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ELECTROPHYSIOLOGICAL EVIDENCE FOR THE EXISTENCE OF A POSTERIOR CORTICAL–PREFRONTAL–BASAL FOREBRAIN CIRCUITRY IN MODULATING SENSORY RESPONSES IN VISUAL AND SOMATOSENSORY RAT CORTICAL AREAS

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Abstract—The prefrontal cortex (PFC) receives input from sensory neocortical regions and sends projections to the basal forebrain (BF). The present study tested the possibility that pathways from sensory cortical regions via the PFC-BF and from the BF back to specific sensory cortical areas could modulate sensory responses. Two prefrontal areas that responded to stimulation of the primary somatosensory and visual cortices were delineated: an area encompassing the rostral part of the cingulate cortex that responded to visual cortex stimulation, and a region dorso-lateral to the first in the precentral-motor association area that reacted to somatosensory cortex stimulation. Moreover, BF neurons responded to PFC electrical stimulation. They were located in the ventral pallidum, substantia innominata and the horizontal limb of the diagonal-band areas. Of the responsive BF neurons 42% reacted only to stimulation of 'visually-responsive,' 33% responded only to the 'somatosensory-responsive' prefrontal sites and the remaining neurons reacted to both prefrontal cortical areas. The effect of BF and PFC stimulations on somatosensory and visual-evoked potentials was tested. BF stimulation increased the amplitude of both sensory-evoked potentials. However, stimulation of the 'somatosensory-responsive' prefrontal area increased only somatosensory-evoked potentials while 'visually-responsive' prefrontal-area stimulation increased only visual-evoked potentials. Atropine blocked both facilitatory effects.

The proposed cortico–prefronto–basalo–cortical circuitry may have an important role in cortical plasticity and selective attention. © 2003 Published by Elsevier Science Ltd on behalf of IBRO.

Key words: cholinergic inputs, cerebral cortex, single units, cortical evoked potentials, sensory processing.

The basal forebrain (BF) has been implicated in a variety of behavioral functions, including learning, memory, attention and arousal (Buzsaki et al., 1988; Fibiger, 1991; Vanderwolf et al., 1993; Nuñez, 1996; Sarter and Bruno, 2000). It contains a heterogeneous population of neurons, including cholinergic and GABAergic projection neurons and several interneurons (Zaborszky and Duque, 2000). The major target of BF projections is the cortex, providing the primary source of cortical acetylcholine (ACh; Mesulam et al., 1983). Single-unit recordings in the BF in combination with electroencephalographic (EEG) recordings indicate that cortical activation depends on BF inputs to the cortex (Metherate et al., 1992; Duque et al., 2000; Manns et al., 2000a). Most of these effects have been explained by the release of ACh in the cortex during wakefulness as well as in the rapid eye movement sleep (Celesia and Jasper, 1966; Jasper and Tessier, 1971; Rasmusson et al., 1992).

Besides its well-known contribution to the control of cortical activity, several experiments have shown that BF stimulation delivered just before the presentation of a sensory stimulus produces long-lasting facilitation of the response in the cortex through a cholinergic mechanism (for review see Rasmusson, 2000). Similarly, ACh iontophoresis enhances the response level of cortical neurons to somatosensory stimulation and increases their receptive field size (Dykes and Lamour, 1988; Metherate et al., 1988). As BF cortically projecting ACh neurons are known to excite cortical cells and GABAergic terminals of BF neurons synapse with GABAergic cortical interneurons (Freund and Meskenaite, 1992; Jimenez-Capdeville et al., 1997), it is possible that the cholinergic and GABAergic corticopetal BF neurons work synergistically to enhance cortical excitability.

Since previous results suggested the participation of the BF in sensory cortical processing, an important issue is to determine how sensory input reaches the BF and results in the release ACh at the appropriate time and location to induce facilitation of sensory responses. Visual, auditory and somatosensory stimulation can each lead to an increase in cortical ACh release in the appropriate cortical areas (Rasmusson, 1993), indicating that the afferent pathways in each of these sensory modalities have access to the cholinergic BF. Since the BF in rodents does not seem to receive specific sensory inputs from the brainstem or via thalamic sensory areas (Zaborszky et al., 1991), such information must be mediated via other routes. Previous anatomical studies have revealed projections from

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Abbreviations: A, anterior; Ach, acetylcholine; BF, basal forebrain; Cg1, cingulate cortex; EEG, electroencephalogram; H, dorso-ventral; L, lateral; M2, secondary motor cortex; PFC, prefrontal cortex; PSTH, peristimulus time histogram.

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prefrontal cortical* (PFC) areas to the BF (Zaborszky et al., 1997). (The prefrontal cortex is generally defined as that part of the frontal cortex that has reciprocal connection with the mediodorsal thalamic nucleus and receives dense dopaminergic input from the ventral tegmental area [Zaborszky et al., 1997]. The parcellation of the prefrontal cortex used in this paper corresponds to that in the recent edition of the rat brain atlas of Paxinos and Watson [1998].) Because the PFC receives inputs from multiple cortical areas (Van Eden et al., 1992), we hypothesized that information from sensory cortical areas would be transferred to the BF via relays from the PFC (Zaborszky et al., 1999). Through their topographical projections, BF cortically projecting neurons would then modify processing in a particular sensory cortical area that initially performed the computation. The goal of the present study is to identify the cortico–prefronto–basalo–cortical routes that could induce facilitation of specific sensory responses. Results have been previously presented in an abstract form (Golmayo et al., 1999).

EXPERIMENTAL PROCEDURES

Animals

The experiments were performed on 38 urethane-anesthetized (1.6 g/kg i.p.) young adult Wistar rats of either sex (from Iffa-Credo, Les Oncins, France), weighing 180–250 g. Animals were placed in a stereotaxic device, with control of the end-tidal CO_2 concentration by a CO_2 monitor (Normocap, Datex) and maintained between 25 and 35 mm Hg by adjusting ventilation rate and tidal volume. The body temperature was maintained at 37 °C. Supplemental doses of anesthetic were given when a decrease in the slow-wave activity of the EEG was observed. Experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC) and with the guidelines set forth in the U.S. Public Health Service manual "Humane Care and Use of Laboratory Animals" and the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health Guide). All efforts were made to minimize animal suffering and the number of animals used.

