

LETTERS

Influence of the thalamus on spatial visual processing in frontal cortex

Marc A. Sommer^{1,2} & Robert H. Wurtz²

Each of our movements activates our own sensory receptors, and therefore keeping track of self-movement is a necessary part of analysing sensory input. One way in which the brain keeps track of self-movement is by monitoring an internal copy, or corollary discharge, of motor commands^{1–13}. This concept could explain why we perceive a stable visual world despite our frequent quick, or saccadic, eye movements: corollary discharge about each saccade would permit the visual system to ignore saccade-induced visual changes^{6–9}. The critical missing link has been the connection between corollary discharge and visual processing. Here we show that such a link is formed by a corollary discharge from the thalamus that targets the frontal cortex. In the thalamus, neurons in the mediodorsal nucleus relay a corollary discharge of saccades from the midbrain superior colliculus to the cortical frontal eye field^{10–12}. In the frontal eye field, neurons use corollary discharge to shift their visual receptive fields spatially before saccades^{14,15}. We tested the hypothesis that these two components—a pathway for corollary discharge and neurons with shifting receptive fields—form a circuit in which the corollary discharge drives the shift. First we showed that the known spatial and temporal properties of the corollary discharge predict the dynamic changes in spatial visual processing of cortical neurons when saccades are made. Then we moved from this correlation to causation by isolating single cortical neurons and showing that their spatial visual processing is impaired when corollary discharge from the thalamus is interrupted. Thus the visual processing of frontal neurons is spatiotemporally matched with, and functionally dependent on, corollary discharge input from the thalamus. These experiments establish the first link between corollary discharge and visual processing, delineate a brain circuit that is well suited for mediating visual stability, and provide a framework for studying corollary discharge in other sensory systems.

The dominant hypothesis of how we perceive visual stability is that advance warning of saccades is sent to the visual system (Supplementary Fig. S1a, b)^{7–9}. The only known pathway for saccadic corollary discharge innervates the cortical frontal eye field (FEF)^{10–12} (Supplementary Fig. S1c), which contains visually responsive neurons that have been shown^{14,15} to use corollary discharge. Neurons of this type, which were discovered in the parietal cortex¹⁶, alter their spatial visual processing just before a saccade (Fig. 1a). Specifically, they shift their visual receptive field (RF) to a new location, the future field (FF), where the RF will reside after the saccade^{14–18}. Because the neurons sample the same region of visual space before and after the saccade (in the FF and postsaccadic RF, respectively), they provide information about whether a visual scene is stable across saccades.

We trained monkeys to make saccades while a visual probe appeared at the RF or FF during initial fixation or just before a saccade (Fig. 1b; Supplementary Fig. S2). An example neuron had

a visual response in its RF, but not in its FF, during initial fixation (Fig. 1c, left column), but this spatial sensitivity reversed just before a saccade: the FF became responsive and the RF unresponsive (Fig. 1c, middle column). Saccades alone evoked no activity as revealed in trials without a probe (Fig. 1c, right column, bottom row). Activity in the FF thus reflected a sudden, presaccadic onset of visual sensitivity—a shifting RF.

We searched in the FEFs of two monkeys for neurons with shifting RFs. Only neurons identified as belonging to the superior colliculus (SC)–FEF circuit as defined by antidromic and orthodromic stimulation criteria were studied (antidromic and orthodromic neurons

