

# Modulation of Cell Firing in the Nucleus Accumbens

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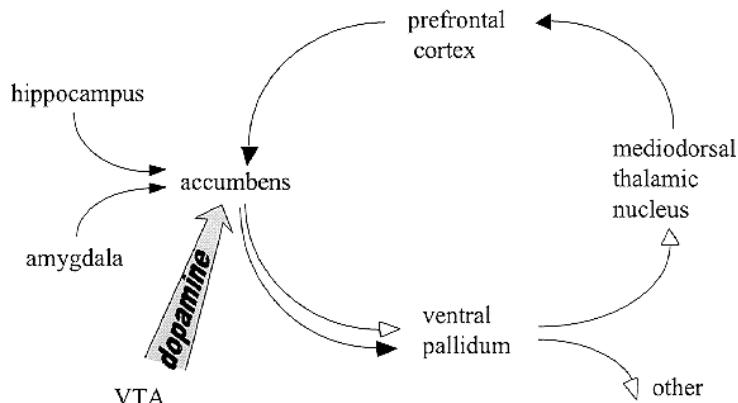
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**ABSTRACT:** Pennartz *et al.*<sup>48</sup> have proposed that functions of the nucleus accumbens (NA) are subserved by the activity of ensembles of neurons rather than by an overall neuronal activation. Indeed, the NA is a site of convergence for a large number of inputs from limbic structures that may modulate the flow of prefrontal cortical information and contribute to defining such ensembles, as exemplified in the ability of hippocampal input to gate cortical throughput in the nucleus accumbens. NA neurons exhibit a bistable membrane potential, characterized by a very negative resting membrane potential (down state), periodically interrupted by plateau depolarizations (up state), during which the cells may fire in response to cortical inputs. A dynamic ensemble can be the result of a distributed set of neurons in their up state, determined by the moment-to-moment changes in the spatial distribution of hippocampal inputs responsible for transitions to the up state. Ensembles may change as an adaptation to the contextual information provided by the hippocampal input. Furthermore, for dynamic ensembles to be functionally relevant, the model calls for near synchronous transitions to the up state in a group of neurons. This can be accomplished by the cell-to-cell transfer of information via gap junctions, a mechanism that can allow for a transfer of slow electrical signals, including "up" events between coupled cells. Furthermore, gap junction permeability is tightly modulated by a number of factors, including levels of dopamine and nitric oxide, and cortical inputs, allowing for fine-tuning of this synchronization of up events. The continuous selection of such dynamic ensembles in the NA may be disputed in schizophrenia, resulting in an inappropriate level of activity of thalamocortical systems.

## INTRODUCTION

The nucleus accumbens (NAcc) is a unique brain region involved in the adaptation of animals to their environment, with a participation in a variety of functions that are appetitive or aversive in nature.<sup>1</sup> This area is part of the basal forebrain and spans striatal and extended amygdala territories.<sup>2</sup> It has at least two distinct compartments that differ primarily with respect to their input/output organization<sup>3</sup> and in specific neurochemical markers,<sup>4,5</sup> with the core being the NAcc region that has more in common with the dorsal striatum and the shell being the NAcc territory that

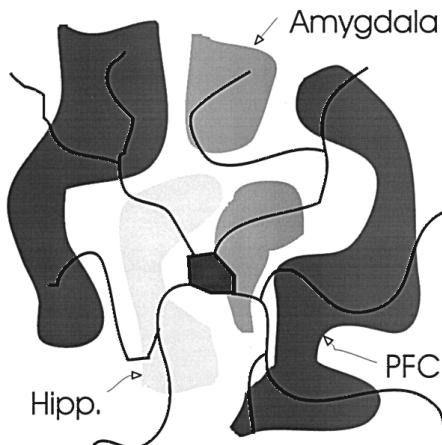
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**FIGURE 1.** Schematic representation of the circuits linking the hippocampus, nucleus accumbens, and prefrontal cortex. The accumbens, as a striatal link within these cortico-subcortical-cortical circuits, projects back to the PFC via its efferents to the ventral pallidum, which, in turn, inhibits specific thalamic nuclei. Open arrows represent GABAergic inhibitory synapses, and filled arrows represent excitatory projections that are mostly glutamatergic, with the exception of the projection from the accumbens to the ventral pallidum that presents substance P.

can be considered a component of the extended amygdala of Heimer and Alheid.<sup>2</sup> The NAcc has been described as participating in feeding mechanisms,<sup>6</sup> sexual behaviors,<sup>7</sup> reward,<sup>8,9</sup> cocaine self-administration,<sup>10,11</sup> stress,<sup>12</sup> spatial learning,<sup>13</sup> antipsychotic drug actions,<sup>14</sup> sensorimotor gating,<sup>15</sup> and probably in the pathophysiology of schizophrenia.<sup>16</sup> As a striatal component within basal ganglia-cortical circuits, the NAcc receives inputs from the prefrontal cortex (PFC) and other “limbic” areas and provides feedback to the PFC<sup>17,18</sup> (FIG. 1). The primary output of the NAcc is directed to the ventral pallidum (VP),<sup>19–22</sup> which among other targets provides an inhibitory input to the thalamocortical system originated in the mediodorsal nucleus (MD) and the reticular thalamic nucleus (RTN) as well.<sup>21,23</sup> Thus, information flowing through this region may be important in gating thalamocortical activity that provides a driving influence to the PFC.

