(average directional preference difference: 138.3 ± 26.2°, range: 89.1°). For cell pairs in which two directions of plaid motion fulfilled these selection criteria, neuronal correlation coefficients (NCCs) were averaged.

Perceptual reports

One monkey reported the direction of moving plaid patterns (six-alternative forced-choice task). During training, the animal viewed plaid patterns with a random-dot texture 'pasted' on the thin bar phase of the gratings (for demonstrations and details see Supplementary section 6). The texture on the two gratings either moved in the same direction (unambiguous coherent motion) or in different directions (unambiguous non-coherent motion). The monkey had one valid choice target for coherent motion and two valid choice targets for non-coherent motion (80% rewards on correct choices). Once performance had reached around 85% correct, we introduced ambiguous probe plaid stimuli on 20% of the trials. On these trials, the monkey was rewarded for reports consistent with either coherent or non-coherent motion.

Data analysis

Baseline firing rates and neuronal synchrony were calculated from 200 ms after fixation onset until stimulus onset (700 ms after fixation onset). Stimulus related activity and synchrony were calculated for three periods: (1) from 200 ms after stimulus onset until 2,000 ms thereafter, avoiding the ON response transient; (2) from the earliest response (30 ms after stimulus onset) until 2,000 ms after stimulus onset; and (3) for the ON response transient only (30–200 ms after stimulus onset). Preferred directions were determined by a vector average method[18] based on direction-of-motion tuning curves in response to gratings. The grating motion direction closest to this vector average was taken as the preferred direction. A neuron was deemed directionally selective if the direction index exceeded 0.5 (direction index = 1 − (anti-preferred activity)/(preferred activity); baseline activity subtracted). All cells in this study were directionally selective by this definition.

Cross-correlograms were calculated for each stimulus and prestimulus condition at 1-ms resolution from −50 to +50 ms averaged over 10–40 trials. In addition, a peristimulus time histogram (PSTH) predictor was calculated to correct for stimulus-locked synchrony[19]. Synchrony was quantified by the NCC[10]. We also calculated z-scores[19,20], which yielded the same pattern of results as the NCC data (see Supplementary section 7). The NCC was calculated over correlogram time intervals of ±5 ms, ±10 ms, ±20 ms and ±30 ms relative to time zero. Our overall results were robust with respect to the choice of time intervals. Most pairs had a synchrony peak width of around 10–20 ms centred at time zero. Accordingly, the data plotted in the figures and the corresponding P-values were derived from ±10-ms time intervals. For an NCC to be included in our data set, the cross-correlograms had to have at least 200 entries. This criterion was usually far exceeded. The CPI was derived from previous work[11,12] (see Supplementary section 8).

To classify neurons as component- or pattern-like, we computed the average CPI across all three plaid pattern configurations for each neuron. Neurons with large average CPI values (in the upper 50%) of this distribution were classified as component-type whereas neurons with small average CPI values (in the lower 33%) were classified as pattern-type (for justification, see Supplementary section 9) To examine neuronal synchrony unaffected by eye movements, we eliminated periods during and immediately after microsaccades, tracking eye-movements, and eye drifts from our data set. Eye-movement-free periods were subdivided into 200-ms sections and these sections were treated as though they constituted individual trials (see Supplementary section 10).

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Selective gating of visual signals by microstimulation of frontal cortex

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Several decades of psychophysical and neurophysiological studies have established that visual signals are enhanced at the locus of attention[1–5]. What remains a mystery is the mechanism that initiates biases in the strength of visual representations[6]. Recent evidence argues that, during spatial attention, these biases reflect nascent saccadic eye movement commands[7,8]. We examined the functional interaction of saccade preparation and visual coding by electrically stimulating sites within the frontal eye fields (FEF) and measuring its effect on the activity of neurons in extrastriate visual cortex. Here we show that visual responses in area V4 could be enhanced after brief stimulation of retinotopically corresponding sites within the FEF using currents below that needed to evoke saccades. The magnitude of the enhancement depended on the effectiveness of receptive field stimuli as well as on the presence of competing stimuli outside the receptive field. Stimulation of non-corresponding FEF representations could suppress V4 responses. The results suggest that the gain of visual signals is modified according to the strength of spatially corresponding eye movement commands.

Important stimuli are generally the targets of eye movements, although they can be selectively processed without direct gaze[1]. The ability of primates to dissociate the point of gaze from the point of interest does not preclude a common mechanism of attention and eye movement control. Instead, this ability may represent a specialized adaptation that allows covert monitoring, while avoiding the consequences of direct eye contact[9]. For example, it may be adaptive to covertly monitor a surly-looking gentleman seated nearby on a train, whereas confronting him with direct gaze could prove hazardous. Under normal circumstances, shifts in gaze occur freely, and visual detection is facilitated at the location of impending saccades even before the eyes move[10,11].

