Visualizing Striatal Networks. Focus on: “Encoding Network States by Striatal Cell Assemblies”

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Central pattern generators (CPGs) comprise coordinated networks of neurons orchestrating motor behavior (Grillner 2006); they were originally described in invertebrates and in the spinal cord. In mammals, the cortex and striatum control spinal CPGs. The question arises whether the synaptic mechanisms operational in CPGs govern coordinated activity in higher centers. Networks of neurons active in defined sequences, so-called syn-fire chains (Abeles 1991), and the coordinated activity of these sequences, so-called cortical songs, have been visualized in the mammalian cortex using Ca2+ imaging (Ikegaya et al. 2004). These landmark observations showed that patterns in the activity of large populations of neurons could be monitored in real time with single-cell resolution.

In the current article, Carrillo-Reid et al. (2008) have extended cellular imaging approaches to deep brain structures of particular interest to the elucidation of neuropsychiatric disorders. While coordinated activity occurs spontaneously in cortex, striatal neurons with their very hyperpolarized membrane potentials do not fire spontaneously. Striatal neurons are driven by cortical afferents (Wilson and Kawaguchi 1996) and so might not possess intrinsic mechanisms for coordinated activity. Moreover, given the inaccessibility of deep brain structures to optical techniques, addressing this issue in the striatum appeared daunting. The authors addressed both issues simultaneously by making striatal brain slices and simulating afferent input with N-methyl-D-aspartate (NMDA) application. They monitored the activity of many striatal neurons using Ca2+ imaging to ask whether striatal networks support patterned activity. They show that when activated by NMDA application, different assemblies of striatal neurons are active in sequence. While these assemblies are dependent on NMDA receptor activation, they are generated by pattern-generation mechanisms intrinsic to the striatal circuitry and do not require patterned afferent input. Because NMDA selectively enhances excitation at active synapses, it can thereby activate or accentuate intrinsic activity. This approach allowed the authors to visualize patterns of active cells in the striatum and to assess capabilities for pattern generation. Specifically, they found that when striatal cells are depolarized and fire at least a couple spikes that the associated Ca2+ influx can be visualized. The fact that the ensembles form in the reduced circuitry of the slice indicates that the modules of neural circuitry that subserve pattern generation may be potentially small and thus a distributed property of the striatal circuitry. It would be interesting to learn how thin or small a chunk of striatal tissue is capable of pattern generation. In other words, are there unitary pattern generators?

The authors go on to show that blockade of GABAergic inhibition freezes the active neurons in one assembly, highlighting the importance of local inhibition in orchestrating ongoing rhythmic activity. A hallmark of the activity of striatal neurons is their alternation between the very hyperpolarized resting, down state, and a depolarized plateau, up state (Wilson and Kawaguchi 1996). Up states depend on Ca2+ influx. Consistent with the importance of up states, inhibition of L-type Ca2+ channels degraded the synchronization of active neurons into assemblies. It would now be of considerable interest to see how dopamine, which is required in other brain regions together with NMDA to elicit rhythmic activity (Tseng and O’Donnell 2005), as well as a range of drugs of neuro-psychiatric relevance, modulate coordinated ensembles of active cells.

Some years ago, Ralph Hoffman (1987) asked how modulation of the strength of connections in neural networks could throw the networks into pathological states modeling pathological patterns of thought disorganization characteristic of psychosis and mania. The present approach provides a way to move to physiological relevance. It will be interesting to see how the network states develop and to then analyze them in transgenic mouse models of neuropsychiatric disorders. With the use of GENSAT mice (Gong et al. 2003) allowing identification of medium-spiny neurons (MSNs) belonging to the direct and indirect pathways (Surmeier et al. 2007), it should be immediately possible to put the ensembles of active neurons into a functional context.

In this regard, the authors made the tantalizing observation that fast-spiking striatal interneurons make up a large number of the core of neurons that are shared among the different cell assemblies. While fast-spiking GABA interneurons comprise 1–2% of striatal neurons, they make up 40% of striatal neurons active in multiple ensembles. Because fast-spiking GABA interneurons function principally in mediating feed-forward inhibition, they are in position to orchestrate the overall excitability of striatal networks (Wilson 2007). Their overrepresentation in the active ensembles may reflect a role in actively inhibiting subsets of MSNs, thereby sculpting the ensembles. Similarly, cholinergic interneurons (Pisani et al. 2007), the other pivotal minority population, bear integration into the next network analyses. Further work along the lines delineated by Carrillo-Reid et al. will likely provide rapidly increasing insight into striatal information processing.

REFERENCES