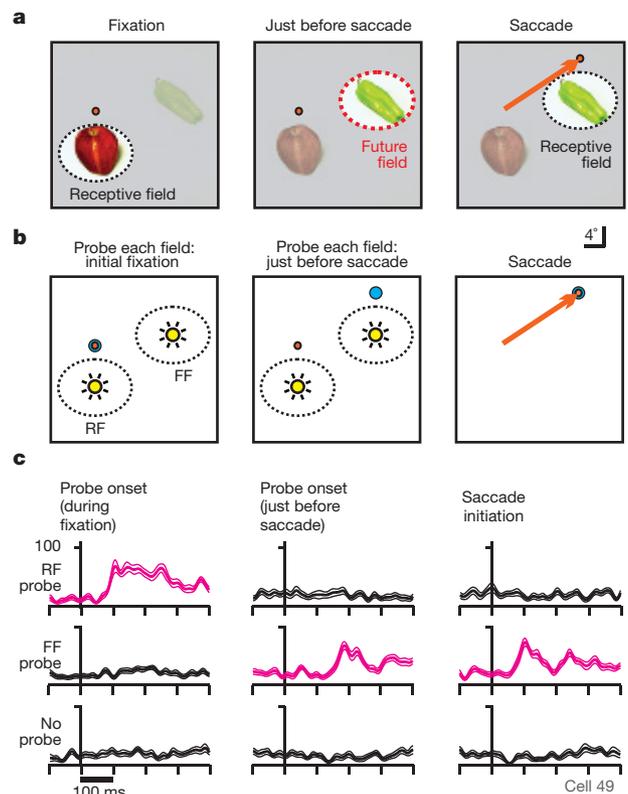


Figure 1 | Shifting receptive fields of visual neurons. **a**, Just before a saccade, visual responsiveness moves from the RF to the FF. **b**, Monkeys looked at (orange dot) a fixation spot (blue dot, left) and made a saccade to a target (blue dot, middle). We flashed a probe (yellow circle) in one of two locations and two times (one probe per trial). **c**, Example FEF neuron. The firing rate (mean \pm s.e.m.; the vertical scale is in spikes s^{-1}) is aligned with events represented in **a** and **b** above. The visual response shifts from the RF (magenta, left) to the FF (magenta, middle) just before the saccade.

¹Department of Neuroscience, the Center for the Neural Basis of Cognition, and the Center for Neuroscience at the University of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA. ²Laboratory of Sensorimotor Research, National Eye Institute, NIH, Bethesda, Maryland 20892, USA.

behaved identically and were pooled; see Supplementary Notes). Of 71 such neurons that had visual responses, 61% ($n = 43$) had shifting RFs. One-third (14 of 43) showed a complete shift from RF to FF just before saccade initiation (for example Fig. 1c), whereas the rest (29 of 43) became active at the FF while maintaining responsiveness at the RF (Supplementary Fig. S3). The basic properties of the neurons with shifting RFs were similar to those described previously^{14–18}.

If FEF neurons with shifting RFs use corollary discharge from the SC, the shifts should be influenced by the spatiotemporal dynamics of SC activity. Spatially, SC activity encodes saccades on a topographic map¹⁹. Localized activity on the map specifies the vector (eccentricity and direction) of the saccadic target (Fig. 2a, 'hill' of activity). Temporally, SC activity encodes the time of saccade initiation with a volley of action potentials (Fig. 2a, arrow representing sudden onset). Thus we predicted that, spatially, shifting RFs should jump as if directed by a vector specification of the saccade, and temporally, they should move in synchrony with the saccade as if driven by a burst of presaccadic activity.

To study the spatial properties of the shift, we added a visual probe at the midpoint between the RF and the FF. If activity at the midpoint were unchanged before a saccade, this would show that visual sensitivity 'jumped' from the RF to the FF (Fig. 2b, top). However, if activity at the midpoint increased before a saccade, this would refute the prediction of a jump and suggest that a gradual spread of visual