The involvement of the FEF in the selection of visual targets for saccades is well established[12]. The FEF contains neurons that have a broad spectrum of properties, from visual to motor, culminating in a map of visual space in which the amplitude and direction of saccades are organized in retinotopic coordinates[13]. Electrical stimulation of the FEF evokes short-latency saccades in both human and non-human primates[13–15]. Stimulation of the FEF with currents below the movement threshold does not evoke saccades, but nonetheless biases the selection of targets for eye movements[16,17]. Subthreshold stimulation of eye movement representations within the FEF can also improve a monkey's ability to covertly filter visual stimuli[8]. This result suggests that microstimulation of the FEF not only initiates the selection of a particular eye movement, but also initiates the selection of particular visual stimuli at the location to which the movement is directed. We studied the influence of subthreshold FEF stimulation on the visual responses of neurons in extrastriate area V4. In each of two monkeys, we electrically stimulated sites within the FEF while simultaneously recording the activity of V4 neurons (Fig. 1a). Modulation of activity in area V4 during both overt and covert spatial attention tasks has previously been observed[5,18]. We reasoned that, if FEF microstimulation initiates both saccade preparation and visual selection, then it should be possible to induce a spatial-attention-like modulation of V4 activity in passively fixating monkeys.

During each experiment, the receptive field (RF) of an isolated V4 neuron was mapped (Fig. 1b, left). With a second electrode, we located a site within the FEF from which saccades could be evoked by electrical stimulation (Fig. 1b, right). Next, we mapped the point in space to which the monkey's gaze was shifted, and measured the current threshold to evoke saccades. At a particular FEF site, the end point of the evoked-saccade vector could fall either within or outside the V4 RF. Finally, using subthreshold currents, we examined the effect of stimulating the FEF site on the visual responses of the V4 neuron. Stimulation was applied to the FEF site 200–500 ms after the appearance of visual stimuli. This delay allowed us to examine the effects of FEF stimulation on visually driven activity in

V4. Thus, stimulation could amplify, have no effect on, or interfere with the V4 representation of the stable stimulus.

An example of the effect of FEF stimulation on the response of a V4 neuron is shown in Fig. 2. Stimulation of the FEF site evoked saccades to a location 11° into the lower contralateral quadrant and into the V4 RF. We applied 50-ms trains of subthreshold current pulses ($20\,\mu A$) to the FEF site during the presentation of stable oriented-bar stimuli while the monkey maintained central fixation. Responses of the neuron during FEF stimulation were excluded from the analysis to avoid contamination by the stimulation artefact. This neuron responded well to the appearance of an optimally oriented bar stimulus in its RF, but adapted within a few hundred milliseconds (Fig. 2a). However, after FEF stimulation, the response was transiently enhanced compared with trials in which there was no stimulation. By contrast, stimulation did not affect the activity of the cell when there was no RF stimulus (Fig. 2b). Therefore, the effect of stimulation was dependent on the presence of the RF stimulus.

