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GABA inactivation of area V4 changes receptive-field properties of V2 neurons in *Cebus* monkeys

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ABSTRACT

To investigate the contribution of feedback circuits from area V4 to the receptive-field properties of V2 neurons, we used tungsten microelectrodes to record extracellular single units in these visual areas, before and after pressure injections of a solution of 0.25 mol/L of GABA in two anesthetized and paralyzed *Cebus apella* monkeys. The visual stimulus consisted of a single bar moving in one of eight directions. Using a device made of four stainless steel pipettes and one central tungsten electrode, we inactivated, with different amounts of GABA, topographically corresponding areas of V4, while studying V2 neurons. We studied a total of 36 V2 neurons during six sessions of GABA injections into area V4. GABA inactivation of visual area V4 produced a general decrease in the excitability of the neurons, which included a decrease in spontaneous and driven activities, followed by changes in direction selectivity. The changes in selectivity were toward an increase in directional selectivity and decrease in orientation selectivity. Thus, feedback connections arising from V4, an area of the ventral steams of visual information processing, are capable of not only modulating the spontaneous and driven activity of V2 neurons, but also of modifying V2 receptive field properties, such as its direction and/or orientation selectivity.

Introduction

In monkeys, visual cortical information has been considered to be the result of ascending projections and local processing through a series of hierarchical cortical visual areas (Hubel and Wiesel, 1968). At each stage, intrinsic horizontal (or lateral) connections reinforce the interplay among groups of neurons with similar properties (McGuire et al., 1991). It is assumed that the retino-geniculo-cortical pathways and the so-called "ascending" cortico-cortical association pathway provide the principal excitatory drive to cortical neurons in both the primary and the "higher-order" visual areas. On the other hand, the extensive cortico-cortical "descending" projections from the higher-order visual areas to the lower-order ones have a modulatory role in the processing of visual information (Felleman and Van Essen, 1991; Zeki and Shipp, 1988). The full network of projections among higher-order and primary areas, however, is likely to be complex, and it is still only partially understood.

Connections between cortical visual areas have been classified as feedforward or feedback, based on the laminar origin and axon termination of the projections (Felleman and Van Essen, 1991; Rockland and Pandya, 1979; Tigges et al., 1977, 1981). Feedback projections are divergent and have a less precise retinotopic organization than feedforward ones (Rockland et al., 1994; Salin and Bullier, 1995). Feedback connections are excitatory and make synapses almost exclusively with excitatory post-synaptic cells at their dendritic spines (Johnson and Burkhalter, 1996). The exuberance of the feedback connections between different cortical areas, the speed of electric signal propagation along these connections, and the latency of visual response all suggest that feedback connections could affect the functional performance of neurons beyond a "modulatory" role (Angelucci et al., 2002; Borra and Rockland, 2011; Bullier, 2001; Hupé et al., 1998; Lamme et al., 1998).

The prestriate visual area V4 is an area of the ventral stream of visual information processing. It is strongly involved in shape and color perception and it contains an abundance of color-coded cells (Hubel and Livingstone, 1987; Tanigawa et al., 2010). It was defined as a strip of cortex from 10 to 12 mm in width prior to V3 that extends dorsally from the anterior margin of the lunate sulcus. V4 contains a topographically organized representation of 35 to 40° of the central visual field. The representation of the central portion of the visual field is greatly expanded compared to the periphery. The receptive field size increases with increasing eccentricity, while the cortical magnification factor decreases (Gattass et al., 1988; Piñon et al., 1998).

V4 receives and projects to visual area V2 (Felleman et al., 1997; Nascimento-Silva et al., 2003; Rockland et al., 1994; Ungerleider et al., 2008; Zeki and Shipp, 1989). The projections from V2 to V4, up to 30° of eccentricity, originate from the supragranular and

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infragranular layers from cytochrome oxidase (CytOx) thin bands and from CytOx-poor interbands of V2. Beyond 30°, the projections from V4 to V2 from the thin bands and interbands are restrict to the infragranular layers (Nascimento-Silva et al., 2003).

In the present work, we investigated whether feedback projections from area V4 directly interfere with orientation and direction selectivity of V2 neurons. We studied the receptive field properties of V2 neurons before and after the inactivation of a large topographically corresponding portion of area V4 in the capuchin monkey (*Cebus apella*). Several aspects of the visual system of this New World monkey, including photoreceptor distribution (Andrade da Costa and Hokoç, 2000); thalamic organization (Gattass et al., 1978a, b, 1979); morphology and physiology of the M and P ganglion cells (Lee et al., 2000; Yamada et al., 1996); intrinsic circuitry of V1 (Amorim and Picanço-Diniz, 1996a,b, 1997); and the topographical characteristics of areas V1, V2, MT, and V4 (Fiorani et al., 1989; Gattass et al., 1987, 2005; Piñon et al., 1998; Rosa et al., 1988), have been studied for almost three decades, making this monkey a suitable experimental model for this study. In addition, we recently studied the effect of GABA inactivation of visual area MT on the direction and orientation selectivity of V2 neurons (Jansen-Amorim et al., 2011), allowing a direct comparison of GABA on the feedback connections from MT and V4. Preliminary results have been presented in abstract form (Jansen et al., 2000).

Material and methods

Animals

Two adult male *C. apella* monkeys were used in once-weekly recording sessions, for a total of six sessions. All experimental protocols were conducted following National Institutes of Health (NIH) guidelines for animal research and were approved by the Committee for Animal Care and Use of the Instituto de Biofísica Carlos Chagas Filho, Federal University of Rio de Janeiro (2011).

Preparation

Prior to the recording sessions, a head bolt and a recording chamber were implanted on the skull of each monkey, under anesthesia and aseptic conditions. We positioned the recording chamber to enable access to areas V4 and V2, using stereotaxic coordinates and the position of the cortical sulci. During each recording session, the animals were anesthetized with a 5% ketamine hydrochloride solution (30 mg/kg, *i. m.*; Ketalar®, Parke Davis, Rio de Janeiro, RJ, Brazil) and maintained with a mixture of 70% nitrous oxide and 30% oxygen, combined with a continuous intravenous infusion of fentanyl citrate (0.003 mg/kg/h). The monkeys were also immobilized with pancuronium bromide (0.1 mg/kg/h). Electrocardiogram readings, body temperature, and end-tidal CO_2 were monitored continuously. Post-surgical analgesia was administered for three days with a fentanyl skin patch (Durogesic®, Janssen-Cilag, São Paulo, SP, Brazil).

Visual stimulation

Prior to the recording sessions, gas-permeable contact lenses were used to focus the eyes on a computer monitor placed 57 cm in front of the animal. The positions of the blind spot and fovea were plotted onto the computer screen with a reversible ophthalmoscope. The stimulus consisted of a thin white bar ($18 \times 0.5°$) that appeared in four random orientations (0°, 45°, 90°, or 135°), crossed the screen in a direction perpendicular to its orientation at a velocity of 6º/s, and passed through the receptive fields of all the recorded neurons. We continuously tested the direction of motion selectivity before and after GABA injection. Note that we did not segregate orientation selectivity from axis-of-movement selectivity. Therefore, the moving bar in the configuration was used to determine both the direction and axis of movement selectivity.

