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Selective Attention from Voluntary Control of Neurons in Prefrontal Cortex

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Abstract

Animals can learn to voluntarily control neuronal activity within various brain areas through operant conditioning, but the relevance of that control to cognitive functions is unknown. We show that monkeys can control the activity of neurons within the frontal eye field (FEF), an oculomotor area of prefrontal cortex. However, operantly driven FEF activity was primarily associated with selective visual attention, and not oculomotor preparation. Attentional effects were untrained, and were observed both behaviorally and neurophysiologically. Furthermore, selective attention correlated with voluntary, but not spontaneous, fluctuations in FEF activity. Our results reveal a specific association of voluntarily driven neuronal activity with “top-down” attention and suggest a basis for the use of neurofeedback training to treat disorders of attention.

Animal and human subjects can learn to alter their own brain activity when provided feedback (1–4). Voluntary control of neuronal activity is likely associated with changes in behavior or cognitive functions, but that relationship is unclear. Operant control of motor cortical neurons is typically dissociated from movement production (5–8), and there are no clear behavioral consequences of operant control of neurons in other brain structures (1, 4). Naturally, one might ask whether a chosen control strategy can elicit *untrained* behavioral or neurophysiological outcomes. To address this question, we examined the consequences of voluntary control of neurons in the frontal eye field (FEF), a visuomotor area within prefrontal cortex with a known role in the programming of saccadic eye movements (9) and visual spatial attention (10) (Fig. 1A).

We first asked whether the activity of FEF neurons can be controlled voluntarily by the monkey without explicit training on any task. We used an operant control paradigm (2) in which the monkey received rewards for alternately increasing and decreasing the firing rates (FRs) of FEF neurons during fixation (11) (Fig. 1B,C) [supporting online materials (SOM)]. During trials the monkey received auditory feedback via pure tones, the pitch of which corresponded to the instantaneous FR of multiunit activity (MUA) at an FEF recording site. In blocks of “Up” trials, the monkey received a reward each time the FR, and thus the tone pitch, reached a high threshold (Fig. 1C). In blocks of “Down” trials, the monkey was rewarded each time a low threshold was reached.

We recorded from 94 FEF sites in two monkeys (Monkey B: 49, Monkey C: 45) during operant control. Figure 2A–C shows the results of a representative experiment. At this site, the MUA FR on Up trials was greater than on Down trials (Fig. 2A; $P < 10^{-4}$), indicating

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that the monkey modulated the MUA in the rewarded direction. This FR difference persisted through the entire trial, and was maintained between blocks of Up and Down trials (Fig. 2B). We quantified neuronal control with a “control index” (CI), with positive CIs indicating changes in activity in the rewarded direction. The overall CI for the example site was 0.064, corresponding to a 13.7% increase in FR from Down to Up trials (Fig. 2C).

Across all experiments, monkeys exerted modest, but reliable, control over the FRs of FEF neurons. The mean CI across sites was 0.031 (Fig. 2D; Monkey B: $P = 0.0086$, Monkey C: $P = 0.0010$; $P = 10^{-4}$), corresponding to a 6.4% difference in FR. However, the magnitude of control varied considerably throughout the course of each experiment ($P = 0.0045$; Fig. S1). Furthermore, for individual FEF sites we found both significant positive and negative effects of control (SOM). Fifty-five experiments (59%) showed individually significant effects of control, and of these, 38 (69%) had positive CIs, with a mean of 0.080 ($P < 10^{-4}$), and 17 (31%) had negative CIs, with a mean of -0.018 ($P = 0.0002$). The effects observed in MUA were also present in isolated single neurons (SOM). We found no correlation between the CI and the visual ($P = 0.4385$) or motor ($P = 0.1204$) properties of the neurons, indicating that both visual- and movement-related neurons (12) could be operantly controlled (Fig. 2E). The FR effect was also accompanied by a difference in the power spectra of local field potentials (LFPs) at the recording site. LFP power in the beta (13–30 Hz) and gamma (30–70 Hz) bands increased during Up versus Down trials (β median difference = 0.059 dB, $P = 0.027$; $\gamma = 0.048$ dB, $P = 0.00068$), while there was no difference for low-frequency theta (4–8 Hz) or alpha (8–13 Hz) bands (Fig. 2F; $\theta = 0.033$ dB, $P = 0.36$; $\alpha = 0.063$ dB, $P = 0.33$).