Figure 2c shows the effect of FEF stimulation as a function of the visually driven activity when no stimulus, the non-preferred, or the preferred stimulus was presented in the RF. We measured the difference in activity between stimulation and control trials during a 70-ms time window immediately after the end of the stimulation train. In this case, FEF stimulation caused a significant enhancement of the firing rate of the V4 cell when there was a preferred visual stimulus in its RF (mean response change, 22.1 spikes s^{-1}; paired t-test, $P < 0.05$). By contrast, there was no effect of FEF stimulation when the cell was not driven by a RF stimulus (mean
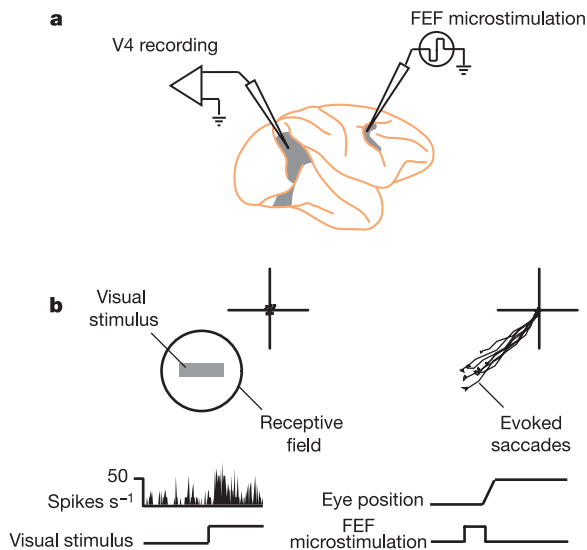
Figure 1 Mapping receptive fields and evoking saccades. **a**, Sites within the frontal eye fields (FEF) were electrically stimulated while recording from neurons in area V4. The cartoon shows a side view of the macaque brain. The locations of the FEF in the arcuate sulcus and of area V4 in the prelunate gyrus are shown (shaded). **b**, Left, the response of a V4 neuron when a visual stimulus appears in its receptive field (RF) while the monkey maintains central fixation (dots at origin). Right, saccades evoked to a location spatially corresponding to the V4 RF following suprathreshold microstimulation of an FEF site.
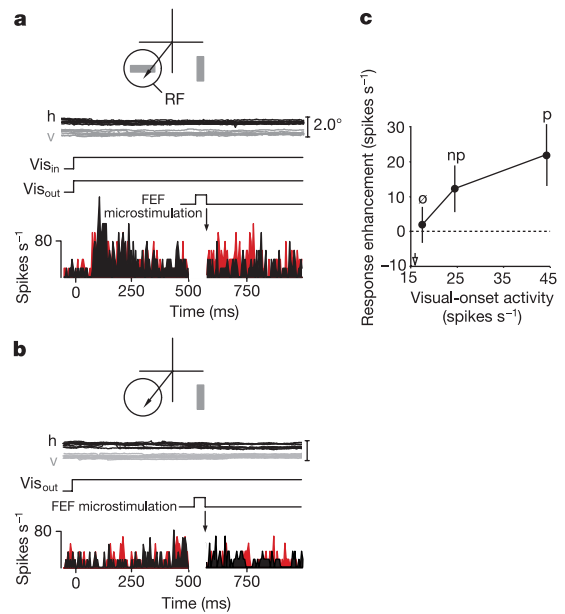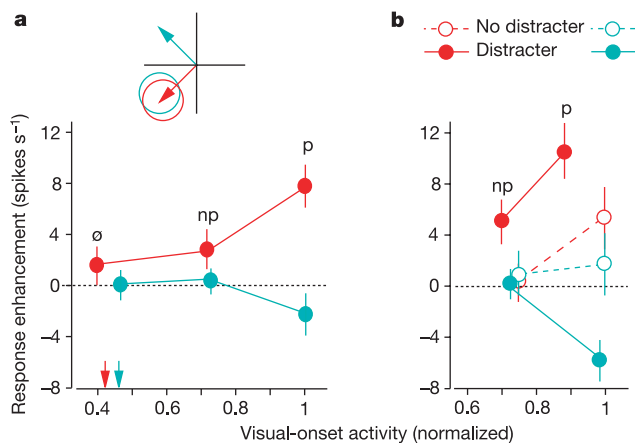

Figure 2 Effect of FEF stimulation on the response of a V4 neuron. The neuron's RF (circle) is aligned with the saccade vector (arrow) evoked with suprathreshold FEF stimulation ($>40\,\mu A$). **a**, Histograms show the V4 neuron's mean response during control (black) and stimulation (red) conditions (ten trials per condition, 5-ms bins). The control histogram is shown superimposed on the stimulation histogram for two time periods: after the onset of RF (Vis$_{in}$) and non-RF (Vis$_{out}$) stimuli and after a 50-ms subthreshold ($20\,\mu A$) stimulation train had been applied to the FEF site. Above, black (horizontal; h) and grey (vertical; v) traces show the monkey's eye position. **b**, As in **a**, except that histograms show the neuron's response when the RF stimulus was not presented. **c**, Response enhancement plotted as a function of visual-onset activity. The x-axis shows the average activity during a 400-ms time window after the onset of the visual display, with Ø (no stimulus), np (a non-preferred stimulus) or p (a preferred stimulus) in the RF. The y-axis shows the mean change in activity (stimulation − control) for a 70-ms time window following the offset of FEF stimulation. Arrow indicates the baseline activity. Error bars represent the s.e.m.

response change, 1.9 spikes s^{-1}; paired t-test, $P > 0.70$). During the presentation of a bar stimulus at a non-preferred orientation, FEF stimulation resulted in an intermediate enhancement (mean response change, 12.3 spikes s^{-1}; paired t-test, $P > 0.05$). Thus, the effect of stimulation seemed to depend on how well the V4 neuron was visually driven.