Recording and stimulating electrodes

Trephine holes were drilled in the skull at preselected stereotaxic coordinates measured from bregma, according to the atlas of Paxinos and Watson (1998). To record the EEG a macroelectrode (120-μm-diameter bluntly cut insulated stainless steel wire; World Precision Instruments, Sarasota, FL) was placed into the frontal cortex (A: +2.2, L: 1–2, H: 0.2 mm; anterior, lateral and dorsoventral coordinates, respectively; left side, contralateral to the unit recording) and referenced against an indifferent electrode placed in the temporal muscle. Insulated tungsten microelectrodes (World Precision Instruments) were used for unit recordings in the BF (A: −1 to −1.6, L: 3, H: 6.5–8 mm) and PFC (A: +2–4.5, L: 0.5–3, H: 0.5–2 mm). Unit firing of BF and PFC neurons was filtered (0.3–3 kHz) and amplified through an AC preamplifier (DAM80; World Precision Instruments). Continuously recorded data were sampled at 8 kHz and fed to a Macintosh computer for off-line analysis. Electrical stimulation was performed through bipolar electrodes (100-μm-diameter bluntly cut stainless steel wire), using rectangular pulses (0.3 ms, 20–200 μA) and aimed at the somatosensory cortex (A: −2, L: 4, H: 1 mm), visual cortex (A: −6.5, L: 4.5, H: 2 mm), PFC or BF (same coordinates as above). Stimulating electrodes were fixed with acrylic to the skull. Trains of electrical stimulation of PFC or BF, lasting 200 ms, were delivered at 100 Hz.

Evoked potentials were recorded with tungsten electrodes (<1 MΩ) placed into the ipsilateral primary somatosensory or visual cortex, at 1-mm depth from the cortical surface. Signals were filtered at 0.3–100 Hz and amplified in an AC preamplifier. Potentials were fed into the computer at a sample rate of 500 Hz. To block muscarinic receptor activation a small piece of cotton soaked with atropine sulfate (1% in saline; Sigma, St. Louis, MO, USA) was placed on the somatosensory and visual cortex after removing the dura mater. In some cases, atropine sulfate was administered i.p. (1% in saline, 0.2 ml).

Sensory stimulation

Somatosensory (tactile) stimulation was performed by an electronically gated solenoid with a probe of 1 mm of diameter that induces <0.5-mm skin deflection. Stimulation consisted in 20-ms stimulation delivered at 0.5 Hz, which could be directed to a small area of the fore- and hind limbs. Visual-evoked potentials were evoked using a Grass PS-22 photo stimulator located 25 cm in front of the rat. Flashes were delivered at 0.5 Hz and the minimal intensity was selected (about 180,000 lumens/m^2).

Data analysis

Recordings were accepted for statistical analysis when the fluctuation of unit amplitudes was lower than 10% throughout the experiment. Statistical analysis consisted of generation of summed peristimulus time histograms (PSTHs; 2-ms bins; 40 stimuli) and averages of the sensory-evoked potentials (20 stimuli), using the Spike 2 software package (Cambridge Electronic Design, Cambridge, UK). The latency of the responses was measured as the time elapsing between the start of the stimulus and the largest peak of evoked activity in the PSTH. The area of the first positive peak (from the zero voltage level) of the sensory-evoked potential was calculated. The two-tailed *t*-test and Wilcoxon matched-pairs statistics were used for comparisons. All data are shown as mean±S.E.

Histological analysis

Upon completion of the experiments, animals were deeply anesthetized with sodium-pentobarbital (50 mg/kg) and then perfused transcardially with saline followed by formalin (4% in saline). The brain was removed, stored in 20% sucrose saline and cut on a freezing microtome. Coronal sections 50 μm thick were stained with the Nissl method to locate the recording and stimulation sites. Experiments were selected for analysis when the tip of the stimulating electrode was found in layer V of the somatosensory, visual cortices or PFC, as well as the electrode track was located in the BF area.

RESULTS

Projections from somatosensory and visual cortices to frontal cortical areas

In order to reveal projections from sensory cortical areas to the PFC, stimulating electrodes were aimed at layer V of the primary somatosensory and visual cortices. Stimulation of either somatosensory or visual cortex evoked orthodromic responses in the PFC, which were identified by their variable latency. Neuronal responses evoked by electrical stimulation of the sensory cortical areas delineated two areas in the PFC. A lateral area, roughly corresponding to the M2 (secondary motor area), contained neurons

