

Prefrontal Contributions to Visual Selective Attention

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Abstract

The faculty of attention endows us with the capacity to process important sensory information selectively while disregarding information that is potentially distracting. Much of our understanding of the neural circuitry underlying this fundamental cognitive function comes from neurophysiological studies within the visual modality. Past evidence suggests that a principal function of the prefrontal cortex (PFC) is selective attention and that this function involves the modulation of sensory signals within posterior cortices. In this review, we discuss recent progress in identifying the specific prefrontal circuits controlling visual attention and its neural correlates within the primate visual system. In addition, we examine the persisting challenge of precisely defining how behavior should be affected when attentional function is lost.

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NEURAL CORRELATES OF VISUAL ATTENTION

Attention describes the basic cognitive function in which behaviorally relevant information is selected in favor of irrelevant information for further sensory processing and for the guidance of behavioral responses. As William James (1890, pp. 403–4) classically described, attention involves the “...withdrawal from some things in order to deal effectively with others.” Neurophysiological investigations have established that in the visual modality, attention involves the amplification of neuronal representations corresponding to selected targets at the expense of other representations (Noudoost et al. 2010). Investigators have observed attention-dependent modulation of visually driven neural activity across multiple stages of the primate visual system, primarily in the form of increases in firing rate (Reynolds & Chelazzi 2004). In more recent years, neurophysiological studies have found that, in addition to increasing firing rates, attention may enhance signaling efficacy for targets by changing other parameters of visually driven neural activity. These parameters include decreases in the trial-to-trial variability of spiking activity (Mitchell et al. 2007), decreases

in low-frequency correlated variability across neuronal ensembles (Cohen & Maunsell 2009), and increases in the phase locking of spiking responses with particular frequency components of local field potentials (LFPs) (Fries et al. 2001), as well as shifts and reductions in the breadth of visual receptive fields (RFs) (Connor et al. 1997). Although we still need to determine which (if any) of these parameters, including firing rate, is most strongly correlated with the behavioral effects of attention, it is nonetheless clear that attentional deployment is associated with robust changes to the signaling properties of neurons within the visual system.

Quite separate from the question of how attention changes the fidelity of visual signals in the brain is the more basic question of which mechanism initiates those changes. Although it is overwhelmingly apparent that attention modulates the visual responses of neurons across many stages of the visual system, the neural circuits underlying that modulation remain unknown. The causal basis of visual selective attention has been an area of much research for well over a century, primarily in the context of lesion studies, yet its origin continues to be one of the more fundamental unresolved questions. As we discuss in the closing section of this review, part of the reason for this missing information is the difficulty in defining precisely what a loss of attention should look like. As a result, for example, competing hypotheses of a critical role of the parietal cortex (Bisley & Goldberg 2010), or of midbrain or thalamic structures (e.g., Shipp 2004), or of the prefrontal cortex (PFC) (Miller & Cohen 2001) in visual attention have persisted in parallel, and almost in spite of one another, for decades. Given that attention has many forms (e.g., spatial versus feature-based), these candidate structures may, in fact, contribute to these different forms in complementary (e.g., Buschman & Miller 2007) or redundant ways. Yet, whether any one of them, or perhaps even some other structure, is indeed a source of attentional modulation of visual signals remains to be determined. In this review, we focus on evidence

that supports a causal role of PFC in visual selective attention. Although it seems unlikely that PFC is both a necessary and a sufficient source of attentional modulation in all its forms, recent work has nonetheless offered important new insights into what is likely a fundamental contribution of PFC to visual attention.

The PFC consists of a multitude of frontal cortical areas anterior to primary and association motor cortices, and it has long been implicated in high-level cognitive functions. In humans, the PFC occupies a much larger proportion of the cerebral cortex than in other species, which prompts the notion that it may contribute more to cognitive capacities unique to humans (Fuster 1995). Consistent with this notion is the evidence that subregions within the PFC play a crucial role in attention, including visual attention. In particular, two regions, the dorsolateral prefrontal cortex (dlPFC) and the frontal eye field (FEF), comprising Brodmann areas 8, 45 and 46, have been implicated (Figure 1). Beginning with the lesion studies in monkeys conducted by David Ferrier in the late nineteenth century, researchers have known that damage to this region of the PFC resulted in behavioral deficits believed to be consistent with a loss of attentional control (Ferrier 1876). More recently, studies in monkeys have yielded similar observations (Wardak et al. 2006), as have studies of human subjects with PFC damage (Knight et al. 1995, Rueckert & Grafman 1996). Moreover, similar to what is observed within the posterior visual cortex, neurophysiological studies of dlPFC and FEF have identified neural correlates of covert visual attention in both of these areas. As in posterior visual areas, visually driven responses in both areas are enhanced when attention is directed to stimuli within the neuronal RF (Lebedev et al. 2004, Thompson et al. 2005, Buschman & Miller 2007, Armstrong et al. 2009, Gregoriou et al. 2009). This enhancement is evident whether attention is directed voluntarily (top-down) (Buschman & Miller 2007, Armstrong et al. 2009, Gregoriou et al. 2009) or shifted to stimuli as the result of their greater salience

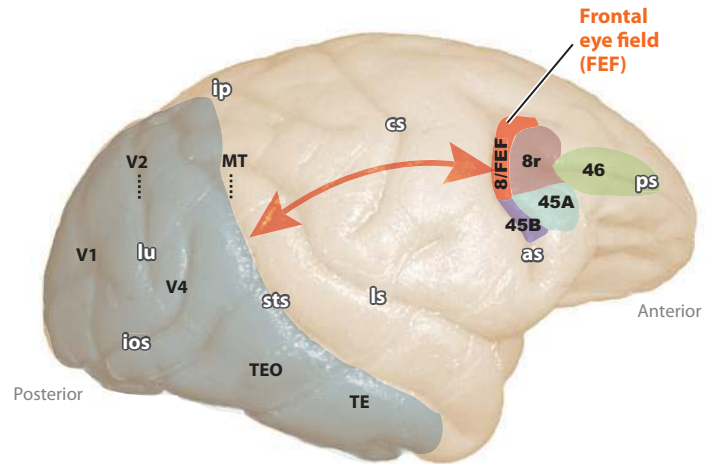


Figure 1

The prefrontal cortex (PFC) of the macaque monkey and its connections with the posterior visual cortex. Shown in the lateral view of the monkey cerebral cortex (right hemisphere) are areas of the PFC with known involvement in visual attention, particularly the frontal eye field (FEF, area 8) in the anterior bank of the arcuate sulcus and the dorsolateral prefrontal cortex (dlPFC) in the principal sulcus (area 46). The arrow between the PFC and the posterior visual cortex depicts the direct and indirect connections of the PFC to areas within the extrastriate cortex [V2, V4, MT (middle temporal), etc.]. Dotted lines denote cortical areas that are mostly buried within a sulcus. Abbreviations: as, arcuate sulcus; cs, central sulcus; ios, inferior occipital sulcus; ip, intraparietal sulcus; lu, lunate sulcus; ls, lateral sulcus; ps, principal sulcus; sts, superior temporal sulcus. PFC areas are shown as defined in Gerbella et al. 2010.

(bottom-up) (Buschman & Miller 2007). Combined with the lesion results, the evidence of neural correlates in these areas has prompted attempts to address the causal role of the PFC in visual attention using more circuit-specific approaches, particularly in the FEF.