Recording sessions

To locate the topographically corresponding portions of areas V4 and V2, we penetrated the cortex with 1 MΩ-impedance tungsten microelectrodes, using stereotaxic coordinates and sulcal landmarks (Piñon et al., 1998; Rosa et al., 1988). The corresponding V4 and V2 stereotaxic coordinates were used to allow access to the central lower field representation of areas V4 and V2 in subsequent recording sessions. After the inactivation site in area V4 was located, a single microelectrode was replaced by an inactivation/recording system.

Inactivation devices

The system consisted of four stainless steel tubes (external diameter: 200 μm) mounted around a large central tube (external diameter: 800 μm), which served as a guide tube for a tungsten microelectrode. A pneumatic pico pump (Model PV 820, World Precision Instrument, Sarasota, FL, USA) delivered the GABA solution to the two external stainless steel tubes though a polyethylene connection. With this system, it was possible to deliver 1–4 μL of a 0.25-mol/L GABA solution.

After the corresponding topographical site was localized in the V2 area, a single microelectrode was replaced by a two-electrode recording system, with the electrodes placed 800 μm apart, to record V2 neuron activity. Single-unit activity from area V2 was recorded using tungsten microelectrodes. The activity was amplified and filtered, and single spikes were sampled by a waveform discriminator system (SPS-8701, Signal Processing System, Malvern, VIC, AU). Extracellular single-unit spike events were stored using CORTEX software (Laboratory of Neuropsychology, NIMH/NIH, Bethesda, MD, USA) for offline analysis. The receptive fields were initially localized and mapped using a hand-plot mapping procedure.

The receptive field automatic mapping procedure was based on computing the latency-corrected neuronal activity in response to elongated bars moving in one of eight directions of motion. Initially, Peristimulus Time Histograms (PSTHs) were computed based on 10 stimulus presentations, using a bin width of 10 ms. Fig. 1A illustrates the PSTHs of a single unit in response to bars moving at 0° and 180°. Single-trial spike trains used to produce the PSTHs were aligned to stimulus onset. The PSTHs were then smoothed, using a normal convolution filter of 200 ms time-window, resulting in the Time Spike Density Function (TSDF). The TSDF characterizes the dynamics of neuronal firing pattern well, as it is a continuous and derivable function (Fig. 1B).

Sensory transduction and synaptic delay impose latency in V2 neuronal response. In order to enable the transformation of the TSDF into the Space Spike Density Function (SSDF), we were required to estimate the response latency of the neuron, and thereby correct the TSDF accordingly. As can be seen in Fig. 1B, the TSDFs (thin and dotted lines for the 0° and 180° directions of motion, respectively) were shifted forward in time, corresponding to the estimated 70 ms response latency of the neuron.

For the SSDF, this corresponds to a correction in the space domain. Thus, in order to integrate the Spike Density Functions (SDFs) at the space domain, the time-corrected functions obtained for bars moving in opposite directions were flipped along the horizontal axis, resulting in a homogeneous space-function.

The averaged TSDFs for one particular axis of movement were thereby converted from time to spatial coordinates (Fig. 1C). Note that the SSDF obtained for one axis of motion cannot provide information regarding receptive field position for the orthogonal axis. Therefore, the SSDF obtained for the 0°–180° axis of motion was smeared (stretched) throughout the 90°–270° axis. The interpolation

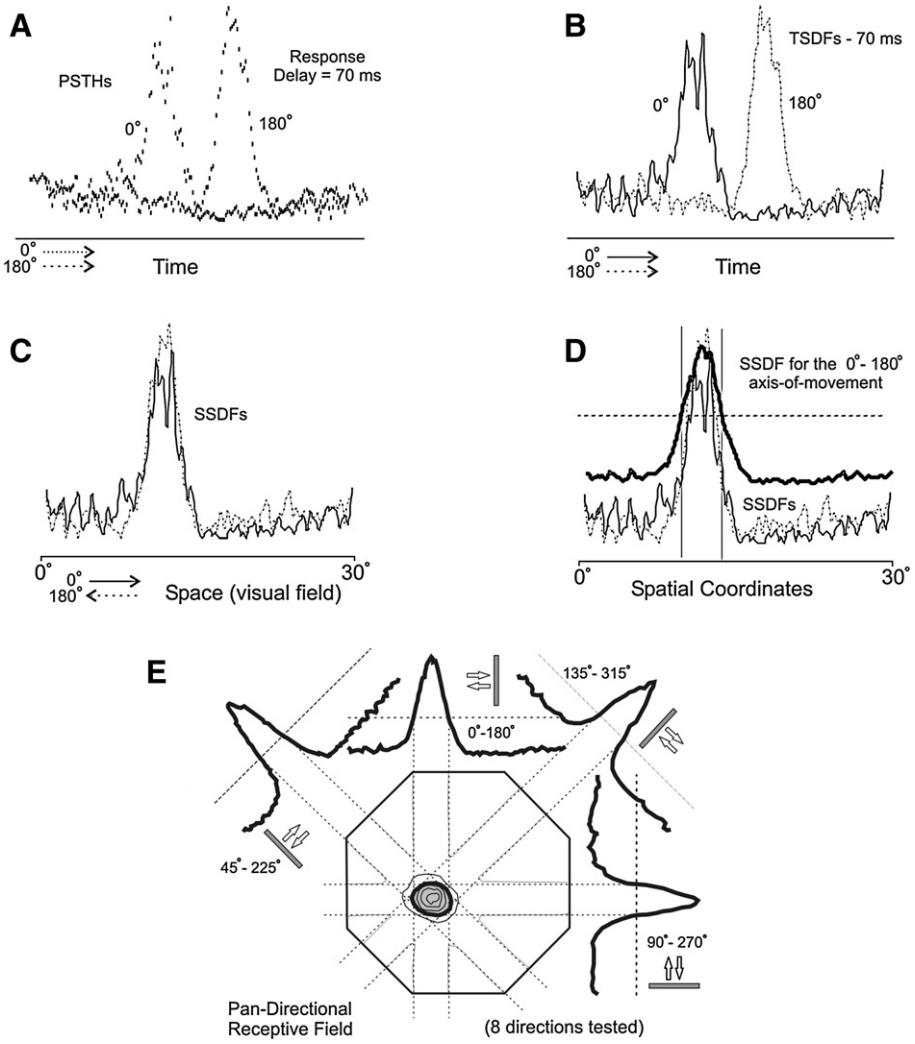

Fig. 1. Steps used to determine a quantitative map of neuronal response. A: PSTHs; B: TSDF corrected for delay; C: SSDF in spatial coordinates (from each direction); D: Sum of the SDF for the axis-of-movement and SSDFs for each direction; E: Quantitative Intersection Map for a pandirectional cell (for details, see text).

of the smeared SSDFs in the space domain for each axis of movement was then used to reveal the location of peak neuronal firing (Fig. 1D). Averaging was performed pixel by pixel after aligning all individual backprojections at the proper orientation, resulting in an averaged backprojection of the neuronal response, named here the Quantitative Intersection Map. The averaged backprojection was then smoothed by a 2D-normal convolution with a 60 ms time-window. A quantitative receptive field intersection map reveals both the size and the location of a single-unit receptive field. Quantitative receptive field mapping of a pandirectional cell is shown in Fig. 1E.

Inactivation paradigm

Area V4 was inactivated until virtually all recorded activity at the injection site was silenced. Data collection resumed immediately before and after the injection, and several blocks of recording protocols were acquired until recovery of V4 cellular activity. The recording sessions typically continued for 24–36 h.