Although a large number of studies have focused on physiological properties of NAcc neurons, several issues related to the information processing taking place in this structure have not been solved. In particular, the interactions among different inputs may be important for the functions in which the NAcc is involved. The NAcc receives afferents from a diverse set of structures involved in higher functions; in addition to the PFC,<sup>24</sup> these include the amygdala,<sup>25,26</sup> hippocampus,<sup>27</sup> and entorhinal cortex.<sup>28,29</sup> The spatial arrangement of these inputs onto their NAcc neuronal targets may determine the functional interactions among these systems. In this regard, anatomical studies have consistently shown that afferents from different sources very rarely overlap within the NAcc.<sup>30</sup> Although this may suggest that different inputs contact distinct populations of neurons in the NAcc, electrophysiological studies have shown a high degree of convergence of synaptic responses on single NAcc neurons evoked by stimulation of these inputs. Extracellular recordings from NAcc neu-



**FIGURE 2.** Hypothetical arrangement of terminal afferent fields and an accumbens neuron with its dendrites crossing the boundaries of nonoverlapping terminal fields. The areas with different shades of gray indicate hypothetical regions in which afferents from the amygdala, hippocampus (Hipp.) and PFC terminate. The location of synaptic contacts relative to the cell body will determine the impact these afferents will have on cell firing.

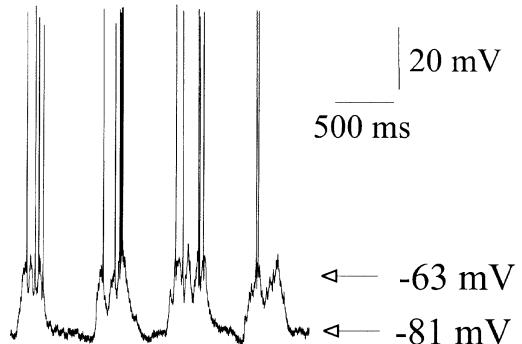
rons reported approximately a 10–30% convergence among inputs from the PFC and amygdala or hippocampus.<sup>31</sup> Furthermore, *in vivo* intracellular recordings revealed a much higher proportion of convergence (95%) for the same inputs.<sup>32</sup> This higher convergence observed with intracellular studies may be due to the ability of this technique to detect subthreshold responses that do not elicit action potential discharge. In that study, convergence was measured as the proportion of neurons showing synaptic responses to several afferents in the form of excitatory postsynaptic potentials (EPSP), which are beyond detection with extracellular recording techniques. The apparent discrepancy between anatomical and electrophysiological data, on the other hand, could be explained by the possibility that dendritic trees of NAcc neurons span areas containing terminals from different afferent systems, even if these do not overlap with each other (FIG. 2). In fact, neuroanatomical studies indicating little overlap among terminal fields from different sources did show a close interdigitization of these terminal fields within the NAcc.<sup>30</sup>

This convergence of “limbic” inputs within the NAcc could be involved in blending affective, cognitive, and motor functions within this ventral striatal region. However, the mechanism underlying such a synthesis is still poorly understood. Several models have proposed different views on the integration of information in the NAcc, differing essentially on the issue of whether there is a primary input that is modulated by others or whether all inputs are equally weighed. If the latter is true, the NAcc may behave as a coincidence detector.<sup>33</sup> Regardless of the relative relevance of different inputs, one of the systems affected by this convergence in the NAcc is the thalamic projection to the PFC via the MD. If the PFC input is the signal to be modulated, filtered or reinforced by other inputs, the question of how such influences are exerted remains open. Furthermore, the extensive monoaminergic innervation of the NAcc suggests that dopamine (DA) and other monoamines may play a role in

this integration of information. Addressing these and related issues is essential for a more thorough understanding of how basal ganglia loops control prefrontal cortical activity. This approach also offers the possibility of integrating into a single neural system the apparently unrelated brain regions that have been implicated in schizophrenia. Here we will review some recent studies on NAcc physiology using both *in vivo* and *in vitro* recording techniques, focusing on the integration of information in this nucleus and the role of dopamine in its information processing mechanisms.

### INTEGRATION OF INFORMATION IN THE NUCLEUS ACCUMBENS

The ability of NAcc neurons to integrate information provided by their inputs is a function of both their afferent organization and their electrophysiological properties. The former is important with respect to assessing the functional relevance of the spatial distribution of inputs to a set of NAcc neurons. Whether a particular set of afferents contacts spines on dendrites located distal from the soma or near the cell body will determine the relative impact these afferents may exert on cell firing. The closer these contacts are to the soma, the stronger will be their effects on membrane potential, resulting in a tighter control over cell activity. NAcc output neurons, the medium-sized densely spiny neurons, receive most of their glutamatergic afferents in the spines located in distal dendrites.<sup>80</sup> However, a fraction of hippocampal, but not PFC, afferents has been shown to contact proximal dendrites and the cell body,<sup>80</sup> positioning them to exert a strong control over cell firing. Furthermore, the electrophysiological properties of individual NAcc neurons are important in determining the relative probabilities that specific individual or groups of inputs will be capable of driving the neuron to firing threshold. NAcc neurons display a characteristic activity pattern in their membrane potential that can underlie complex interactions among afferent synaptic inputs. Most NAcc neurons exhibit a bistable membrane potential; that is, their resting membrane potential, typically very negative (*down state*), is periodically interrupted by plateau depolarizations (*up state*) that are 100–1,000 ms in duration and 10–25 mV in amplitude<sup>32,34</sup> (FIG. 3). These depolariza-