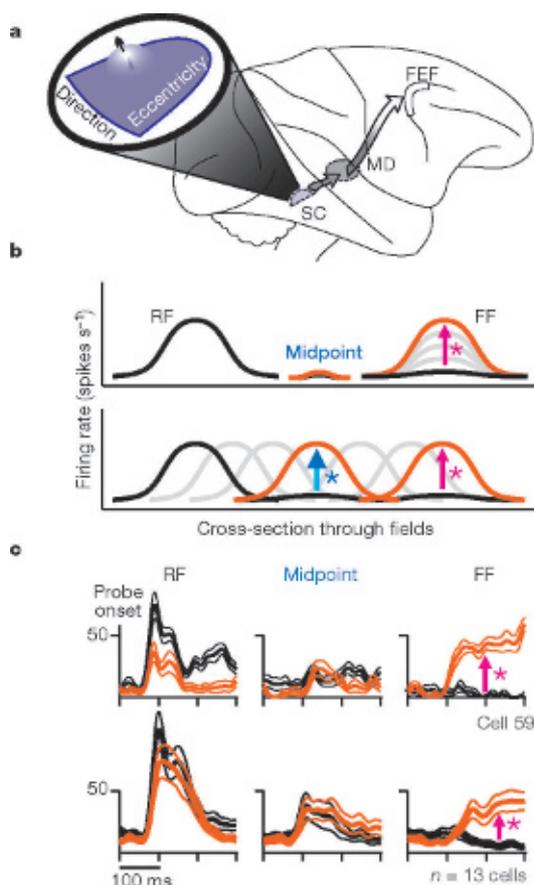


Figure 2 | The spatial properties of shifting RFs are predicted by corollary discharge from the SC–MD–FEF pathway. **a**, The corollary discharge arises from the SC, which encodes saccades spatially, using a map of direction and eccentricity, and temporally, using a burst of activity. **b**, Spatially, we predicted that shifting RFs jump (top), as indicated by a significant (asterisk) increase in activity at the FF (magenta arrow) but no significant difference at the midpoint. Alternatively, shifting RFs could spread (bottom). Probe onset time: black, initial fixation; orange, just before saccade. **c**, Example neuron (top) and population (bottom); data aligned to probe onset. Shifting RFs moved as a jump. The vertical scale is in spikes s⁻¹.

sensitivity travelled from the RF to the FF (Fig. 2b, bottom). An example neuron responded to a probe in the RF during initial fixation (Fig. 2c, top) but had little if any response at the midpoint and was unresponsive at the FF. Just before the saccade, the neuron suddenly became visually responsive at the FF ($P < 0.0001$), whereas the midpoint location showed no significant change ($P > 0.05$; measured 100–300 ms after probe onset). We isolated 13 neurons long enough to test the midpoint, and every one exhibited no change there as activity jumped to the FF. The pooled data from all 13 neurons (Fig. 2c, bottom) showed that just before a saccade, the average activity dropped slightly at the RF, rose markedly at the FF (by 43 spikes s⁻¹, $P < 0.0001$) and did not change significantly at the midpoint ($P > 0.05$). A minor, late increase at the midpoint was due to a slight overlap of the probe onto the edge of the FF (see further analyses in Supplementary Figs S4–S6). Shifting RFs therefore jump, rather than spread, to their new locations.

Next we tested our prediction that shifts were synchronized to saccade initiation by flashing probes earlier to impose a substantial delay (about 200 ms) between probe onset and saccade initiation. If shifts were synchronized to saccade initiation they would start after the delay, when the saccades begin, but if shifts were synchronized to probe onset they would start at a normal visual latency after the probes. On a trial-by-trial basis, we found that the times of shift onset and saccade initiation were tightly correlated in single neurons (Fig. 3a, left; $R = 0.97$, $P < 0.001$) and in the population (Fig. 3b; mean $R = 0.50$, greater than 0 at $P < 0.002$, t -test; $n = 13$ neurons having more than ten trials). In addition, there was a higher peak in the average firing rate when aligned to saccade initiation (Fig. 3a, right) as opposed to probe onset (Fig. 3a, left; true for 24 of 26 individual neurons, an average increase of 6 spikes s⁻¹; $P = 0.001$, paired t -test). In contrast, shift onset had no clear relation to probe onset; the shift started long after the normal visual latency (green arrow) in the single example (Fig. 3a, left) and in the population (not shown; average shift onset time 174 ± 92 ms (mean \pm s.d.) versus average visual latency 86 ± 16 ms; $P < 0.0001$). In sum, shifting RFs were synchronized with saccades. On average they started with saccade initiation (Fig. 3c; mean 24 ± 74 ms (mean \pm s.d.),