GAZE CONTROL, VISUAL ATTENTION, AND THE FEF

Before studies well established that covert attention involves a widespread modulation of visual activity, researchers knew that saccadic eye movements (overt attention) involve their own form of visual response modulation. In their early studies of the visual and motor properties of neurons within the superficial layers of the superior colliculus (SC) in alert monkeys,

Wurtz & Goldberg (1972a,b) observed that the neuronal responses elicited by visual stimuli were enhanced when monkeys used those stimuli as the targets of saccades. Similar effects were observed subsequently within the FEF (Goldberg & Bushnell 1981) and within the posterior parietal cortex (Mountcastle et al. 1975). Later studies demonstrated that the presaccadic visual enhancement is also observed within the posterior visual cortex, specifically in area V4 (Fischer & Boch 1981), and the inferior temporal cortex (Chelazzi et al. 1993). These neurophysiological observations appear consistent with the long-appreciated relationship between visual spatial attention and gaze control. Gaze shifts, which are most often achieved by saccades, appear to occur in conjunction with shifts of visual attention, as shown by the decrement in target-detection thresholds observed near the end points of upcoming saccades (Hoffman & Subramaniam 1995, Peterson et al. 2004). In the 1980s, Rizzolatti and colleagues proposed a “premotor theory of attention,” which hypothesized that the mechanisms responsible for spatial attention and the mechanisms involved in programming saccades are the same, but that in the covert case “the eyes are blocked at a certain peripheral stage” (Rizzolatti et al. 1987, p. 37). Subsequent studies demonstrated that visual detection and discrimination are in fact facilitated at the end points of saccades, even when subjects are instructed to attend elsewhere (Shepherd et al. 1986, Hoffman & Subramaniam 1995, Deubel & Schneider 1996). These results led to the hypothesis that the selection of objects for perceptual processing and the preparation of appropriate motor responses are controlled by a common mechanism. Later neurophysiological experiments provided crucial tests of that hypothesis.

The FEF provides an interface between the saccadic system, the representation of visual stimuli within posterior cortices, and the executive control functions of PFC. The FEF is the region from which contraversive saccadic eye movements can be elicited with electrical stimulation (Robinson & Fuchs 1969, Bruce

et al. 1985). Subthreshold FEF stimulation, i.e., stimulation with currents below that required to evoke a saccade, nonetheless increases the likelihood that an animal will subsequently initiate the saccade represented by neurons at the stimulation site. That is, subthreshold FEF stimulation can bias saccade planning (Schiller & Tehovnik 2001). The dynamics of FEF spiking responses recorded during saccade tasks reveal a continuum of visual and movement functions among neurons within the FEF. Some neurons exhibit purely visual activity in response to the onset of a stimulus (visual neurons), and others respond exclusively before a saccade is initiated (movement neurons), although most FEF neurons (visuomovement neurons) exhibit a combination of visual and movement properties (Bruce & Goldberg 1985, Sommer & Wurtz 2000). The aforementioned finding of attentional modulation among FEF neurons includes the observation that only visual and visuomovement neurons, and not movement neurons, are modulated during covert attention (Thompson et al. 2005, Gregoriou et al. 2012).

Prompted by the psychophysical evidence of a link between saccades and attention, Moore and Fallah (Moore & Fallah 2001, Moore & Fallah 2004) examined whether manipulating neural activity within the FEF could affect the deployment of spatial attention. The authors stimulated FEF sites using subthreshold currents while monkeys monitored a target stimulus among distracters for a small change in luminance. On trials in which microstimulation occurred, monkeys were able to detect smaller luminance changes than they could on control trials. This effect was spatially and temporally specific: An increase in sensitivity was observed only if the target location matched the end point of saccades evoked from the microstimulation site, and the effect was strongest when onset of microstimulation immediately preceded, and temporally overlapped, the luminance change. Moreover, the magnitude of the change in sensitivity produced by microstimulation was comparable to removing the distracters altogether.

In addition to the behaviorally defined effects of FEF microstimulation on attention, a series of related studies found that FEF microstimulation alters the visual responses of neurons within the posterior visual cortex, specifically area V4. Moore & Armstrong (2003) found that subthreshold microstimulation of the FEF enhanced the visual responses in V4 neurons at retinotopically corresponding locations, whereas responses at other locations were suppressed. This modulation was stronger in the presence of distracters and was critically dependent on an overlap in the RF of the V4 neuron and end point of saccades evoked from the microstimulation site. The enhancement also depended on the placement of the visual stimulus precisely at the end point of evoked saccades and not merely anywhere within the larger V4 receptive field (Armstrong et al. 2006). In addition, the microstimulation-driven enhancement was larger for the V4 neuron's preferred stimulus than for a non-preferred stimulus, resulting in an increase in the ability of a V4 cell to discriminate between preferred and nonpreferred stimuli (Armstrong & Moore 2007). Placing both a preferred and nonpreferred stimulus within a V4 neuron's RF produces a response that is intermediate in magnitude between its responses to either stimulus alone (Reynolds et al. 1999). The responses of V4 neurons to such competing RF stimuli could be biased toward one stimulus or the other with FEF microstimulation, depending on which stimulus was aligned with the stimulated FEF vector. This effect mirrors the known influence of voluntary attention on the responses of visual cortical neurons to competing RF stimuli (Moran & Desimone 1985, Reynolds et al. 1999). A subsequent study by Ekstrom et al. 2009 examined the influence of FEF microstimulation on visual cortical activity using functional magnetic resonance imaging (fMRI), thus allowing them to see effects in all visual areas. They observed modulations in visually driven BOLD responses throughout the visual cortex, including V1, and found that the impact of microstimulation depended on the presence of distracters.

CONTROL OF VISUAL CORTICAL MODULATION BY FEF NEURONS

The fact that FEF microstimulation produces attention-like modulation within area V4 suggests that FEF neurons themselves are the source of that modulation. But such a conclusion cannot be made. Electrical stimulation is known to antidromically activate neurons within areas projecting to the stimulated site, in addition to orthodromic activation of downstream neurons, and stimulation may even activate cells in remote regions whose axons pass in proximity to the electrode tip (see Clark et al. 2011 for review). Thus, the possibility remains that neurons antidromically activated by stimulation, for example those within parietal area LIP (lateral intraparietal) (Bisley & Goldberg 2010), are in fact those directly responsible for producing the observed modulation. In addition, the more recent observation of an increased coupling of spiking and gamma-band local field activity between the FEF and V4 during attention (Gregoriou et al. 2009) has been interpreted by some as evidence of a direct effect of FEF neurons on V4 (e.g., Anderson et al. 2011). Moreover, a Granger causality analysis of the direction of gamma-band local field potential increases suggests an early causal influence of the FEF on V4 and a later causal influence of the latter on the former (Gregoriou et al. 2009). Though elegant, these results, like the stimulation results, leave open the possibility that neurons within one or more other structures not being studied are in fact the ones driving modulation within both V4 and the FEF. Resolving the question of a direct influence of FEF neurons on visual cortical modulation instead requires testing whether changes in FEF neuronal activity are sufficient to bring about that modulation. Such a test was recently carried out by Noudoost & Moore (2011a).