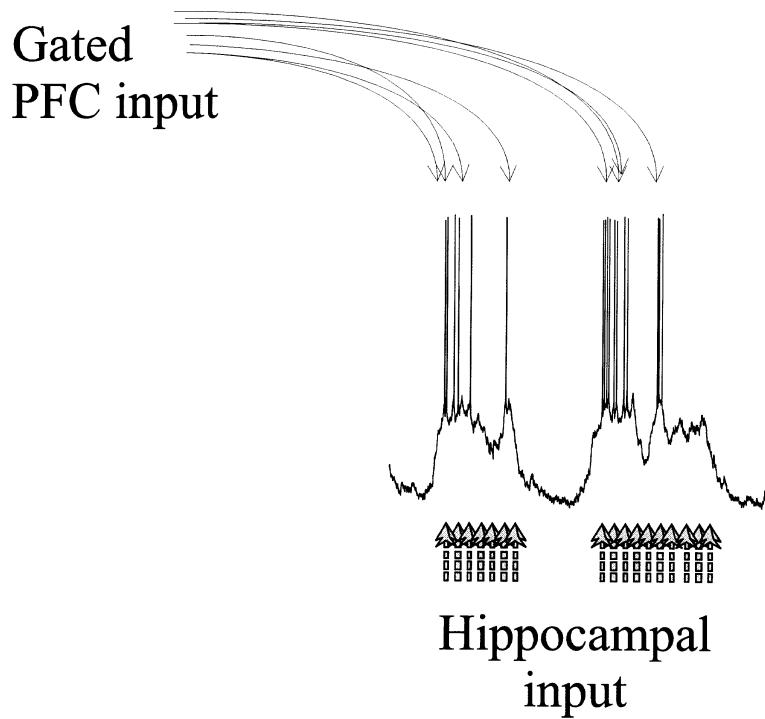


**FIGURE 3.** Most NAcc neurons exhibit up and down states in their membrane potential. The tracing shows a typical pattern of activity from a bistable neuron. Four up events are shown, and action potential firing is only observed during these events.

tions, or up events, bring the membrane potential of selected neurons close to their firing threshold during a relatively discrete time window. Such bistable membrane potential had been initially observed with *in vivo* intracellular recordings from dorsal striatal neurons as depolarizations underlying bursts of action potentials.<sup>35</sup> Yim and Mogenson<sup>36</sup> reported similar depolarizations in NAcc neurons. Using extracellular recordings, NAcc neurons were found to fire at very slow rates, with occasional bursts of 3 or 4 spikes.<sup>37</sup> It is likely that these bursts correspond to up events in NAcc neurons, because in studies using *in vivo* intracellular recordings, spontaneous action potential firing could only be observed during the up state.<sup>32</sup> The alternations between up and down states may provide a means to selectively gate the transfer of information in NAcc neurons by bringing their membrane potential close to their firing threshold, where afferent inputs are more likely to result in neuronal discharge. Any factor governing the transitions between states will thus have a strong impact on the ability of these neurons to convey to the thalamocortical system the messages they receive from different sources. This control of transitions between states in NAcc neurons can therefore be a very effective means of controlling thalamo-PFC activity.

The resting membrane potential of these neurons, the down state, is maintained at such negative values by a number of factors. A very important one is the inward rectifier K<sup>+</sup> conductance that medium spiny neurons exhibit.<sup>81</sup> As a result of this, any change in membrane potential is very effectively attenuated. However, with sufficient converging and synchronous arrival of glutamatergic excitatory inputs, a strong depolarization may occur. At this point, the inward rectifier current will be shut down, letting the membrane shift to a more depolarized value. This can explain why transitions between states occur abruptly, giving the impression of an all-or-none event rather than a gradual one.

Up events, on the other hand, are dependent on synaptic activation of NAcc cells. This is indicated by the fact that intracellular recordings *in vitro* yield silent neurons with a very negative and stable membrane potential, that lies within the range of the down state observed *in vivo*.<sup>38-40</sup> Furthermore, we have shown that stimulation of the fimbria-fornix system results in transitions to the up state in NAcc neurons.<sup>32</sup> The involvement of this fiber system in driving up events was further supported by *in vivo* intracellular recordings from animals that had received a transection to the fimbria-fornix. In this condition, neurons with a bistable membrane potential could not be detected in the NAcc, although they were still found in the caudate-putamen.<sup>32</sup> Most NAcc neurons recorded in these experiments were silent and exhibited a very negative membrane potential, which was within the range of the down state observed in control animals. Additional recordings were performed in rats before and after administration of the local anesthetic, lidocaine, into the fimbria-fornix. In these cases, up events were temporarily suppressed and returned to control levels approximately 15 to 20 min following the lidocaine injection.<sup>32</sup> Overall, these results indicate that afferents arriving to the NAcc via the fimbria-fornix are important, if not necessary, for the transitions to the up state (FIG. 4). The most likely source of such afferents is the hippocampal formation,<sup>41</sup> particularly the ventral subiculum. It should be noted that these recordings were performed from neurons located in the medial NAcc (either in the shell or the medial core), an area known to receive a dense projection from the ventral subiculum.<sup>27</sup>



**FIGURE 4.** Hippocampal gating of prefrontal cortical throughput in NAcc neurons. Tracing from a bistable NAcc neuron, with the vertical arrows indicating the influence of inputs arriving via the fimbria-fornix system that can induce and maintain up events. Because the up state elicited by these inputs brings the membrane potential close to firing threshold, afferent inputs arriving from the PFC (curved arrows) during these periods will easily elicit action potential firing. On the other hand, PFC inputs arriving during the down state will be largely ineffective with respect to action potential firing.

