various aspects of parietal- and prefrontal-cortical functions, as well as more generally, in studies on spatial memory, cortical circuitry, and more. What are the reasons for the longstanding influence of the paper? In part, this stems from the paper's notable rigor and quality: the careful attention to implementation detail, and thoughtful application of analytical tools, and its eloquent writing. Beyond that, one may argue, the study's task design strikes a unique balance between simplicity and concreteness on the one hand, and relevance to broader questions on the other. This 'sweet spot' has appealed to researchers approaching the topic from a variety of perspectives, including modelers, cognitive psychologists, and neurophysiologist. In the context of questions around coding stability, for instance, recent studies have found that single-unit activity could be combined to obtain population-level stimulus mnemonic coding that is robust during the whole delay period (Figure 2; [9,12]). Other recent studies examined the issues of temporal timescales across cortical regions, and argued, for instance, that frontal areas are endowed with intrinsic timescales (∼180 ms) much longer than those found in sensory cortex areas (∼65 ms, [13]). This feature could allow frontal lobe circuits to maintain information more easily than early sensory cortices.

The idea of working memory encoding via persistent neural activity, one should mention, has also generated controversy and debate over the years. Some of the complexity here stems from the difficulty of fully disentangling the various components involved in working memory tasks, for example, the time component (mentioned earlier) or reward expectation. Some also questioned, for instance, whether the same mechanism is relevant when subjects have to memorize fine visual features, typically encoded in upstream visual areas that do not tend

to show persistent activity patterns during working memory. Recent studies using blood oxygenation level-dependent signals have shown that it is possible to decode information during working memory from the activity in early sensory cortices [14,15]. However, single-unit recordings from sensory cortices during working memory tasks have found that neurons only code their own principal sensory modality within the stimulation period [11,15]. These seemingly contradictory findings open up the door for new studies necessary to reconcile both results. In this sense, a possible line of research is the relationship between these signals and top–down mechanisms that influence stimulus processing in early sensory areas. In addition, working memory was systematically observed across parietal and frontal lobe circuits [6,9,10,11,15] and the role of this distributed coding is an open question for future work. In short, the discovery of a visual space memory map in the PFC and the associated theoretical framework remains relevant to this day. As long as careful attention is paid to the implementation of appropriate controls and the application of analytical tools, as the late Patricia Goldman-Rakic and colleagues did, neuroscience can still gain much from similar studies into perception and memory, using cognitively demanding tasks.

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References
1. Jung, R. (1984) Sensory research in historical perspective: some philosophical foundations of perception. In *Handbook of Physiology* (Brookhart, J.M. and Mountcastle, V. B., eds), pp. 1–74, American Physiological Society
2. Adrian, E.D. (1928) *The Basis of Sensation. The Action of the Sense Organs,* Christophers
3. Funahashi, S. *et al.* (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* 61, 331–349
4. Fuster, J.M. and Alexander, G.E. (1971) Neuron activity related to short-term memory. *Science* 173, 652–654
5. Kubota, K. and Niki, H. (1971) Prefrontal cortical unit activity and delayed alternation performance in monkeys. *J. Neurophysiol.* 34, 337–347
6. Chafee, M.V. and Goldman-Rakic, P.S. (1998) Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *J. Neurophysiol.* 79, 2919–2940
7. Romo, R. *et al.* (2003) Correlated neuronal discharges that increase coding efficiency during perceptual discrimination. *Neuron* 38, 649–657
8. Brody, C.D. *et al.* (2003) Timing and neural encoding of somatosensory parametric working memory in macaque prefrontal cortex. *Cereb. Cortex* 13, 1196–1207
9. Rossi-Pool, R. *et al.* (2017) Decoding a decision process in the neuronal population of dorsal premotor cortex. *Neuron* 96, 1432–1446
10. Romo, R. *et al.* (1999) Neuronal correlates of parametric working memory in the prefrontal cortex. *Nature* 399, 470–473
11. Vergara, J. *et al.* (2016) A neural parametric code for storing information of more than one sensory modality in working memory. *Neuron* 89, 54–62
12. Murray, J.D. *et al.* (2017) Stable subspace coding for working memory coexists with heterogeneous neural dynamics in prefrontal cortex. *Proc. Natl. Acad. Sci. U. S. A.* 141, 394–399
13. Murray, J.D. *et al.* (2014) A hierarchy of intrinsic timescales across primate cortex. *Nat. Neurosci.* 17, 1661–1663
14. Harrison, S.A. and Tong, F. (2009) Decoding reveals the contents of visual working memory in early visual areas. *Nature* 458, 632–635
15. Mendoza-Halliday, D. *et al.* (2014) Sharp emergence of feature-selective sustained activity along the dorsal visual pathway. *Nat. Neurosci.* 17, 1255–1262

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Building on a Solid Baseline: Anticipatory Biases in Attention

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A brain-imaging paper by Kastner and colleagues in 1999 was the first to demonstrate that merely focusing attention at a spatial location changed the baseline activity level in various regions of human visual cortex even before any stimuli appeared. The study provided a touchstone for investigating cognitive–sensory interactions and

understanding the proactive endogenous signals that shape perception.