Recordings from areas V4 and V2 were obtained before (control) and during several sequential time blocks at different time-points (1–150 min) after GABA inactivation of area V4. The neuronal responses at the injection site and at the topographically corresponding region in area V2 were analyzed by comparing an effective direction-selective polar plot (polargram) with a post-stimulus raster in a histogram plotted as the SDFs of the neuronal discharge.

Data analysis

The changes in V2 neuron direction selectivity before and immediately after GABA injection into area V4 were also evaluated using analysis of variance (ANOVA) (MATLAB toolbox, MathWorks Inc., Natick, MA, USA). To determine the significance of changes in the directionality of V2 neurons in response to visual stimulation, data from each stimulus direction were submitted to a one-way ANOVA, followed by a post-hoc least significant difference test. To determine the statistical significance of the effects on V2 neuron direction selectivity before and after GABA injection into area V4, cell activity under each condition was analyzed using a two-way ANOVA. We also performed a statistical evaluation of the recovery after GABA injection by evaluating cell activity in the control condition, before GABA injection and after the GABA-induced effects had vanished, using a two-way ANOVA. Finally, some cells that did not exhibit a statistically significant directional component showed, instead, a significant bidirectional response. By grouping the conditions with the same stimulus orientation moving in opposite directions, we tested the bidirectional component. The four groups of data generated by this procedure were then submitted to a one-way ANOVA to

evaluate changes in the selectivity of the cell for axis of movement. Probability values mentioned in the text, which were related to the changes in direction selectivity, were evaluated by ANOVA, unless specified otherwise in the text.

Selectivity of the neurons was examined with a standard test of circular tuning in order to determine the magnitude of the GABA-induced changes in both direction and orientation selectivity across the population. The orientation selectivity index (OI) was calculated for each neuron according to the following formula, proposed by Sato et al. (1996):

$$OI = \left[\left(\Sigma\ R_i \sin(20_i)\right)^2 + \left(\Sigma\ [R_i \cos(2\ 0_i)\right)^2\right]^{0.5} / \Sigma\ R_{i,}$$

where R_i represents the magnitude of response to each stimulus orientation, 0_i. The rate of spontaneous activity, which was measured for the 700-ms window before stimulus presentation, was subtracted from the stimulus-driven responses. The response to each stimulus orientation is expressed as a vector with direction 20_i and length R_i. This index varies between 1 and 0, with an OI value of 1 indicating complete selectivity to a particular orientation, while a value of 0 indicates equal responsiveness to all orientations.

Direction selectivity indices (DI) were also quantified by the directional index, as described by Wang et al. (2000). An index of 1 indicates sharply tuned cells, whereas an index of 0 indicates non-tuned cells. We used a paired Student's *t*-test to evaluate changes in the mean OI and DI in the cell population. Using this test, we also evaluated the recovery time after GABA injection by comparing cell activity in the control condition, before the GABA injection and after the GABA-induced effects had vanished. In addition, we used the individual index values to reveal any bias in the population. We considered a change greater than 0.20 in the OI or DI to be significant. Population bias was evaluated using the χ^2 test.

Histological procedures

After a complete set of inactivation sessions, the animals were euthanized for histological processing and localization of the injection and recording sites. At the end of the last recording session, the animals were deeply anesthetized with sodium pentobarbitone (30 mg/kg) and perfused intracardially with saline, followed by 2% paraformaldehyde in phosphate-buffered saline (PBS), 2% paraformaldehyde in PBS supplemented with 2.5% glycerol, PBS supplemented with 5% glycerol, and PBS supplemented with 10% glycerol. Frozen sections (70-μm thick) were cut on a cryostat and mounted on glass slides or kept in PBS at 4 °C. The sections were stained using Nissl (cresyl violet) and were analyzed on a slide projector and microscope to determine the locations of the electrode tracks.

Results

GABA inactivation of visual area V4 produced a general decrease in the excitability of the neurons, which included a decrease in spontaneous and driven activities, followed by changes in direction and/or orientation selectivity. The changes in selectivity were toward increase of direction selectivity and loss of orientation selectivity.

Pressure injections of GABA (1–4 μL 0.25 mol/L) in area V4 induced early and late effects in the activity of neurons in area V2. These effects were observed in the properties of the topographically corresponding receptive fields of the neurons in both areas. We studied a total of 36 neurons in V2. Eleven neurons were studied only before and after GABA inactivation and their data were not included in the quantitative evaluations. Twelve neurons were studied more than one time after GABA inactivation, for 60 min, but their activity did not return to the control level. The data from such cells were used only for qualitative evaluation of the short-term effect of GABA inactivation, and they support the quantitative results derived from the 13 neurons that were studied for more than 2 h.

GABA inactivation of V4 induced a statistically significant effect in the majority (72%) of V2 neurons studied. Statistical analysis of the first 5 min of the response of the V2 neurons after GABA inactivation of V4 showed a change in direction selectivity in 46% of these neurons; of these, 23% showed a change from pandirectionality to directional selectivity. The remaining 23% showed a change from directional selectivity to pandirectionality. In seven neurons, there was no change of direction selectivity, although there was a statistically significant effect on the strength of the response. There was no significant effect in the remaining three cells.

We studied eight V2 neurons after pressure injections of 1.6 μL of 0.25 mol/L GABA in V4, three other neurons after pressure injections of 1 μL of GABA, and two other neurons after pressure injections of 4 μL of GABA. In the first two cases, the median value for spontaneous activity of V2 neurons decreased approximately 20% in the first 5 min. The inhibition of spontaneous activity was followed by a rebound of the activity, which lasted for an additional 5 min. After this period, spontaneous activity returned to control levels. The median value of the response of the neurons to the preferred direction of the stimulus decreased approximately 35% in the first 5 min after GABA injection, returning to control levels after 20 minutes. After injections of 4 μL of GABA, we observed the same results, but with greater intensity than observed after injections with smaller volumes. The median value of spontaneous activity of the V2 neurons decreased 50% in the first minute after injection. After a sustained suppression of 30 minutes, there was a rebound of activity, which lasted for an additional 100 min. The median value of the response of the neurons to the preferred direction decreased 70% in the first 15 min, returning to control levels after 70 min.

Local effect in V4

Fig. 2 illustrates typical recordings obtained in area V4 during GABA-induced inactivation of area V4. Injection of 4 μL of 0.25 mol/L GABA in V4 caused a local decrease in spontaneous and driven activity of V4 neurons. Before the injection, there was high spontaneous activity and good response to the moving bar. After the injection in V4, the neuron showed a significant decrease ($p<0.01$) in spontaneous activity and a decrease in driven activity, with loss of directional selectivity.

Effect on V2 neurons

Fig. 3 illustrates the response of one neuron that lost its bidirectional selectivity ($p<0.05$) as a result of GABA-induced inactivation in area V4. Neurons in both V2 and V4 had receptive fields in topographically corresponding locations of the visual field. The neuron illustrated was recorded in V2 before and after pressure injections of 4 μL of 0.25 mol/L GABA in area V4. After 1 min of inactivation, this neuron showed a significant decrease ($p=0.9$) in directional selectivity. In this figure, three panels represent, respectively, the activity of the neuron before (Fig. 3C), 1 min after (Fig. 3D), and 30 min after (Fig. 3E) GABA injection. The polargrams and SDFs represent concurrent recording intervals. The bidirection-selective V2 neuron ($p<0.05$) shown in Fig. 3C was inhibited (Fig. 3D) for the first minute ($p=0.9$) after a 4-μL injection of 0.25 mol/L GABA. After 30 min, the cell recovered its bidirection selectivity ($p<0.05$) (Fig. 3E). Thus, the feedback projections from V4 are capable not only of modulating the spontaneous and driven activity of V2 neurons, but also of modifying V2 receptive field properties.