Although synaptic inputs are essential for the presence of up events, the relatively stable membrane potential and the long duration of these events may indicate that certain membrane properties may limit the extent of depolarization, whereas others may contribute to its persistence. Recent studies from striatal medium spiny neurons (which also show up and down states) have described the presence of slowly inactivating K<sup>+</sup> currents ( $I_A$ )<sup>42</sup> that may limit the extent of depolarizations, such as those constituting the up state,<sup>43</sup> maintaining the membrane potential during these depolarizations just below firing threshold. In addition, striatal and NAcc neurons exhibit a slow voltage-dependent Na<sup>+</sup> current<sup>44</sup> and slow Ca<sup>2+</sup> conductances<sup>38,45</sup> that may contribute to the persistence of such depolarizations. As a consequence of the interaction between these forces driving and limiting these depolarizations, up events may take the form of a stable plateau depolarization.

If the subicular afferents are an important factor driving up events in NAcc neurons, then these inputs may have a crucial role in determining the ability of NAcc

neurons to trigger action potential discharge in response to other inputs. Indeed, activation of PFC afferents elicits action potential firing only during the up state, independently of whether it occurs spontaneously or is evoked by fornix stimulation.<sup>32</sup> Because the spontaneously occurring up events can be eliminated by transection or local anesthetic application into the fimbria-fornix, it is possible that they are dependent on hippocampal inputs. Thus, this could be envisioned as a gating mechanism, by which the hippocampal afferents are driving a distributed set of NAcc neurons into the up state, allowing them to fire in response to ongoing cortical afferent input activity.

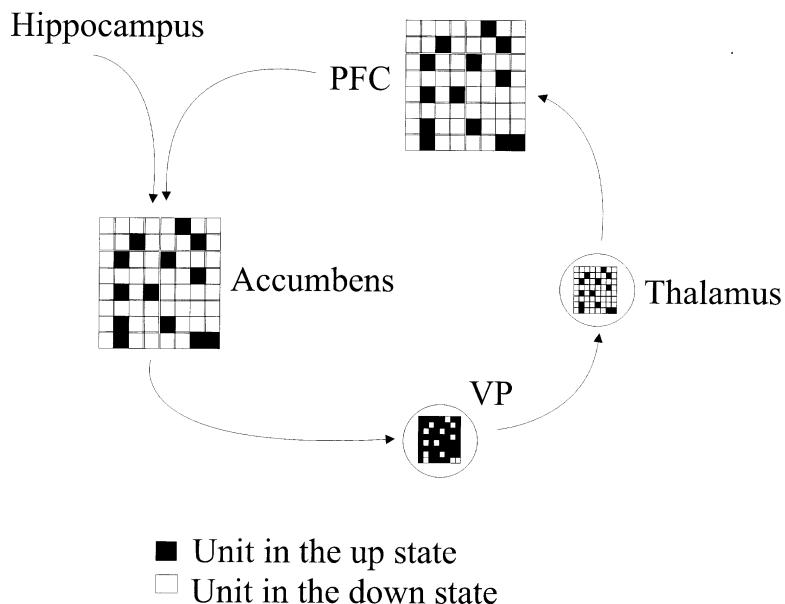
The hippocampal input to the NAcc may also control the activity of the DA innervation of this region. For example, D<sub>2</sub> DA receptors in the NAcc increase two weeks after hippocampal kindling.<sup>46</sup> Moreover, neonatal hippocampal lesions have recently been observed to decrease the DA transporter (DAT) in mesencephalic DA neurons.<sup>47</sup> In short, hippocampal afferents may have a role in the control of the flow of information through the NAcc by a variety of mechanisms.

### ENSEMBLE CODING IN THE NUCLEUS ACCUMBENS

Pennartz *et al.*<sup>48</sup> have proposed that NAcc functions are subserved by the activity of ensembles of neurons rather than by an overall neuronal activation. We believe that this concept can be extended to suggest that ensembles can be dynamic and based on activity states, rather than solely on connectivity patterns.<sup>49</sup> Indeed, the NAcc is a site of convergence for a large number of inputs from limbic structures that may modulate the flow of prefrontal cortical information and contribute to defining such ensembles, as exemplified in the already reviewed ability of hippocampal input to gate cortical throughput in the nucleus accumbens. Thus, a distributed set of neurons in their up state could actually represent an ensemble<sup>49</sup> (FIG. 5). This is similar to what has been described in the hippocampus as "ensemble coding,"<sup>50,51</sup> reflecting the distribution of activity in a population of neurons. Ensembles in the NAcc may change as an adaptation to the contextual information provided by hippocampal inputs<sup>49</sup> or to the affective information provided by the amygdala.<sup>52</sup>

### DOPAMINE AND INFORMATION PROCESSING IN THE NUCLEUS ACCUMBENS

The NAcc receives a dense DA innervation<sup>53</sup> that has been shown to play a role in practically every function attributed to this brain region. Despite their importance, our knowledge of the actions of DA is obscured by the inconsistency of results obtained in the attempt to unveil their mechanisms. The concept of DA being a transmitter controlling information processing in the NAcc is beyond doubt. However, there is still considerable confusion regarding the actions of DA at a cellular level. It is common to envision this issue as a debate regarding whether DA is inhibitory or excitatory, with rather unconvincing evidence supporting either possibility. On the other hand, it is becoming increasingly apparent that this dichotomy is an oversim-