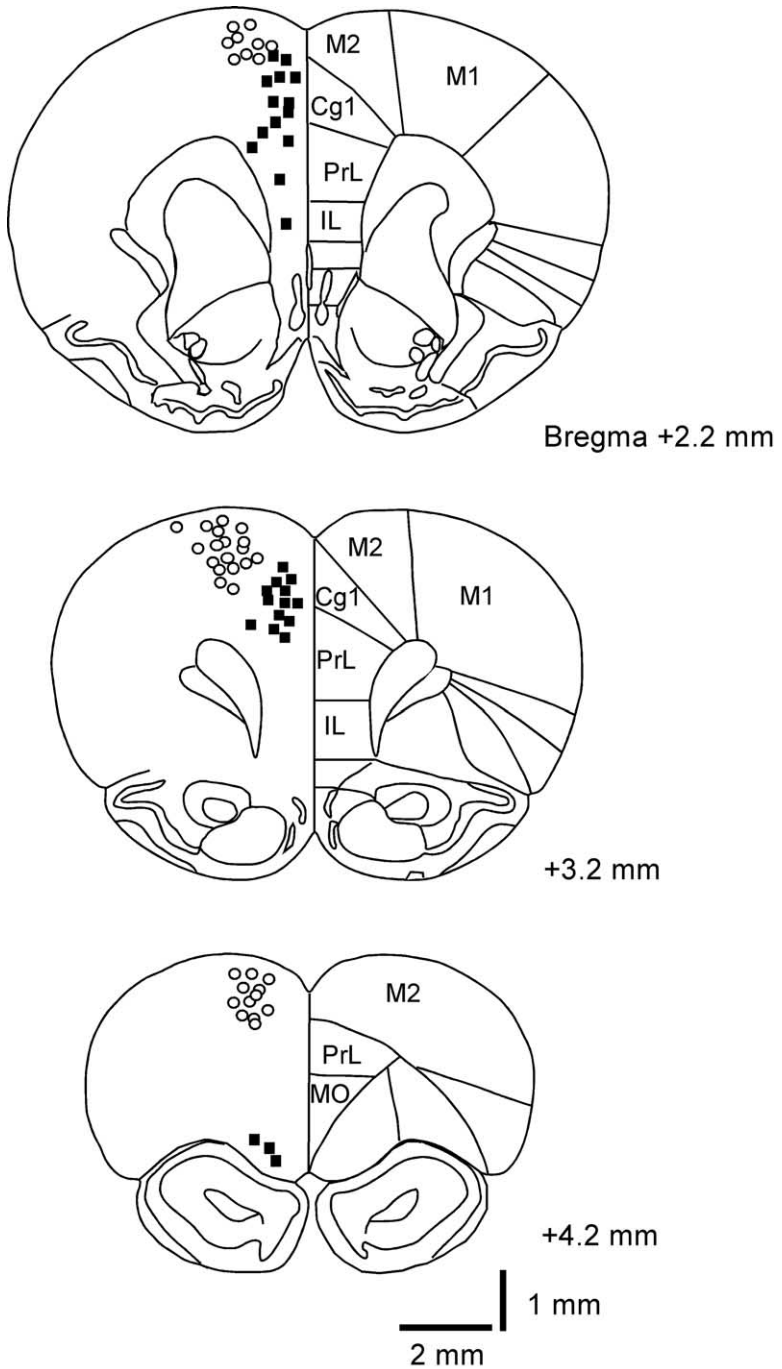

Fig. 1. Location of PFC neurons orthodromically activated from electrical stimulation of primary somatosensory (open circles) or visual (solid squares) cortical areas reconstructed on coronal sections from the atlas of Paxinos and Watson. Anterior–posterior distances (mm) from the bregma are indicated in the lower right. Neurons activated from the somatosensory cortex are located more lateral than neurons responding to stimulation of the visual cortex.

showing responses to electrical stimulation of the somatosensory cortex, termed here as *somatosensory-responsive* PFC area and a medial area, located in the rostral part of the cingulate cortex (Cg1), that responded to electrical stimulation of the visual cortex, termed here as *visual-responsive* PFC area. Visually reactive cells were also noted in the ventral orbital area. The position of each unit recorded was determined by stereotaxic coordinates and verified later by the electrode track in Nissl-stained sections observed under a microscope. The positions of recorded neurons displaying orthodromic responses to sensory cortex stimulation were plotted on three coronal plates of the Paxinos and Watson atlas (1998) as shown in Fig. 1. All recorded units were located from 2.0–4.5 mm rostral to

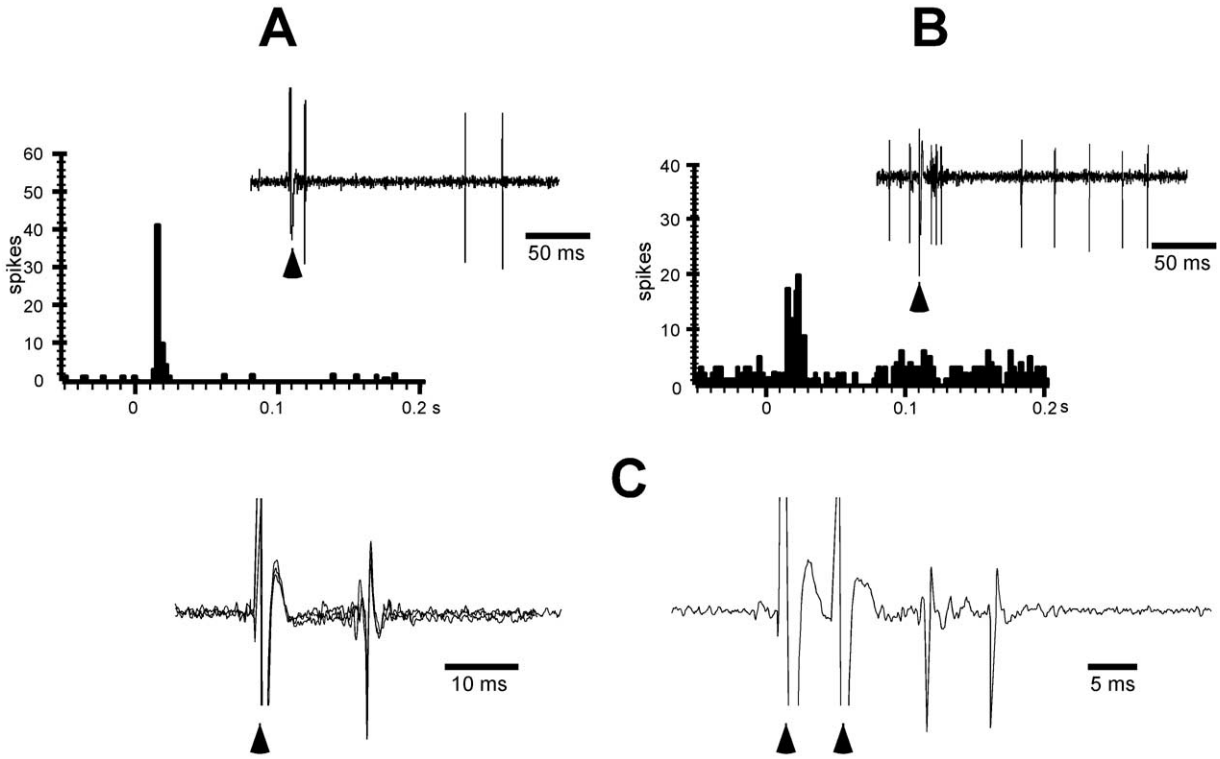

Fig. 2. Orthodromic activation of PFC neurons. (A) PSTH (40 stimuli) of a PFC cell during electrical stimulation of the somatosensory cortex. (B) PSTH of a different PFC cell activated from the visual cortex. Insets show raw data. (C) antidromic activation of a PF cell from the somatosensory cortex Antidromic spikes display a constant latency (three superimposed traces are shown on the left) and follow pair-pulse stimulation at high frequency (200 Hz; right record).