Experimental and clinical evidence suggests that dopamine (DA) within the PFC plays an important role in cognitive functions, including attention (Ernst et al. 1998, Castellanos & Tannock 2002, Robbins & Arnsten 2009). Noudoost & Moore (2011a) exploited this

evidence and hypothesized that perhaps DAergic activity within the FEF mediates the apparent influence that FEF neurons have on signals within the visual cortex. They reasoned that if DA plays a role in visual attention, then changes in DAergic activity within the FEF should in some way alter signals within the visual cortex. DAergic innervation of the PFC originates from neurons within the ventral midbrain, including those within the ventral tegmental area (VTA) (Björklund & Dunnett 2007). Compared with other subtypes, D1 receptors (D1Rs) are more abundant in the PFC and are believed to play a more prominent role in regulating cognitive functions (Lidow et al. 1991, Goldman-Rakic et al. 1992, Santana et al. 2009). Although the effects of DA on PFC

neuron activity are rather complex, evidence from a variety of experimental approaches suggests that when acting via D1Rs, DA can alter the strength and reliability of converging excitatory (glutamatergic) synapses (Gao et al. 2001). This property suggests a means by which D1Rs could mediate the selection and maintenance of particular FEF signals and the influence of those signals on other areas.

To address the direct role of FEF neuronal activity in the modulation of visual cortical signals as well as the role of DA in mediating that modulation, Noudoost & Moore (2011a) studied the impact of manipulating D1R-mediated activity within the FEF on the visual responses of extrastriate area V4 neurons (Figure 2a). Manipulation of D1R-mediated

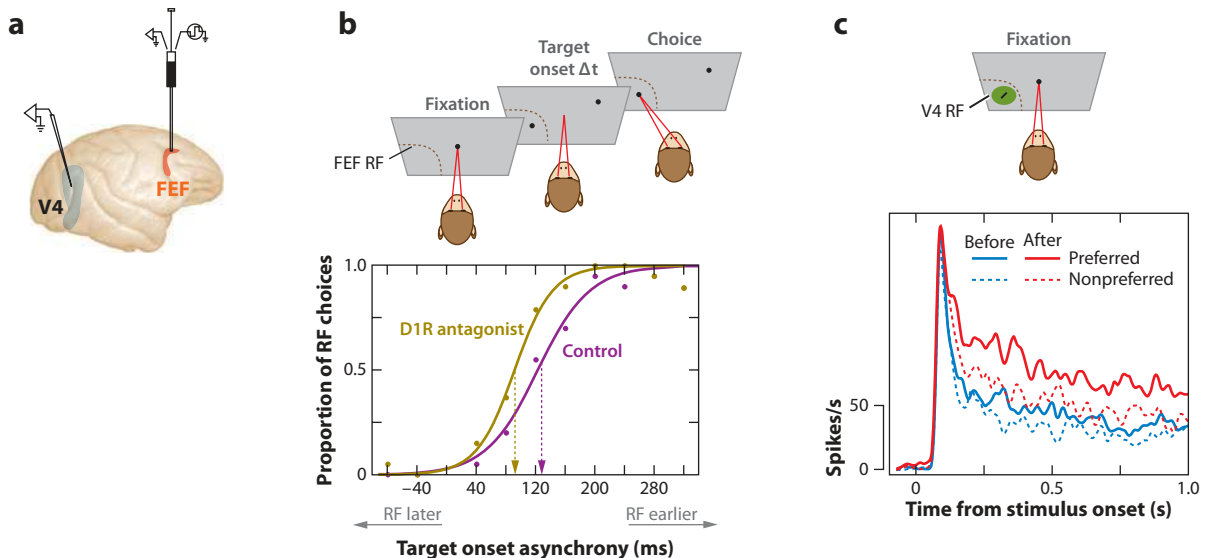


Figure 2

Dopamine-mediated frontal eye field (FEF) control of saccadic target selection and visual cortical responses. (a) Local manipulation of D1 receptor (D1R)-mediated activity within the FEF during single-neuron electrophysiology in area V4. Lateral view of the macaque brain depicts the location of a recording microinjectrode within the FEF and of recording sites within area V4. (b) A free-choice saccade task was used to measure the monkey's tendency to make saccades to targets within the part of visual space represented by neurons at the drug infusion site (FEF RF) versus targets at a location in the opposite hemifield. In the task, the two targets appeared at varying temporal onset asynchronies (Δt). The receptive field (RF) target appeared either earlier or later than the target outside the RF. The monkey's bias toward either target was measured as the asynchrony at which targets were chosen with equal probability (dotted arrows in bottom plot). Following a local infusion of a D1R antagonist into the FEF, there was a leftward shift in the psychometric curve (gold), indicating an increase in the tendency to make saccades to targets within the FEF RF. (c) Visual responses of a V4 neuron with an RF within the FEF RF; responses were measured during passive fixation. The plot shows mean visual responses over time to oriented bar stimuli presented at the preferred (solid lines) or nonpreferred (dotted lines) orientation both before (blue) and after (red) the FEF D1R manipulation. Adapted from Noudoost & Moore 2011a.

FEF activity was achieved via small (a microliter or less) injections of the selective D1 antagonist SCH23390 into sites within the FEF. The authors then measured the spiking responses of area V4 neurons that had RFs within the part of space affected by the D1R manipulation. Thus, measurements of visually driven V4 activity could be made before and after manipulating the D1R-mediated activity of FEF neurons projecting to the recorded V4 neurons. In addition, given the evidence mentioned above that attentional deployment tends to coincide with the preparation of saccades, the authors also measured the effects of the D1R manipulation on the selection of visual stimuli as targets for saccades (**Figure 2b**). They observed that visual stimuli presented within the part of space affected by the D1R manipulation were consistently more likely to be selected as saccadic targets compared with control trials. Thus, the manipulation increased saccadic target selection. Most importantly, within area V4, the authors observed that responses to visual stimuli were altered in three important ways. First, the manipulation produced an enhancement in the magnitude of responses to visual stimulation (**Figure 2c**). Second, visual responses became more stimulus selective. Third, visual responses became less variable across trials. Notably, all three of the observed changes in V4 visual activity are known effects of visual attention (Motter 1993, McAdams & Maunsell 1999, Mitchell et al. 2007). Moreover, the magnitude of the observed modulation was nearly equal to that seen in attention studies. Thus, manipulation of D1R-mediated FEF activity not only increased saccadic target selection within the corresponding part of space but also increased the magnitude, selectivity, and reliability of V4 visual responses. In essence, the manipulation effectively elicited correlates of covert attention within the extrastriate cortex in the absence of a behavioral task.

The effects of the FEF D1R manipulation on V4 neurons show that changes to FEF neuronal activity are sufficient to exert a long-range influence on signals within the visual cortex.