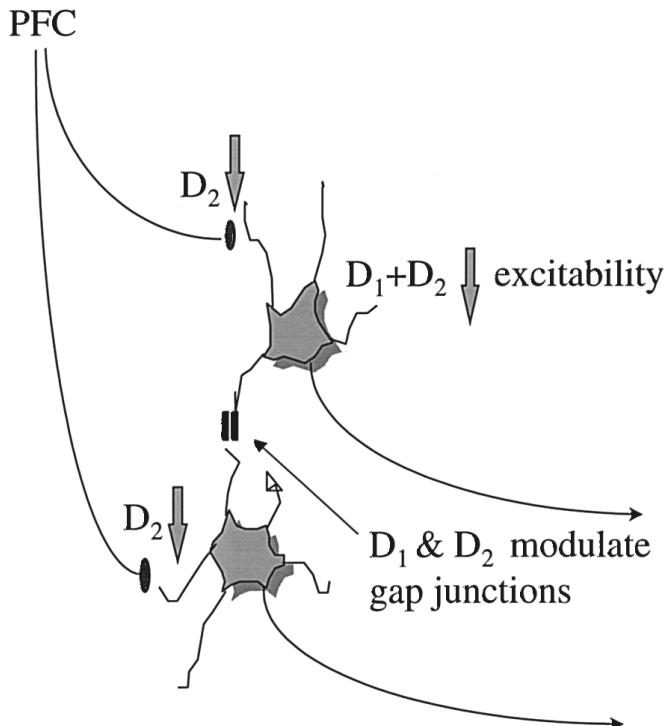


**FIGURE 5.** Ensemble coding in the nucleus accumbens. Information processing in the NAcc may be based on a sequence of neuronal ensembles that can be defined by the spatial distribution of neurons in their active, or up, state (black squares in the boxes representing NAcc and PFC neurons). A particular ensemble in the NAcc is determined by PFC afferent inputs and modulated by hippocampal inputs providing contextual and spatial information, and perhaps amygdaloid inputs providing affective information. This distribution of neurons in the up state will determine the activity of neurons in the ventral pallidum (VP) and MD thalamus, which in turn may exert control over activity states in PFC neurons.

plification of the actions of DA. Instead, more recent studies have provided evidence that DA is a modulatory agent that alters the functional impact of other afferent systems. Indeed, such a function may be commonplace for many G protein-linked receptors, which do not exert a direct control over ionic channels on their target neurons. Thus, although DA can be described as either inhibitory nor excitatory, an alternate possibility could be that it is actually both. DA may have different effects on an individual neuron, depending not only on which receptor subtypes or which afferents it is affecting, but also on the state of the system. For example, DA may exert different actions depending on whether a neuron is in the up or down state of its membrane potential.

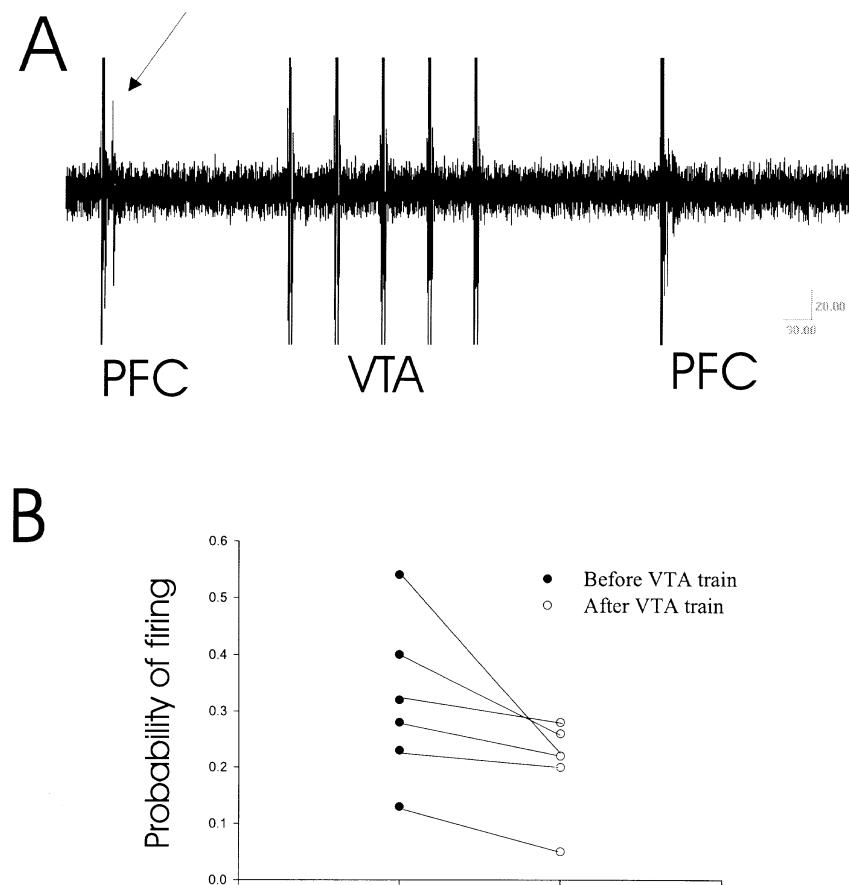
#### *Dopaminergic Control of Nucleus Accumbens Cell Excitability*

DA has a multiplicity of effects, many of which can affect information processing within the NAcc (FIG. 6). DA actions on NAcc neuron membrane potential are inconsistent, consisting of either depolarizing or hyperpolarizing responses.<sup>54,55</sup> However, a common finding is that action potential firing is more difficult to obtain in the



