Brain Structure and Function
https://doi.org/10.1007/s00429-021-02311-x

REVIEW

The role of feedback projections in feature tuning and neuronal excitability in the early primate visual system

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Received: 8 September 2020 / Accepted: 26 May 2021

Abstract

A general assumption in visual neuroscience is that basic receptive field properties such as orientation and direction selectivity are constructed within intrinsic neuronal circuits and feedforward projections. In addition, it is assumed that general neuronal excitability and responsiveness in early visual areas is to a great extent independent of feedback input originating in areas higher in the stream. Here, we review the contribution of feedback projections from MT, V4 and pulvinar to the receptive field properties of V2 neurons in the anesthetized and paralyzed monkey. Importantly, our results contradict both of these assumptions. We separately inactivated each of these three brain regions using GABA pressure injections, while simultaneously recording V2 single unit activity before and hours after inactivation. Recordings and GABA injections were carried out in topographically corresponding regions of the visual field. We outline the changes in V2 activity, responsiveness and receptive field properties for early, mid and late post-injection phases. Immediately after injection, V2 activity is globally suppressed. Subsequently, there is an increase in stimulus-driven relative to spontaneous neuronal activity, which improves the signal-to-noise coding for the oriented moving bars. Notably, V2 tuning properties change substantially relative to its pre-injection selectivity profile. The resulting increase or decrease in selectivity could not be readily predicted based on the selectivity profile of the inactivated site. Finally, V2 activity rebounds before returning to it pre-injection profile Our results show that feedback projections profoundly impact neuronal circuits in early visual areas, and may have been heretofore largely underestimated in their physiological role.

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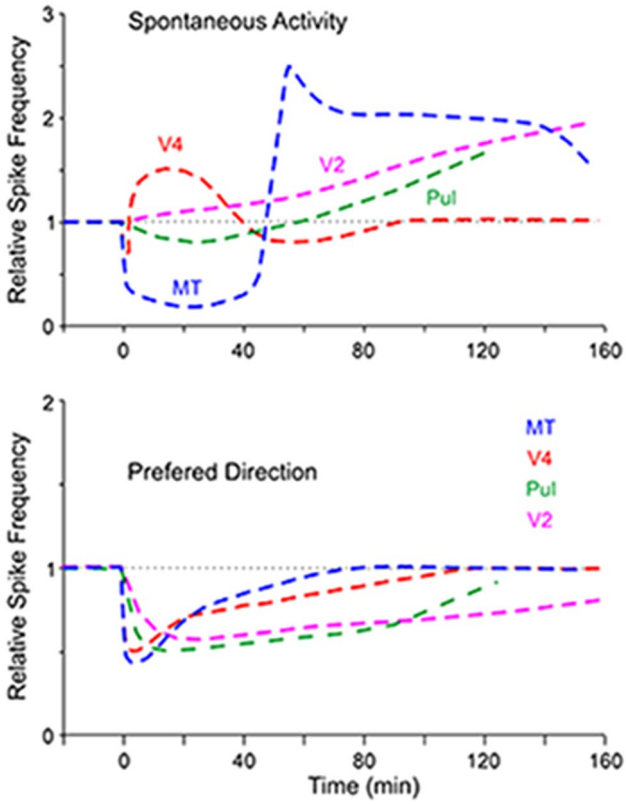
Published online: 04 June 2021

Graphic abstract



Keywords Feedback projections · GABA inactivation · Feature tuning · Primate visual system · Area V2

Introduction

Since the seminal work by Hubel and Wiesel (1968) it has been assumed that the most basic receptive field properties in the early visual system are constructed by means of ascending feedforward projections and lateral (i.e., intrinsic) circuits. Indeed, both feedforward and intrinsic circuits contribute to the extraction of complex attributes of the visual scene at each successive processing stage (Galuske et al. 2002). The feedforward connections are excitatory and make nonspecific synaptic contacts with different compartments of the target cell (Johnson and Burkhalter 1996). These connections are topographically organized, converge in clusters, and are paramount to the receptive field properties of postsynaptic neurons (Lamme et al. 1998; Sincich et al. 2004). On the other hand, some receptive field properties, such as orientation and direction selectivity, have been related to the inhibitory influence of intrinsic circuits on incoming information (Sato et al. 1996). Indeed, inhibitory GABAergic circuits contribute to directional tuning in V1 (Sillito 1977; Sato et al. 1995; Crook et al. 1998; Murthy and Humphrey 1999; Roerig and Kao 1999). The inactivation of intrinsic inhibitory processes impairs both orientation and direction selectivity (Sillito 1975a, b). In primary (V1) and secondary (V2) visual areas of monkeys and cats, the orientation and direction selectivity depend on the inhibitory influence of basket cells projecting to orientation- and direction-selective functional modules (Sato et al. 1996, 1995; Crook et al. 1998, 1996, 1997). There is also experimental evidence that the excitatory network contributes to orientation and direction selectivity (Sato et al. 1995, 1996; Crook et al. 1996; Sillito et al. 1980a, b; Hata et al. 1988; Tsumoto et al. 1979). For example, Sato et al. (1995) showed that bicuculline injection decreased direction selectivity in macaque V1. However, the originally preferred direction continued to yield the best neuronal response even after inactivation. This suggests that the excitatory network may be the basis for building direction selectivity. Cortical inhibition would play a subsequent role in increasing selectivity by strengthening the bias of the excitatory input (Vidyasagar and Eysel 2015).

On the other hand, the neurophysiological role of feedback projections is far less clear. Their abundance, their propagation speed along the axons, and their short response latency all suggest that their influence on the receptive field

properties of target neurons is not restricted to a simple modulatory role (Hupé et al. 1998; Mignard and Malpeli 1991; Alonso et al. 1993; Rockland and Knutson 2000; Bullier 2001; Angelucci et al. 2002; Huang et al. 2004; Borra and Rockland 2011). Notwithstanding, other studies have failed to pinpoint any influence at all of feedback projections (Sandell and Schiller 1982; Hupé et al. 2001).

Here, we review the contribution of feedback projections from MT, V4 and pulvinar to the receptive field properties of V2 neurons in the anesthetized and paralyzed monkey. Area MT is a small area (~ 70 mm^2 in area in capuchin monkeys) located in the temporal lobe of primates and contains a full representation of the contralateral visual field (Gattass and Gross 1981; Fiorani et al. 1989). It is part of the dorsal stream of visual information processing (Ungerleider and Mishkin, 1982) and is strongly involved in visual motion perception, including in humans (Kaas and Collins 2001). Area V4, on the other hand, is part of the ventral stream of visual information processing. It is located anterior to V3 and contains a topographically organized representation of the central 40º of the contralateral visual field (Gattass et al. 1988; Piñon et al. 1998). It is involved in shape and color perception and contains an abundance of color contrast-coding neurons (Hubel and Livingstone 1987; Tanigawa et al. 2010). The third region to be inactivated was the pulvinar nucleus, a diencephalic structure located in the posterior region of the thalamus. The expansion of the occipital, parietal and temporal lobes largely paralleled the development of the pulvinar during evolution, whose involvement in visual function has been demonstrated by the multiple visuotopic maps it harbors (Gattass et al. 1979, 2018; Adams et al. 2000; Soares et al. 2001).