We tested the effect of FEF microstimulation on a total of 64 V4 neurons in the two monkeys. Of these, 31 neurons had RFs into which the evoked saccade shifted the monkey's gaze, whereas 28 had RFs that the saccade end points fell outside and were displaced from by an angle of $>45°$. Two further neurons were tested in both conditions by advancing the FEF electrode to a new site between experiments while recording from the same V4 cell. The remaining three neurons had RFs that partially overlapped the FEF representation and/or were tested with visual stimuli that bridged the two representations, and therefore were excluded from the analysis. The FEF was always stimulated with currents below the site's movement threshold current. The mean test current (40.7 μA) was 55% of the mean threshold current (73.5 μA). During each experiment, optimal and non-optimal visual stimuli were presented within the V4 RF, outside it, or at both locations simultaneously. These conditions allowed us to examine whether the stimulation effect depended on how well the RF stimulus drove the V4 cell, and whether it depended on the presence or absence of a potentially distracting stimulus outside the RF.

When the evoked saccade shifted the monkey's gaze into the V4 RF, subthreshold FEF stimulation resulted in a visually dependent enhancement of the population response (Fig. 3a). In this analysis, data were collapsed across the distracter conditions. When a stimulus was presented in the RF, stimulation enhanced V4 responses (paired t-test, $P < 0.0001$). By contrast, FEF stimulation had no effect on the response of the population when there was no RF stimulus (paired t-test, $P > 0.25$). The dependence of the stimulation effect on the visually driven activity was also evident when we excluded the conditions with no RF stimulus. That is, the enhancement depended on whether the preferred or non-preferred stimulus appeared in the RF, the preferred stimulus yielding greater response enhancement (analysis of variance (ANOVA), $P < 0.02$). Thus, the enhancement grew with increasing visual drive.

Figure 3 Effect of FEF stimulation on the responses of populations of V4 neurons. Data were obtained from experiments in which the evoked saccades (arrows) shifted the monkey's gaze to a point within (red, $n = 33$) or outside (blue, $n = 30$) the RF (circles) of the recorded V4 neuron. **a**, The mean response difference between stimulation and control conditions (stimulation − control) plotted as a function of visual-onset activity. The onset activity of each neuron in the population was normalized to its response to the preferred stimulus presented alone. Arrows indicate the mean baseline activity for each population subset. **b**, Same as **a**, but conditions with and without a non-RF stimulus (distracter) are shown separately.

We also examined the dependence of the stimulation effect on the presence or absence of a distracter stimulus outside the RF. We compared the conditions in which the RF stimulus was presented either alone or simultaneously with the distracter stimulus (Fig. 3b). The effect of FEF stimulation was greater when a non-RF stimulus was presented simultaneously with the RF stimulus than when the RF stimulus was presented in isolation (ANOVA, $P < 0.02$). The effects of distracter and RF stimuli did not significantly interact (ANOVA, $P > 0.5$). As a result, we observed the largest response enhancement when the preferred stimulus was presented in the RF simultaneously with a distracter outside the RF. In this condition, FEF stimulation increased the response of V4 neurons by an average of 10.4 spikes s^{-1}. The population response to the onset of the preferred stimulus averaged 48 spikes s^{-1}. Thus, stimulation enhanced visual responses by more than 20% of the maximum.

The effect of subthreshold stimulation was different when the evoked saccade shifted the monkey's gaze to a location outside the V4 RF. In these experiments, the distracter stimulus was placed at the end point of the evoked-saccade vector. When the preferred visual stimulus was presented in the RF simultaneously with the non-RF distracter, the condition that produced the largest enhancement during stimulation of overlapping representations, we observed a suppression of V4 responses (paired t-test, $P < 0.01$) (Fig. 3b). Following FEF stimulation, the population response was reduced by an average of 5.1 spikes s^{-1}. In all other conditions, FEF stimulation did not alter V4 responses (Fig. 3b). Thus, FEF stimulation could enhance or suppress the visual response depending on whether the two cortical representations overlapped retinotopically.

Microstimulation of the FEF could have altered the activity of V4 neurons in a number of ways. Stimulation could have directly activated V4 neurons antidromically, given that at least some cells in V4 project to the FEF[19]. However, our failure to change the activity of these neurons when they were not driven by a RF stimulus indicates that direct antidromic effects were absent. Furthermore, the dependence of stimulation effects on the presence of a RF stimulus indicates that activation of the FEF site did not impose an extraneous visual signal on V4 neurons. This interpretation is consistent with the failure of human subjects to report visual sensations during cortical stimulation of their homologous FEF[14,15]. Second, although we stimulated the FEF with subthreshold currents, we may have nonetheless destabilized the monkey's fixation and increased the frequency of microsaccades. Such an increase could have raised the visual responsiveness of each neuron by effectively moving the stimulus within the RF[20]. However, this effect would not depend on the overlap between the FEF and V4 representations, contrary to our observations.