**FIGURE 6.** Actions of dopamine on information processing within the nucleus accumbens. DA effects with an impact on NAcc cell firing include (a) control of cell excitability mediated by D<sub>1</sub> and D<sub>2</sub> receptor coactivation; (b) presynaptic modulation of glutamatergic afferents via D<sub>2</sub> receptors in the case of PFC afferents and an atypical D<sub>1</sub> receptor in hippocampal afferents; and (c) control of gap junction permeability, with regional differences, including different DA receptor subtypes involved.

presence of DA agonists. *In vitro* studies have shown that the threshold for firing is moved to a more depolarized membrane potential<sup>55,56</sup> and the rheobase (i.e., the minimum amplitude of intracellularly injected current required to elicit an action potential) is increased<sup>56,57</sup> following administration of DA agonists. These results could be interpreted as DA's decreasing cell excitability in the NAcc. Although this may suggest an inhibitory effect, caution should be taken in interpreting these results. First, they are not observed in every cell tested. Second, these involve activation of NAcc neurons by intracellular injection of current; DA may have additional effects on the afferent-mediated activation that may cancel or even reverse any effect due to changes in membrane properties. Also, NAcc neurons recorded in the slice preparation may be the equivalent to a permanent down state, given their lack of spontaneous firing and their very negative membrane potential. In this regard, DA actions observed *in vitro* could provide information relevant to actions on NAcc neurons in the down state.



**FIGURE 7.** VTA stimulation decreases the probability of PFC-evoked action potential firing. **A:** Extracellular recording showing a spike (arrow) in response to a PFC stimulus that is followed by a train of stimuli to the VTA. A second stimulus to the PFC has a reduced probability to evoke action potential firing, as shown in **B**.

#### Dopamine Actions on Synaptic Responses

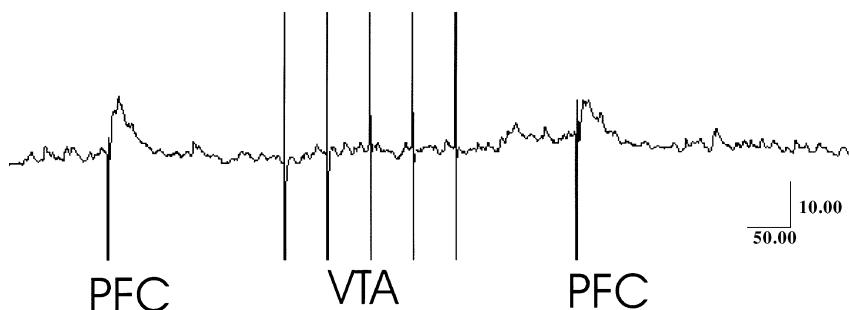
Cortical glutamatergic afferents to striatal regions possess presynaptic DA hetero-receptors that modulate glutamate release.<sup>58,59</sup> *In vivo* studies have suggested that DA may exert an inhibition of synaptic responses; in this sense, DA has been described as providing an increase in the signal-to-noise ratio.<sup>60</sup> Stimulation of the ventral tegmental area (VTA), which is the source of DA innervation to the NAcc, as well as the local DA application by iontophoresis, attenuated synaptic responses in NAcc neurons evoked by hippocampal stimulation<sup>61</sup> and amygdala stimulation.<sup>62</sup>

We have also found that VTA stimulation decreases the probability of spike firing elicited by PFC stimulation. During extracellular recordings from 13 NAcc neurons, VTA train stimulation (5 pulses of 0.1 ms, 0.1–1 mA at 20 Hz) was preceded and

followed by single shocks to the medial PFC (0.1 ms, 0.1–1 mA). The stimulus intensity of the pretrain PFC stimulation was adjusted to elicit action potential firing in around one half of the trials. In seven of these neurons, the same stimulus intensity delivered after the VTA train stimulation was less likely to elicit spike discharge (FIG. 7). In these neurons, the probability of action potential firing following PFC stimulation was reduced from  $0.32 \pm 0.05$  (mean  $\pm$  SEM) to  $0.21 \pm 0.03$  ( $p = 0.03$ , paired  $t$ -test). These results indicate that VTA stimulation may decrease the ability of PFC afferents to elicit synaptic responses that may reach threshold for action potential firing.

Similar experiments were performed using *in vivo* intracellular recordings from NAcc neurons. The amplitudes of PFC-evoked EPSP were compared before and after a train of stimuli was delivered to the VTA. In these experiments, the intensity of cortical stimulation was set to around one half of that needed to evoke an action potential. The ratio between the amplitudes of EPSP evoked by the second (post-VTA train) pulse to the PFC and the EPSP evoked by the first (pretrain) pulse was measured. In four neurons, this ratio was  $0.75 \pm 0.08$  when all the stimuli were delivered during the down state or at very negative membrane potentials ( $-77.7 \pm 11.1$  mV), indicating that the amplitude of synaptic responses to PFC afferent stimulation was decreased in NAcc neurons in the down state following a burst of stimuli to the VTA (FIG. 8). The EPSP amplitudes had some variability from cell to cell, but even with this small sample, a paired  $t$ -test using raw amplitude values indicated a significant decrease ( $8.9 \pm 2.8$  mV before;  $6.8 \pm 2.2$  mV after the train;  $p = 0.04$ , paired  $t$ -test).