MT, V4 and the pulvinar share in common a rich repertoire of reciprocal projections with area V2. Direct feedback projections from area MT, V4 and pulvinar to area V2 in primates have been previously described (Rockland et al. 1994; Ungerleider et al. 2008; Rosa et al. 1993; Soares et al. 2001; Nascimento-Silva et al. 2014). Cortical layers II, III, V, and VI of area V4 contain mainly pyramidal neurons (Zeki and Shipp 1988), which constitute the source of feedback projections to hierarchically lower areas. In V2, the same layers are the recipients of V4 feedback projections (Tigges et al. 1981). By studying the V2-V4 connectivity in the macaque monkey, Zeki and Shipp (1988) found that V2 pyramidal neurons in layer IIIB were the main source of projections to area V4, followed by neurons in layers IIIA and II and then by neurons in layer V. Conversely, feedback projections from V4 to V2 targeted mainly layer I and, less intensely, layers II, III, V and VI. Notably, these feedback projections were dispersed throughout all three types of V2 cytochrome oxidase-defined bands.

Area V2 is the largest extrastriate area in primates. Our group described the visuotopic organization of V2 in the capuchin monkey using extracellular electrophysiological recordings (Rosa et al. 1988). It is located anterior to V1 and contains a complete visuotopic representation of the contralateral visual hemifield (Gattass et al. 2015; Amorim and Picanco-Diniz 1996, 1997, 1998). V2 is part of both ventral and dorsal streams of visual information processing. The functional anatomy of these four regions (V2, V4, MT and pulvinar) offers a unique opportunity to combine multisite recordings and inactivation techniques to access the contribution of feedback projections to cortical circuits and dynamics. This review is largely based on publications from our own group, where we have separately inactivated each of these three brain regions using pressure injections of GABA, while simultaneously recording V2 single unit activity before and hours after inactivation (Soares et al. 2004; Jansen-Amorim et al. 2011, 2012, 2013). Recordings and GABA injections were carried out in topographically corresponding regions of the visual field.

When we started these experiments in the late 1990's, other groups had largely focused on local injections to investigate intrinsic neuronal circuits, or on injections in hierarchically lower areas (e.g., V1) to investigate their contribution to receptive field properties of hierarchically higher visual areas (e.g., V2). At the time, the expectation was that regions higher in the hierarchy (e.g., MT or V4) had minor (if any) contribution to feature selectivity in hierarchically lower areas (e.g., V2). Our results contradict this basic assumption. We showed an early decrease in V2 excitability for both spontaneous and stimulus-driven activity 1–20 min after GABA injection. However, since we observed a more pronounced decrease in spontaneous relative to stimulus-driven activity, the net outcome was an intermediate (20–40 min post-GABA injection) improvement in the signal-to-noise coding of oriented moving bars. We also observed profound changes in V2 direction and orientation selectivity after injection. Nevertheless, we were not able to draw any clear prediction on how V2 selectivity would change based on the stimulus selectivity of the injection site. Indeed, the V2 neuron stimulus tuning curve could become more or less selective after injection. Two possible explanations can account for this observation. First, feedback projections are not as specific as intrinsic connections in attributes such as orientation and direction selectivity. Second, GABA may have inactivated regions nearby to the injection site with different direction and/or orientation selectivities, but which nevertheless influenced V2 activity.

Below, we discuss the issues outlined above in more detail. In all, and despite the lack of any explicit model accounting for how feedback projections influence the coding attributes and responsiveness of early visual areas, our results corroborate the notion that feedback projection may have been heretofore largely underestimated in their physiological role.

Methodological considerations

This review is based on neural data acquired in 16 capuchin monkeys. Details regarding the methodological procedures used in each of our experiments can be found in the original articles. All experiments, originally published in Soares et al. (2004), Jansen-Amorim et al. (2011, 2012, 2013), used an equivalent GABA inactivation protocol. The location of areas V2, V4, MT and the pulvinar were initially estimated using stereotaxic coordinates and sulcal landmarks (Rosa et al. 1988; Fiorani et al. 1989; Piñon et al. 1998; Gattass et al. 1978a, 1987; Gattass and Gross 1981).

Subsequently, we used microelectrode electrophysiological recordings to probe the receptive field properties of the neurons in the assumed region to ascertain we had reached the correct target. One basic requirement in all experiments was that the inactivation (MT, V4 or pulvinar) site and the recording site in V2 represented overlapping regions of the visual field. The first technical challenge was to insert the inactivation apparatus, which consisted of a syringe and a tungsten electrode, inside the target brain region. This had to be done with the least tissue compression and tissue damage possible not to compromise neuronal circuitry sending the projections to V2. After mapping the visual field representation of the inactivation site, we sought the V2 region with the corresponding overlapping representation in the visual field. GABA was injected only when stable recordings were obtained at both sites. The criterium was to slowly inject GABA until all neuronal activity at the inactivation site was silenced. GABA injection was immediately stopped once this was achieved. Finally, in additional control experiments, we performed simultaneous inactivation and neuronal recordings in V2. In this case, we used lidocaine and GABA.

The visual stimulus was presented on a computer monitor placed at a distance of 57 cm in front of the animal. The stimulus consisted of a full contrast thin white bar (18×0.5 degrees), presented in one of four possible orientations (0°, 45°, 90°, or 135°), and which moved in a direction perpendicular to its orientation at a velocity of 10 degrees/sec. Therefore, the receptive field properties were probed with a set of 8 stimulus directions (conditions). Neuronal activity was acquired before and after GABA injection. Data were acquired in successive blocks consisting of 10 trials for each stimulus condition. Conditions were presented in a pseudo-random order. We continued to acquire data until after the inactivation site fully recovered its neuronal activity.

Throughout the years that we have been carrying out these experiments we have gradually migrated from hand mapping to the automatic mapping of the receptive fields (see Fiorani et al. 2014 for a precise description of the automatic receptive field mapping method). In short, this method interpolates the spike density functions (after latency correction) obtained in response to the elongated bars moving in different directions. This computation provides us with a precise estimate of the center and size of the receptive field. Despite the fact that hand mapping and automatic mapping of the receptive fields yield comparable results, automatic mapping is a much faster procedure.

We used multiunit neuronal activity to initially assess receptive field properties. However, all data subsequently acquired that were stored for further analysis were based on single unit activity. Spikes were sorted online using a waveform discriminating system (SPS-8701; Signal Processing System, Malvern, Australia). The resulting spike events were stored using the CORTEX software (Laboratory of Neuropsychology, NIMH/NIH, Bethesda, MD) for off-line analysis. We computed neuronal activity for the time window during which the moving bar was present within the receptive field. Much of our analyses was based on plotting neuronal activity in the form of a polargram for the various directions of motion tested. This allowed us to visually inspect directional tuning before and after inactivation, as well as to compare stimulus selectivities across regions. We quantified selectivity by means of indexes for both orientation (Sato et al. 1996) and direction (Wang et al. 2000). Finally, we employed standard statistical tests, such as Student's t-test, one- and two-way ANOVA and the least significant difference (LSD) test to decide whether the observed changes in neuronal activity were significant.

The impact of V2, V4, MT and pulvinar inactivation on the receptive field properties of V2 neurons

Figure 1 illustrates the general inactivation paradigm used in our studies. It shows the impact of V2 GABA inactivation on a neuron located near to the inactivation site (also in V2). The location of the inactivation and recording sites were identified by histological processing (Fig. 1a–d). The cell was classified as unidirectional with preferential response to bars moving at 315° (Fig. 1e). One minute after inactivation, the spontaneous activity decreased, as expressed by the decrease in the radius of the circle located at the middle of the polargram (Fig. 1f). In addition, the stimulus-driven activities changed its selectivity, now favoring bars moving in the direction of 180°. Thus, local inactivation is able to alter the direction selectivity of V2 neurons.

