

ESSAYS ON APS CLASSIC PAPERS |

Discovering spatial working memory fields in prefrontal cortex

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This essay looks at the historical significance of one APS classic paper that is freely available online:

Funahashi S, Bruce CJ, and Goldman-Rakic PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 61: 331–349, 1989 (<http://jn.physiology.org/cgi/reprint/61/2/331>).

THE PREFRONTAL CORTEX is considered to be a key cortical substrate of the highest-level mental processes. Yet, despite the bewildering gamut and complexity of cognitive processes that depend on the prefrontal cortex, over the last decades significant progress has been made in linking the prefrontal function with its cellular and circuit mechanisms in a field at the interface between cognitive sciences and cellular electrophysiology. A landmark paper that helped usher prefrontal research into neurophysiology is Funahashi, Bruce, and Goldman-Rakic's article published in 1989 in the *Journal of Neurophysiology* (3).

The tale began with W. S. Hunter (10) who 90 years ago introduced delayed-response tasks. In these tasks, the sensory stimulus and motor response are separated by a brief delay period, during which time the sensory information must be actively held in mind by the subject. The behavior goes beyond simple stimulus-response reflexes and engages active short-term memory or "working memory." In the 1930s, C. F. Jacobsen (11) demonstrated that frontal ablations in monkeys induced specific deficits in delayed response tests. Subsequent work by K. H. Pribram, H. E. Rosvold, M. Mishkin, and others substantiated Jacobsen's finding and established delayed response tasks as a paradigm of choice for prefrontal studies. Therefore, a critical brain substrate of working memory was identified and prefrontal function could now be studied in a simple task amenable to rigorous experimentation.

The next pivotal event took place when single neuron recordings from awake monkeys became possible. Using this electrophysiological technique in a delayed response task, Kubota and Niki (12) and Fuster and Alexander (6) discovered "memory cells" in the prefrontal cortex that displayed elevated spike discharges throughout the delay period while the animal was required to maintain sensory information internally in the absence of sensory stimulation. Persistent neural activity was immediately recognized as a candidate neural correlate of working memory. However, in these early studies, the behavioral responses were manual and the monkey's eye positions were not controlled. This raised uncertainty about the functional interpretation of the observed persistent neural activity.

For example, if the animal kept its gaze at the prospective response location continuously during the delay period, it would not need to remember the cue position at all.

The situation changed completely in 1989 with the publication of Funahashi, Bruce, and Goldman-Rakic (3). This work was the fruit of 6 years of work, beginning in 1983 when S. Funahashi arrived at Yale University and joined the laboratory of P. S. Goldman-Rakic (Fig. 1), a pioneer in prefrontal research. Together with C. J. Bruce, they decided to adopt an oculomotor version of a delayed response task to study visuospatial working memory. A major methodological advantage of the oculomotor paradigm developed by R. H. Wurtz and collaborators (9, 15), is that the animal's eye positions are accurately controlled and monitored with a search coil. The monkey is required to fixate its eyes at the center spot of a computer monitor, and a peripheral visual stimulus is briefly flashed followed by a delay period of a few seconds. The disappearance of the fixation light spot signals the end of the delay. At that moment, the monkey must make an accurate saccadic eye movement to the location where the cue was shown before the delay period to collect a liquid reward. Because the eyes are fixed at the center spot through the delay period, whereas during the response period there is nothing on



FIG. 1. Patricia S. Goldman-Rakic.

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the computer monitor and the room is dark, the monkey must use working memory to perform the task. Thus the oculomotor paradigm offers an unprecedented degree of experimental control.

Funahashi et al. found that many neurons in the dorsolateral prefrontal cortex including and surrounding the principal sulcus and in the frontal eye field, exhibited mnemonic persistent activity during the delay period. Remarkably, the delay activity of a recorded neuron was selective for preferred spatial cues (the cell's memory field), and this selectivity could be quantified by a Gaussian tuning curve. This delay activity was disrupted in error trials when the cue was in a neuron's memory field and the monkey made a wrong saccadic response, indicating that neuronal mnemonic activity could predict the animal's behavioral outcome. A second salient finding was that neurons in each hemifield of the prefrontal cortex prefer spatial cue locations in the contralateral hemifield. In a later paper, the working memory lateralization was confirmed at the behavioral level with small dorsolateral prefrontal cortex lesions in the same oculomotor task (4). On the basis of the observation that all spatial locations tested in the experiment were represented across recorded neurons, the authors concluded that different prefrontal cells encode and store in working memory different spatial locations so that, "this area of the cortex contains a complete 'memory' map of visual space" (3).

Goldman-Rakic previously proposed that representational working memory holds the key to understanding how the prefrontal cortex regulates behavior (8). That is, the prefrontal cortex does not simply send out nonspecific "control signals." Explicit representation of information that is internally sustained, rather than externally driven, enables the prefrontal cortex to subserve time integration, planning, decision-making, and other executive processes. The discovery of memory fields elegantly and convincingly demonstrated an internal representation of visuospatial information in the prefrontal cortex. This representation is observable and can be quantitatively described in terms of a Gaussian tuning of persistent delay activity at the single cell level. But Gaussian tuning is commonplace among cortical neurons. Perhaps the best known example is orientation selectivity in the primary visual cortex, the mechanisms of which have been extensively studied in cellular and synaptic physiology. With the Funahashi paper, the question of prefrontal microcircuitry underlying working memory could now be formulated in cellular and synaptic terms. What are the excitatory-inhibitory synaptic mechanisms for the formation of memory fields? What are the microcircuitry properties of the prefrontal cortex, such as local horizontal connections, that generate reverberatory dynamics underlying persistent activity? These questions have served as a catalyst and motivated much of the forthcoming research in the field, including the work of Patricia Goldman-Rakic until her untimely death in 2003.

The Funahashi et al. (3) paper also raised key conceptual issues that have occupied cognitive and systems neuroscientists

to this day. Given that persistent activity is also present in other cortical areas such as the parietal cortex (1, 7), what are the differential functions of prefrontal cortex and more posterior areas in spatial working memory? Is there a subregion in the prefrontal cortex dedicated to spatial working memory? Are different types of information (such as spatial vs. object visual streams) processed in different subdivisions in the prefrontal cortex (2, 13, 14)? Does delay neural activity in the prefrontal cortex represent (retrospective) sensory information or selection and planning of (prospective) motor response (5)?

The paper of Funahashi, Bruce, and Goldman-Rakic (3) revealed representational working memory in its simplest and purest form. This work ushered prefrontal research into the fields of in vivo and in vitro electrophysiology as well as computational modeling. It will remain a landmark in our quest for understanding prefrontal function in terms of synaptic microcircuitry, neuronal biophysics, and collective cortical network dynamics.

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