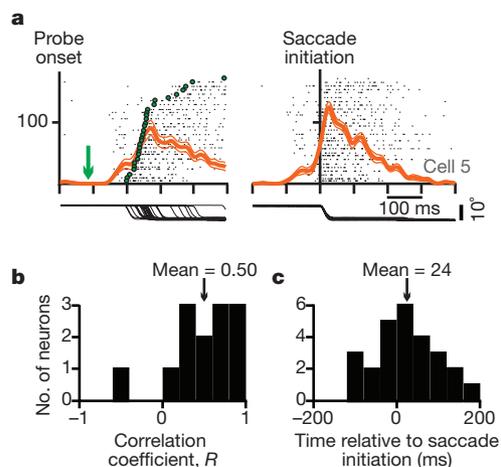


Figure 3 | The temporal properties of shifting RFs are predicted by corollary discharge from the SC–MD–FEF pathway. **a**, Our hypothesis predicts that shifting RFs are synchronized with saccades. Shift activity (in the FF) for an example neuron is aligned to probe onset (left) and saccade initiation (right). Rasters of action potentials from each trial are sorted by saccadic latency (green dots). Eye position traces (horizontal component) are shown below. The green arrow indicates the average visual latency of this neuron. The vertical scale is in spikes s⁻¹. **b**, Strength of correlation (Pearson's R) between shift onset time and saccadic latency for the population. Mean $R > 0$ at $P < 0.002$. **c**, Shift onset time relative to saccade initiation for the population. There is no significant difference in shift onset time from 0 ms.

not significantly different from 0; range -94 to 164 ms). A visual response gated by saccadic initiation would be critical for perceiving visual stability, because saccades can be cancelled about 100 ms before initiation²⁰; only after this 'point of no return', when a saccade is inevitable, should neurons shift their RFs.

Next we looked for evidence that corollary discharge from SC through the thalamus caused the shifting RFs in the FEF. In an experimental session, first we isolated a visually responsive FEF neuron that was connected to the SC and had a shifting RF (as described for the 43 neurons above). While maintaining isolation of the neuron, we inserted an injection syringe needle targeted at the previously identified relay nucleus from the SC to the FEF in the mediadorsal (MD) thalamus (Fig. 4a). We then returned to the FEF neuron, quantified its visual sensitivity at the RF and the FF, and inactivated the MD nucleus with muscimol, an agonist of the inhibitory neurotransmitter γ -aminobutyric acid (GABA)²¹. Finally, we retested the visual sensitivity of the same neuron at the RF and the FF. Our prediction was that MD inactivation should reduce activity at the FF.

We completed the lengthy sequence of procedures required in this experiment for eight FEF neurons (Supplementary Fig. S7). In an example neuron, the major effect was a 70% decrease ($P < 0.0001$) in FF activity (Fig. 4b, lower middle and right), whereas the visual response in the RF was spared (Fig. 4b, upper left), as was low-level

activity in the trials without a probe (not shown). Inactivating the corollary discharge pathway through the MD therefore caused a marked reduction in the ability of this neuron to shift its RF.

Because the SC–MD–FEF pathway on each side of the brain represents only contraversive saccades¹⁰, a further prediction was that our unilateral inactivations would eliminate corollary discharge for contraversive saccades only. Therefore shifts accompanying contraversive saccades, but not ipsiversive saccades, should be impaired. This is exactly what we found (Fig. 4c).

Overall, we found that activity at the FF decreased during inactivation for every neuron (16–70%, individually significant for seven of eight neurons; Supplementary Fig. S7). The average deficit (Fig. 4d, left) was severe in the FF for contraversive saccades (53.9% deficit, $P < 0.001$) but not significant in the RF ($P = 0.48$) or in the FF for ipsiversive saccades ($P = 0.76$). In terms of firing rates (Fig. 4d, right), the average visual response decreased from 69.6 to 30.3 spikes s^{-1} in the FF for contraversive saccades (paired t -test, $P = 0.019$) but was unchanged in the RF ($P = 0.2$) and in the FF for ipsiversive saccades ($P = 0.4$). Data from the trials without a probe never showed a significant deficit (not shown). Most of the neurons were antidromically activated from the SC, but the one orthodromically activated neuron showed the same effect (55% deficit; Supplementary Fig. S7a). Injections as small as $0.4 \mu\text{l}$ were effective and larger volumes did not cause larger effects, suggesting that inactivation beyond the targeted MD relay neurons was inconsequential (Table in Supplementary Fig. S7). A side-product of MD inactivation, bilaterally increased saccadic latencies, did not cause the deficits (Supplementary Fig. S8). For more consideration of these issues see the Supplementary Discussion.