Figure. 2a shows an example V2 neuron after inactivation of the corresponding topographical representation in the pulvinar. This neuron exhibited a bidirectional response to the axis of motion 0180°. After pulvinar inactivation,

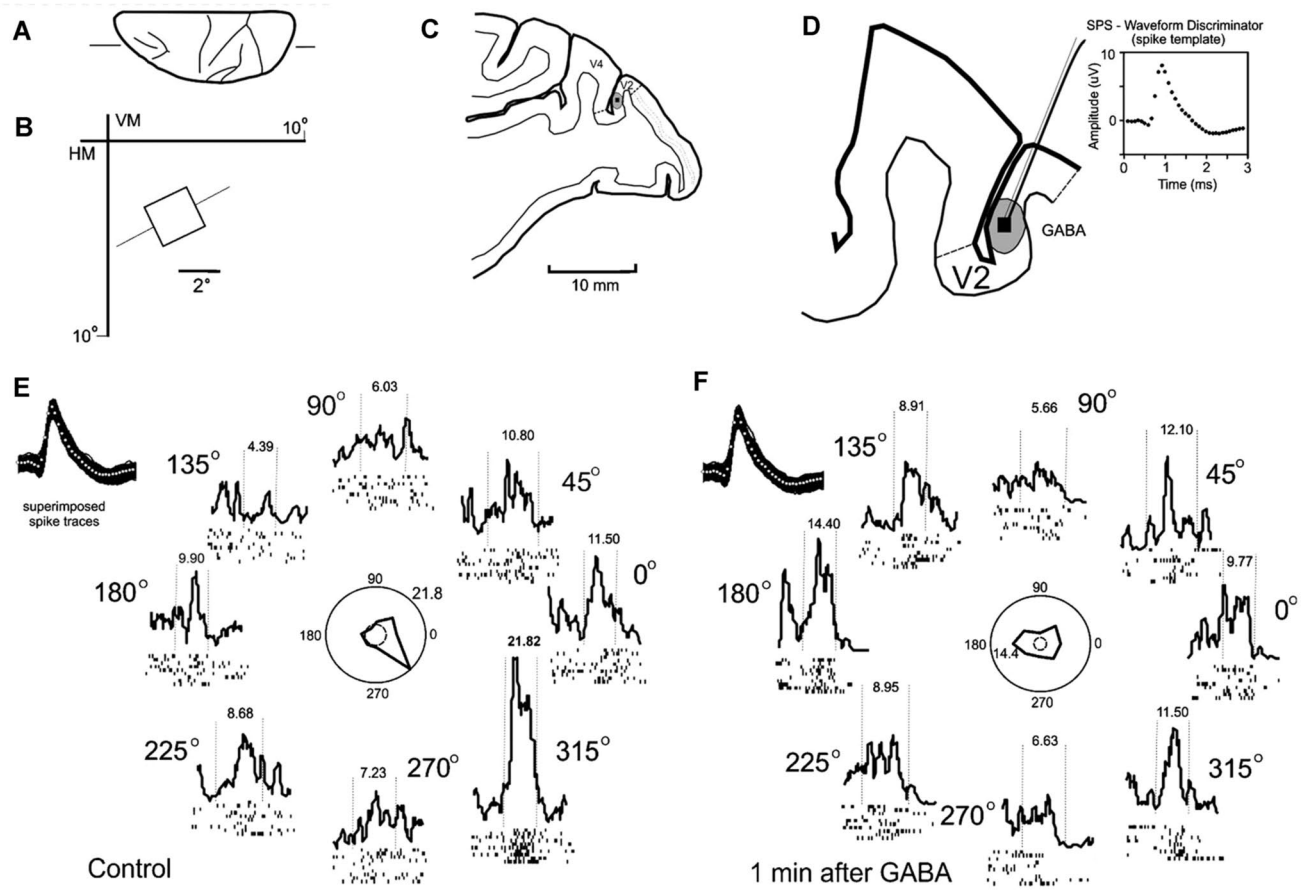


Fig. 1 Effect of GABA injection on the intrinsic circuit of V2. **a** Dorsal reconstruction of the capuchin brain, indicating the medial–lateral level of the parasagittal section illustrated in (**c**). **b** Location of the receptive field (square) for an example V2 neuron. *HM* horizontal meridian; *VM* vertical meridian. **d** Parasagittal section showing the location of the recording and GABA injection site in area V2 (inset: SPS-8701: waveform discriminator spike template). **e** Direction selectivity of a V2 neuron prior to the GABA inactivation of V2. The polargram represents the response magnitude relative to each direction of motion. It illustrates the unidirectional neuronal peak firing rate elicited by bars moving toward 315°. Left inset shows superimposed spike waveforms (black solid lines) and the spike template (white dots). Spike density function and spike rasters from 10 trials are illustrated for each direction. **f** Loss of direction selectivity (P 0.05, one-way ANOVA) 1 min after GABA inactivation. (Modified from Fig. 1 of Jansen-Amorim et al. 2013)

spontaneous and stimulus-driven activities were drastically reduced in V2. A preferential response to 180° (relative to 0º) appeared 21 min after inactivation (Fig. 2a – middle panel). Response to 0º started to recover 83 min after the injection. The original selectivity profile gradually recovered at around 133 min. The other example V2 cell shown in Fig. 2b showed high spontaneous activity. Pulvinar inactivation induced an inhibitory response at V2 receptive field. At the same time, the tuning of the response changed slightly, and the inhibition at the 0–180° axis started to be statistically significant at 13 min and peaked at 57 min after inactivation.

Figure 3a compares the effects of GABA and lidocaine inactivation at the same recording site in V2. Note that lidocaine injection induces a general decrease in neuronal activity, but does not change selectivity in any substantial way, as compared to GABA injection. The time course of the immediate observed changes is similar for both GABA and lidocaine, but the recovery to original selectivity is faster for lidocaine than for GABA. This may be due to the mechanism of lidocaine action. Lidocaine blocks voltage-dependent sodium channels, while GABA is the endogenous agonist of GABAergic channels. After V2 inactivation, approximately 37% of V2 neurons showed changes in their direction and orientation tuning. Some cells increased while other decreased their direction selectivity (16% versus, 21%, respectively). Regarding changes in orientationality, a similar proportion of V2 neurons either increased or decreased their selectivity (8% versus 13%, respectively).

Figure 4 compares the effect of GABA inactivation across the regions we investigated. We observed similar changes in V2 responses during inactivation of V2, V4, MT and the pulvinar. The effects of MT inactivation were quantitatively