We wondered whether voluntary modulation of FEF activity might have associated effects on behavior, or on the function of the controlled neurons. Neuronal control could be achieved through nonspecific means such as changes in general arousal or vigilance, or perhaps through means that were motor in nature but that did not require a saccade (Figs. S4–S6). Alternatively, voluntary control might be achieved by a cognitive or behavioral strategy specific to the presumed role of FEF neurons (10, 14). We therefore employed visual search trials to probe psychophysical and neuronal performance during operant control. On 29% of operant control trials, the monkey was presented with a visual search array at an unpredictable time (Fig. 3A). Feedback then ceased, and the monkey was no longer rewarded for controlling neuronal activity. Instead, the monkey received a reward for directing a saccade to the search target (an oriented bar) if it was present at any location, or for maintaining fixation if no target was present.

In 82 experiments (Monkey B: 41, Monkey C: 41), the mean probe trial performance was 86.3% correct (Monkey B: 81.9%, Monkey C: 90.7%). The overall percentage of saccades targeting the RF was the same during Up and Down trials (Fig. 3B; Up = 22.6% of 4441, Down = 23.0% of 4346, $P = 0.65$; Monkey B: $P = 0.43$; Monkey C: $P = 0.80$). Likewise, the latencies of saccades to RF targets were similar during Up and Down trials (Fig. S7; z-score normalized Up latency = -0.001 ± 0.033 ; Down = 0.001 ± 0.032 ; $P = 0.967$). Thus, we found no evidence that operant control was associated with saccade preparation. The saccadic main sequence was also unaltered by voluntary control (Fig. S8).

In contrast, neuronal control had a spatially specific effect on visual search performance. The proportion of trials on which the monkey failed to detect the target in the RF (“misses”) was significantly greater during Down trials in both monkeys (Fig. 3C; Up = 5.7% of 1098, Down = 9.3% of 1124, $P = 0.0017$; Monkey B: $P = 0.020$; Monkey C: $P = 0.032$). In contrast, the proportion of misses at locations opposite the RF was statistically indistinguishable between Up and Down trials (Fig. 3D; Up = 2.7% of 1120, Down = 3.4% of 1114, $P = 0.31$; Monkey B: $P = 0.39$; Monkey C: $P = 0.70$). The influence of voluntary

control on search performance was confined to locations less than $\sim 6^\circ$ from the controlled neuron's RF (Fig. S9). We confirmed that search performance was specifically correlated with the direction of voluntary control and not with spontaneous fluctuations in pre-probe neural activity (Fig. S10 and SOM).

Next, we measured the effect of voluntary control on the ability of FEF neurons to identify the search target. As in previous studies (15) we found that the responses of FEF neurons ($n = 150$; Monkey B: 61, Monkey C: 89) could indicate whether a search target or a distracter appeared within the RF (Fig. 3E and SOM). However, we also found that the response to RF targets was 16.5% greater on Up than on Down trials (Fig. 3F; Up mean peak-normalized rate = 0.668, Down = 0.573, $P = 0.0054$). In contrast, there was no difference between responses to distracters during Up versus Down trials (Fig. 3G; Up = 0.265, Down = 0.313, $P = 0.9207$). Thus, neuronal control selectively enhanced FEF responses to targets but not to distracters, resulting in a significant enhancement in target *discrimination* during Up trials compared to Down (Fig. 3H; Up = 0.404, Down = 0.259, $P = 0.004$; Monkey B: $P = 0.046$; Monkey C: $P = 0.037$).

As with the behavior, target discrimination by FEF neurons was specifically related to operant control rather than non-controlled fluctuations in spontaneous pre-probe activity. Overall pre-probe activity for combined Up and Down trials did not predict the FEF responses to targets (median regression coefficient = 0.0145, $P = 0.9337$). However, dividing trials according to the direction of voluntary control revealed that pre-probe activity was positively correlated with the target response during Up trials (Fig. 4E,F; median regression coefficient = 0.0633, $P = 0.0303$), but anti-correlated during Down trials (median = -0.1128 , $P = 0.0468$; Up versus Down: $P = 0.0033$). In contrast, responses to distracters were uncorrelated with pre-probe activity for both Up (Fig. 4G; median = -0.0072 , $P = 0.6560$) and Down trials (median = 0.00, $P = 0.9853$; Up versus Down: $P = 0.7431$). Thus pre-probe FR combined constructively with target-driven activity only during upward control.