the bregma, 1.0–3.0 mm lateral from the midline and 0.5–1.0 mm deep from the cortical surface. Although both the 'somatosensory' and 'visual' PFC areas roughly appeared at the same antero-posterior levels, PFC neurons responding to visual cortex stimulations tended to be located in a more caudal region than that of the somatosensory-responsive PFC neurons. A small overlapping area could be observed. However, no neurons that responded to both sensory cortical areas were recorded.

Most recorded cortical neurons (69 of 80 neurons; 86%) displayed a low spontaneous activity (range 0.5–3.0 Hz), as has been described previously in cats anesthetized with urethane (Steriade et al., 1993). The remaining 11 neurons (14%) showed higher spontaneous firing rates (15–30 Hz). Electrical stimulation of somatosensory cortex evoked orthodromic responses in 38 of 46 PFC cortical cells (83%), with a mean latency of 13.6±6.2 ms (Fig. 2A). Visual cortex stimulation induced orthodromic responses in 30 of 34 neurons located in the visual-responsive PFC area (88%) with a mean latency of 19.1±4.9 ms (Fig. 2B). Electrical stimulation of somatosensory or visual cortex elicited one or two evoked spikes in those neurons with low spontaneous activity and a train of two to five spikes in neurons with higher spontaneous activity, as the neuron depicted in Fig. 2B. Response latencies indicated that axons responsible for these corticocortical connections were slowly conducting (0.3–0.6 m/s).

A few PFC neurons showed antidromic responses by somatosensory (8 of 46 cells; 17%) or visual cortical stimulation (8 of 34 cells; 12%) with a mean latency of 10.5±6.5 ms and 20±5 ms, respectively (Fig. 2C). Antidromic responses were identified by their constant latency and the possibility to follow high-frequency stimulation (>100 Hz). All antidromically driven cells displayed a spon-

Abbreviations used in the figures

AHC	*anterior hypothalamic area*
B	*basal nucleus*
CPu	*caudate putamen*
GP	*globus pallidus*
HDB	*nucleus of the horizontal limb of the diagonal band*
IL	*infralimbic cortex*
LH	*lateral hypothalamic area*
LPO	*lateral preoptic area*
M1	*primary motor cortex*
MnPO	*median preoptic nucleus*
MO	*medial orbital cortex*
OX	*optic chiasm*
PrL	*prelimbic cortex*
Rt	*reticular thalamic nucleus*
SI	*substantia innominata*
VP	*ventral pallidum*

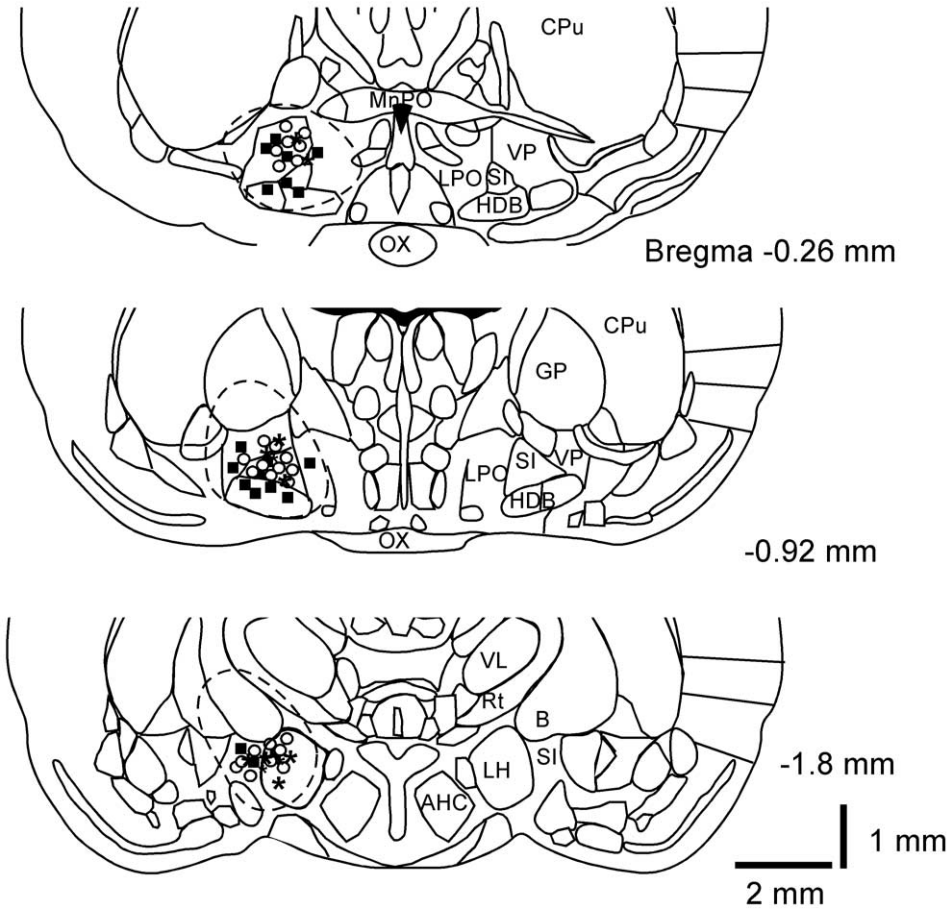

Fig. 3. Location of BF neurons orthodromically activated by stimulation of the PFC. Neurons activated from the somatosensory-responsive PFC area (open circles), from the visual-responsive PFC area (solid squares) or from both PFC areas (asterisks) are located in the ventral pallidum, substantia innominata and in the horizontal limb of the diagonal band. BF areas containing cortically projecting neurons are shown with broken lines, according to previous results (see introduction).

taneous low firing rate. These response latencies showed that axons involved in corticocortical connections were slowly conducting (0.3–0.6 m/s), as has been indicated above using orthodromic activation of PF neurons, and in agreement with other cortico-cortical connections (e.g. Lohmann and Rorig, 1994; Nowak et al., 1997).