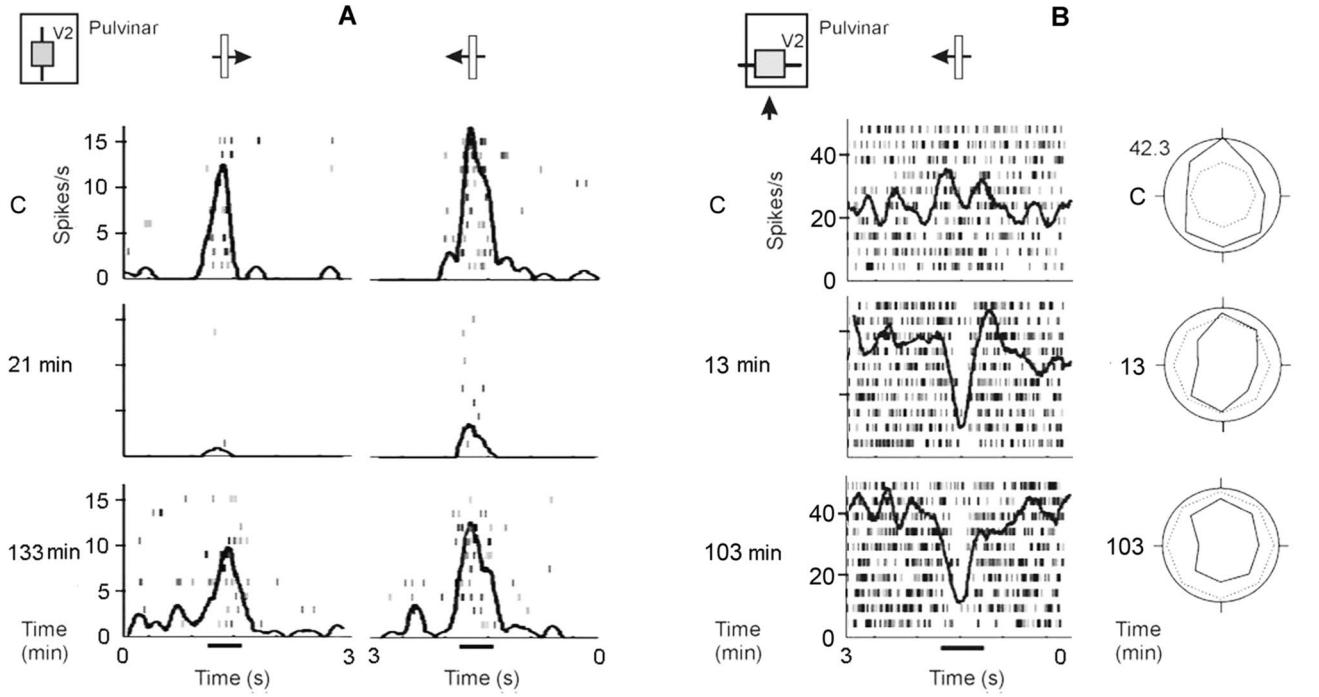


Fig. 2 Response change of two V2 cells after GABA injection in the pulvinar. **a** Single unit activity of an excitatory cell was recorded before (0) and at different time intervals (21 and 133 min) after injection of GABA. The inset shows the receptive field of the cell of V2 relative to the receptive field recorded at the injection site in the pulvinar. Peristimulus time histograms (PSTH) of the response to stimulus movement in the preferred direction (180°) and in the opposite direction. Right columns: PSTH of the responses to stimulus movement in orthogonal directions. Vertical ticks represent spikes (10 trials shown). Note the large reduction of the cell response at 21 min after the injection. **b** Inhibitory effect in another cell. Prior to inactivation, this cell showed an excitatory receptive field with a better response to movements along the 90–270° axis. After GABA injection, the spontaneous activity increased, and the cell started to exhibit an inhibitory receptive field along the 0–180° direction. The right column shows polar diagrams displaying the mean response rates computed from the regions corresponding to the receptive fields (dark bars below the PSTH) for different directions of movement at 45° steps. Dotted-line circles in the center of the polar diagrams correspond to the mean spontaneous activity of the cell. The radii of the external circles indicate the maximum value of the cell's response (42.3 spikes/s) obtained throughout the recording. (Modified from Figs. 4, 5 of Soares et al. 2004)

different from those of V4 inactivation. While inactivation of MT, on average, decreased DI, inactivation of V4 increased DI (Jansen-Amorim et al. 2011, 2012; Hupé et al. 1999). In addition, inactivation of MT, on average, increased OI, while inactivation of V4 or pulvinar decreased OI (Hupé et al. 1999; Jansen-Amorim et al. 2011, 2012). Thus, the feedback projections from MT have a different impact from those of V4, but both promote inhibitory modulations in V2, while the projection from pulvinar produces both excitatory and inhibitory modulations.

Some cells became direction or orientation selective after GABA injection in areas MT, V4 or pulvinar. For example, a pan-directional V2 neuron that had high spontaneous activity before GABA injection became directionally selective 1 min after injection in MT due to inhibitory flanks at the orthogonal axis (for example, see Fig. 5 in Jansen-Amorim et al. 2011). The loss of selectivity was the most frequently observed effect on V2 receptive field property after GABA inactivation in areas MT, V4 or pulvinar. For example, two V2 neurons that exhibited directional selectivity during the control condition became pan-directional 1 min after GABA injection in area MT. After 14–15 min, the cells recovered their directional selectivity (for examples, see Figs. 6, 7 in Jansen-Amorim et al. 2011).

Inactivation of V4 caused both an increase (72.2%) and a decrease (27.7%) in direction circular tuning of V2 cells. In addition, 72.2% of these cells decreased while 27.7% increased their orientation selectivity after GABA injection, thus presenting an opposite effect for direction and orientation circular tuning. The number of cells that increased their orientation index (OI) was similar to the number that decreased their directionality index (DI). During the first 5 min after V4 GABA inactivation, approximately 46% of V2 neurons changed their direction selectivity profile. Half of these cells became selective for the direction of stimulus motion, while the other half lost their tuning.

Following inactivation of area MT, V2 neurons also showed diverse responses: the large majority (62%)

