous limbic input seems to *gate* neocortical information processing in the NAcc (Goto and O'Donnell, 2001a).

The nature of the "enabling signal" and the "gated inputs" acting upon DSt MSNs is less well understood. Because the neocortex drives up states in the DSt (see Section I), Stern *et al.* (1997, 1998) proposed that the specific cortical input that provokes MSN firing is embedded within the enabling neocortical signal. Our recent findings support that the prevailing neocortical activity state defines the temporal features of the striatal gate involved in the analysis of the more specific inputs. In a DSt region overwhelmed by a neocortical "activated" area, the striatal gate would remain open for as long as the cortex remains desynchronized (Kasanetz *et al.*, in press).

It is well known that DSt neurons can exhibit sustained firing for several seconds in behaving animals (Apicella *et al.*, 1992; Boussaoud and Kermadi, 1997; Schultz and Romo, 1992). Schultz and Romo (1992) showed that monkey caudate/putamen neurons display sustained activations lasting up to several tens of seconds during a delayed response task, and that longer delays resulted in activations of increasing length. The authors noticed that sustained neuronal activity related to movement preparation progresses in large areas of the frontal cortex and caudate/putamen concurrently, but it begins slightly earlier in the cerebral cortex (Romo and Schultz, 1992; Schultz and Romo, 1992; see also Alexander and Cruchter, 1990). We have postulated that persistent up states underlay the sustained activation of striatal neurons that takes place during behavioral operations requiring unremitting cortical activity (Kasanetz *et al.*, 2002).

A distinction of up states on the basis of their length deserves attention because of the meaningfulness of the cortical activity patterns that probably drive them. The excitability of MSNs depends on intrinsic membrane currents that are strongly modulated by DA receptors and exhibit elaborate voltage-dependent activation and inactivation kinetics (Nicola *et al.*, 2000). Because of their voltage-dependence, the availability of these currents would be determined by the recent V_m history. Recent studies support that both the MSN response to electrical stimulation of cortical foci (Mahon *et al.*, 2000), and the effect of dopamine agonists on MSN excitability (Hernández-López *et al.*, 1997; see Section III), vary as function of the recent V_m history, which in vivo is dictated by the prevalent cortical activity state. For instance, Mahon *et al.* (2000) provided in vivo data showing a time-dependent facilitatory effect of depolarizing current prepulses on the response of DSt MSNs to cortical stimulation. The authors proposed that this time-dependent facilitation reflects the kinetics of a potassium current which is available at around -60 mV and recovers slowly from inactivation. These observations suggest that MSNs may process specific cortical input differently depending on the general pattern of cortical activity in which the specific input is embedded (Kasanetz *et al.*, 2002).

VIII. CONCEIVING THE ROLE OF THE DORSAL STRIATUM AND DOPAMINE IN SHAPING THE NEURAL REPRESENTATIONS OF COGNITIVE AND SENSORIMOTOR ACTIVITY

The DSt occupies a critical position within a multisynaptic loop that is involved in translating higher order cognitive activity into action (Graybiel *et al.*, 1994; Hollerman *et al.*, 2000; Houk and Wise, 1995; Salinas *et al.*, 2000). This process is

believed to involve reverberating activity in the loop during time windows of variable length. For instance, the preparatory activity that precedes movement may last several seconds and builds-up concurrently in the frontal cortex and basal ganglia (see Section VI). Translating cognitive activity into action is further believed to require a classification of the input patterns (Plenz and Kitai, 2000), an extraction of the "salience" of the input patterns (Gurney *et al.*, 2001), or a reduction of the dimensionality of the input space (Bar-Gad and Bergman, 2001), because the cortical representations of higher order cognitive states are supposed to be more widely distributed and involve a higher number of neurons than the cortical representation of the better adapted behavioral output. Indeed, higher order cognitive states are believed to be encoded by widely distributed ensembles of cortical neurons displaying synchronized activity in the gamma band (Engel *et al.*, 2001; Pulvermuller *et al.*, 1997; Rodriguez *et al.*, 1999; Varela *et al.*, 2001) while a behavioral output representation is supposed to consist of synchronized neuronal ensembles oscillating at high frequencies in the motor cortical areas (Brown, 2000). Even though interactions between the direct and indirect pathways at the level of the basal ganglia output nuclei presumably contribute to the process of mutation of one neural representation into another (Hikosaka *et al.*, 2000; Mink, 1996), it is likely that the striatum supports a large part of the computational load.

How would this operation be reflected in the activity of MSNs? The duration of up states probably reflects iterations of the loop. Among the enabled MSNs the probability of firing would be higher for those receiving finely correlated input through the most efficient corticostriatal connections. The gated cortical inputs (reflected in MSN firing) will result in positive feedback to the neocortex (Fig. 1; Hikosaka *et al.*, 2000; Mink, 1996), which may help to outline and stabilize the distributed representation that impelled the MSNs to threshold. During the iterative process the striatal representation would progressively shrink and positive feedback would progressively slide from frontal association to motor cortical areas, resulting in the development of a "winner" behavioral output representation. Phasic DA release may contribute to this process in "real time" by sustaining the up states and increasing firing probability of the most depolarized neurons (Hernández-López *et al.*, 1997; Lewis and O'Donnell, 2000), and by inducing potentiation of favored corticostriatal connections (Reynolds *et al.* 2001; Schultz, 1997). The local network of GABAergic axon collaterals of MSNs may also contribute significantly to delineate the ensembles of active MSNs (Bar-Gad and Bergman, 2001; Groves, 1983; Plenz and Kitai, 2000; Wickens, 1993).