In addition, the above effects show that DA, acting via D1Rs, is involved in the FEF's influence on visual cortical signals as well as its influence on saccadic preparation. Because a wealth of evidence implicates D1Rs in the neural mechanisms of spatial working memory, specifically in regulating the persistent activity of neurons within the dlPFC (Williams & Goldman-Rakic 1995), the above results suggest that D1Rs are part of a common mechanism underlying spatial attention and spatial working memory (Noudoost & Moore 2011b). Like dlPFC neurons, FEF neurons also exhibit persistent, delay-period activity, even in tasks not involving saccades (Armstrong et al. 2009) (**Figure 3**). Persistent activity within the PFC is thought to be generated by recurrent glutamatergic connections between prefrontal pyramidal neurons (Gao et al. 2001, Seamans & Yang 2004). DAergic modulation of persistent activity within the PFC appears to be achieved by the influence of D1Rs on these recurrent connections. The above results suggest a model in which D1Rs contribute to signatures of attention within the visual cortex by a mechanism similar to their influence on persistent activity, namely by modulating long-range, recurrent connections between the FEF and the visual cortex (**Figure 4**). Consistent with this idea is the finding that FEF neurons exhibiting persistent activity tend to exhibit greater attentional modulation than do those without (Armstrong et al. 2009). In the model, attention (and/or saccadic preparation) is directed toward particular locations according to the pattern of activity across the map of visual space within the FEF, similar to what Bisley & Goldberg (2010) proposed for parietal area LIP. Cortical columns with greater activity would then correspond to locations of greater attentional deployment (and/or saccadic preparation) and consequently higher gain of spatially overlapping visual cortical signals, compared with nonoverlapping signals. A possible role of DA would be to control the extent of the FEF gain modulation, effectively setting the breadth of the so-called attentional window. Thus, optimum DA levels would translate into larger differences between

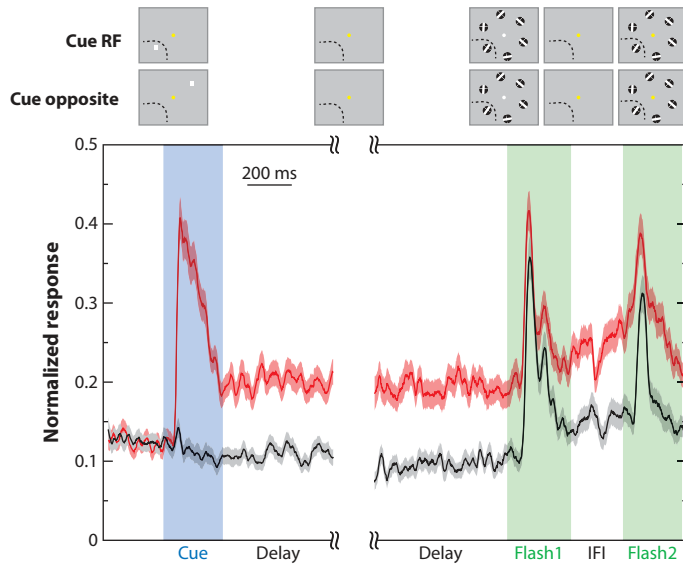


Figure 3

Modulation of frontal eye field (FEF) neuronal responses in monkeys performing an attention task. In the task, monkeys fixated on a central fixation spot (*yellow dot in gray panels*) and depressed a manual lever. The brief appearance of a peripheral cue (*white square, first panels*) instructed the monkey that, after a delay (~1 s), a change in the orientation of a flashed grating stimulus may occur at the cued location (50% of trials). During the grating flash epoch that followed the delay, an array of six oriented gratings was flashed twice, and the monkey was rewarded for releasing the lever if the grating at the cued location changed its orientation and for holding the lever if a change did not occur. The diagram depicts trials without a change. The five remaining gratings were distracters. The neuronal response histograms below show the average response of a population of 106 FEF neurons on correct trials in which monkeys were cued to attend either to the location coinciding with the receptive field (RF) of a FEF neuron (*red*) or to a location in the opposite hemifield (*gray*). The dotted half circle in each panel depicts the neuronal RF. Note that the average neuronal response not only signals the visual appearance of the brief cue but also continues to encode the attended location throughout the trial. Data are from only trials on which the grating orientation did not change. Adapted from Armstrong et al. 2009.

attended and unattended stimuli, whereas sub-optimal DA levels would mean small differences and perhaps a less stable attentional focus. At least superficially, such a role of DA in attentional deployment would be consistent with the perceptual deficits characteristic of attention deficit hyperactivity disorder (ADHD) patients (Mason et al. 2003), who generally exhibit abnormal PFC DA levels (Ernst et al. 1998).

Noudoost & Moore (2011a) also observed that manipulation of D2 receptor (D2R)-mediated activity increased saccadic target selection in a manner equivalent to the D1R manipulation. However, only the D1R manipulation produced attention-like effects within area V4; the D2R manipulation exerted no measurable effects on the visual activity of V4 neurons. Thus, in addition to being dissociable at the level of functional subclasses of FEF neurons (Thompson et al. 2005, Gregoriou et al. 2009), the control of visual attention and saccadic target selection appear to be dissociable at the level of DA receptor subtypes. This dissociability appears to result, at least in part, from differing patterns of D1R and D2R expression across cortical laminae (**Figure 4**). Within the cortex, D1Rs exhibit a bilaminar pattern of expression, appearing in both supragranular and infragranular layers. In contrast, D2Rs are less abundant and tend to be expressed primarily within infragranular layers (Lidow et al. 1991, Santana et al. 2009). In the FEF, the principal source of output to the brain stem oculomotor nuclei and to the SC emanates from pyramidal neurons in layer V (Segraves & Goldberg 1987), where both DA receptor subtypes are expressed. This finding proposes how both the D1R and D2R manipulations could have altered saccadic target selection. On the other hand, FEF neurons projecting to the posterior visual cortex reside primarily within superficial layers II and III (Pouget et al. 2009), where D1Rs are the dominant receptor subtype and are thus more likely to mediate the FEF's influence on visual cortical activity.

OPERANT CONTROL OF FEF NEURONS AND VISUAL ATTENTION

The aforementioned attention studies demonstrate that when monkeys are engaged in a learned task in which they must deploy attention, the activity of visual and visuo-movement FEF neurons (as in many other areas) reflects that deployment. They do not,