The time-courses of the changes in spontaneous activity and response at the preferred directions during GABA inactivation with 1.0-μL and 1.6-μL injections were similar. Fig. 4 illustrates the time-course of the changes observed in ten V2 neurons during inactivation

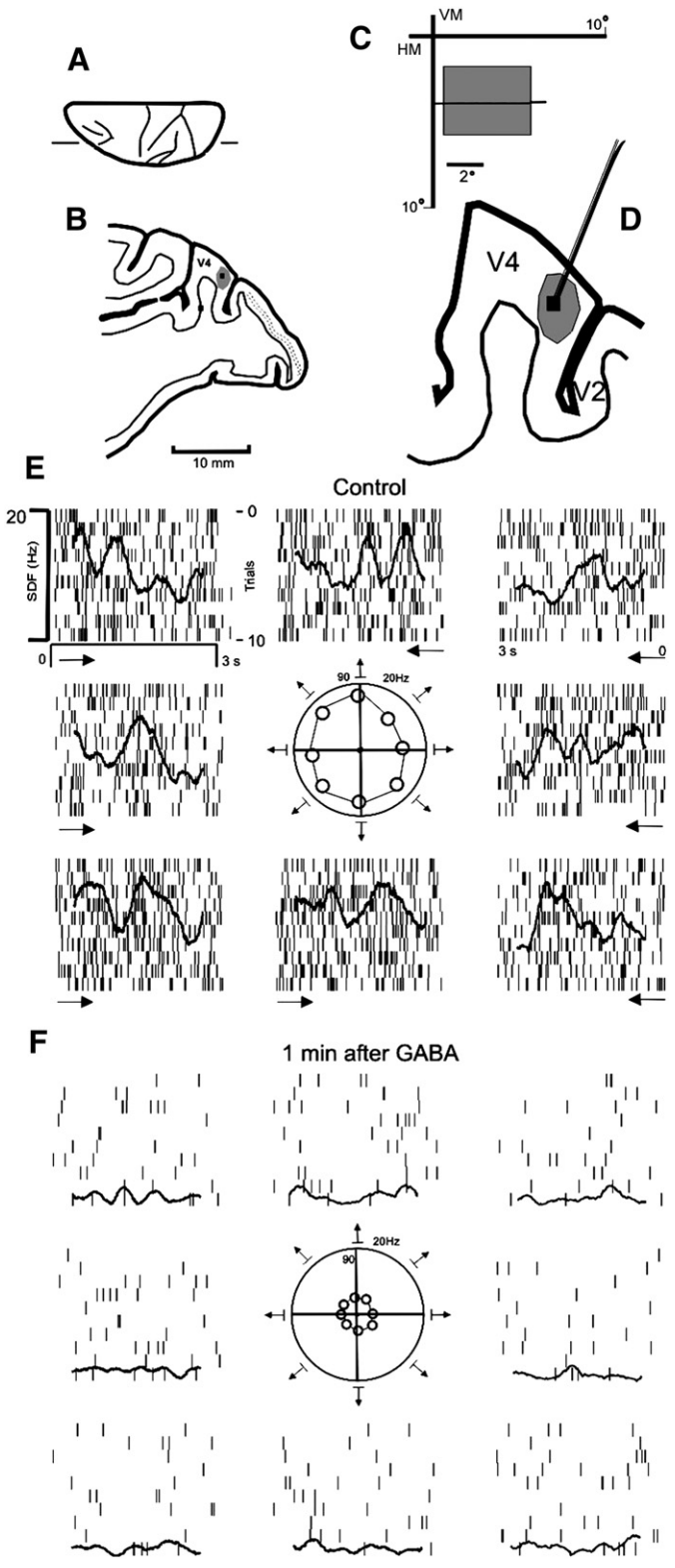

Fig. 2. Local effect of GABA inactivation in V4. A: Dorsal reconstruction of the *Cebus* brain, indicating the levels of the section illustrated in B; C: Visual field location of the receptive field of V4 that were studied in this experiment. D: Parasagittal sections of the *Cebus* brain, showing the location of inactivation and recording in V4. The large rectangle correspond to the V4 receptive field. E: The bidirection selective V4 neuron recorded at the V4 site. The polargrams depicted at left illustrate the V4 neuron mean firing rate elicited by bars moving in eight directions orthogonal to its preferred orientation before (control condition, polargram at the top) and, F: 1 min after GABA inactivation.

with 1.6-μL injections of 0.25 mol/L GABA in V4. Spontaneous activity of the V2 neurons decreased approximately 35–50% in the first min in 40% of the cases. After a suppression of up to 5 min, an increase in spontaneous activity was observed in all cases. This increase persisted for 15–35 min. The strength of the response decreased in the first 15 min and remained depressed for up to 30–40 min. The effect on the strength of the preferred direction varied with the amount of GABA injected. The 4-μL injections induced a stronger and longer-lasting decrease in the strength of the response than did the 1.0-μL and 1.6-μL injections.

An example of a V2 pandirectional neuron studied before and after pressure injections of 4 μL of 0.25 mol/L GABA in area V4 is illustrated in Fig. 5. After 1 min of inactivation, this neuron showed no significant decrease ($p = 0.3$) in directional selectivity. The change of the neuronal activity in V2 is similar to that of Fig. 2. The activity of the neuron before ($p = 0.4$) (Fig. 5C), 1 min after ($p = 0.3$) (Fig. 5D), and 21 min after ($p = 0.3$) (Fig. 5E) GABA injection show the transitory effect of GABA inactivation of V4. The polargrams and SDFs represent concurrent recording intervals. Thus, the feedback projections from V4 are capable not only of modulating the spontaneous and driven activity of V2 neurons, but also of modifying V2 receptive field properties.

We found six inhibitory V2 cells that were excluded from the circular statistic sample. Both increase (13/18) and decrease (5/18) of direction tuning were observed in the V2 neurons. In addition, we found that these cells decreased (13/18) and increased (5/18) their orientation selectivity, thus presenting an opposite effect for direction and orientation. Fig. 6 shows changes in the direction and orientation tuning of V2 neurons after GABA-induced inactivation of the topographically corresponding portion of area V4. When changes greater than 0.2 were used as the criterion, only four neurons (25%) changed their direction or orientation tuning. There is no statistical segregation of GABA effect for DI or OI in this sample (χ^2 test $p = 0.1$). Although the number of cells that increased OI is similar to the number that decreased DI (5/18), there was no bias toward increase or decrease (5 vs.13) in the sample (χ^2 test $p = 0.1$).

Discussion

Previous studies have described the divergent nature of the feedback connections from visual area V4 to area V2 (Rockland et al., 1994; Salin and Bullier, 1995). Thus, the descending projections onto a given V2 neuron represent a larger portion of the visual field than that encompassed by the feedforward afferents on the same unit (Salin and Bullier, 1995). Consequently, to remove all feedback influence of area V4 on a given V2 neuron, a large portion of area V4 must be inactivated. For this reason, we injected 1.0–4.0 μL (0.25 mol/L) of GABA into V4 and studied the topographically corresponding portions of V2.