Projections from medial PFC to BF

To determine whether BF neurons receive inputs from specific PFC cortical areas, unitary activity was recorded in the BF during electrical stimulation of both somatosensory-responsive and visual-responsive PFC areas. Thirty-six neurons out of 76 neurons (47%) were recorded in the BF region that responded to electrical stimulation of either the visual-responsive or the somatosensory-responsive PFC areas. They were located in the ventral pallidum, in the substantia innominata and in dorsal part of the horizontal limb of the diagonal band areas (Fig. 3). Of these neurons, 42% (15/36) responded only to stimulation of the visual-responsive PFC area and 33% responded only to stimulation in the somatosensory-responsive PFC area (12/36). Responses consisted in one to three spikes with a mean latency of 17.8±5.1 ms and 16.9±5.6 ms, to stimulus delivered in the visual-responsive or somatosensory-responsive PFC areas, respectively (Fig. 4B). Nine of the 36 responsive BF neurons (25%) reacted to stimulation of both cortical areas with a mean latency of 15.3±8.3 ms (Fig. 4C). Although these neurons responded to stimulation of both cortical areas they typically responded stronger to one of the areas. Assuming a cortical projection length of 6-9 mm, the conduction velocity can be estimated between 0.4 and 1.1 m/s, similar to the velocity of fibers projecting from PFC cortex to the caudate-putamen (Trzcinska and Bielajew, 1998). In all cases PFC stimulation did not modify the spontaneous activity of BF neurons. In a previous report two types of BF neurons were defined on the basis of their firing pattern under anesthesia (Nuñez, 1996). Bursting neurons (50/76; 66%) were characterized by periodic bursts of two to five spikes at 0.2–2 Hz whereas tonic neurons (26/76; 34%) showed spontaneous spike firing at 8–15 Hz. In this study no differences between bursting and tonic neurons were observed in the latencies or in the response characteristics by PFC electrical stimulations. Antidromic responses were not observed. Al-

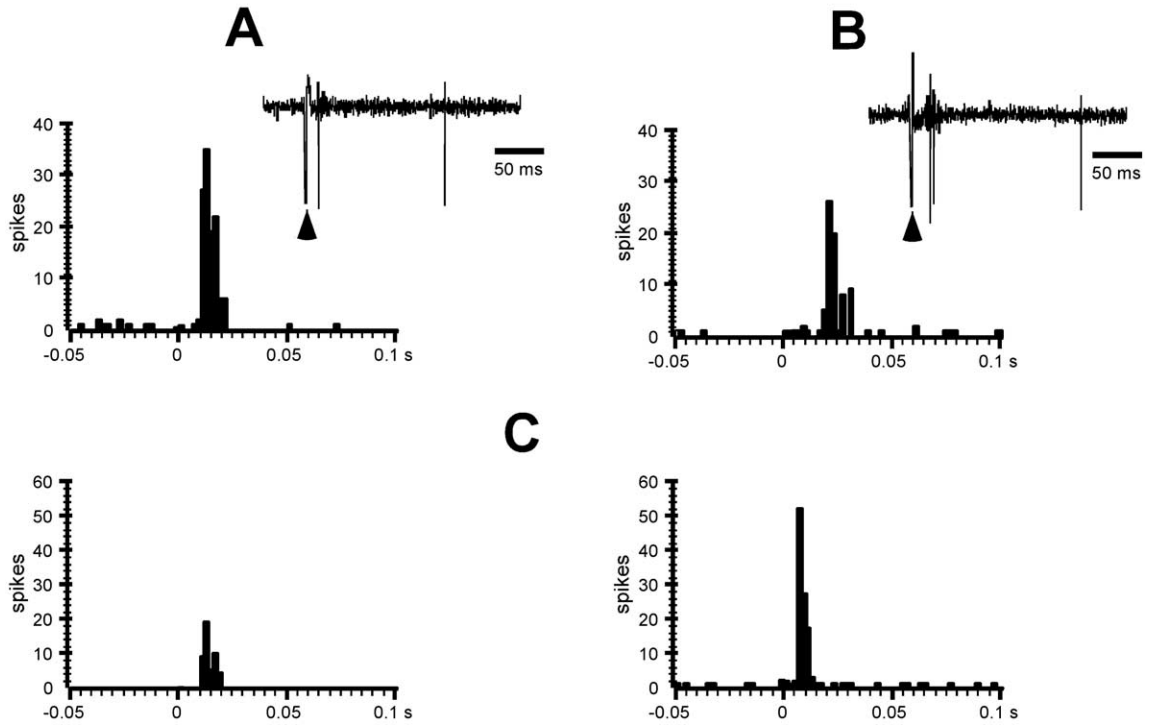

Fig. 4. Orthodromic activation of BF neurons by PFC stimulation. (A) PSTH (40 stimuli) of a representative BF cell during stimulation of the visual-responsive PFC area. (B) PSTH (40 stimuli) of a different BF cell activated from the somatosensory-responsive PFC area. Insets show raw data. (C) PSTHs of a BF neuron during stimulation of the visual (left) and somatosensory (right) PFC areas. Typically, the responses are higher to one of the cortical areas.

though an important percentage of BF neurons were orthodromically driven from stimulation of PFC areas that receive inputs from somatosensory and visual cortex, no sensory-evoked responses were elicited in BF neurons by means of flash or somatosensory stimulations.