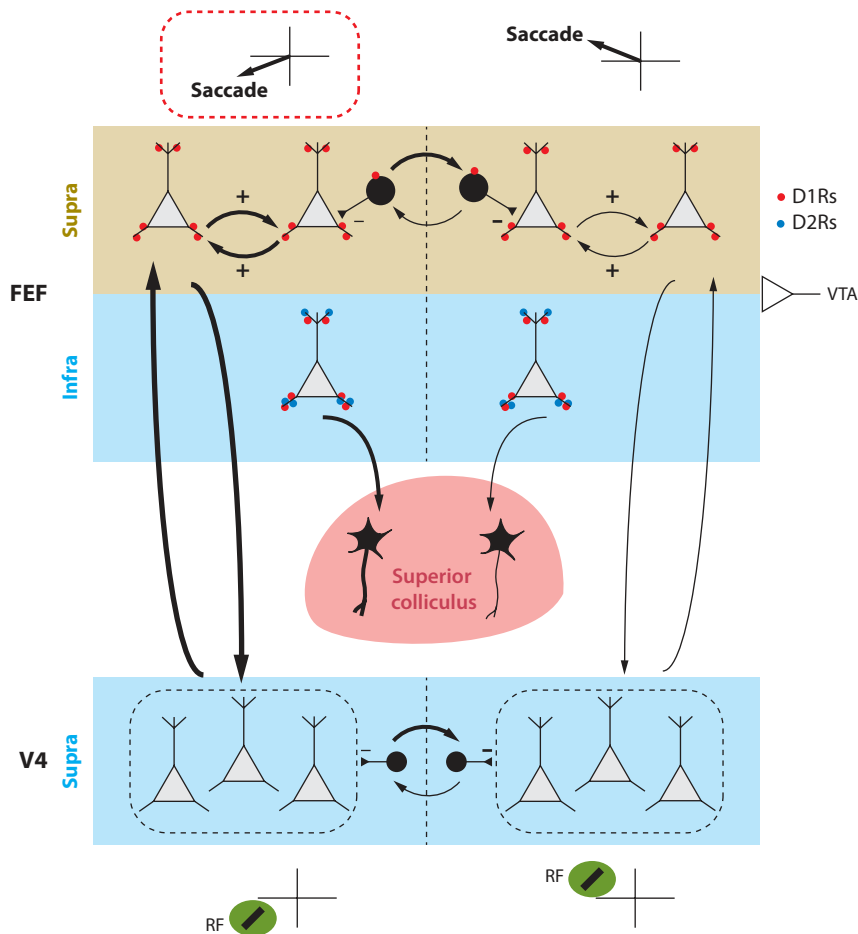


Figure 4

Possible influence of D1 receptors (D1Rs) on recurrent networks within the frontal eye field (FEF) and between the FEF and V4. The diagram depicts two adjacent FEF or V4 columns representing different, but adjacent, locations in saccadic or visual space, respectively. The columns are assumed to interact competitively (*black inhibitory neurons*). Positive arrows between FEF neurons within the same column depict the recurrent excitatory connections thought to underlie the persistence of spatial signals during remembered saccades or locations. Recurrent activity between the FEF and V4 is proposed to underlie the influence of FEF on the gain of visual inputs within V4. Diffuse dopaminergic input from the ventral tegmental area (VTA) (*input at right*) to the FEF (all columns) may modulate recurrence both within the FEF and between FEF and V4 through D1Rs and may influence competition between spatial representations. For example, increases in recurrence in a particular column while remembering or attending to a corresponding location (*dotted rectangle, thicker arrows at left*) may be modulated by dopamine levels. Biases in competitive interactions between columns within the visual cortex can also be achieved by experimental manipulation of D1R-mediated FEF activity. Also shown are the projections from infragranular FEF neurons to the superior colliculus (SC). Red circles represent D1Rs, and blue circles indicate D2Rs. Note the localization of D2Rs primarily in infragranular, SC-projecting, layers, which is consistent both with anatomical evidence and with the observation that changes in D2R-mediated FEF activity affect only saccadic target selection and not visual cortical activity. Adapted from Noudoost & Moore 2011b.

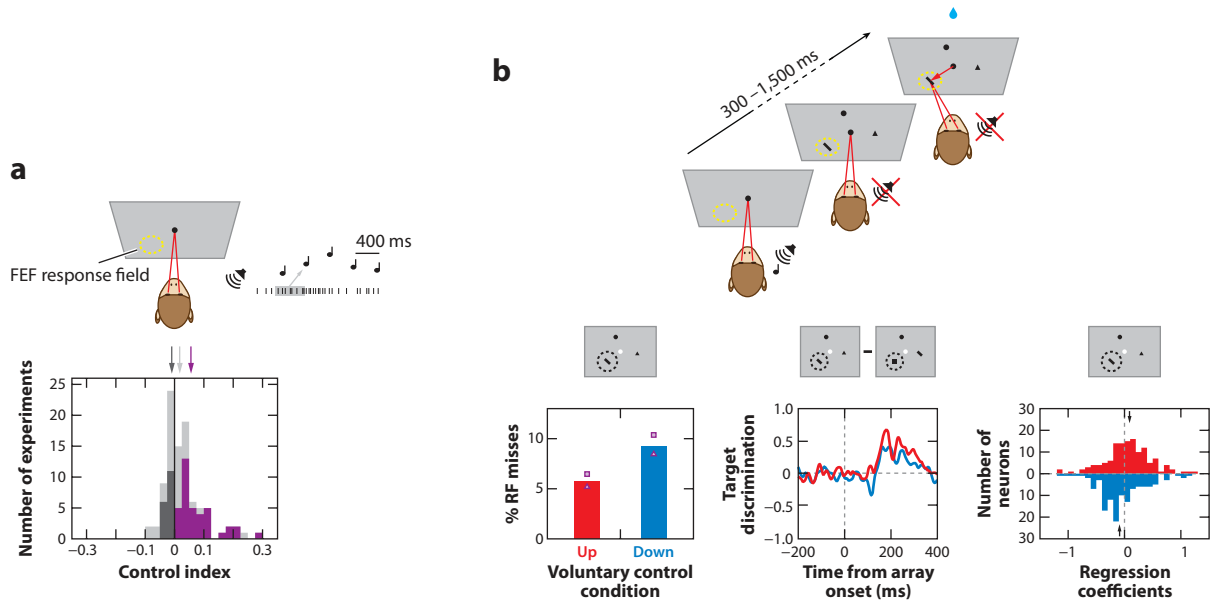


Figure 5

Operant control of frontal eye field (FEF) neurons and its effects on selective attention measured behaviorally and neurophysiologically. (a) In the operant control task, the monkey fixated a central spot on an otherwise blank video display and was rewarded for increasing or decreasing the firing rate of FEF neurons. The dotted circle shows the FEF receptive field (RF). Speaker icon and musical notes depict auditory feedback of FEF neuronal activity (spike train) during a sliding 500-ms window (*gray rectangle*). Bottom plot shows a histogram of operant control indices across a population of FEF neurons. The control index measures the change in FEF firing rate in the rewarded direction (UP or DOWN); positive values denote correct control. The light gray histogram shows all experiments, the purple histogram shows experiments with individually significant positive control, and the dark gray histogram shows experiments with significant negative control. (b) Behavioral and neurophysiological consequences of operant FEF control. (Top) Visual-search probe trials, in which a search array appeared, the auditory feedback ceased (*red "X" on speaker icon*), and the monkey was rewarded (*blue droplet*) for directing a saccade toward an oriented bar target. (Bottom left) Mean proportion of target misses opposite the RF was increased during DOWN operant control of FEF activity in both monkeys (*square and triangle symbols*). (Bottom middle) Target discrimination by FEF neurons was increased during upward (*red*) operant control relative to downward (*blue*). (Bottom right) Correlation of spontaneous activity with FEF responses to the target array. The direction of operant control determined the sign of the relationship between baseline and target-driven FEF activity. Adapted from Schafer & Moore (2011).

however, show that changes in endogenously generated neuronal activity in the absence of an explicit task are sufficient to bring about that deployment. Schafer & Moore (2011) tested the hypothesis that behaviorally conditioned, voluntary changes in FEF neuronal activity are sufficient to bring about the deployment of visual attention. The authors took advantage of the evidence from previous studies that demonstrated humans' and monkeys' ability to manipulate activity voluntarily within motor-related brain structures, even in the absence of movement (Fetz & Finocchio 1975). Schafer & Moore (2011) used similar operant training

techniques to examine the impact of voluntary control of FEF activity on visually driven behavior. Monkeys were given real-time auditory feedback based on the firing rate of FEF activity and rewarded for either increasing or decreasing that activity (in alternating UP and DOWN blocks of trials), while maintaining central fixation on a blank visual display (Figure 5a). In each behavioral trial that lasted several seconds, monkeys were rewarded every time neuronal activity measured within a moving time window exceeded (for UP trials) or dropped below (for DOWN trials) an arbitrary spike rate threshold. Reward therefore depended

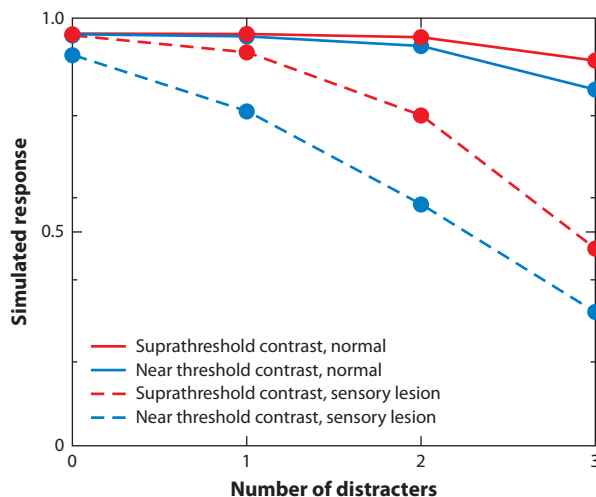
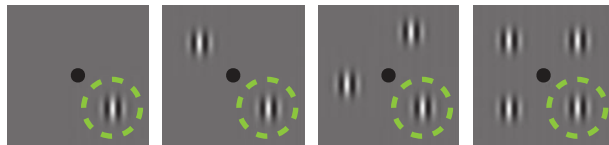
solely on the rate of neural activity during fixation and not on any explicit behavioral task.