*In vitro* studies in the NAcc shell have shown that D<sub>1</sub> receptor activation decreases synaptic responses to fornix stimulation, presumably by affecting hippocampal afferents.<sup>63</sup> In the core, our electrophysiological studies *in vitro* have shown that activation of D<sub>2</sub>, but not D<sub>1</sub>, receptors decreases synaptic responses elicited by PFC afferent activation.<sup>64</sup> On the other hand, other studies have reported that D<sub>1</sub> receptors may be involved in the DA-mediated decrease of synaptic responses in the NAcc.<sup>65,66</sup> However, these changes were blocked only by exceedingly high concentrations of the D<sub>1</sub> antagonist, SCH 23390,<sup>66</sup> and could not be affected by manipulations of adenylate cyclase,<sup>65</sup> suggesting that they may involve an atypical D<sub>1</sub>



**FIGURE 8.** *In vivo* intracellular recordings from NAcc neurons using a combination of stimuli similar to that shown in FIG. 7 revealed a decreased amplitude in PFC-evoked EPSP following a train of stimuli to the VTA.

receptor. It now appears that this D<sub>1</sub>-like receptor may reduce synaptic responses to hippocampal afferents, but not to cortical afferents<sup>67</sup> that are under D<sub>2</sub> DA control.<sup>64</sup>

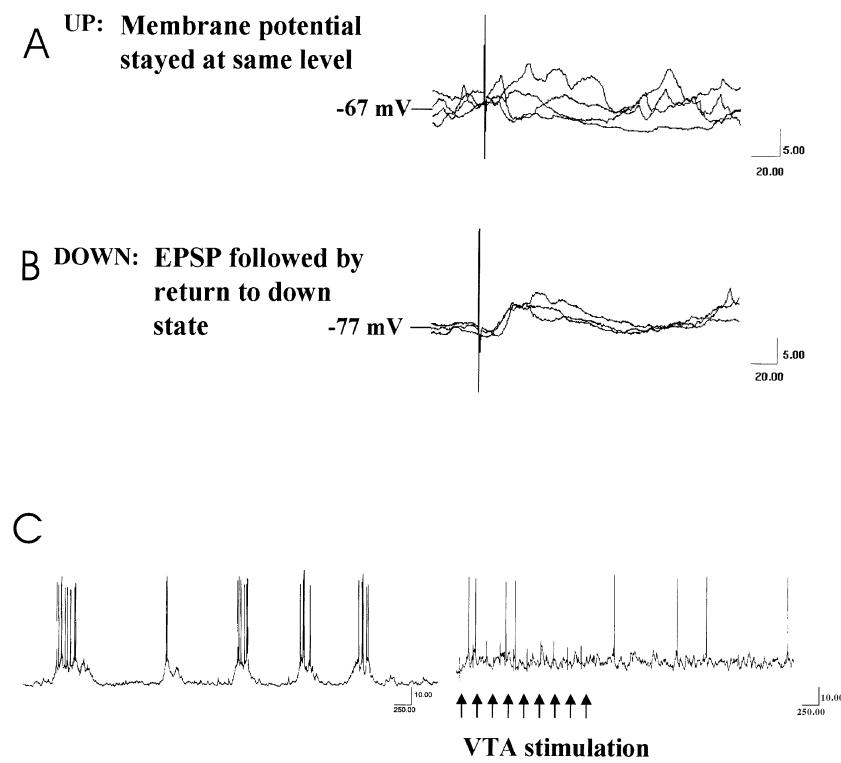
#### *Dopamine and Ensemble Coding in the Nucleus Accumbens*

Overall, interpreting the net effect of DA on the activity of NAcc neurons presents several paradoxes. For instance, if as some data suggests, DA decreases cell excitability, how is it that DA agonists can be behavioral activators? Some authors have claimed that a general “inhibitory” action of DA could serve as a means to decrease background activity and therefore to increase signal-to-noise ratio.<sup>56,68</sup> In addition, although evidence has shown that DA cells fire “en bloc” upon presentation of behaviorally relevant stimuli,<sup>69</sup> there is also clear data showing that DA neurons exist in functionally distinct cell groups (i.e., motor vs. limbic). An alternative view about DA actions that emphasizes its influence on ensemble coding<sup>49</sup> may circumvent these conflicts. Thus, DA action may vary depending on the membrane potential, even within the same cell.

An elegant series of studies in Michael Levine’s laboratory has revealed that D<sub>1</sub> and D<sub>2</sub> receptors may play different roles in the modulation of glutamatergic responses in striatal neurons and that the type of interaction depends on the glutamate receptor subtype involved. Thus, activation of D<sub>1</sub> receptors may enhance NMDA-mediated responses.<sup>70</sup> This is consistent with claims that D<sub>1</sub> receptors may be excitatory in nature.<sup>71</sup> A D<sub>1</sub>-NMDA interaction will be substantially different between up and down states. At the very negative membrane potential that characterizes the down state, NMDA receptors are effectively blocked by Mg<sup>2+</sup>, rendering D<sub>1</sub> receptors ineffective in this action. However, with the membrane depolarization characteristic of the up state, the Mg<sup>2+</sup> blockade is partially removed, allowing for NMDA responses to be expressed and eventually to be increased by D<sub>1</sub> receptor activation. Thus, a D<sub>1</sub>-NMDA interaction may only take place during up events, perhaps contributing to sustaining these depolarizations. Furthermore, D<sub>1</sub> receptors also enhance the activity of L-type Ca<sup>2+</sup> channels,<sup>45</sup> another effect that may contribute to the sustained depolarization of the up state. On the other hand, activation of D<sub>2</sub> receptors may shunt AMPA-mediated responses. It is during the down state that this modulation can occur without being masked by NMDA activation. Thus, D<sub>2</sub> receptors may effectively attenuate synaptic responses during the down state and contribute to its persistence. In addition, DA can enhance the inwardly rectifying K<sup>+</sup> current that in medium spiny neurons may contribute to holding their membrane potential down. As a consequence, DA actions on glutamatergic transmission could have the effect of stabilizing the current state of the membrane in the neurons affected.

