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Dynamic Landscape of the Frontal Lobe: A Tribute to Patricia S. Goldman-Rakic

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A rod going through the frontal lobe of Phineas Gage in 1848 signaled the beginning of the quest to understand the enigma of this fascinating region of the cortical mantle. In the ensuing 100 years, progress was extraordinarily slow, save for the work of Jacobsen in 1935 revealing that the lateral prefrontal cortex was necessary for monkeys to hold stimuli for a short delay. In the 40 years after Jacobsen's work, neuroscientists such as Teuber, Nauta, and Luria were unable to pin down the neural basis of the prefrontal cortex in organized behavior. These eminent scientists referred to the frontal cortex as "a riddle," "mystifying," and the "youngest and most complex portion of the cortex." The situation began to change in the 1970s, and the last decade has witnessed an accelerated growth in the field of prefrontal research. Today, empowered with techniques like single-cell recording from behaving nonhuman primates, functional brain imaging, and genomic mapping, neuroscientists are striving to elucidate the central role of the frontal lobe in a wide array of cognitive functions, such as working memory, attention, decision making, and social interaction. Indeed, one can find an important influence of prefrontal cortex on almost all key human behaviors including language, memory, perception, and emotion. Experimental findings have provided the impetus for developing increasingly sophisticated computational theories for conceptualizing prefrontal function and neural circuit models to test specific hypotheses about the inner workings of the frontal lobe. Lately, the field has also attracted increasing interest from the general public as evidence is accumulating that the prefrontal cortex holds the key to many educational, social, and mental health issues, including development of intellectual abilities, making moral judgments, and understanding and ultimately treating psychiatric diseases.

Against this backdrop of an unprecedented opportunity and challenge for prefrontal research, a Kavli Symposium was held at Yale on 4–5 May 2006 in memory of Patricia Goldman-Rakic, a pioneer in the field. The meeting was attended by a diverse group of neuroscientists, whose lectures exemplified recent advances in a wide spectrum of topics and approaches, converging on the common goal of understanding the functional organization of the prefrontal cortex: brain evolution, neurophysiology in behaving animals or in vitro brain slices, computational modeling, functional imaging of the human brain, neuropharmacology, and molecular psychiatry. Pat would have been delighted by this gathering as her work embodied the multidisciplinary spirit of the meeting and of the field in general. This "Special Issue" is based on the Kavli symposium and contains articles representative of themes currently pursued in the field.

Working memory, the brain's ability to actively hold and manipulate information online, was identified by Pat as a major prefrontal function and motivated much of the ensuing research in the field. Indeed, without working memory all other cognitive abilities fail, and Pat understood that dissecting this process was a key step to understanding how the brain enables behavior. The underlying neurobiological substrate of working memory remains an area of active inquiry and was amply reviewed in the Kavli Symposium. Arnsten shows that this issue can now be examined at the cellular and even subcellular level, by demonstrating the influences of neuromodulator-specific systems on persistent neural activity in prefrontal cortex of monkeys engaged in working memory tasks. Based on results from a physiologically based neural network model, Carter and Wang suggest that mnemonic persistent activity underlying the robustness of working memory depends on an interplay between recurrent synaptic excitation and cannabinoid-mediated activity-dependent disinhibition. Interestingly, they showed that cannabinoid signaling in the prefrontal cortex represents a double-edged sword: the endocannabinoids facilitate working memory, but the exogenous cannabinoid marijuana disrupts it.