Our perception derives from the interaction between incoming sensory stimulation and endogenous factors linked to task goals, expectations, and memories. Selective attention comprises the functions that prioritize and select relevant information from the incoming sensory stream based on these endogenous signals and, thus, is an essential building block of cognition. In 1999, *Neuron* published a brain-imaging study by Kastner and her colleagues [1] that significantly advanced our understanding of selective attention in the human brain. In their task, participants viewed colored stimulus patterns appearing sequentially or simultaneously in four locations of the upper right-hand quadrant, and were instructed to detect a prespecified stimulus pattern (target) appearing at a given, fixed location. Similar to previous and contemporaneous studies, results highlighted the involvement of dorsal parietal and premotor–prefrontal areas in controlling spatial attention, and revealed modulation throughout multiple visual areas, including the primary visual cortex. In addition, the study made two important novel contributions. By framing the study within theoretical and methodological approaches developed using nonhuman primate models, the results supported two central tenets of the influential biased-competition model of selective attention [2].

The first tenet of the biased-competition model of attention [2] is the existence of an anticipatory signal that biases the analysis of incoming sensory stimuli. This anticipatory signal is based on goal-related stimulus templates and, in the context of visual processing, facilitates processing of the visual features and spatial locations of task-relevant items. Kastner and colleagues [1] were the first to observe a putative anticipatory biasing signal in the human brain. Even before any stimulus was presented in the trials, significant tonic elevation of brain activity occurred in visual areas responsive to the task-relevant spatial location, as well as in dorsal frontal and parietal areas implicated in controlling spatial attention [3]. This 'baseline shift' was compatible with spatially selective preactivation in early visual areas to facilitate subsequent processing of the relevant target stimulus. Notably, and somewhat curiously, the observed baseline shift was pronounced, whereas in previous single-unit recordings in animal studies, prestimulus modulations were often modest or even absent [4]. The reasons for discrepancies in the nature and magnitude of effects in imaging versus single-unit studies are not entirely settled [5]. Nevertheless, the finding of Kastner and colleagues provided persuasive evidence for preparatory attention signals and, thus, represents one of the first important novel contributions from human FMRI studies.

The second, related tenet of the biased-competition model is that attentional modulation is primarily directed at resolving competition among visual stimuli. Accordingly, Kastner and colleagues observed greater attentional modulation when stimuli appeared simultaneously and, thus, competed for neural processing, than when they appeared sequentially and competition was (presumably) minimal. The stimulus-related hemodynamic response in multiple visual areas was significantly larger when the stimuli were attended compared with when they were passively viewed in a control condition. This difference between attended and unattended conditions was accentuated when stimuli competed for visual processing. Although it remains puzzling to understand the mapping between modulations at the single-neuron level and those observed at the regional level using hemodynamic signals, the study suggested that population-imaging measures preserved important functional properties seen at the cellular level.

The findings have stood the test of time, and provided an anchor point for the refinement of our knowledge and understanding of the neural basis of attention. The dorsal frontoparietal network implicated in the control of attention [3] is investigated with increasing granularity, subcortical areas are recognized to integrate network activity, and brain-stimulation studies probe the causal influence of its constituent functional areas on visual processing [6–8]. The plurality of modulatory sites is ever more striking as the sensitivity of imaging methods increases [7,9]. It is intuitive to propose that sensory modulation starts in brain areas processing stimulus attributes that are relevant to task goals and that differentiate target from competing distractor stimuli. However, in reality, tracking the evolution of neural modulation within the nodes of the rich and highly interconnected visual network remains challenging. This will be a fruitful area for investigation with methods that sample multiple sites simultaneously with high spatial and temporal resolution (e.g., simultaneous intracranial recordings or electrocorticography).

Human MRI methods improve relentlessly. In addition to ever-increasing improvements in hardware and imaging sequences, research over the past decade has revolutionized analytical methods, enabling researchers to investigate the informational content within brain areas and networks, and to relate it to behavioral performance at the level of single trials. Multivariate methods were developed to compare the pattern of small variations in the fMRI signal within a population of imaging units (voxels). Using multivariate pattern analysis, attention-related anticipatory biasing signals were shown to share informational content with the anticipated target stimulus within visual areas [10]. Going further, the use of multivariate methods to derive encoding models based on tuning

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functions of voxels [11] has enabled more precise investigations into the nature of anticipatory and modulatory signals. These methods have also been adapted for human electrophysiology with electro- and magnetoencephalography (EEG and MEG), which have the necessary temporal resolution to chart the temporal dynamics of anticipatory and modulatory signals as they unfold [12].