Preliminary data indicate that at least in the PFC, DA can act as a state stabilizer. It may be possible that a similar mechanism exists in the NAcc, although this remains to be studied. As an initial step to address this issue, experiments were performed with VTA stimulation as a means to elicit DA release. In these experiments, neurons were recorded from the PFC, an area that also has neurons with a bistable membrane potential and receives DA innervation from the VTA. *In vivo* intracellular recordings from 17 neurons located in the medial or orbital PFC were performed in anesthetized rats. Immunostaining with Neurobiotin, a marker injected into the cells at the end of the recording session, revealed that these were pyramidal neurons. Nine out of 17 neurons recorded exhibited a bistable membrane potential (down state: -81.3 ±

5.7 mV; up state:  $-67.1 \pm 7.8$  mV). Electrical stimulation of the VTA elicited a variety of responses in PFC neurons, depending on whether the neuron was in the up or down state at the time of stimulation. Only neurons with a bistable membrane potential showed responses to VTA stimulation.<sup>78,79</sup> During the up state, the most common response was the permanency of the cell in the up state for more than 100 ms, and during the down state, a brief and small EPSP was followed by a return to the down state (FIG. 9). Stimulation of VTA with a train of pulses elicited similar responses. These results suggest that DA may have different effects depending on the membrane potential of the PFC pyramidal neurons and that in most cases DA may act as a state stabilizer.<sup>78,79</sup>



**FIGURE 9.** In PFC pyramidal neurons, VTA stimulation exhibited a variety of responses. In cells with up and down states in their membrane potential, the most common response was a long-lasting permanence in the state at which the neuron was during VTA stimulation. **A:** Overlay of responses to VTA stimulation obtained from a medial PFC pyramidal cell during the up state. **B:** Overlay of tracings from the same neuron during the down state, showing a brief EPSP followed by a return to the down state. **C:** A train of stimuli to the VTA elicited long-lasting responses; the tracings show the membrane potential from a bistable pyramidal neuron before (left) and during (right) a VTA train stimulation. In this case, the membrane potential stayed in the up state for several seconds.

Since DA is released massively in the striatum and NAcc upon presentation of behaviorally relevant stimuli,<sup>69</sup> this DA message may be interpreted as fixing the state of a distributed set of neurons in these areas; in other words, DA may reinforce a distributed pattern of activation (or ensemble) that may, for example, be associated with appetitive or aversive stimuli.<sup>49</sup> This may be an important mechanism involved in the learning processes in which DA cell firing plays a role. For example, upon successfully learning a task, DA cell activation switches from being reward related to being conditioning-stimulus related.<sup>72</sup> Although highly speculative, this could be interpreted as the DA signal tagging an ensemble that can be associated with obtaining a reward-predicting stimulus and, therefore, reflecting a behavioral pattern that is worth reinforcing.

#### *Gap Junctions and Ensemble Coding*

Neuronal ensembles in the NAcc can be defined by a distributed set of neurons in the up state at any given moment. To be functionally meaningful, these up events may require some extent of synchronization. This can be accomplished by the cell-to-cell transfer of information via gap junctions, a mechanism that can allow for a transfer of slow electrical signals, including “up” events, between coupled cells. Furthermore, gap junction permeability is tightly modulated by a number of factors, including dopamine,<sup>73</sup> nitric oxide, and cortical inputs,<sup>74</sup> allowing for fine-tuning of this synchronization of up events.

Although studies attempting to establish the presence of connexin (gap junction protein) or a typical seven-layer electron microscopic image in the brain have not been conclusive regarding their presence in the NAcc, electron microscopy studies have found cell pairings within the NAcc with close membrane appositions (30–90 nm gap) similar to those seen in gap junctions.<sup>75</sup> The difficulties in ascertaining connexins within the NAcc could reflect either a remote site of contact (such as dendrodendritic) or a sparse distribution of connexin channels.

### CLINICAL IMPLICATIONS

Current hypotheses of schizophrenia emphasize the presence of temporal lobe (hippocampal) disturbances, hypofrontality, and altered DA systems, among others. The NAcc is a brain region in which each of these systems may interact. Specifically, the convergence of PFC, hippocampal, and DA inputs in this region may provide mechanisms, such as the gating of PFC throughput by limbic afferents, which could become disturbed in schizophrenia. There is also indirect evidence supporting the idea that the hippocampal drive of up events in the NAcc may be affected in schizophrenia. Phencyclidine, perhaps the best pharmacological model of schizophrenia, can reduce the frequency and duration of up events when administered systemically while recording from bistable NAcc neurons.<sup>34</sup> Furthermore, intracellular recordings from NAcc neurons in animals that had received PCP provided a smaller proportion of bistable neurons.<sup>34</sup> These results indicate that this NMDA channel blocker, a psychotomimetic that can reproduce endogenous symptoms in schizophrenics, may exert its action via interfering with the hippocampal gating of up events in NAcc neurons; this could be a neurochemical model that reflects the patho-

physiological disturbance caused by a hippocampal deficit in the schizophrenic brain.

The control over the flow of information discussed here can be a means by which a putative developmental hippocampal deficit could cause hypofrontality.<sup>76</sup> Neonatal hippocampal pathology and the consequent disturbance in PFC architecture may result in altered ensemble coding in the NAcc. When coupled with a pathological increase in phasic activity of DA systems,<sup>77</sup> an excessive reinforcement of inappropriate ensembles may arise, thereby giving rise to the positive symptoms of the schizophrenia psychosis.<sup>16</sup>

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