Facilitation of sensory responses by electrical stimulation of the BF

To study the effect of BF stimulation on sensory cortical responses, evoked potentials were elicited in the primary somatosensory or visual cortex by tactile or flash stimulations, respectively. Intensity of the sensory stimulation was set close to the threshold in order to discern sensory facilitation. At this intensity, tactile stimulation elicited an evoked potential in the primary somatosensory cortex that consisted of an initial negative wave at 36.3±4.6 ms of latency, followed by a positive wave at 74±6.3 ms (Fig. 5A). Similarly, flash stimulation elicited evoked potential in the visual cortex at 32.5±7.4 ms and 71±3.3 ms for the negative and positive waves, respectively (Fig. 5B). Although the components of the somatosensory or visual evoked potentials were similar to the evoked potentials described previously in rats (Jellema and Weijnen, 1991; Brankack et al., 1990), the amplitude was lower and the latency was longer due to the low intensity of the sensory stimuli.

After a control period of 20 tactile or visual stimuli, two trains of electrical stimulation were delivered in the BF (pulses of 0.3 ms, 20–200 μA at 100 Hz; train duration 200 ms; interval between trains 2 s). The BF stimulation induced desynchronization of the EEG for 30–60 s. In order to compare the sensory evoked potentials in the same EEG conditions, twenty tactile or visual stimuli were applied at 1, 10, 20 and 30 min after the BF stimulation. Both somatosensory and visual evoked potentials showed larger amplitudes than those under control conditions (Fig. 5A, B; thick versus thin traces). No differences in the latency of the evoked potentials were observed. To quantify the changes in amplitude and duration of sensory-evoked potential, the area of the positive wave was calculated. The proportion of the evoked-potential area relative to values obtained before BF stimulation (test/control areas) revealed a facilitation of both somatosensory- and visual-evoked potentials by the BF stimulation (Fig. 5C). The evoked-potential facilitation appeared in both sensory modalities 1–2 min after BF stimulation and lasted, at minimum, for 30 min of recording after stimulation. Comparison of evoked potential areas in control condition and after the stimulation train in BF showed a statistically significant increase ($n=8$; $P<0.01$). Further stimulation of the BF did not increase more the evoked potentials. Atropine sulfate, applied on the somatosensory ($n=3$) or visual cortex ($n=3$), or administered i.p. ($n=4$) evoked an increase of the slow waves recorded in the EEG. Under atropine, BF stimulation did not modify the evoked-potential amplitudes (Fig. 5C), suggesting that the facilitatory

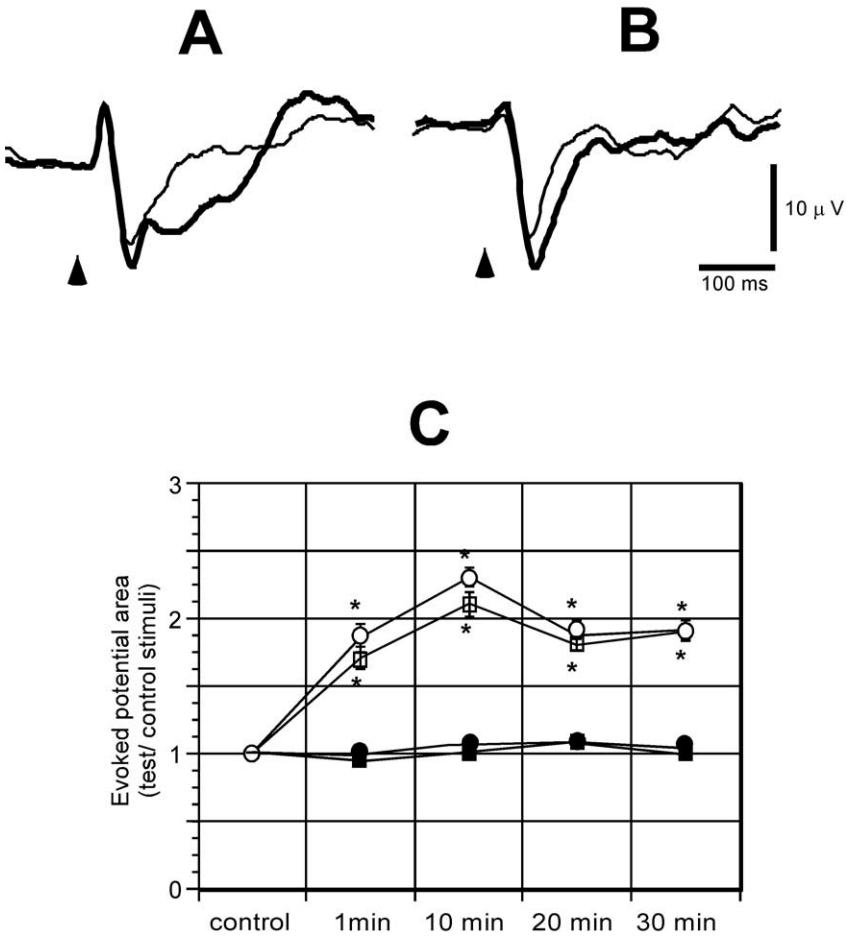

Fig. 5. Effect of BF electrical stimulation on cortical evoked potentials. (A, B) Averages (20 stimuli) of the somatosensory and visual evoked potentials, respectively, before (thin trace) and after (thick trace) two trains of stimulus delivered in the BF (100 μA, 200 ms at 100 Hz). BF stimulation induces an increase in the amplitude and duration of sensory-evoked potentials. (C) Plots of the proportion between evoked-potential area after BF stimulation (test) and before the stimulation (control; $n=8$). Both somatosensory- (open circles) and visual- (open squares) evoked potential areas increase after a train of stimulus delivered in the BF during at least 30 min of the recording. However, under atropine (1%; 0.2 ml; $n=4$) BF stimulation does not modify the somatosensory- (solid circles) and visual- (solid squares) evoked potential areas. In this and in the following figure asterisks indicate values significantly different from respective control at $P<0.01$.

effect evoked by BF stimulation was mediated by the activation of muscarinic receptors.

