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Motor "Binding:" Do Functional Assemblies in Primary Motor Cortex Have a Role?

In this issue of *Neuron*, Jackson and colleagues describe a functional correlate of neural synchrony related to movement control. Synchrony strength in cortico-motoneuronal output neurons in primary motor cortex depended upon similarity of these neurons' connectivity pattern with the spinal cord. These results could form the foundation for subsequent investigations of motor binding.

Neural synchrony has been observed throughout the CNS, particularly in sensory systems, and theories have abounded concerning its functional role. Preeminent among them is the theory that synchrony is the basis for perceptual binding (von der Malsburg and Schneider, 1986; Eckhorn et al., 1988). Since debate swirls about the meaning of neural synchrony in certain sensory processing areas (e.g., see Bair et al., 2001; Thiele and Stoner, 2003), a definitive role for neural synchrony in functional brain organization necessarily remains elusive. In this issue of *Neuron*, Jackson and colleagues (Jackson et al., 2003) explore the synchrony problem within the context of brain control of voluntary movement. Not unlike processing needed to form coherent percepts, the brain systems mediating voluntary actions must aggregate disparate spiking patterns to form spatially and temporally coherent neural codes that then drive α motor neurons and their associated muscles. Essentially, motor binding seems exactly what motor structures of the mammalian brain do—high-level coordination of simple and complex voluntary movements.

Movement control and the primary motor cortex (M1) of primates have particularly useful features in determining the functional significance of neural synchrony and its potential role for motor binding. Movement provides an extensive repertoire of experimental variables to manipulate and to assess from input to output streams. In contrast, richness in perceptual binding work focuses fundamentally on input manipulations and a single, binary response variable: perceived or not perceived. M1 seems a model site to investigate functional significance of synchrony. Preeminent among neocortical areas, M1 is ideally situated as the collector of multifarious, highly processed integrated inputs that then become relayed to the brain stem and spinal cord to express neural computations related to sensation, perception, and thought for voluntary action. Functional and anatomical features of M1 make it a particularly likely neocortical candidate site for implementation of motor binding. The intrinsic organization of M1 has distributed and overlapping movement representations, suggestive of intrinsic substrates for coordination (Sanes and Schieber, 2001). Additionally, M1 has profuse intracortical horizontal connections that exhibit short-term and long-term plasticity (Sanes and Donoghue, 2000), a feature likely needed for a structure devoted to synthesizing information to yield highly complex output.

Jackson et al. (2003) focused their work on a special type of neuron in M1: the cortico-motoneuronal (CM) cell (see Porter and Lemon, 1993, for a comprehensive review of CM cells). Anatomical and functional properties of the CM cell contribute to its use as a model for understanding neuromotor control and for investigating neural synchrony. CM cells have monosynaptic excitatory contacts on multiple α motor neurons in a single motor neuron pool, and via interneurons exert inhibitory effects on other, antagonist motor neurons. The synaptic effects of direct M1 input onto α motor neurons have been well characterized. Axons of individual CM cells also branch to contact neurons in other motor neuron pools; their aggregate branching pattern yields a muscle field that describes the functional coupling, both facilitatory and suppressive, of a CM cell to a set of muscles. Commonly, a muscle field for a CM cell comprises motor neuron pools having synergistic actions, potentially representing distal and proximal voluntary movements. While CM cells constitute a small proportion of all layer V cells—approximately 10%–20% of pyramidal tract neurons (PTN) in M1—their known anatomic and functional properties can be exploited to reveal general neural processing properties. A further advantage of studying neural synchrony of CM cells is that it can be done in awake preparations.

Synchrony in M1 was first observed nearly 20 years ago (see Jackson et al., 2003, for a review of relevant work). More recently, neural synchrony in M1 has been related to movement direction coding and specific aspects of task performance. However, these studies have not placed neural synchrony into the larger context of motor binding. New findings from Jackson et al. (2003) and Hatsopoulos et al. (2003) bring the connection between motor binding and M1 neural synchrony substantially forward.

Jackson et al. took advantage of the muscle field feature of the CM system to investigate the relationship between M1 neural synchrony and CM output. The spiking of neurons was recorded with a multiple-electrode array in a zone of M1 expected to yield functional relationships to muscles related to hand function; this sample was further restricted to CM cells. The spike triggered averaging (STA) method was used to characterize the muscle field of each CM cell. As commonly employed in neuromotor control, STA implemented between spiking and the electromyogram (EMG) can reveal both post-spike facilitation from CM cell action, a short-latency and transient increase in the EMG, or post-spike suppression, a transient decrease in the EMG. As expected, STA revealed the functional connection of CM cells to

spinal cord, with each cell having a muscle field of one to six of the relatively small set of sampled intrinsic and extrinsic hand muscles. Additionally, the sampled CM cells had muscles fields that spanned a variety of presumed functionality, such as finger extension, flexion, adduction, or abduction.