The authors made several important observations. First, monkeys were indeed able to alter the average firing rate of FEF neurons significantly in UP versus DOWN trials at a majority of recorded sites. Second, they found that the magnitude of voluntary modulation was uncorrelated with the visual or motor properties of the individual FEF neurons being recorded. That is, neurons that responded to visual stimuli, but not in advance of saccades, were just as likely to be operantly controlled as neurons with little or no visual activity but with a great amount of saccade-related activity. Third, the authors observed significantly greater power in the gamma band of FEF local field potentials (LFPs). Fourth, and perhaps most importantly, the authors probed the behavioral and neurophysiological consequences of operant control of FEF activity. They introduced probe trials in which the monkey performed a visual search task while exerting operant control over FEF activity. Partway through randomly chosen trials, the auditory feedback would cease and a search array appeared on the screen consisting of different shapes of equal area. The monkey was then rewarded for making a saccade to the oriented bar (the target) or withholding a saccade if the search target was absent from the array (**Figure 5b**). Saccades to other shapes were counted as incorrect and were not rewarded. The authors reasoned that if the monkeys' strategy for altering FEF firing rates was one of general vigilance or arousal, any effects of UP versus DOWN modulation on behavior should generalize across target locations. Instead, they found behavioral effects of operant control that were limited to trials in which the target appeared in the RF. Specifically, when the target appeared in the RF, monkeys were less likely to detect the target (i.e., they had more misses) on the DOWN trials than they were on the UP trials. Unlike the effects on search performance, however, neither saccade probability nor saccade metrics were affected by operant

conditioning, demonstrating a dissociation between the attention-related and motor-preparatory effects of FEF activity. In addition, the authors found that FEF neurons could discriminate targets from distracters better during UP trials compared with DOWN trials. This change in target discriminability was dependent on the direction of operant control and not on spontaneous fluctuations in firing rate. Lastly, splitting UP and DOWN trials revealed a positive correlation between preprobe spontaneous firing rate and neuronal responses to the target in the RF during UP trials but revealed a negative correlation during DOWN trials. Thus, the direction of operant control seemed to determine the nature of the relationship between spontaneous and target-driven neural activity. Taken together, the above results show that endogenous, voluntary changes in FEF neural activity are sufficient to bring about both the behavioral and the neurophysiological effects of visual attention and that explicit learning of an attention task is not required.

USING LOSS OF FUNCTION TO IDENTIFY SOURCES OF ATTENTIONAL CONTROL

Understanding what controls a particular behavior ultimately requires demonstrating a specific loss in that behavior when the suspected underlying mechanism is damaged. But what constitutes a loss of attention? Researchers have proposed a number of recent models to account for the effects of attention on visual signals (Desimone & Duncan 1995, Reynolds et al. 2000, Reynolds & Heeger 2009, Lee & Maunsell 2010). These models provide a useful framework for understanding the interaction of attentional control with the encoding of visual information, thus potentially allowing one to distinguish between deficits in either process. Attention is generally thought to affect the competitive interactions inherent in visual processing. For example, although a representation with larger stimulus drive will tend to exert greater suppression on its competitors than one with lower stimulus drive, attention



to one stimulus or the other is expected to mitigate (or exacerbate) that effect. However, when attention is held constant, decreases in the strength of a representation can be brought about not only by reduced competitiveness with that of other stimuli, but also by reduced stimulus drive, including reduced drive due to brain damage. For example, cortical visual representations are distributed across a large set of highly connected retinotopic maps, and damage to a portion of one of them (e.g., V4) should result in significant (yet incomplete) loss of stimulus drive at retinotopically corresponding portions in the others [e.g., V2, MT, MST (medial superior temporal area)]. This loss in stimulus drive should result in a competitive disadvantage at that spatial location within the intact maps. As a result, because stimulus drive and attention both interact competitively, the above models suggest that altering stimulus drive in such a way should affect the magnitude of neural responses in a manner consistent with a loss of attention, even when attention is functioning normally.

This idea can be illustrated using one of the above-mentioned models, for example, with the normalization model described by Reynolds & Heeger (2009). In their model, stimulus drive combines with an attentional gain signal (the “attention field”), and then competitive interactions between multiple stimuli reciprocally inhibit one another as a function of their activity (normalization). Using this model, we simulated a lesion in the sensory drive independent of attentional gain and examined its effects on downstream encoding (Figure 6). The simulation shows that weakening the stimulus drive can produce a deficit in the sensory encoding that is dependent on the presence of other competing stimuli. In the absence of competing stimuli (distracters), there may be no observable deficit in encoding, particularly when stimuli are sufficiently suprathreshold (e.g., at high contrast). But with multiple competing or less salient stimuli, a significant deficit emerges. Thus, even when attentional gain remains intact, a diminution in the strength of visual input could be sufficient to produce a distracter-dependent deficit. Unfortunately, distracter dependency is often what is used to define a loss in attentional function (e.g., De Weerd et al. 1999, Wardak et al. 2006, Lovejoy & Krauzlis 2010). Such a definition may thus be overly broad in many cases (Desimone & Duncan 1995) and may make it difficult to distinguish a role of brain structures in visual attention and a role in visual processing, as in the case of area V4 (e.g., Schiller & Lee 1991, De Weerd et al. 1999).