Facilitation of sensory responses by electrical stimulation of the PFC

To test whether PFC stimulation could facilitate responses in sensory cortical areas, sensory stimulation was applied after trains of electrical stimulation were delivered in PFC areas. As indicated above, the intensity of the sensory stimulation was adjusted close to the threshold in order to enhance the detection of sensory facilitation. Two trains of electrical stimulation delivered in the somatosensory-responsive PFC area (pulses of 0.3 ms, 20–200 μA at 100 Hz; train duration 200 ms; interval between trains 2 s) induced EEG desynchronization for about 20–30 s and after that a facilitation of the somatosensory-evoked potentials was observed in nine of 10 cases (90%; Fig. 6 left). Stimulation of the somatosensory-responsive PFC area did not modify the visual-evoked potentials (Fig. 6A, right). The facilitation consisted of a statistically significant increase ($n=9$; $P<0.01$) in the evoked-potential area that appeared 1 min after the PFC stimulation and lasted at least 30 min (Fig. 6A, plot).

Electrical stimulation of the visual-responsive PFC area facilitated visual-evoked potentials (five of six cases; 83%; $P<0.01$) and no statistically significant difference was observed in the somatosensory-evoked potentials (Fig. 6B, traces on the right and on the left, respectively). The facilitatory effect in the visual cortex appeared immediately after the electrical stimulation but was shorter in duration than the effect of stimulations in the somatosensory-responsive PFC area on the somatosensory-evoked potentials (Fig. 6B, plot).

To test whether facilitatory effects induced by PFC stimulation were mediated by cholinergic mechanisms, the muscarinic receptor antagonist atropine sulfate was applied topically to the somatosensory cortex ($n=4$) or to the

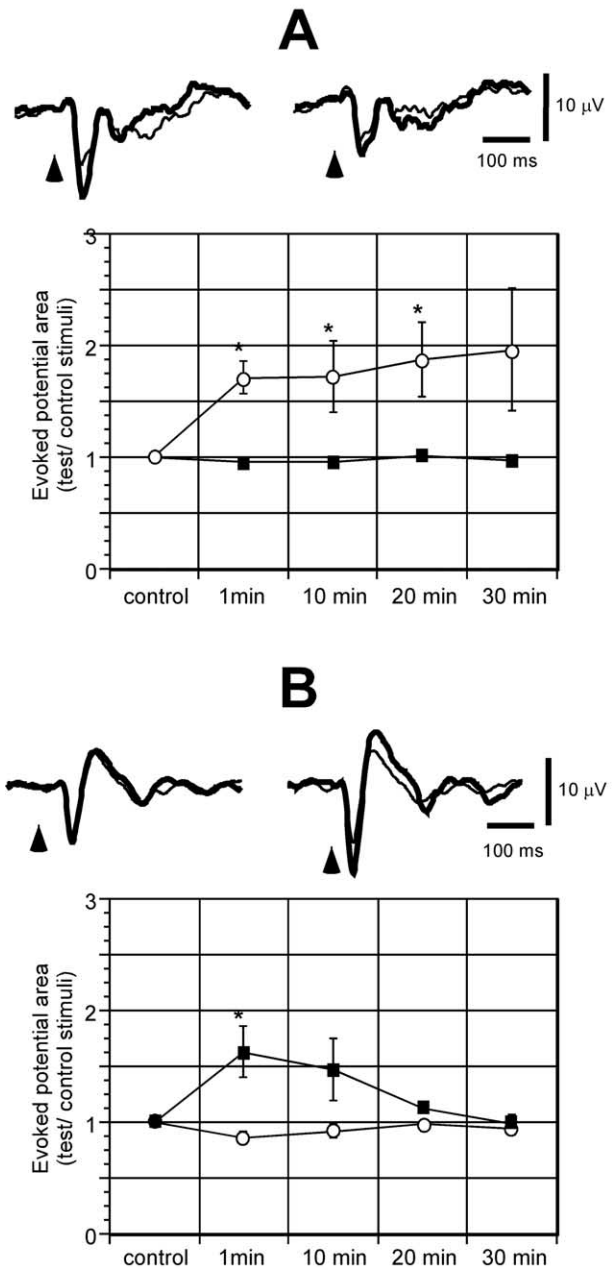

Fig. 6. Effect of PFC electrical stimulation on sensory cortical-evoked potentials. (A) Averages (20 stimuli) of the somatosensory- (left) and visual-evoked potentials (right) before (thin trace) and after (thick trace) two trains of stimulus delivered in the somatosensory PFC area (100 μA, 200 ms at 100 Hz). Stimulation of the somatosensory-responsive PFC area facilitates somatosensory-evoked potentials but does not modify the visual-evoked potentials. Plots of the proportion of evoked-potential areas (n=8) displaying the long-lasting effect on the somatosensory-evoked potentials (open circles); however, visual-evoked potentials (solid squares) are not modified. (B) Same records and plot as in (A) after stimulation of the visual-responsive PFC area (100 μA, 200 ms at 100 Hz). Stimulation slightly, but not statistically significantly, decreases somatosensory-evoked potentials (left and open circles on the plot) but induces a short-lasting facilitation of the visual-evoked potentials (right and solid squares on the plot).