Several contributions are devoted to understanding open issues concerning working memory and prefrontal cortex. Petrides and Cadoret report single-cell activity in a task that requires controlled retrieval of specific information about a remembered stimulus in behaving monkeys. Their data support the conclusion emerging from human functional magnetic resonance imaging (fMRI) studies that retrieval of memories of events critically depends on the midventral prefrontal cortex. Warden and Miller describe a task that was designed to probe neural processes correlated with memory storage of 2 items; they found evidence that different items are not coded by distinct neural populations but by overlapping neural populations in the lateral prefrontal cortex. Barcelo and Knight examine another aspect of working memory, namely processing of novelty-based contextual information, which is impaired in patients with prefrontal cortical damage. Romanski addresses the question of how inputs from the visual and auditory pathways are combined in ventrolateral prefrontal neurons for multimodal processing and possibly vocal communication. Another outstanding question is whether mnemonic persistent activity is formed through long-term learning, addressed by Meyer, Qi, and Constantinidis, who found persistent activity in prefrontal neurons even in naive monkeys. This result suggests that the prefrontal cortex is equipped with suitable microcircuit properties to support working memory, even without training for a particular task. Zhou, Ardestani, and Fuster argue that working memory engages a large-scale brain system encompassing interconnected prefrontal cortex and posterior cortical areas.

There has been a debate as to whether prefrontal function should be conceptualized in terms of internal representations (memory maintenance) or processes (decision making and executive control). Interestingly, computational models have revealed that reverberatory dynamics in a single microcircuit can instantiate both working memory and decision making functions. Experimental studies from several laboratories have provided evidence that single-cell activity in prefrontal cortex is correlated with specific aspects of reward-dependent decision behavior. Watanabe and Funahashi report that prefrontal neurons showing delay-period activity in a memory-guided saccade task also exhibit directional delay-period activity in a free choice task, suggesting a shared network for these tasks. Watanabe and Sakagami review evidence that the orbitofrontal cortex signals the motivational context, whereas the lateral prefrontal cortex integrates the motivational and cognitive contexts that determine the behavioral meaning of sensory stimuli. Seo, Barraclough, and Lee describe a dynamic decision task in which monkeys play an interactive game with the computer, and single-neuron activity from dorsolateral prefrontal cortex is modulated by the subject's choices, rewards, or the computer opponent's choices. These findings should motivate future search to identify circuits and precise rules that determine how different types of cognitive and reward information are combined in prefrontal cortex.

Another current debate centers on the relationship of working memory and selective attention. Physiological studies in monkeys and human imaging point to a shared network for working memory maintenance and top-down attention signaling to guide sensory processing. Interestingly, the paper of Woodman, Schall, and Luck shows that, in a visual search task, the working memory system is involved in sustained attention only when the target varies from trial to trial. Their findings suggest that the engagement of the working memory system by attention could depend on the (short or long) timescale over which the attended cue must be updated. Gazzaley et al. apply the "seed region"–based correlation analysis of human fMRI to strengthen the case that the middle frontal gyrus interacts with visual association cortices during visual attention. It is worth noting that although a dynamic interplay between the prefrontal cortex and the posterior visual system is believed to be critical to selective attention, very little is known about the circuits for such cross talk. It has been argued that this interaction should be both excitatory (for a boost of sensory processing by attention) and inhibitory (for suppressing unattended processes). Medalla et al. in this volume describe specialized pathways that project from the frontopolar area 10 and cingulate area 32 to subtypes of local inhibitory neurons in auditory areas of the temporal lobe, providing the basis through which the prefrontal cortex may implement inhibitory control of sensory processing.

A final set of papers are devoted to building a firm neurobiological and neuropharmacological foundation to understand psychiatric diseases. Robbins and Roberts review a long series of experiments using behaving rodents in support of differential modulation of the prefrontal executive function by monoamines and acetylcholine, respectively. Diamond reports recent studies that link genes affecting dopamine signaling to prefrontal functions. Finally, Tan, Callicott, and Weinberger discuss how genetic research combined with neural imaging can provide a powerful set of tools to decipher the molecular and circuit basis of cognitive deficits in schizophrenia.

Thus, the papers printed in these pages illustrate the fast evolving field of prefrontal research. It is our hope that this "Supplement Issue" will stimulate new research and foster dialogs among neuroscientists from different disciplines to work together toward a coherent and shared framework for understanding the prefrontal circuits underlying cognition. For this progress in unraveling the "mystery of the frontal lobe," we are deeply indebted to the groundbreaking contributions of Pat.