Instead, microstimulation of FEF sites appears to have activated a network that controls the gain of visually driven signals. Moreover, our results show that activation of this network biases not only the selection of eye movements[16,17], but also the strength of visual cortical signals, revealing a common network for the control of visual and oculomotor selection. In addition, the dependence of the stimulation effects on the features of the RF stimulus as well as on the presence of a non-RF distracter indicates that the above network may be involved in previously reported attentional modulations in area V4. Studies in which changes in V4 responses are observed during spatial attention tasks have shown that the magnitude of modulation depends on how well the RF stimulus drives the V4 cell[21] and on the number of distracter stimuli[5]. In our study, the display conditions in which FEF stimulation produced the largest effect were similar to those that gave rise to the largest V4 modulation in monkeys trained to direct attention either inside or outside a V4 RF. It is also noteworthy that, under these conditions, the magnitude of the enhancement effect (~20%) was comparable to that previously observed in V4 during spatial-attention tasks[21]. Although it is tempting to speculate that the

observed effects resulted from orthodromic activation of FEF neurons with top-down projections to posterior visual areas[22], including direct projections to V4 as well as to parietal and temporal areas, this is only one of many possible ways in which stimulation could gate signals in area V4. Future experiments should aim to specify further the pathway or pathways that are sufficient to bring about the observed gain modulation.

Primate vision consists of a sequential sampling of the details contained within a scene[23]. The extraction of information from a scene depends on the continual shifting of perceptual resources, such as the foveas, across locations in space. This process must include the reciprocal interaction of brain mechanisms that are involved primarily in coding the visual stimulus with those that are involved primarily in moving the eye[24]. The results of the current study reveal an equivalence of biases in oculomotor preparation and biases in the gain of spatially corresponding visual signals when oculomotor plans are not carried out. As such, covert spatial attention may simply reflect one emergent property of visuomotor integration. □

Methods

We recorded the responses of V4 cells to oriented-bar stimuli while the monkey fixated a central spot and while subthreshold stimulation trains lasting 20–50 ms (200 Hz, biphasic, 0.2-ms pulse duration) were applied to the FEF. We determined the metrics of the evoked saccade and the movement threshold of each FEF site in a separate behavioural paradigm in which stimulation with varying current amplitude was delivered to the site during the performance of a fixation task[8]. During the experiment, visual stimuli (50–93% Michaelson contrast) were presented for 1.5–2 s inside and outside the RF of a V4 neuron. RFs were mapped in a further behavioural paradigm in which oriented bars were swept across the display during fixation while monitoring the activity of the recorded cell[25]. Bar stimuli were presented either at the preferred orientation or orthogonal to the preferred orientation during successive trials. All visual stimuli were displayed on a video monitor (30 cm vertical × 40 cm horizontal, 60 Hz) positioned 57 cm in front of the monkey. Throughout behavioural testing, eye position was monitored through a scleral search coil and stored at 200 Hz. All general surgical and experimental procedures, which have previously been described[26], were approved by the Princeton University Animal Care and Use Committee and were in accordance with National Institutes of Health guidelines.

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Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders

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The expansion of a CAG repeat coding for polyglutamine in otherwise unrelated gene products is central to eight neurodegenerative disorders including Huntington's disease[1]. It has been well documented that expanded polyglutamine fragments, cleaved from their respective full-length proteins, form microscopically visible aggregates in affected individuals and in transgenic mice[2–7]. The contribution of polyglutamine oligomers to neurodegeneration, however, is controversial. The azo-dye Congo red binds preferentially to β-sheets containing amyloid fibrils[8,9] and can specifically inhibit oligomerization[10] and disrupt preformed oligomers. Here we show that inhibition of polyglutamine oligomerization by Congo red prevents ATP depletion and caspase activation, preserves normal cellular protein synthesis and degradation functions, and promotes the clearance of expanded polyglutamine repeats *in vivo* and *in vitro*. Infusion of Congo red into a transgenic mouse model of Huntington's disease, well after the onset of symptoms, promotes the clearance of expanded repeats *in vivo* and exerts marked protective effects on survival, weight loss and motor function. We conclude that oligomerization is a crucial determinant in the biochemical properties of expanded polyglutamine that are central to their chronic cytotoxicity.

To assess directly the role of oligomerization in the cytotoxicity of expanded polyglutamines, we determined whether anti-amyloid compounds that are known to bind to β-sheet-containing amyloid fibrils, including polyanions[11], tetracyclines[12] and azo-dyes such as Congo red[8,10] and chrysamine G[13], could prevent expanded poly-