We conclude that corollary discharge from the SC–MD–FEF pathway is both appropriate and necessary to produce shifting RFs in FEF neurons. These results delineate a link between an identified corollary discharge and a sensory system in the primate brain. More specifically, the data provide a circuit-level explanation for our percept of visual stability across saccades—an aim of neuroscience for at least 50 years^{1,8,9}. Corollary discharge from the SC causes the visual system to shift its RFs spatially, and these shifting RFs are proposed to promote the percept of visual stability across saccades¹⁶ (although exactly how this would be achieved has not yet been modelled).

Our findings permit the first direct test of the visual-stability hypothesis. In monkeys trained to detect visual motion, one could inactivate MD relay neurons to reduce shifting RFs; if these shifts underlie perceptual stability, the monkeys should report that static visual stimuli move with saccades. More generally, our approach may open up the study of other corollary discharge circuits such as those mediating the percept of a stable soundscape during head movements.

METHODS

Two rhesus monkeys (*Macaca mulatta*), 'T' and 'Y', were prepared for neurophysiological experiments as described in detail elsewhere^{10,22}. Details on physiology, task design and analysis are given in Supplementary Methods. To record from FEF neurons, we used standard extracellular methods combined with antidromic and orthodromic stimulation^{10,22} to confirm a connection with the SC (Supplementary Notes). To inactivate MD relay neurons, we first mapped their location in the thalamus by activating each one antidromically from the FEF and orthodromically from the SC. Relay neurons of the SC–MD–FEF pathway were concentrated in a restricted volume along the lateral edge of the MD thalamus^{10,23}. We inactivated them by inserting the tip of a 30-gauge cannula at their location and injecting $5 \mu\text{l} \mu\text{l}^{-1}$ muscimol.

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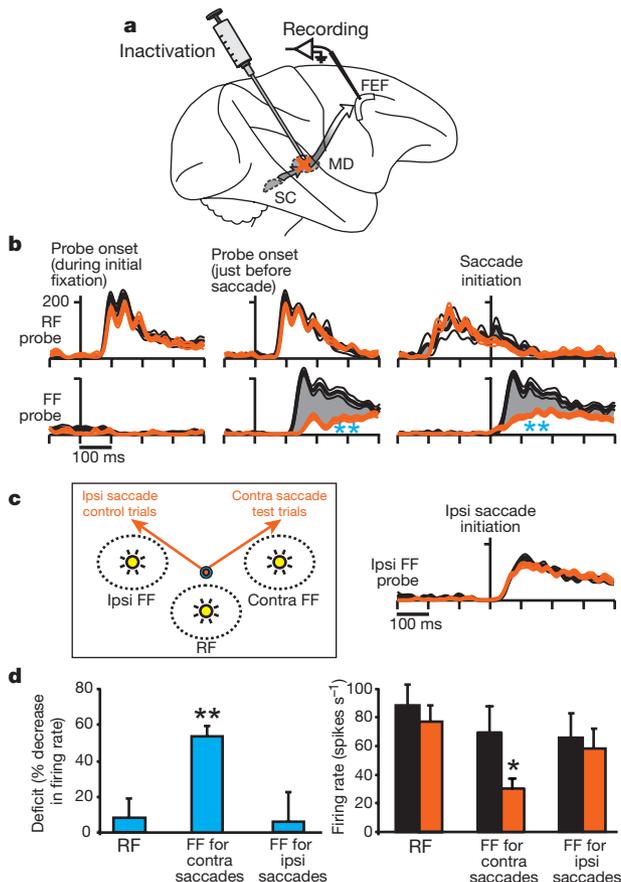


Figure 4 | Shifting RFs require corollary discharge from the pathway. **a**, We recorded from FEF neurons while inactivating MD relay neurons that convey corollary discharge. **b**, Example neuron (the same one as in Supplementary Fig. S3), with the difference in activity between during inactivation (orange) and before inactivation (black) highlighted in grey. Visual responsiveness in the FF just before the saccade—the shift—decreased severely during MD inactivation. The vertical scale is in spikes s^{-1} . **c**, In contrast, in ipsiversive (ipsi) saccade trials for the example neuron (left) there was no deficit (right). Contra, contraversive. **d**, Population data. Left, average percentage deficits; right, average changes in raw visual response (means and s.e.m.). Asterisk, $P < 0.05$; two asterisks, $P < 0.0001$.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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