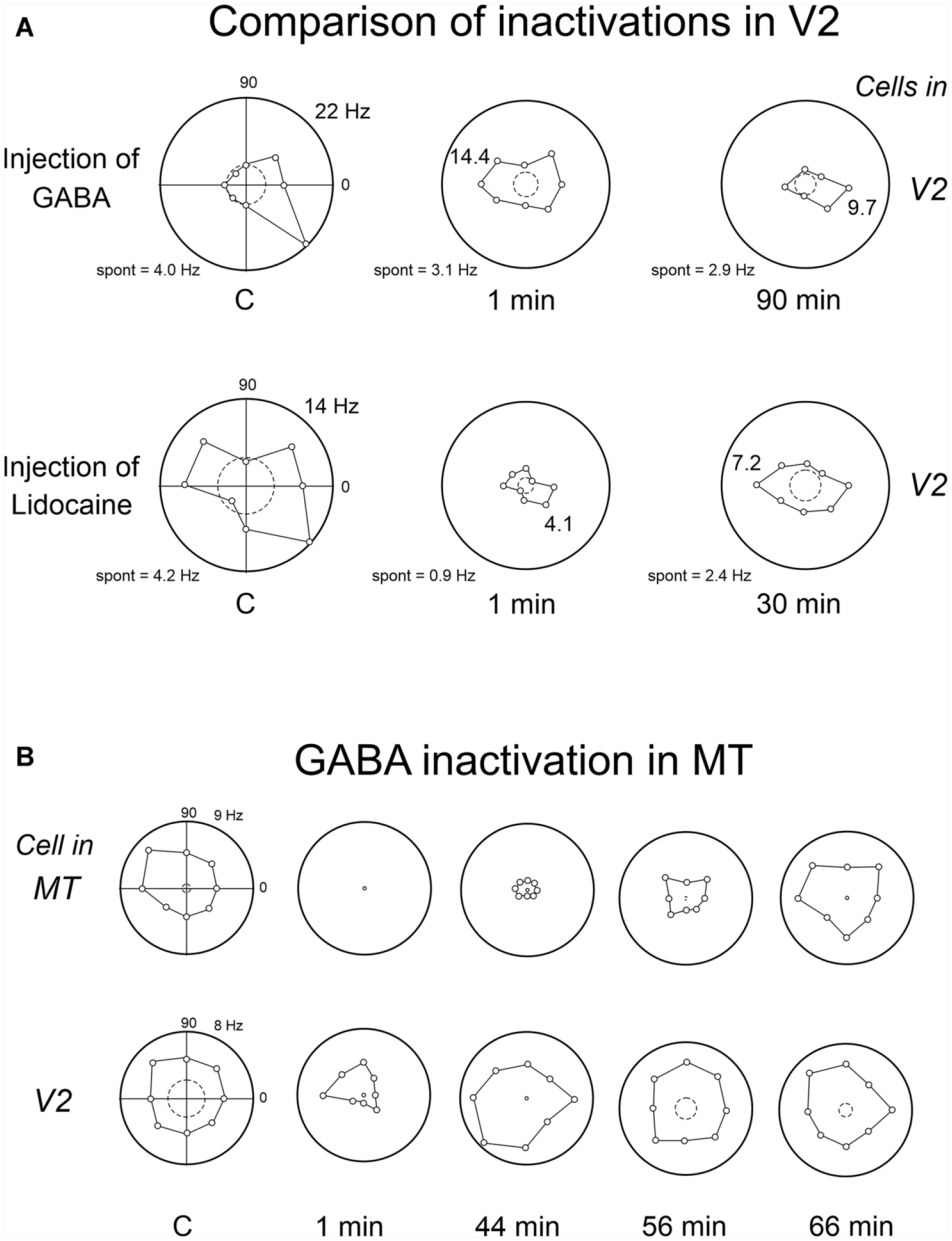


Fig. 3 Changes in V2 response after inactivation. **a** Comparison of changes in V2 selectivity after injections of GABA and lidocaine. **b** Comparison of the changes at the injection site in MT and at the corresponding topographical location in V2. The polar diagrams displaying the mean response rates computed from the regions corresponding to the receptive fields for different directions of movement, at 45° steps and at different times. Dotted-line circles in the center of the polar diagrams correspond to the mean spontaneous activity of the cell. The radii of the external circles indicate the maximum value of the cell's response obtained throughout recording. The numbers inside the circle indicate the maximum firing rate of the response. In (**a**), the effect of GABA lasts longer than that of Lidocaine. In B, there is a parallel between the inactivation and the V2 response, with a recovery by 66 min. (Data from Jansen-Amorim et al. 2011 and 2013)

increased their direction tuning (compared to 38% that decreased their tuning), while some neurons changed their orientation selectivity. The time course and the recovery of neuronal responses were similar for MT and V4 inactivation. During the first 15 min of inactivation, we observed a clear inhibition of the V2 cell response. In 6% of the cells, a general suppression of activity was observed with no associated change in direction selectivity.

Finally, the inactivation of the pulvinar induced both excitatory and inhibitory changes in V2 neurons. All cells recorded ($N=33$) had their receptive fields within 10 degrees of the foveal representation. Most cells in V2 (67%) showed changes in the response to visual stimuli and/or spontaneous activity. A change in the direction and/or orientation selectivity was observed in 91% of the cells. Most of these neurons (55%) showed changes in both their orientation and directionality indexes, 21% showed changes only in their orientationality and 15% only in directionality.

Table 1 summarizes the effect of V2, V4, MT and pulvinar inactivation on V2 neurons. Cortical injections caused changes in most (72–80%) V2 cells, while injections in the pulvinar affected approximately 67% of V2 cells. The injections caused differential changes in spontaneous activity at the intermediate and late phases of inactivation. The changes in the visual response in most (58–77%) V2 cells were mainly in the initial and intermediate phases of inactivation. Many (28–72%) V2 cells showed a significant change in direction selectivity, with most of them showing

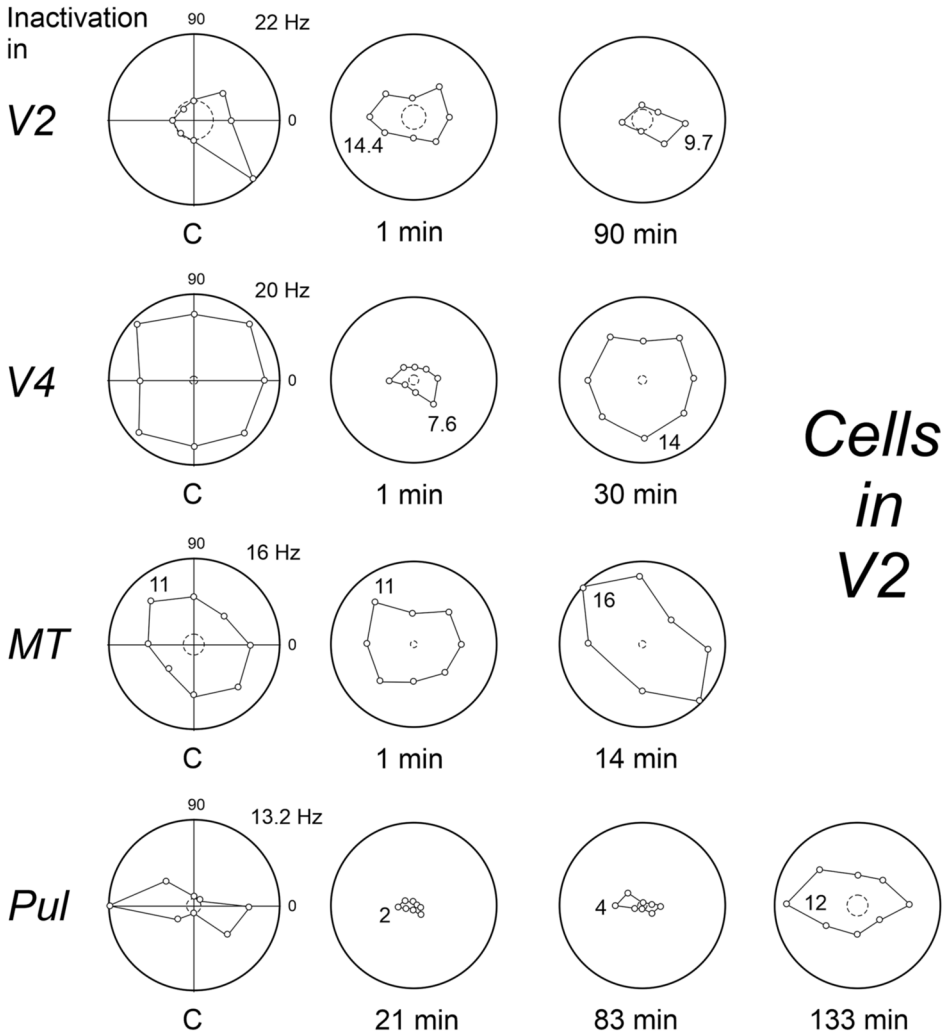


Fig. 4 Changes in V2 response after V2, V4, MT and pulvinar inactivation. The polar diagrams displaying the mean response rates computed from the regions corresponding to the receptive fields for different directions of movement, at 45° steps and at different times. Conventions as in Fig. 3. (Data from Soares et al. 2004 and Jansen-Amorim et al. 2011, 2012 and 2013)

a decrease in direction selectivity in the initial and intermediate phases of inactivation. A smaller number of cells showed an increase in direction selectivity after inactivation.

Time course of V2 activity after inactivation across brain regions

In a typical inactivation experiment, one expects to see a transient effect on neuronal activity that disappears with time. Previous inactivation experiments have shown a very short time effect on neuronal activity after local GABA inactivation of the cortex (Crook et al. 1996, 1997; Martin et al. 1993). Other studies have shown that the duration of inactivation is directly proportional to the injected volume and to the concentration of the GABA solution. Repeated injections increase the duration of inactivation and the strength of its effect (Hupé et al. 1998; Martin et al. 1993; Casanova et al. 1992).