Hupé et al. (1999) performed a quantitative study on the spread of GABA after pressure injections into the cortex and predicted that the injected volume would spread throughout the extracellular space, occupying an ellipsoid shape. They also determined that, with a greater quantity of GABA injected, the inactivation period and the time needed for the neurons to recover also would be greater. This last result is in agreement with our observations. In Hupé et al. (2001), the neurons required 40 min to recover to baseline after a 0.9-μL injection of GABA (0.1 mol/L). This recovery period coincided with the time required by V2 neurons to regain baseline activity after a 1.0-μL GABA (0.25 mol/L) injection into area V4 in the present study. Considering the extent of area V4 determined by Piñon et al. (1998), we extended the predictions of Hupé et al. (1999) regarding the relationship of injected volume and occupied extracellular volume. We predicted that injection volumes between 1.0 and 4.0 μL would inactivate 0.7–3.22% of area V4.

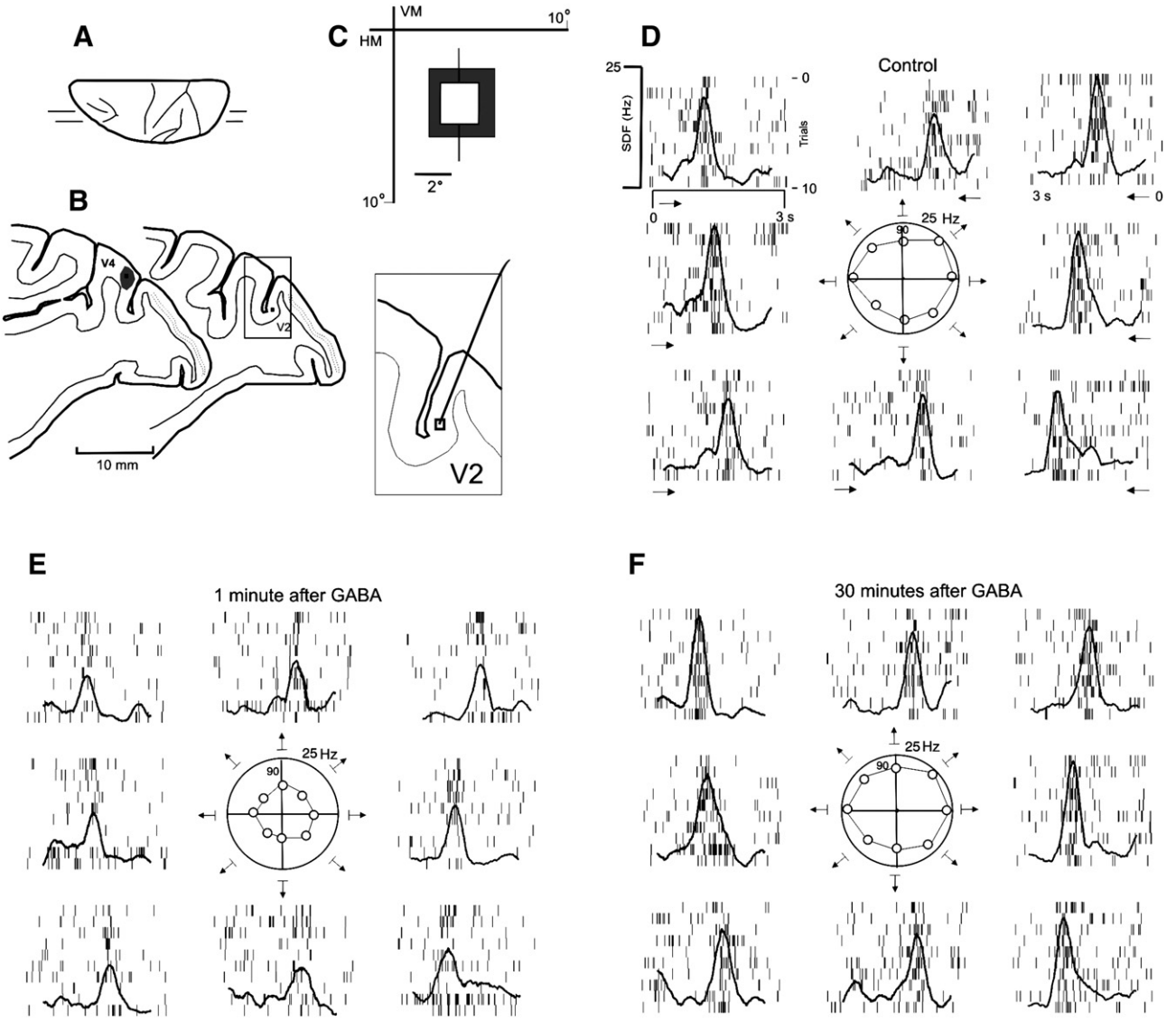

Fig. 3. Effect of GABA inactivation of a portion of V4 in the visual response of a V2 neuron. A: Dorsal reconstruction of the *Cebus* brain, indicating the levels of sectioning; B: Para-sagittal sections of the *Cebus* brain, showing the locations of V4 and V2. The approximate positions of the recordings sites are indicated by small rectangles; C: Visual field location of receptive fields of the neurons of V4 and V2 that were studied in this experiment. The large and small rectangles correspond to the V4 and V2 receptive fields, respectively; D: The bidirection selective V2 neuron ($p<0.05$) recorded at the V2 site. The polargrams depicted at left illustrate the V2 neuron mean firing rate elicited by bars moving in eight directions orthogonal to its preferred orientation before (control condition, polargram at the top) and 1 min after GABA (E) ($p=0.9$), and 30 min (F) after GABA ($p<0.05$). The polargrams represent response magnitude relative to each direction of motion. For each polargram, pairs of SDFs corresponding to the best and opposite directions of motion are shown in the right side of the figure. These SDFs represent cellular activity in the space domain. Vertical ticks represent spikes, and each line of spikes corresponds to the total span of visual stimulation during each trial. The thick black line represents the SDF, obtained by the Gaussian convolution (product summation) of the action potentials. The scale on the left indicates the frequency rate, and the scale on the right indicates the number of trials.

Evaluation of the early and late effects of GABA inactivation

Independent of the amount of GABA injected, the inactivation of V4 produced a decrease of approximately 30% (relative to control level) in the spontaneous activity of V2 neurons for the first 40 min. This was typically followed by a rebound in activity, where the spontaneous firing increased beyond the pre-inactivation period level. The greater the injected volume, the greater the activity rebound and its duration. For the 4-μL injection, a period of 100 min was required for V2 activity to return to control level. Regarding V2 driven activity, it normally fell below 50% of control level in the first 10 min post-injection. For the 1- and 1.6-μL GABA injections in area V4, the driven activity in V2 neurons began to recover to control levels 5 min after the onset of inactivation. For the 4-μL injection, this period was 15 min, achieving a complete recovery after 40 min. The dissociation between spontaneous and driven activity is difficult to explain based only on the operation of GABAergic channels. For injections of 1 and 1.6 μL, a rebound effect of spontaneous activity was already observed, while the response in the preferred direction was still below control level. This dissociation suggests that different and possibly independent mechanisms underlie changes of the driven response and that of spontaneous activity in the cortex. A hypothesis to explain the late rebound effects could involve a downregulation of the enzyme glutamic acid decarboxylase (GAD), which is responsible for GABA biosynthesis. The intermediate-to-late effect of activity rebound could be explained by an inhibition of GAD by GABA in the circuitry projecting from V4 to V2. Downregulation has been demonstrated in chick retina after seven-hour incubation with GABA (de Mello, 1984).