Findings based on these novel analytical methods have led us away from the long-held notion of attention-related anticipatory preparation carried by a static sustained signal that preactivates ensembles of neurons based on receptive fields matching the spatial locations or features of goal-related stimulus templates. Instead, anticipatory control has revealed itself to be more flexible, adaptive, and dynamic than had been previously assumed. For example, in a functional MRI task requiring participants to decide whether the orientation or contrast of two peripheral gratings matched, analysis using an encoding model revealed that foreknowledge about stimulus orientation could increase activity in neuronal populations coding nontarget orientations [13]. When off-target orientations were particularly useful to guide performance, activity in their population receptive fields were elevated and correlated with behavioral performance. Thus, rather than simply preactivating neuronal populations receptive to target-related templates, attention proactively and selectively prepares neuronal populations that are most informative. Complementing MRI studies, human neurophysiology has revealed the dynamic nature and time course of attention-related biases. MEG recordings taken when individuals matched incoming visual orientation stimuli against a mental template revealed reliable dynamic trajectories of brain activity patterns carrying template-related content [14]. Rather than being sustained, the decoding of the template content ebbed and flowed

with the temporal rhythm of stimulus presentation, suggesting the possibility of latent codes that become 'energized' by temporal expectations and incoming sensory stimulation [15].

The recent discoveries outlined above have prompted researchers to reconsider the idea of tonic delay activity. Under the hood of seemingly sustained signals over an average of trials lie many interesting and non-mutually exclusive possibilities of short-lived bursts of processing, dynamic sequences of activations, reverberating network states, and latent traces of stimulus information left behind by short-term synaptic plasticity. Whatever form these signals take, they are not merely passive reproductions of memory templates, but rather active prospective constructs to facilitate goal-based adaptive behavior.

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References

1. Kastner, S. *et al.* (1999) Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron* 22, 751–761
2. Desimone, R. and Duncan, J. (1995) Neural mechanisms of selective visual attention. *Annu. Rev. Neurosci.* 18, 193–222
3. Corbetta, M. *et al.* (1993) A PET study of visuospatial attention. *J. Neurosci.* 13, 1202–1226
4. Luck, S.J. *et al.* (1997) Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *J. Neurophysiol.* 77, 24–42
5. Boynton, G.M. (2011) Spikes, BOLD, attention, and awareness: a comparison of electrophysiological and fMRI signals in V1. *J. Vis.* 11, 12–12
6. Nobre, A.C. and Mesulam, M.M. (2014) Large-scale networks for attentional biases. In *The Oxford Handbook of Attention* (Nobre, A.C. and Kastner, S., eds), pp. 105–151, Oxford University Press
7. Serences, J.T. and Kastner, S. (2014) A multi-level account of selective attention. In *The Oxford Handbook of Attention* (Nobre, A.C. and Kastner, S., eds), pp. 76–104, Oxford University Press
8. Moore, T. and Fallah, M. (2001) Control of eye movements and spatial attention. *Proc. Natl. Acad. Sci.* 98, 1273–1276
9. Sprague, T.C. *et al.* (2015) Visual attention mitigates information loss in small-and large-scale neural codes. *Trends Cogn. Sci.* 19, 215–226
10. Stokes, M. *et al.* (2009) Shape-specific preparatory activity mediates attention to targets in human visual cortex. *Proc. Natl. Acad. Sci.* 106, 19569–19574
11. Serences, J.T. *et al.* (2009) Estimating the influence of attention on population codes in human visual cortex using voxel-based tuning functions. *Neuroimage* 44, 223–231
12. Garcia, J.O. *et al.* (2013) Near-real-time feature-selective modulations in human cortex. *Curr. Biol.* 23, 515–522
13. Scolari, M. *et al.* (2012) Optimal deployment of attentional gain during fine discriminations. *J. Neurosci.* 32, 7723–7733
14. Myers, N.E. *et al.* (2015) Testing sensory evidence against mnemonic templates. *Elife* 4, e09000
15. Nobre, A.C. and van Ede, F. (2018) Anticipated moments: temporal structure in attention. *Nat. Rev. Neurosci.* 19, 34–48

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Cell Type-Specific Optogenetic Dissection of Brain Rhythms

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A pair of 2009 papers by Cardin *et al.* and Sohal *et al.* marked a watershed moment as optogenetics exploded onto the scene of systems neuroscience. This pair of back-to-back papers in the June issue of *Nature* leveraged a powerful combination of the Cre/lox