In our experiments, GABA inactivation of areas MT, V4, V2 and of the pulvinar nucleus produced early (up to 20 min) and late (20—160 min after injection) effects on V2 cells. We observed an early general decrease in neuronal excitability due to a suppression in both spontaneous and stimulus-driven activities. On the other hand, late effects generally reflected changes in the orientation and/or direction selectivity of V2 cells. A loss of direction or orientation selectivity was observed during the first 25 min after inactivation. As an intermediate effect, we observed a stimulus-driven increase in activity inside the classical receptive field 15 to 25 min after injection, which was followed by a longer-lasting decrease in neuronal excitability. Different areas showed different time courses and durations of the decrease in directional selectivity. The duration of the effects varied from neuron to neuron. MT inactivation revealed shorter effects than those in the pulvinar.

Figure 5 shows the population results (based on data from all of our experiments) regarding the time course of V2, V4, MT and pulvinar inactivation on V2 neuronal activity.

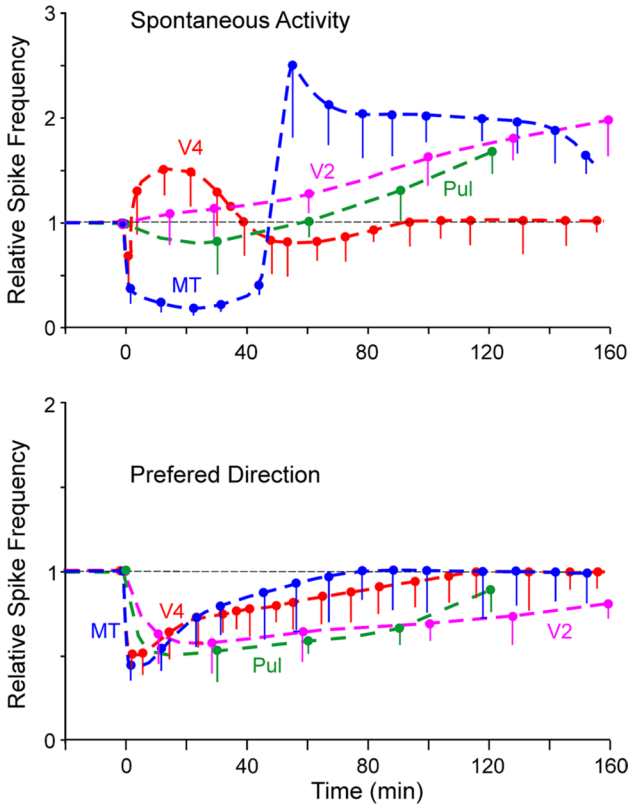


Fig. 5 Effects of GABA injected into areas MT, V4, V2 and pulvinar and the time course of changes in the spontaneous (**a**) and stimulus-driven activity (**b**) of neurons in area V2. The curves were fitted to the mean relative firing rate (filled circles) for each time point after inactivation. On average, the 2 µL injections in each area had a similar effect on the stimulus-driven activity at the preferred direction. However, the effects were different from those on the spontaneous activity. Injections of 2 µL induced an immediate decrease in the response to the preferred direction (**b**), as well as a decrease followed by an increase in the spontaneous activity (**a**). The duration of the effect on the stimulus-driven activity varied from area to area, and it lasted longer after GABA injection in V2 and pulvinar than after injections in V4 and MT. While injections in V2 and pulvinar gradually increased spontaneous activity, the injections in V4 and MT showed opposite effects during the first 30 min, reversing after 50 min. Vertical bars on each data point correspond to the standard error of the mean. (Data from Soares et al. 2004 and Jansen-Amorim et al. 2011, 2012 and 2013)

Specifically, we depict the time course for both spontaneous activity (upper panel) and for the response to the preferred direction of motion (lower panel) as a function of inactivation onset. The effect of the GABA injection in these four areas lasted for at least 80 min (up to around 160 min). The injections caused differential changes in spontaneous activity at the intermediate and late phases of inactivation. The inactivation in all areas caused a decrease in the spontaneous activity during the first 5 min. From 5 to 50 min, we observed increases in neuronal activity for V4 and V2 and decreases for MT and the pulvinar. After 50 min, inactivation in all areas (except in V4) caused an increase in the spontaneous activity. Many cells showed significant changes in direction selectivity, with most cells showing a decrease in direction selectivity in the initial and intermediate phases of inactivation. Greater amounts of injected GABA yielded longer-lasting neuronal inactivation. Consequentially, it also required longer recovery intervals (Hupé 1995; Hupé et al. 1999). Neurons required approximately 40 min to recover to baseline after a 0.9-µL injection of a 0.1 M GABA solution (Hupé et al. 2001). This recovery period was similar to the time required for V2 neurons to return to baseline activity after a 0.8–1.0 µL GABA (0.25 M solution) injection into areas MT and V4. Considering the extent of areas MT and V4 (Fiorani et al. 1989; Piñon et al. 1998), our findings corroborate predictions made by Hupé (1995) and Hupé et al. (1999) regarding the relationship between injected volume and the occupied extracellular volume. We estimate that injection volumes between 0.8 and 10 µL would inactivate, respectively, between 2.3 and 33.3% of area MT and 0.7–3.22% of area V4.

In Soares et al. (2004), we made multiple 1–2 µL injections of a 0.5 M GABA solution at three different depths, 500 µm apart, to inactivate a large volume of the pulvinar. Neuronal activity decreased immediately after injection and only returned to its original level after 70–150 min. This long-lasting action could be due either to the high concentrations of GABA used or to the large volumes injected. The histological processing performed after 5–8 inactivation sessions showed a lesion in the region of GABA application, which may have been caused by the large volume injected or by repeated injections at the same site. Casanova and collaborators also observed lesions after more than three injections at the same site in the cortex (Casanova et al. 1992). Lesions due to the injection were more common in the pulvinar than in areas V4 or MT. This is probably due to fact that in the pulvinar we targeted the same stereotaxic coordinates across experiments, which increased the chance of tissue lesion. Experiments with a given animal were discontinued once we observed any deterioration in the quality of the recordings (Soares et al. 2004). This was less of an issue in V4 and MT, where cannula position varied across experiments. We do not believe that potential tissue lesions compromised our data in any significant way for two main reasons: (1) in most experiments we were able to recover robust neuronal activity at the injection site, indicating that cortical tissue remained healthy. (2) we performed experiments with the same animal every 1–2 weeks. Across experiments, we were able to observe healthy neuronal activity at the area was targeted for inactivation.

In the pulvinar, GABA can act upon several structures that constitute the complex synaptic glomeruli of its neurons. GABA can hyperpolarize the postsynaptic cells that project to the visual cortex. In the case of the excitatory

pulvinar projections, GABA injection could cause V2 cells to lose this direct excitatory drive. Pulvinar projections could also play an inhibitory role by directly activating inhibitory V2 interneurons. Indeed, we observed that the majority of V2 cells decrease their visually-driven response after GABA injection in the pulvinar. This suggests that inhibitory projections may be a critical component of the pulvinar's effect on V2. The prolonged effect of pulvinar GABA injections on V2 activity could also be explained by the influence of GABA on pulvinar neurochemistry. In this case, the injection of large amounts of GABA could inactivate the glutamic acid decarboxylase enzyme (GAD), thereby reducing the synthesis of endogenous GABA. In cultured cells of chicken embryos, the administration of GABA reduces the expression of GAD in a dose-dependent manner. After the withdrawal of GABA, the activity of this enzyme takes several hours to return to its normal levels (de Mello 1984).