What then should an attention deficit look like? The answer to this question will only grow in importance as we contemplate future studies investigating the neural mechanisms that are causally related to the filtering and selection of behaviorally relevant sensory information (visual or otherwise). Carefully defined attention deficits are particularly important for studies that employ cell- and circuit-specific experimental tools (Fenno et al. 2011) and for those that employ animal models with more rudimentary forms of attention-related behavior than primates (Muir et al. 1992). Subsequent attempts to pinpoint the neurons, neural circuits,

Figure 6

Distracter-dependent deficits from a loss of visual inputs in a normalization model of attention. (*Top, left to right*) Schematic representations of a visual display with a target stimulus (Gabor grating) in isolation or with one, two, or three distracters. In each display, the gray dot depicts the point of fixation during a covert attention task. The dotted green line depicts the region of space affected by the lesion (the scotoma), the attended location, and the receptive field of the simulated neuron. Both the location of attention and the target stimulus are constant across the different distracter conditions, and the distracters have the same contrast as the target. (*Bottom*) Responses of a simulated neuron as a function of the number of distracters in the display. Without a lesion (*blue and red solid lines*), the responses remain nearly constant across the number of distracters. With a visual lesion (*dotted lines*), which weakens the stimulus drive while leaving the attention gain intact, responses become compromised as more distracters are added to the display. The distracter-dependent deficits are less severe for high-contrast stimuli (*red lines*) than for near threshold, low-contrast stimuli (*blue lines*). Model: The set of Matlab routines provided by the normalization model of attention (NMA) (Reynolds & Heeger 2009) was used to implement the present simulation. In the NMA, stimulus-driven inputs (stimulus drive) are multiplied by an attention gain signal (attention field), after which competitive interactions between all units reciprocally inhibit one another as a function of their activities (normalization) to yield the responses of the neurons in the model. Here, four significant additions were made. First, the script for figure3F.m (Reynolds & Heeger 2009) was augmented to simulate multiple distracters. Second, for more control over the spread and magnitude of the inhibition underlying the competitive interactions between neurons (i.e., normalization), an additional variable, *IxKernelHeight*, was added. *IxKernelHeight* allowed the user, along with the preexisting variable *IxWidth*, to independently control the height and width of the Gaussian inhibition kernel, respectively. Third, to simulate a lesion in the stimulus drive, independent of the attention gain, the stimulus drive was multiplied by a lesion matrix before any other computations were performed. This produced a lesioned stimulus drive matrix that the model used in place of the original stimulus drive. The lesion matrix consisted of values ranging between 0 and 1, and it can be visualized as an inverted Gaussian (specified by the variables *lesionWidth* and *lesionDepth*) centered on the spatial center of the lesion. Multiplying the lesion matrix with the stimulus drive to create the lesioned stimulus drive is equivalent to a gain down-modulation of the original stimulus drive. Fourth, to simulate model neurons with saturating responses, final responses in the present simulation were computed by passing the output of the NMA through a simple sigmoidal function: Final Response = $1/(1 + e^{\beta*(H-x)})$, where e is the natural number, β modifies the slope of the sigmoid, H is equal to the half-max value of the sigmoid, and x is equal to the output of the NMA. Parameters: *Apeak* = 2; *AxWidth* = 7; β = 0.75; H = 7; *IxKernelHeight* = 0.0175; *IxWidth* = 100; *lesionWidth* = 7; *lesionDepth* = 0.5; *stimWidth* = 7.

and neural computations that confer a nervous system with the unique capacity to distinguish a target from distracters will need to determine more definitively when a behavioral phenotype reflects a loss in that capacity rather than a loss in some other function. In this review of recent evidence for the PFC's contribution to visual attention, we have highlighted studies that demonstrate experimentally produced benefits in visual processing, either by neurons (Noudoost & Moore 2011a, Schafer & Moore 2011) or in behavioral performance (Schafer & Moore 2011). Such benefits in processing,

separate from processing itself, appear to be what most specifically defines attention. We therefore suggest that the loss of function one should expect when attentional mechanisms are absent is a loss of such benefits rather than a deficit in sensory processing per se. We assume that independent of the absolute level of perceptual performance, or even the degree of distracter dependency, a loss of attentional control should result in performance that cannot be improved by attentional cues. Remarkably, most, if not all, of the experimental literature is devoid of such results.

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LITERATURE CITED

- Anderson JC, Kennedy H, Martin KA. 2011. Pathways of attention: synaptic relationships of frontal eye field to V4, lateral intraparietal cortex, and area 46 in macaque monkey. *J. Neurosci.* 31:10872–81
- Armstrong KM, Chang MH, Moore T. 2009. Selection and maintenance of spatial information by frontal eye field neurons. *J. Neurosci.* 29:15621–29
- Armstrong KM, Fitzgerald JK, Moore T. 2006. Changes in visual receptive fields with microstimulation of frontal cortex. *Neuron* 50:791–98
- Armstrong KM, Moore T. 2007. Rapid enhancement of visual cortical response discriminability by microstimulation of the frontal eye field. *Proc. Natl. Acad. Sci. USA* 104:9499–504
- Bisley JW, Goldberg ME. 2010. Attention, intention, and priority in the parietal lobe. *Annu. Rev. Neurosci.* 33:1–21
- Björklund A, Dunnett SB. 2007. Dopamine neuron systems in the brain: an update. *Trends Neurosci.* 30:194–202
- Bruce CJ, Goldberg ME. 1985. Primate frontal eye fields. I. Single neurons discharging before saccades. *J. Neurophysiol.* 53:603–35
- Bruce CJ, Goldberg ME, Bushnell MC, Stanton GB. 1985. Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *J. Neurophysiol.* 54:714–34
- Buschman TJ, Miller EK. 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science* 315:1860–62
- Castellanos FX, Tannock R. 2002. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat. Rev. Neurosci.* 3:617–28
- Chelazzi L, Miller EK, Duncan J, Desimone R. 1993. A neural basis for visual search in inferior temporal cortex. *Nature* 363:345–47
- Clark KL, Armstrong KM, Moore T. 2011. Probing neural circuitry and function with electrical microstimulation. *Proc. Biol. Sci.* 278:1121–30
- Cohen MR, Maunsell JHR. 2009. Attention improves performance primarily by reducing interneuronal correlations. *Nat. Neurosci.* 12:1594–600
- Connor CE, Preddie DC, Gallant JL, Van Essen DC. 1997. Spatial attention effects in macaque area V4. *J. Neurosci.* 17:3201–14
- De Weerd P, Peralta MR 3rd, Desimone R, Ungerleider LG. 1999. Loss of attentional stimulus selection after extrastriate cortical lesions in macaques. *Nat. Neurosci.* 2:753–58
- Desimone R, Duncan J. 1995. Neural mechanisms of selective visual attention. *Annu. Rev. Neurosci.* 18:193–222
- Deubel H, Schneider WX. 1996. Saccade target selection and object recognition: evidence for a common attentional mechanism. *Vis. Res.* 36:1827–37
- Ekstrom LB, Roelfsema PR, Arsenault JT, Kolster H, Vanduffel W. 2009. Modulation of the contrast response function by electrical microstimulation of the macaque frontal eye field. *J. Neurosci.* 29:10683–94
- Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. 1998. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. *J. Neurosci.* 18:5901–7
- Fenno L, Yizhar O, Deisseroth K. 2011. The development and application of optogenetics. *Annu. Rev. Neurosci.* 34:389–412
- Ferrier D. 1876. *Functions of the Brain*. London: Smith, Elder and Co.
- Fetz EE, Finocchio DV. 1975. Correlations between activity of motor cortex cells and arm muscles during operantly conditioned response patterns. *Exp. Brain Res.* 23:217–40
- Fischer B, Boch R. 1981. Enhanced activation of neurons in prelunate cortex before visually guided saccades of trained rhesus monkeys. *Exp. Brain Res.* 44:129–37