Our results demonstrate that voluntary control of FEF neuronal activity is associated with spatially selective visual attention, measured behaviorally and neurophysiologically. In controlling FEF activity, monkeys converged on a strategy that dissociated spatial attention from saccadic preparation. This untrained dissociation provides a naturalistic demonstration that the two functions are not wholly interdependent, a point that has proven difficult to substantiate (10). We also observed that the attentional consequences of operant control were correlated with voluntarily driven, rather than spontaneous, FEF activity. This selective linkage might occur if control alters interactions between the FEF and visual cortex, a possibility supported by the enhanced LFP power at frequencies with suspected involvement in long-range interactions during attention (16). Finally, our results suggest a basis for recent evidence that neurofeedback training may be therapeutic in patients with attention-deficit hyperactivity disorder (17, 18) as they demonstrate that voluntary modulation of neural activity can indeed produce specific changes in cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Operant control paradigm. **(A)** Location of the FEF in the arcuate sulcus (shading) shown in a lateral view of a monkey brain (top). Eye traces at bottom-left show saccades evoked with $50\mu\text{A}$ microstimulation of an FEF site. Bottom-middle and right show saccadic and visual responses, respectively, at the same FEF site during a visually guided delayed saccade task. **(B)** Operant control task. The monkey fixated a central spot on an otherwise blank video display. Dotted circle shows the FEF RF, speaker icon and musical notes depict auditory feedback of FEF neuronal activity (spike train) during a sliding 500 ms window (open rectangle). **(C)** Spike counts and rewards. Histograms show binned spike counts during Up and Down operant control for the example site in **A**. Rewards (blue droplets) were delivered each time a spike count reached the high threshold (red dotted line) on Up trials, or the low threshold (blue dotted line) on Down trials.

Fig. 2.

Voluntary control of FEF neurons. **(A)** Average MUA over the course of Up (red) and Down (blue) trials during an example experiment. **(B)** Firing rates for each Down and Up trial in **A** are indicated by blue and red triangles, respectively, with the mean firing rate for a block of trials represented by a horizontal line. Gray vertical bars mark the first ten trials after each block transition, which were excluded from analysis. **(C)** Time course of the control index for the experiment in **A**. **(D)** Population histogram of multiunit CIs. Light gray histogram shows all experiments, purple histogram shows experiments with individually significant positive control, and dark gray histogram shows experiments with significant negative control. Inset shows the mean time course of voluntary control (colors as in the histogram). Thickness of each envelope is $\pm$ s.e.m. **(E)** The control index of single FEF neurons as a function of their visual (left) and saccadic response indices (right). **(F)** Population histograms showing Up-Down differences in LFP power in four frequency bands. * = significant difference at $P < 0.05$, *** is $P < 0.001$.

Fig. 3.

Behavioral and physiological consequences of operant FEF control. **(A)** Visual search probe trials, in which a search array appeared and the monkey was rewarded (blue droplet) for directing a saccade toward an oriented bar target. **(B)** Percentage of probe trials in which a saccade was directed into the RF, correctly or incorrectly during all conditions (ellipses), and during Up (red) and Down (blue) operant control. Purple triangles: Monkey B; purple squares: Monkey C. **(C)** Proportion of target misses in the RF. **(D)** Proportion of target misses opposite the RF. **(E)** FEF responses to the visual search array. The normalized population response of 150 FEF neurons aligned to array onset for trials with the target in the RF (black) or opposite the RF (gray). Gray bar along abscissa indicates the interval during which the target and distracter responses were significantly different. **(F)** FEF responses to targets in the RF on Up and Down trials. Data are the same as the black line in **E**, but red and blue lines show responses on Up and Down trials, respectively. **(G)** FEF responses to distracters in the RF, when the target was opposite. Data are the same as the gray line in **E**. **(H)** Target discrimination by FEF neurons, defined as the difference in responses between “Target in RF” and “Target opposite” trials. Bar plot shows mean target discrimination on Up (red) and Down (blue) trials. ** = significant difference at $P < 0.01$.

Fig. 4.

Correlation of spontaneous activity with FEF responses. **(A)** Linear regression between the probe trial response of an example FEF neuron and its spontaneous pre-probe activity during Up (red) and Down (blue) control. **(B and C)** Population histogram of regression coefficients describing the relationship between spontaneous activity and responses to targets **(B)** or distracters **(C)** in the RF. Arrows denote medians of each distribution. * = significant difference at $P < 0.05$, ** is $P < 0.01$.