The main finding from Jackson et al. is that CM cells with overlapping muscle fields exhibited greater neural synchronization than CM cells without overlapping muscle fields. Consistent with the finding between CM cell-pair synchrony and overlapping muscle fields was a corollary finding of diminished, or "negative," synchrony for CM cell pairs that exhibited divergent muscle fields. The manner of characterizing the observations—that is, with muscle field overlap—provide an important connection to the functional significance of these results. Note that neural synchrony could be a marker of neuronal engagement within a functional neural assembly, minimally of two neurons, but more likely of significantly more neurons. Recall that axons of CM cells branch to contact multiple α motor neurons within a specific motor neuron pool and also branch to influence neurons within agonist or antagonist motor neuron pools. Additionally, multiple CM cells influence numerous motor neuron pools. The net effect is that CM cells have a potentially powerful amplification factor, and neuronal synchrony could amplify this further. The finding of M1 synchrony having a functional role regarding output creates a unique opportunity to explore the ramifications of neural synchrony in a defined output system.

Along these lines, one might expect that neural synchrony would yield supralinear effects on the post-synaptic target, but Jackson et al. (also see Supplementary Data online at http://www.neuron.org/cgi/content/full/38/1/3/DC1) did not find this. Consider the case of two inputs closely spaced in time, with each generating an excitatory post-synaptic potential on the target neuron. These two inputs might yield nonlinear excitation. Jackson et al. used a novel method, the double STA (dSTA), to demonstrate only linear post-synaptic effects by synchronous pairs of CM cells. For each CM cell pair, simultaneous (synchronous) and time-lagged spikes of the two cells are then taken as trigger events for the dSTA, allowing the observation of both the isolated and combined (perhaps synchronous) facilitation effects of the two CM cells spikes on the triggered EMG averages. Say FA and FB are the amplitudes of the isolated peak facilitation effect from cell A and B, respectively. A linear model of the synchronous effects of the two cells would simply be given by FA + FB. Next, the ratio (FA + FB)/FO, where FO is the actually observed amplitude peak facilitation for the synchronous spikes, is computed. A predominantly linear effect would give a ratio that is very close to 1. By computing this ratio for all the CM cell pairs in the selected ensemble, the authors find that the sampled cells fell within a 95% confidence interval around an expected linear response. In other words, the observed synchronous effects behaved mostly linearly, with perhaps only small nonlinearities not being detected by the dSTA analysis. The authors elaborate on the implications of this result to the functional role of synchrony, but more importantly, the result rules out the possibility that the observed relation between synchrony and muscle field similarity occurred due to an artifact related to the disproportionate contribution of synchronous spikes to the STA of a single CM cell.

The work of Jackson et al. does have some limitations. First, the number of CM cell pairs evaluated was necessarily small, which might have prevented the identification of some CM cell with supralinear properties. Second, the CM pairs studied in this study were selected specifically for their functional relationship with hand muscles. Phylogenic analyses suggest that the development of the pyramidal tract and particularly of CM cells has a special relationship to hand function. However, M1 also exerts precise control over more proximal arm movements, and CM cell axons make monosynaptic contacts upon both distal and proximal muscles of the upper limb. Third, the important findings of Jackson et al. on synchrony of CM cells and motor output do not address the role of synchrony and correlation within the neocortex and how it actually might relate to motor binding. Hatsopoulos et al. (2003) do address this issue.

In their work, Hatsopoulos et al. (2003) evaluated coarsely correlated spiking of paired M1 neurons while monkeys performed a "bound" and an "unbound" sequential movement. Note that these workers did not classify the recorded M1 neurons, though the neural sampling methods created a bias toward evaluation of large neurons in layer 5 of M1, exactly the position of PTNs and CM cells. During the recordings, monkeys performed either a preplanned, continuous, sequential movement (the bound movement) or a sequential movement following the same path but having a brief intermediate stop and a secondary target. The second type of movement could not be planned in advance and was considered the unbound movement. The concept behind the choice of movements was that the continuous movement would require a bound set of neural signals needed to control the movement. By contrast, the neural signals needed for the movement having an intermediate stop would have a signature of two independent movements. A significant point about the results was that the pattern of neural firing for the planned and unplanned sequences had rough equivalence, even though one movement was preplanned and the other partially planned. Independent of that finding was the key observation that occurred before any movement occurred; M1 neural correlations increased during the period immediately preceding movement onset. With the assumption that neural synchrony reflects grouping of neurons into assemblies, the finding by Hatsopoulos et al. (2003) suggests that M1 neurons aggregate into assemblies more often when a bound, sequential movement is about to be performed.