Hypothetical circuit

Figure 6 lays out a model of a hypothetical circuit, which takes into account the essential features we observed in our experimental data involving the inactivation of feedback circuits. Corticocortical connections in the visual system seem to be solely excitatory (Salin and Bullier 1995). Feedback circuits can thereby influence receptive field properties of upstream visual areas by targeting both excitatory and inhibitory intrinsic neuronal circuits. The most common effect during the first 10 min after GABA injection in MT, V4 or the pulvinar was a decrease in V2 excitability, both spontaneous and stimulus driven. Our model is based on assumptions that rely on a cascade of events that start in upstream areas and then affect V2. Initially, the injected GABA would produce an inhibitory effect on V4, MT and pulvinar neurons containing $GABA_A$ receptors on their surface (Sato et al. 1995, 1996). Subsequently, there would be a decrease in neurotransmitter released within these areas. In MT and V4, we would observe this decrease both in superficial and deep cortical layers. The diminished feedback excitatory drive would account for the initial decrease in spontaneous and stimulus-driven activity of V2 neurons. Note that the decreased excitatory drive would also suppress the activity of intrinsic inhibitory interneurons in V2. Due to the role of inhibitory interneurons in shaping orientation and direction tuning, less inhibition would eventually lead to a decrease in selectivity, explaining why some cells were orientation or direction selective during control and then became pan-directional after injection.

However, we also observed neurons that were pan-directional under control conditions, but which became selective after inactivation of upstream areas. We believe

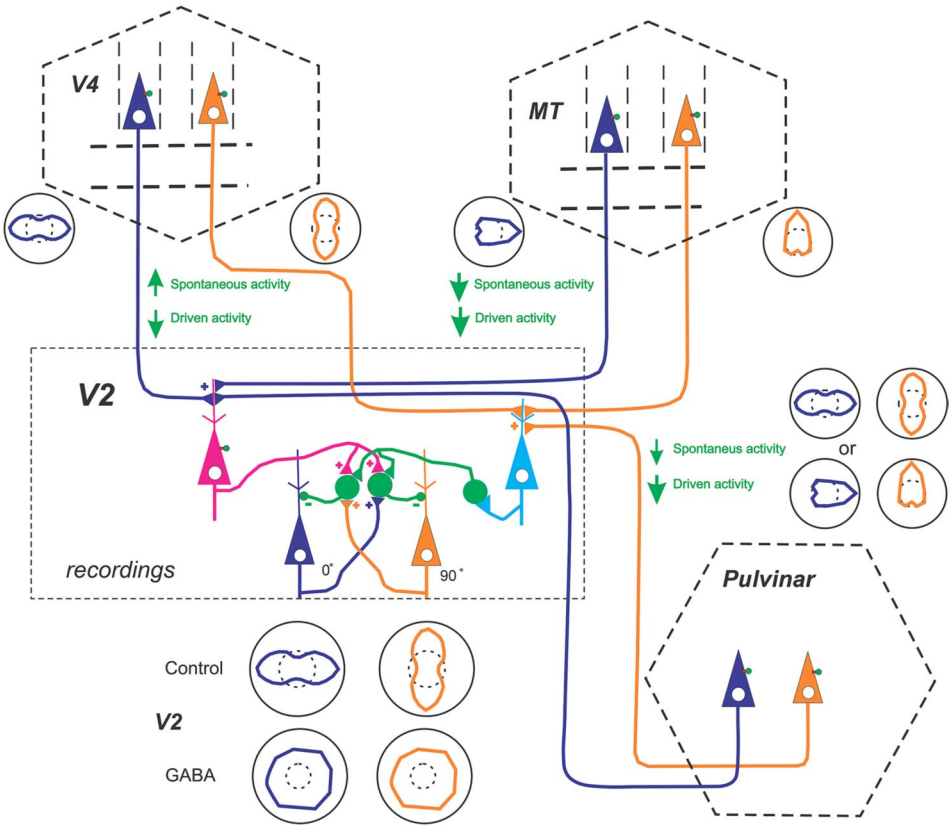


Fig. 6 Hypothetical circuit depicting the effect of feedback circuits on V2 selectivity. Schematic diagram of cortical and pulvinar circuits capable of altering V2 selectivity after GABA injection in MT, V4 or pulvinar. Direction selective neurons in these latter areas sense the injected GABA by means of $GABA_A$ receptors on their surface and thereby decrease their firing rate. Consequentially, their projecting axons decrease their levels of excitatory neurotransmitter released in V2, leading to a decrease in firing rate at their V2 target neurons

this can be explained by a nonsymmetrical influence of feedback projections upon columns surrounding our V2 recording site. A pan-directional neuron, with supposedly balanced inhibition arising from surrounding cortical columns representing the full spectrum of selectivities, has now a biased inhibition profile that generates some level of selectivity for orientation or direction.

In a more general context, we believe that the feedback projections are important in engaging the neuronal activity of cortical modules within a wider brain network. For example, the selectivity of V1 neurons may be strongly dependent on feedback from downstream areas. This is schematically illustrated in Fig. 7 for a network representing a small region located in the upper left visual field (Gattass et al. 1990). Retinal ganglion cells project to the lateral geniculate nucleus (LGN) and to the superior colliculus (SC). LGN neurons have direct access to the cortex, primarily projecting to cortical area V1. On the other hand, SC neurons access the cortex indirectly; first they project to the pulvinar, which subsequently projects to several cortical regions. From its very early stages, visual processing occurs through both serial and parallel pathways. Moreover, mostly every node shown in Fig. 7 is able to send feedback projections to the same areas it received feedforward input.

Area MT is generally considered the main hub for the analysis of visual motion (Dubner and Zeki 1971; Albright 1984; Britten et al. 1992). Movshon and Newsome (1996) suggested that neurons in MT inherit their directional selectivity from areas V1, V2, and V3. Their argument is that the neurons from these three MT-projecting areas already exhibit selectivity to the direction of stimulus motion. Indeed, overall responsiveness and direction selectivity of MT neurons are greatly reduced after V1 inactivation (Girard et al. 1992; Rodman et al. 1989). However, our results showing that MT feedback projections can considerably change the orientation/direction selectivity of an upstream early visual area (e.g., V2) offer a complementary mechanism to the notion that serial hierarchical processing and lateral interactions are the only pathways responsible for the construction of receptive field properties. Indeed, if cortical interactions can be explained by recurrent dynamical networks as suggested in Fig. 7, then multiple cycles of feedforward and feedback iterations between V1, V2, V3 and MT (and possible V4) may play an important role by which selectivity to orientation and direction emerges across

