Use of Behavioral Outcome to Assess Cognitive State

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ABSTRACT

Historically neurological, psychological, and physiological measures have been used to assess the neural status or "brain state" corresponding to cognitive performance and behavior. We have recently demonstrated a means by which behavioral assessments can begin to assess cognition and brain state by searching for distinct patterns of neural activity and observing the behavioral results of those patterns. This presentation will explore the use of mean neural activity derived across specific behavioral states, then examining the neural patterns on single trials/events to determine how that behavioral or cognitive state may be altered on a trial-by-trial basis. Within this context it is then possible to determine how a given state arises from the preceding state, and further assess the effects of cognitive workload, stress, and pharmacological manipulation. Studies from rodent and nonhuman primate reveal correlations between past and present neural state with behavior that can be used to predict future cognitive state along with behavioral outcome. Facilitation or impairment of the animal's ability to perform mnemonic tasks can thus be produced by pharmacologically manipulation to confirm the role of specific neural circuits as well as neurotransmitters and neuromodulators within those circuits. Mathematical modeling of the relationship between recorded neural patterns and underlying cognitive state is currently underway to yield algorithms and devices that may eventually allow restoration of impaired cognitive function due to neural damage. These studies have concentrated on three primary brain regions within which it is possible to correlate specific neural firing patterns with behavior and vice versa. The first of these areas is the prefrontal cortex or PFC. which is responsible for executive function, and some forms of short-term memory. The second area is the basal ganglia, particularly the striatum, which mediates behavioral motivation and reward. The third area is the hippocampus and medial temporal lobe, which mediate memory, association and cognitive decision. Current theories view prefrontal cortex, basal ganglia and medial temporal lobe as a functional circuit that allocates specific types of cognitive processing (i.e. memory, rule implementation, response execution) proportionally across each but that each has neuronal representation that can independently or conjointly correlate with specific behavioral events.

Prefrontal cortical function has been the emphasis of several new theoretical notions which integrate it with other frontal cortical regions and also structures in the basal ganglia. The more traditional notion of the dorsal prefrontal cortex subserving "executive function" as prominent in human clinical literature, appears to have evolved into the role of "rule planning and use." Neurons in the prefrontal cortex (ventral and dorsal) appear to be "most" responsive to task features that are unrelated to particular stimulus features or response components of the task, but rather rules or strategies that must be employed to satisfy experimental contingencies. Thus PFC neural firing patterns frequently correlate with specific behavioral events that signal context switching or application of different behavioral "rules." Likewise experimental design that emphasize a switching context, increasing cognitive workload, or application of various response rules can reveal the status of prefrontal neural activity on the basis of behavioral measures. Specifically we have shown that prefrontal neurons correlate with cognitive workload in a behavioral task. At the same time we have measured the frequency of pupil dilation, an independent measure of cognitive workload, that correlates with behavioral outcome as well as response latency (Hampson et al. ***Behav. Brain Res***., ***212*** (2010), 1-11). Thus in this instance, the behavioral outcome reveals as much about prefrontal neural activity, as the neural activity reveals about the behavior.

Neurons recorded in the basal ganglia often encode the reward or outcome properties of behavioral tasks that feature rule-based learning and performance. Single neurons in the putamen showed a progressive increase in firing with learning. Dorsal striatal neurons appear to function in the role of "error detection" within a behavioral task, while ventral striatal neurons respond to salience and magnitude of reward. In addition, striatal neurons

differentially respond to drug versus natural rewards (Opris et al. ***Neuroscience***, ***163*** (2009), 40-54) as well as which type of reward the subject will select. Thus, while basal ganglia play a major role in controlling responsiveness, the response to a behavioral stimulus can in turn be used to predict the underlying neural state, thereby predicting future behavioral responses.

For more than 50 years, the hippocampus and medial temporal lobe have been linked to learning and memory. Although there has been continual refinement of theories of hippocampal function, it is clear that damage to the hippocampus and associated areas impair spatial, as well as nonspatial memory. It has become apparent from lesion studies that the hippocampus is essential to representing not just position or "place", but relationships between stimuli (especially spatial stimuli). A novel role for hippocampus has been demonstrated in a visual delayed-match-to-sample task for nonhuman primates in which we have identified patterns of task-specific firing in the hippocampus that (1) fire differentially depending on the phase of the DMS trial, and (2) encode aspects of the stimuli that facilitate retention of object specific information over the interposed delay period. This latter characteristic was unexpected, in that hippocampal neurons demonstrated a "cognitive rule" by responding to specific categories of visual stimuli which could quickly discriminate between distractor stimui and identify the appropriate stimulus which matched prior encountered daily within the task (Hampson et al., ***Proc. Nat. Acad. Sci. USA***, 101 (2004), 3184-3189). In another example of behavior revealing the underlying cognitive processing, it was possible to predict stimuli to which hippocampal neurons would respond, on the basis of specific visual features of the stimulus.

This laboratory has taken advantage of the identification of discrete spatial and temporal patterns of hippocampal neural activity that can predict behavioral outcome in rodents performing a delayed match to sample task. Hippocampal neural activity within the task is analyzed via nonlinear systems analysis to identify the fine temporal structure and predict not only behavioral outcomes but the subsequent status of neural activity within hippocampus. Further correlation of sequences of behavioral trials with each new neural and cognitive state have yielded a model of the interaction between detection of a stimulus, cognitive decision-making, behavioral response, and the underlying cognitive state on top of which subsequent processing will occur. In this model we find that the behavioral history modulated neural encoding on any given trial. Subsequently the neural encoding on each trial predicts the behavioral outcome on that trial. This neural-behavioral circuit illustrates the importance of behavioral measures as a means of assessing underlying cognitive state on par with the use of neural cognitive recording to assess behavioral performance. In addition future development of prosthetic devices intended to replace or restore damaged brain areas will rely heavily on behavioral validation in studies such as those cited here in which neural recordings inform behavioral studies and behavioral outcome reveal the underlying brain activity.