Taken together, the findings of Jackson et al. (2003) and Hatsopoulos et al. (2003) advance the cause for revealing functional significance of neural synchrony and correlations, certainly within the motor system, and also possibly for other systems. Jackson et al. have taken a well-described neuron—the CM cell—and related its functional output properties with a particular feature of intracortical processing—neural synchrony. They show that neurons with similar functional output have an increased likelihood to exhibit neural synchrony, a possible signature of grouping into neural assemblies. Hatsopoulos et al. (2003) provide important evidence for a link between neural correlations and movements

that require binding at the behavioral level. While these findings provide some new answers, they also require additional observations and extensions to determine whether neural synchrony in motor structures truly represents motor binding.

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Declarative versus Episodic: Two Theories Put to the Test

The question of whether the hippocampus plays a selective role in episodic memory or a more general role in both episodic and semantic memory (together termed declarative memory) is an unresolved and much-debated topic in the current literature. In two back-to-back articles in this issue of *Neuron*, Squire and his colleagues describe findings from a group of six patients with damage thought to be limited to the hippocampus. The reported findings provide new evidence toward resolving this much-debated controversy.

It would be fair to say that most neuroscientists polled today would agree with the statement that the hippocampus plays an important role in memory. Asked specifically what form of memory the hippocampus participates in, and this initial consensus will quickly dissolve into a raucous clash of two strongly divergent views. One camp has proposed that the hippocampus plays a selective role in episodic memory with little or no contribution to semantic memory. This has been termed the episodic theory of hippocampal function. Perhaps the most dramatic evidence in support of this view comes from the description of a group of patients who sustained damage to the hippocampus early in life and who exhibit impaired episodic memory in the face of surprisingly good semantic memory (Vargha-Khadem et al., 1997). Related to this view, others have argued that the hippocampus is not only specifically involved in laying down new episodic memories, but that even very remote episodic memories remain dependent on the hippocampus (Fujii et al., 2000). The opposing camp argues that the hippocampus together with the surrounding entorhinal, perirhinal, and parahippocampal cortices contribute to both semantic and episodic memory. This has been termed the declarative theory of medial temporal lobe function. This view is supported by a large body of convergent findings from studies in human amnesic patients together with parallel findings in animal model systems (Manns and Squire, 2002; Squire and Zola, 1998). The declarative view also holds that the medial temporal lobe plays a time-limited role in the consolidation of declarative memory such that memory for both episodic and semantic information encountered well before the onset of amnesia is unaffected.

A handy feature of such diametrically opposed theories is that each of them makes very distinct and testable predictions. For example, the episodic theory predicts that selective damage to the hippocampus should result in little or no impairment in semantic memory. In contrast, the declarative theory predicts significant semantic memory impairment resulting from selective hippocampal damage. A second clear prediction of the episodic theory is that remote episodic memories should be impaired in patients with selective hippocampal lesions. In contrast, the declarative theory predicts that remote episodic memories would be intact. One might ask, how is it that these clear and obvious predictions have not yet been tested? The short answer is that it is very difficult to gather a large enough group of patients with the kind of selective bilateral hippocampal damage necessary to test these predictions in a robust way. Using a rare group of six such amnesic patients with damage thought to be restricted primarily to the hippocampal region, Squire and his colleagues have tested these key predictions of the episodic and declarative views in two studies published in this issue of *Neuron* (Bayley et al., 2003; Manns et al., 2003).

The first experiment in the study by Manns et al. examined the performance of this group of hippocampal-damaged patients and matched controls on semantic memory for news events. The news events were either encountered before (retrograde memory) or after (anterograde memory) the onset of amnesia. The patients with hippocampal damage exhibited significant impairments on either recalling or answering multiple choice questions about the news events occurring after the onset of amnesia (i.e., anterograde amnesia for semantic information). On the retrograde component of this task, Manns et al. found evidence for a temporally graded retrograde amnesia such that recall for new events occurring 0–10 years before the onset of amnesia was impaired relative to the performance of control subjects. In contrast, remote memory for events occurring 11–30 years before the onset of amnesia did not differ from control performance. One potential problem in interpreting these findings is that control subjects but not amnesic patients may have access to episodic details that may, in turn, help them recall the related semantic infor-