Hierarchical processing or recurrent network

The hierarchical processing theory suggests that the visual information progresses serially through several synaptic stations by way of rostrally directed, feed-forward projections (Hubel and Wiesel,

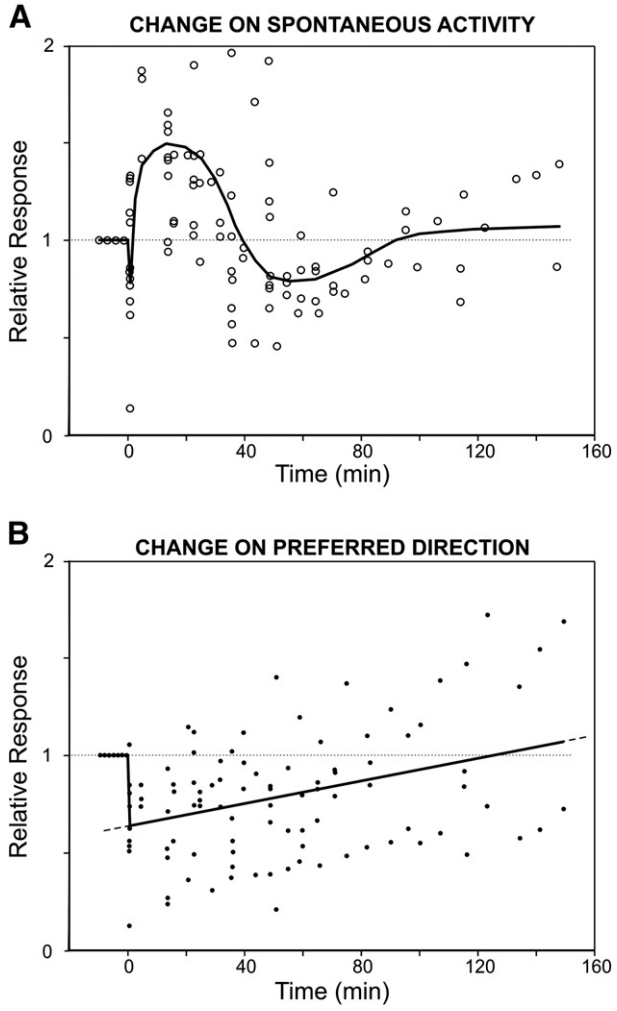

Fig. 4. Time-course of the effect GABA injected in V4 on changes in spontaneous (A) and driven activity (B) of neurons of V2. The relative firing rate (firing rate/firing rate before inactivation) of each neuron, before and after inactivation is plotted against time. On average, injections of 1.6 μL 0.25 mol/L of GABA induce an immediate decrease of the response in the preferred direction (B), as well as an increase in spontaneous activity (A). After the immediate general decrease in the firing rate at the preferred direction, there is an increase in spontaneous activity, which lasts for 15–35 min, and then the response strength at the preferred direction returns to normal (for details, see text).

1968). At each station, horizontal connections reinforce the interplay between groups of neurons with similar properties (McGuire et al., 1991). Based on this theory, feed-forward projections and intrinsic circuits contribute to the extraction of complex attributes of the visual scene, at each successive processing stage. The role of caudally directed feedback projections is less clear. It has been proposed that these connections are related to perceptual organization, attention, visual consciousness, memory and sensory integration (Lamme and Roelfsema, 2000; Payne et al., 1996; Salin and Bullier, 1995). Some studies have demonstrated the influence of feedback circuits on the receptive field properties of target neurons (Alonso et al., 1993; Galuske et al., 2002; Huang et al., 2004; Hupé et al., 1998; Mignard and Malpeli, 1991; Rockland and Knutson, 2000; Wang et al., 2000), whereas others found no influence on these neurons (Hupé et al., 2001; Sandell and Schiller, 1982). However, the exuberance of these connections among different cortical areas, the fast speed of electric signal propagation along these connections, and the latency of visual response suggest that feedback connections may contribute significantly to receptive field properties (Angelucci et al., 2002 ; Borra and Rockland, 2011; Bullier, 2001). The feedback projections are divergent and have a crude topographical organization in the cortical visual areas already studied (Salin and Bullier, 1995; Sousa et al., 1991; Ungerleider et al., 2008).

It has been suggested that some receptive field properties of cortical neurons, such as orientation selectivity and direction selectivity, may be attributed to the inhibitory influence of intrinsic circuits on incoming information. (Crook et al., 1998; Sato et al., 1996). The inactivation of intrinsic inhibitory processes disrupt both orientation and direction selectivity (Sillito, 1975).

In visual areas V1 and V2 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 (Crook et al., 1996, 1997, 1998; Sato et al., 1995, 1996). However, evidence indicates that excitatory intrinsic inputs also contribute to V1 orientation selectivity and direction selectivity (Sato et al., 1995, 1996).

Using a reversible inactivation technique in monkey visual area MT, Hupé et al. (1998) have shown that feedback connections serve to amplify and focus activity of neurons in lower-order areas, and that they are important in the differentiation of figure from ground, particularly in the case of stimuli of low visibility. More specifically, they show that feedback connections facilitate responses to objects moving within the classical receptive field; enhance suppression evoked by background stimuli in the surrounding region; and have the strongest effects for stimuli of low salience (Hupé et al., 1998).

Reciprocal connections of V4 with V2 and pulvinar could be modulated by the connection of the pulvinar to V4 and V2. In this study we cannot rule out the possibility that the changes in V2 neurons derive from indirect elimination of a functional pathway from V4 to the pulvinar, and from that nucleus to V2. To better understand the interactions between these areas and the role of each node of a large network we would need to record simultaneously from these areas while injecting GABA in each area. In separate occasions we studied the effect of GABA inactivation of MT, V4 and the pulvinar. We observed different effects of the inactivation of the cortical areas and that of the pulvinar. The inactivation of the lateral pulvinar induces excitatory and inhibitory modulations at neuronal responses in V2, while inactivation of MT or V4 induces only inhibitory modulations in these neurons (Jansen-Amorim et al., 2011; Soares et al., 2004).

The results of GABA inactivation challenge the notion that serial hierarchical processing and lateral projections are responsible for the construction of receptive-field properties in early cortical visual areas. They suggest that a large wide recurrent network may also contribute to the construction of response properties of single cells and that those proprieties could be established after several cycles of feed-forward and feedback information (Gattass et al., 2005).