We propose that the impact of DA on the operation of the cerebral cortex – basal ganglia loop can be interpreted in terms of the size of the cortical activity window that the MSN "reads" (Fig. 7). The restraining effect of ECF DA may help to define the span of the DSt gate, by maintaining the MSNs that receive weak cortical inputs far from threshold. In the parkinsonian condition, a reduction of the restraining effect of ECF DA should result in weak inputs from cortical regions that normally do not recruit a given MSN in an information processing channel becoming an effective enabling input. Firing probability should increase, as a result of the enlargement of the cortical activity window that the MSN reads. As a consequence, the number of iterations needed to sculpt a behavioral output representation in the motor cortical areas should increase, delaying movement initiation.

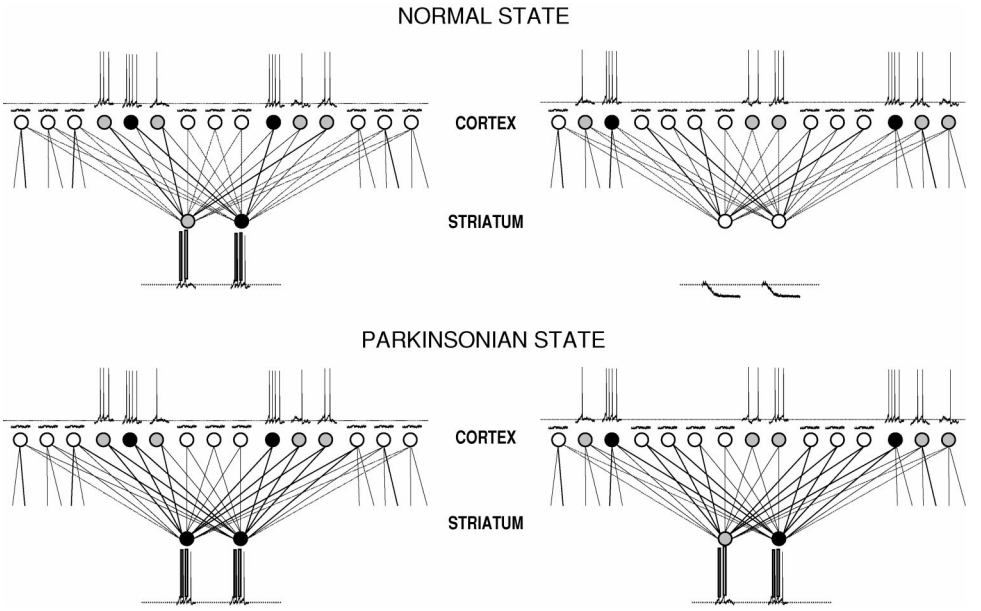

Fig. 7. The behavior of the V_m of a DSt MSN probably reflects interactions between global features of cortical network activity (enabling input) and focal features in the cortical areas providing the strongest synaptic input (specific input). *Normal state:* Cortical neurons provide either very strong (*thick solid lines*), strong (*thin solid lines*), or weak (*dotted lines*) input to a given MSN. The activation of a sufficient number of cortical neurons providing strong input (*gray somas*) will sustain the MSN V_m near threshold (*left*). Among the enabled MSNs, those receiving correlated input through the strongest input lines will fire (*black somas*). MSN are not impelled to the up state or are only slightly depolarized by weak inputs (*right*). *Parkinsonian state:* Chronic nigrostriatal lesions increase the impact of cortical input on MSNs (represented as a thickening of input lines), increasing the likelihood of firing in response to poorly correlated cortical inputs (*left*) and the probability of being recruited in a wrong information processing channel (*right*).

Remarkably, MSNs exhibit high-frequency V_m modulations in the top of the up states that eventually provoke firing (Kasanetz *et al.*, in press; Stern *et al.* 1997, 1998). Even though these high-frequency V_m modulations probably reflect finely correlated neocortical inputs, we failed to detect a significant coupling between the frontal EEG and the V_m of DSt MSNs at the "gamma band" during EEG desynchronization (Kasanetz *et al.*, in press; see also Mahon *et al.*, 2001). This failure might be accounted for by several facts. Anatomical matching between the EEG and intracellular recordings might had not been good enough as to detect high frequency oscillatory synchronization, or the phenomenon might had not been strong enough as to be detected in an anesthetized preparation. Furthermore, high frequency cortical oscillations might reflect inhibitory synaptic input to pyramidal neurons rather than neocortical output (Steriade, 2000). In order to definitively prove that firing of MSNs reflects coincident input from transiently bound distributed ensembles of cortical neurons, it should be necessary to record multiunit activity from functionally related cortical sites together with the V_m of MSNs in a nonanesthetized preparation. These demanding experiments will undoubtedly be performed in the near future.

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