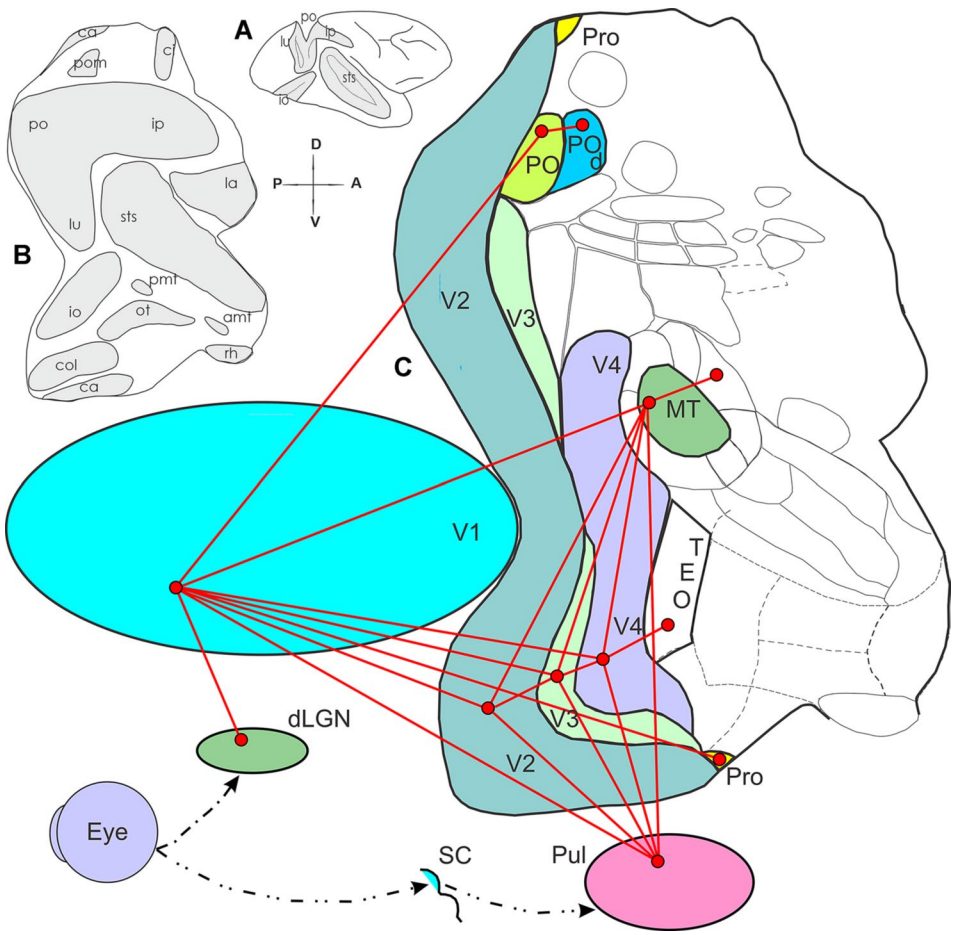


Fig. 7 Cortical feature selectivity built by means of recurrent dynamic networks. The right hemisphere (**a**), shown with opened sulci, underwent a physical flattening procedure (**b, c**). The reiterating highly interconnected network (**c**) is depicted on a two-dimensional reconstruction of the monkey cortex, showing striate and extrastriate visual areas. Axons from ganglion cells in the eye project to the superior colliculus (SC) and the dorsal lateral geniculate nucleus (dLGN). Cells of the dLGN project mainly to the primary visual cortex (V1), while cells from the SC project to the pulvinar, which in turn projects to several cortical areas. Note the extensive topographically organized feedforward and feedback connections, which may play an important role in determining the activity of each module in the network

Table 1 Effect of injections of GABA on V2 neurons

Area injected	V2 (intrinsic)	V4	MT	Pulvinar
Number of cells studied	24	18	50	33
% of cells affected in V2	60%	78%	64%	64%
Spontaneous activity				
Initial phase (0–5 min)	–	–	–	–
Intermediate phase (5–40 min)	–	–	–	–
Late phase (> 60 min)	< = >	< = >	< = >	< = >
Visual Response				
Significant Change	58,3% (14/24)	77,7% (14/18)	64% (32/50)	64% (21/33)
Initial phase (0–5 min)	–	– – / + +	–	– / + + +
Decrease	33,3%	38,8%	34%	27%
Increase	24,8%	38,8%	28%	39%
Intermediate phase (5–40 min)	–	+	+ +	+
Late phase (> 60 min)	< = >	< = >	< = >	< = >
Orientation Selectivity				
Significant Change	20,8% (5/24)	38,8% (7/18)	36% (18/50)	76% (25/33)
Initial phase—Decrease	12,5% (3/24)	22,2% (4/18)	14% (7/50)	49% (16/33)
Increase	8,3% (2/24)	16,6% (3/18)	22% (11/50)	27% (9/33)
Intermediate phase (5–40 min)	–	+ +	–	+ +
Late phase (> 60 min)	< = >	< = >	< = >	< = >
Direction Selectivity				
Significant Change	37,5% (9/24)	38,8% (7/18)	28% (14/50)	72% (24/33)
Initial phase—Decrease	20,8% (5/24)	22,2% (4/18)	22% (11/50)	33% (11/33)
Change				
Increase	16,6% (4/24)	16,6% (3/18)	6% (03/50)	37% (12/33)
Intermediate phase (5–40 min)	–	–	–	+ +
Late phase (> 60 min)	< = >	< = >	< = >	< = >

Conventions: – decrease; + increase; < = > variable; – / + decrease followed by increase

multiple cortical regions. Thiele et al. (2004) injected the GABA blocker bicuculline-methiodide into MT to study the contribution of local circuits to direction selectivity. Direction selectivity was preserved during the late phase, but was abolished during the initial 50 ms of the response. This suggests that MT neurons are able to locally compute motion direction shortly after stimulus presentation. However, after that time window MT relies on input from upstream cortical areas to further process motion. In a subsequent work, the same group injected a more specific $GABA_A$ blocker (gabazine) into MT to observe the effect on local direction selectivity (Thiele et al. 2012). They analyzed longer time windows and observed that inhibition indeed played a role in increasing selectivity to the direction of stimulus motion. Importantly, the authors contrasted the role of the GABAergic system with that of the cholinergic system in shaping MT response properties, such as direction selectivity, the robustness of neuronal firing and the reliability of the responses. As predicted, the GABAergic system was more associated with shaping the selectivity to stimulus features, while the cholinergic system paralleled the effects observed during attentional modulation.

Concluding remarks

We work with the notion that cortical modules are essential processing units of visual information. This premise is particularly relevant to the present work since several processes of cortical computation, such the construction of orientation and direction tuning are associated and bound to cortical columns, one of the most prominent modules found in the primate cortex. Cortical columns were first discovered in Area 2 of the somatosensory cortex by Vernon Mountcastle (Mountcastle 1957). The traditional view is that columns rely upon ascending and intrinsic circuits in order to decode specific attributes of the sensory stimulus. In the visual system, columns were first described by David Hubel and Torsten Wiesel (Hubel and Wiesel 1968).

Hubel and Wiesel also proposed a hierarchical model for visual processing, which is the basis for the serial processing of attributes of the visual stimulus. For example, neurons with concentric receptive fields found in the dorsolateral geniculate nucleus (dLGN) project colinearly to area V1 to build orientation selective cells. Subsequently, these cells would contribute in shaping the activity of complex

and hypercomplex cells (Hubel and Wiesel, 1968), which in turn would be instrumental to the neuronal responses of the inferotemporal cortex, such as the face cells described by Gross and collaborators (Gross et al. 1972).

Concomitantly to these findings, several groups described another important feature of cortical organization: vision is processed through several areas, each containing a topographically organized map of the visual field (Daniel and Whitteridge 1961; Allman and Kaas 1974a, b; Gattass and Gross 1981; Gattass et al. 1978a, b, 1990). Moreover, the feedforward and feedback connectivity across these areas we also found to be topographically organized (Sousa et al., 1991; Gattass et al., 2005). Finally, columns and larger-scale modules are embedded within and across the topographical representation of the various areas, and are associated with the selective processing of attributes such as motion or color of the stimulus (Zeki et al., 1978). This architecture of cortical organization creates the basis for parallel processing in the visual cortex, and offers one additional dimension of complexity to the original model of a serial feedforward framework as proposed by Hubel and Wiesel (1968).

When considering cortical computation in general, and the generation of orientation and direction selectivity in particular, we have to take into account the role of feedback projections within the perspective that cortical networks operate both serially and in parallel, that they are recurrent, and that the dynamics that emerges from this architecture may be paramount to the response properties what we observe at the single neuronal level in early visual areas.

Funding This study was supported by grants of the Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq), FAPERJ (FAPERJ E-26/210.917/2016—PRONEX), and FINEP (0354/16).

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