- Fries P, Reynolds JH, Rorie AE, Desimone R. 2001. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291:1560–63
- Fuster JM. 1995. *Memory in the Cerebral Cortex*. Cambridge, MA: MIT Press
- Gao WJ, Krimer LS, Goldman-Rakic PS. 2001. Presynaptic regulation of recurrent excitation by D1 receptors in prefrontal circuits. *Proc. Natl. Acad. Sci. USA* 98:295–300
- Gerbella M, Belmalih A, Borra E, Rozzi S, Luppino G. 2010. Cortical connections of the macaque caudal ventrolateral prefrontal areas 45A and 45B. *Cereb. Cortex* 20:141–68
- Goldberg ME, Bushnell MC. 1981. Behavioral enhancement of visual responses in monkey cerebral cortex. II. Modulation in frontal eye fields specifically related to saccades. *J. Neurophysiol.* 46:773–87
- Goldman-Rakic PS, Lidow MS, Smiley JF, Williams MS. 1992. The anatomy of dopamine in monkey and human prefrontal cortex. *J. Neural Transm. Suppl.* 36:163–77
- Gregoriou GG, Gotts SJ, Desimone R. 2012. Cell-type-specific synchronization of neural activity in FEF with V4 during attention. *Neuron* 73:581–94
- Gregoriou GG, Gotts SJ, Zhou HH, Desimone R. 2009. High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science* 324:1207–10
- Hoffman JE, Subramaniam B. 1995. The role of visual attention in saccadic eye movements. *Percept. Psychophys.* 57:787–95
- James W. 1890. *Principles of Psychology*, Vol. 1. New York: H. Holt
- Knight RT, Grabowecy MF, Scabini D. 1995. Role of human prefrontal cortex in attention control. *Adv. Neurol.* 66:21–34; discussion 34–36
- Lebedev MA, Messinger A, Kralik JD, Wise SP. 2004. Representation of attended versus remembered locations in prefrontal cortex. *PLoS Biol.* 2:e365
- Lee J, Maunsell JH. 2010. The effect of attention on neuronal responses to high and low contrast stimuli. *J. Neurophysiol.* 104:960–71
- Lidow MS, Goldman-Rakic PS, Gallager DW, Rakic P. 1991. Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]Sch23390. *Neuroscience* 40:657–71
- Lovejoy LP, Krauzlis RJ. 2010. Inactivation of primate superior colliculus impairs covert selection of signals for perceptual judgments. *Nat. Neurosci.* 13:261–66
- Mason DJ, Humphreys GW, Kent LS. 2003. Exploring selective attention in ADHD: visual search through space and time. *J. Child Psychol. Psychiatry* 44:1158–76
- McAdams CJ, Maunsell JH. 1999. Effects of attention on orientation-tuning functions of single neurons in macaque cortical area V4. *J. Neurosci.* 19:431–41
- Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24:167–202
- Mitchell JF, Sundberg KA, Reynolds JH. 2007. Differential attention-dependent response modulation across cell classes in macaque visual area V4. *Neuron* 55:131–41
- Moore T, Armstrong KM. 2003. Selective gating of visual signals by microstimulation of frontal cortex. *Nature* 421:370–73
- Moore T, Fallah M. 2001. Control of eye movements and spatial attention. *Proc. Natl. Acad. Sci. USA* 98:1273–76
- Moore T, Fallah M. 2004. Microstimulation of the frontal eye field and its effects on covert spatial attention. *J. Neurophysiol.* 91:152–62
- Moran J, Desimone R. 1985. Selective attention gates visual processing in the extrastriate cortex. *Science* 229:782–84
- Motter BC. 1993. Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. *J. Neurophysiol.* 70:909–19
- Mountcastle VB, Lynch JC, Georgopolous A, Sakata H, Acuna C. 1975. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J. Neurophysiol.* 38:871–908
- Muir JL, Robbins TW, Everitt BJ. 1992. Disruptive effects of muscimol infused into the basal forebrain on conditional discrimination and visual attention: differential interactions with cholinergic mechanisms. *Psychopharmacology (Berl.)* 107:541–50

- Noudoost B, Chang MH, Steinmetz NA, Moore T. 2010. Top-down control of visual attention. *Curr. Opin. Neurobiol.* 20:183–90
- Noudoost B, Moore T. 2011a. Control of visual cortical signals by prefrontal dopamine. *Nature* 474:372–75
- Noudoost B, Moore T. 2011b. The role of neuromodulators in selective attention. *Trends Cogn. Sci.* 15:585–91
- Peterson MS, Kramer AF, Irwin DE. 2004. Covert shifts of attention precede involuntary eye movements. *Percept. Psychophys.* 66:398–405
- Pouget P, Stepniewska I, Crowder EA, Leslie MW, Emeric EE, et al. 2009. Visual and motor connectivity and the distribution of calcium-binding proteins in macaque frontal eye field: implications for saccade target selection. *Front. Neuroanat.* 3:2
- Reynolds JH, Chelazzi L. 2004. Attentional modulation of visual processing. *Annu. Rev. Neurosci.* 27:611–47
- Reynolds JH, Chelazzi L, Desimone R. 1999. Competitive mechanisms subserve attention in macaque areas V2 and V4. *J. Neurosci.* 19:1736–53
- Reynolds JH, Heeger DJ. 2009. The normalization model of attention. *Neuron* 61:168–85
- Reynolds JH, Pasternak T, Desimone R. 2000. Attention increases sensitivity of V4 neurons. *Neuron* 26:703–14
- Rizzolatti G, Riggio L, Dascola I, Umiltá C. 1987. Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. *Neuropsychologia* 25:31–40
- Robbins TW, Arnsten AF. 2009. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu. Rev. Neurosci.* 32:267–87
- Robinson DA, Fuchs AF. 1969. Eye movements evoked by stimulation of frontal eye fields. *J. Neurophysiol.* 32:637–48
- Rueckert L, Grafman J. 1996. Sustained attention deficits in patients with right frontal lesions. *Neuropsychologia* 34:953–63
- Santana N, Mengod G, Artigas F. 2009. Quantitative analysis of the expression of dopamine D1 and D2 receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. *Cereb. Cortex* 19:849–60
- Schafer RJ, Moore T. 2011. Selective attention from voluntary control of neurons in prefrontal cortex. *Science* 332:1568–71
- Schiller PH, Lee K. 1991. The role of the primate extrastriate area V4 in vision. *Science* 251:1251–53
- Schiller PH, Tehovnik EJ. 2001. Look and see: how the brain moves your eyes about. *Prog. Brain Res.* 134:127–42
- Seamans JK, Yang CR. 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog. Neurobiol.* 74:1–58
- Segraves MA, Goldberg ME. 1987. Functional properties of corticotectal neurons in the monkey's frontal eye field. *J. Neurophysiol.* 58:1387–419
- Shepherd M, Findlay JM, Hockey RJ. 1986. The relationship between eye movements and spatial attention. *Q. J. Exp. Psychol. A* 38:475–91
- Shipp S. 2004. The brain circuitry of attention. *Trends Cogn. Sci.* 8:223–30
- Sommer MA, Wurtz RH. 2000. Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *J. Neurophysiol.* 83:1979–2001
- Thompson KG, Bichot NP, Sato TR. 2005. Frontal eye field activity before visual search errors reveals the integration of bottom-up and top-down salience. *J. Neurophysiol.* 93:337–51
- Wardak C, Ibos G, Duhamel JR, Olivier E. 2006. Contribution of the monkey frontal eye field to covert visual attention. *J. Neurosci.* 26:4228–35
- Williams GV, Goldman-Rakic PS. 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376:572–75
- Wurtz RH, Goldberg ME. 1972a. Activity of superior colliculus in behaving monkey. IV. Effects of lesions on eye movements. *J. Neurophysiol.* 35:587–96
- Wurtz RH, Goldberg ME. 1972b. The primate superior colliculus and the shift of visual attention. *Invest. Ophthalmol.* 11:441–50



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