The effect of inactivation

We injected local anesthetic in V2 (manuscript in preparation) while recording from nearby neurons and we found that there was no change direction or orientation selectivity of V2 neurons. Thus, we concluded that the decrease in response magnitude of the V2 neurons, by itself, does not cause changes in direction and orientation tuning. We propose that GABA inactivation cause either a decrease of directional selective feedback signals or an asymmetrical inactivation of feedback projections to the V2 neuron. To determine how large and how extensive were the GABA-induced changes in direction and orientation selectivity across the population, we examined neurons tuning using a standard test of circular tuning before and after injection GABA in V4 and in MT (Jansen-Amorim, et al., 2011). The result presented here showed a significant change in orientation selectivity which is consistent with the role and properties of neurons of visual area V4 and a significant change in the direction selectivity, showed previously (Jansen-Amorim et al., 2011) is consistent with the role of visual area MT. We, however, could not

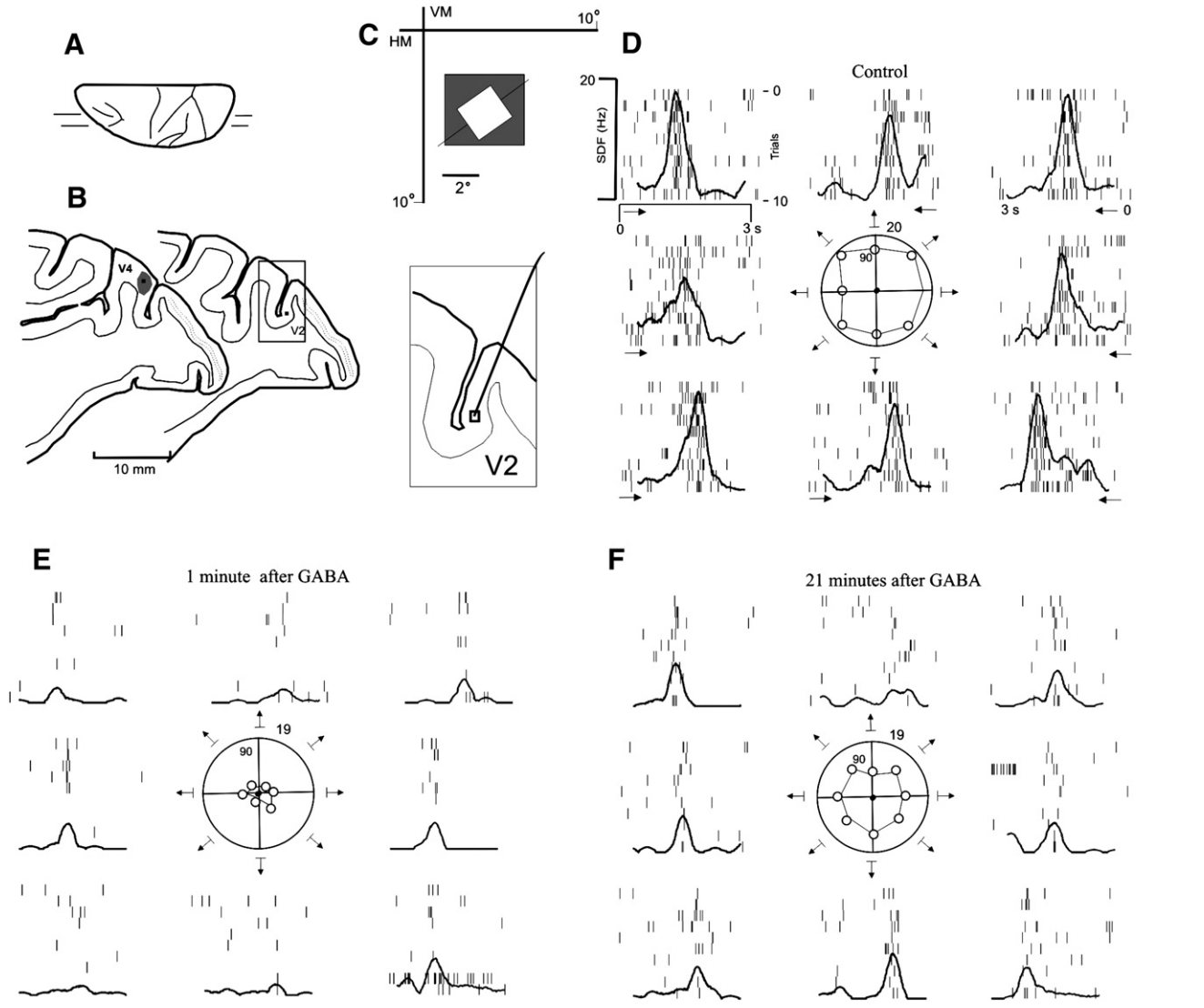

Fig. 5. Effect of GABA inactivation of a portion of V4 in the visual response of a V2 neuron. A: Dorsal reconstruction of the *Cebus* brain, indicating the levels of sectioning; B: Parasagittal sections of the *Cebus* brain, showing the locations of V4 and V2. The approximate positions of the recordings sites are indicated by small rectangles; C: Visual field location of receptive fields of the V4 and V2 neurons that were studied in this experiment. The large and small rectangles correspond to the V4 and V2 receptive fields, respectively. D: The pandirectional V2 neuron ($p = 0.3$) recorded at the V2 site. The polargrams depicted at left illustrate the V2 neuron mean firing rate elicited by bars moving in eight directions orthogonal to its preferred orientation before (control condition, polargram at the top) and 1 min after GABA (E) ($p = 0.4$), and 21 min (F) after GABA ($p = 0.3$). The polargrams represent response magnitude relative to each direction of motion. For each polargram, pairs of SDFs corresponding to the best and opposite directions of motion are shown in the right side of the figure. See also legend for Fig. 3.

differentiate between an intrinsic change in direction/orientation selectivity and a change in the shape of the receptive fields or their surrounds. The paradigm used in this study does not allow such distinction. For instance, if GABA caused the RFs to become smaller, this would presumably show up as a decrease in responsiveness. Likewise, if the receptive field became asymmetrical, this would result in a change in orientation selectivity. Subjective analysis of the changes in the receptive field structure of V2 neurons with GABA inactivation of V4 did not revealed, however, any systematic trend in the change of the receptive fields. Future experiments with a selected sample of cells are necessary to further exam the spatial structure of the V2 neurons intersection maps before and after GABA inactivation to better understand the nature of the change of the receptive fields.

Duration of inactivation

Prior to the start of these experiments, we could not predict the long-lasting effects of GABA injection in area V4; we believed that the inhibitory effects were equivalent to the effects of iontophoretic GABA injections, as described in the literature (Crook et al., 1996, 1997, 1998; Sato et al., 1995, 1996). With iontophoresis, however, the amount of GABA released is usually much smaller than that released from a pressure injection. Therefore, it is possible that, in addition to an initial inactivation effect, a pressure injection causes late effects in neuronal activities that are not observed when lower quantities of GABA are injected. Several changes occurred in the V2 neurons while the V4 cells were still silent, suggesting that V2 neurons could be induced by GABA inactivation. These effects persisted for 40–120 min.

Pharmacological inactivation paradigms are based on post-injection effects, which disappear over time. The effects are usually reversible and are evaluated in comparison with the pre-injection state. A return to the resting or pre-injection spontaneous and driven activity is indicative of a non-toxic or non-destructive effect on central nervous tissue. Therefore, we based our results on a sample of cells in which a clear trend toward the recovery of driven activity was observed.

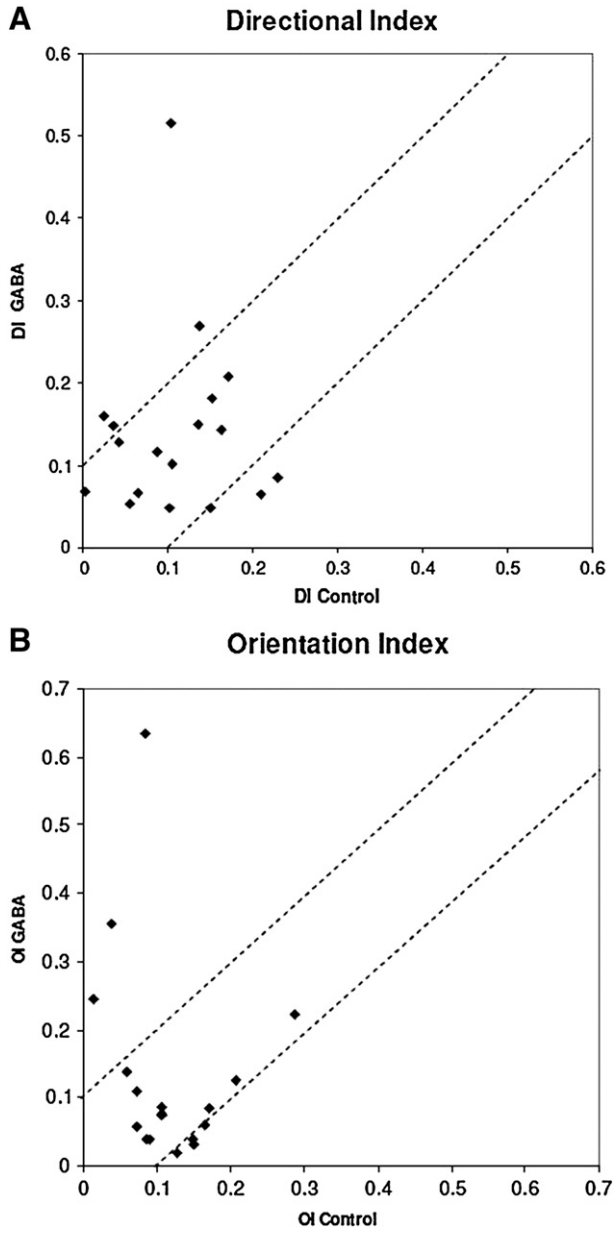

Fig. 6. Changes in the direction and orientation tuning of 18 V2 cells; A: Correlation between the directional indices before (control DI) and after GABA injection (GABA DI) into area V4. B: Correlation between the orientation indices before (control OI) and after GABA injection (GABA OI). Broken lines with a slope of 1 represent the limits of significance for the changes in the indices (>0.2). A significant change in the DI and OI was observed for 38% of the cells. In addition, GABA injection in V4 tended to increase the DI and decrease OI in V2.

Comparison of GABA inactivation of V4, MT, and pulvinar

Visual area V2 receives direct projections from V4, MT, and several areas of the pulvinar (Gattass et al., 2005; Rockland et al., 1994; Rosa et al., 1988; Ungerleider et al., 2008; Zeki and Shipp, 1989). GABA inactivation of areas MT and V4 produced an early and short decrease in both spontaneous activity and responsiveness, followed by a transitory increase of the spontaneous activity and change in V2 neuronal direction and orientation selectivity. GABA inactivation of the pulvinar induces both excitatory and inhibitory change in the V2 neuronal activity and produces a decrease in orientation selectivity. The effects of inactivation of the visual area MT are quantitatively different from those of inactivation of area V4. While inactivation of MT, on average, decreases DI, the inactivation of V4 increases DI (Jansen-Amorim et al., 2011; Soares et al., 2004). In addition, inactivation of MT, on average, increases OI, while inactivation of V4 or the pulvinar decreases OI (Jansen-Amorim et al., 2011; Soares et al., 2004). Thus, the feedback connections of MT are different from that of V4, but both promote inhibitory modulations in V2, while the projection of pulvinar produces both excitatory and inhibitory modulations on the target cells in V2.

Cortical modules and inactivation

Direct feedback projections from area V4 to area V2 in primates have been described previously (Rockland et al., 1994). Layers II, III, V, and VI of V4 contain mainly pyramidal neurons (Zeki and Shipp, 1989), which constitute the source of feedback circuits to the hierarchically lower areas. In V2, the same layers (II, III, V, and VI) (Tigges et al., 1981) receive projections from the feedback circuits of V4. Zeki and Shipp (1989) evaluated the anterograde and retrograde connections from V4 to V2 in Macaca, using peroxidase conjugated to wheat germ. The labeled cells in V2 are pyramidal cells and were found mainly in lamina III (lamina IIIB). These cells are outnumbered in layers IIIA and II, and even less in V. Labeled terminals were mainly in lamina I and less intensely in II, III, V and VI. The projection from V4 back to V2 is fully dispersed in the tangential plane, invading the territories of all three types of CytOx bands.

We did not test the effects of V4 deactivation on sites at non-overlapping retinotopic loci in V2. We focused this study on topographically corresponding portions of both areas, because there is accumulated evidence that the spread of GABA was very small and that the effect was restrict to topographically corresponding regions of the areas (Hupé et al., 1999). However, based on the work of Hupé et al. (1999) it is possible that some of our large injections have spreaded into neighboring extracellular space as to include non-topographic neighboring sites in V4. On the study of GABA inactivation of the pulvinar (Soares et al., 2004) we added control injections in the lateral geniculate nucleus and in other subcortical structures with no effect on the neuronal response of V2 neurons.

We propose the following hypothetical inactivation circuits to explain the results described in the present study. The feedback circuits modify the properties of the receptive field, probably through excitatory and inhibitory neurons from intrinsic circuits. The most common effect observed after the first 10 min of GABA injection in V4 was a decrease in both spontaneous and driven activity of V2 neurons. We propose that pyramidal neurons of directional selectivity modules in V4 containing $GABA_A$ receptors (Sato et al., 1996) capture the injected GABA and produce a modification of the membrane potential of those neurons toward the negative potential. This change results in the inhibition of the propagation of activity of the neurons that project to the superficial and deep layers of V2. There is a decrease in the liberation of the neurotransmitters in the neurons of area V4. As a result, the excitatory feedback synapses decrease, causing a decrease in spontaneous and driven activity of the V2 neurons. The injections affect all direction selectivity columns, resulting in a decrease in spontaneous and driven activity of the neurons in all directions.

For the majority of neurons, the intrinsic inhibitory interneurons decrease their influence on their afferents to neighboring direction columns and cause a loss of direction selectivity. For the remainder of the neurons that were not direction selective and became selective after the GABA injection, we propose that the inactivation of V4 had a partial and asymmetrical effect and, therefore, some direction columns remained active, while other were inhibited. This asymmetrical inhibition generates direction selectivity in neurons that were pandirectional before the injection, when V4 was intact.

Conclusions

The inactivation of feedback connections of V4 to area V2 produces a general decrease in the excitability of the V2 neurons, which included an increase in spontaneous activity, decrease of the driven activities, and changes in direction selectivity. The changes in selectivity were toward an increase in directional selectivity and decrease in orientation selectivity.

The effects of inactivation of the cortical visual area V4 is different from those of inactivation of visual area MT or from inactivation of the subcortical nuclei, the pulvinar. Inactivation of the feedback connections of V4 and MT promote inhibitory modulations in V2, while inhibition of the pulvinar produces both excitatory and inhibitory modulations on the target cells in V2.

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