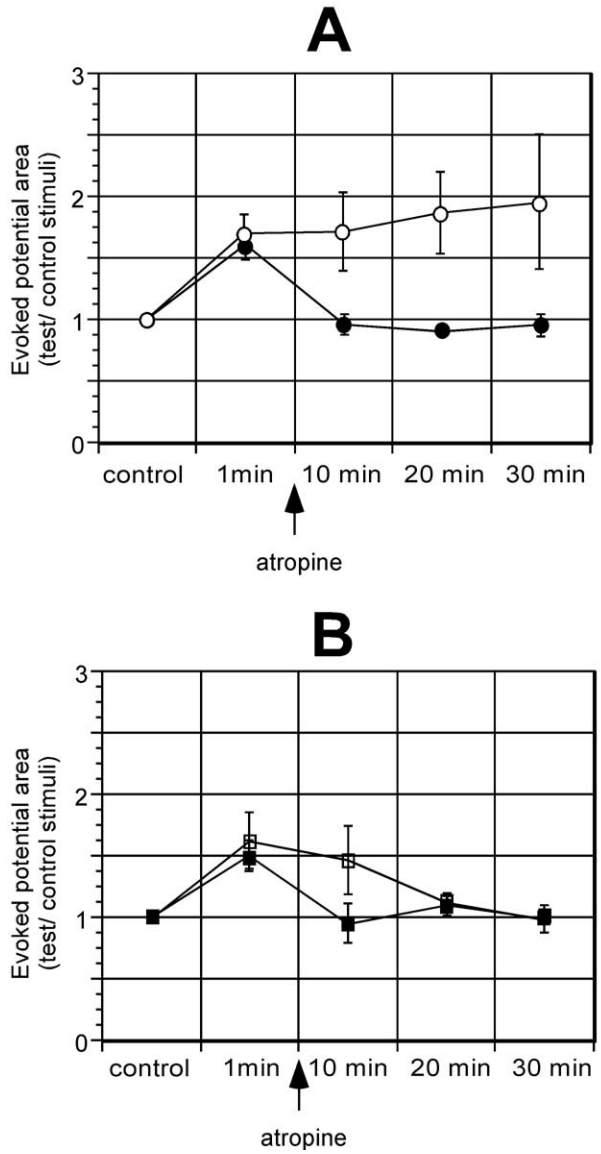

Fig. 7. Atropine blocks the facilitatory effect evoked by PFC stimulation. (A) Plots (n=4) of the proportion between test and control somatosensory-evoked potential areas after a train of stimulus delivered in the somatosensory-responsive area of the PFC (open circles). Atropine (1%; 0.2 ml) delivered on the somatosensory cortex 5 min after PFC stimulation blocks the facilitation (solid circles). (B) Plot (n=4) of visual-evoked areas after electrical stimulation of the visual-responsive PFC area (open squares). Atropine also blocks the facilitation (solid squares).

visual cortex (n=3), or administrated i.p. (n=3), 5 min after PFC stimulation. Plots of evoked-potential areas show an increase in the somatosensory- or the visual-evoked potentials 1 min after stimulation of the somatosensory or visual PFC areas. Atropine blocked the facilitatory effect elicited by stimulation of the respective PFC areas (Fig. 7).

DISCUSSION

Our results indicate that somatosensory and visual inputs to the PFC are segregated in two distinct areas and that

the projections of these PFC areas to the BF remain also largely segregated. The topographical organization in the projections from sensory cortex to the PFC and from PFC-BF–sensory cortex may have an important role in selective modulation of sensory processes via a cholinergic mechanism. The discussion is focused on the following topics: 1) technical considerations; 2) short- and long-term changes in cortical excitability following prefrontal and BF stimulations, including the various transmitters involved; 3) how the organization of PFC or BF can support selective processes in sensory-related cortical areas; 4) behavioral significance of the topographical organization in the projections from sensory cortex to the PFC and from PFC-BF–sensory cortex.

Technical considerations

Neurons in the BF receive input from multiple transmitter systems (for review see Zaborszky et al., 1991; Smiley and Mesulam, 1999; Zaborszky and Duque, 2000), it is unclear whether or not sensory information reaches BF neurons. In our studies, no sensory responses or receptive fields were found in the BF using urethane anesthesia. In freely moving rats, waking monkeys and guinea-pigs, however, visual and auditory responses were recorded in BF areas (Bringmann and Klingberg, 1990; Santos-Benitez et al., 1995; Chernyshev and Weinberger, 1998). This discrepancy may be due to decreased responses in BF neurons to sensory inputs due to the anesthesia.

Short- and long-term changes in cortical excitability following prefrontal and BF stimulations or lesions

BF or PFC stimulations induced a short-lasting desynchronization of the EEG (30–60 s). However, sensory responses, especially in the somatosensory cortex, were facilitated for tens of minutes. Studies of firing properties of chemically identified neurons in the BF as they relate to EEG suggest that both cholinergic and GABAergic cortically projecting BF neurons participate in short-lasting cortical desynchronization (Duque et al., 2000; Manns et al., 2000a,b). Similar to our studies, electrical stimulation of the lateral orbitofrontal cortex produced bilateral low-voltage fast electrical activity and suppression of the large irregular slow activity and administration of atropine (50 mg/kg, i.p.) abolished this response (Dringenberg and Vanderwolf, 1997), suggesting that this activating effect involves, at least in part, the cholinergic input to the cortex from the BF.

Long-lasting changes in the stimulation-evoked responses in somatosensory and auditory cortex were reported in cats, raccoons, guinea-pigs and rats when sensory stimulation was paired with BF stimulation (Rasmusson and Dykes, 1988; Webster et al., 1991; Howard and Simons, 1994; Bakin and Weinberger, 1996). Similarly, iontophoretically administrated ACh induces long-lasting increase of sensory responses, including uncovering new receptive fields and increasing receptive field size in the somatosensory (Donoghue and Carroll, 1987; Metherate et al., 1988), visual (Sillito and Kemp, 1983) or auditory cortex (Ashe et al., 1989; Metherate and Ashe, 1991). Local application of the specific cholinergic immunotoxin, 192-saporin (Sachdev et al., 1998), microiontophoresis of atropine in barrel cortex (Maalouf et al., 1998), or BF lesions prevent cortical barrel field reorganization after whisker trimming (Baskerville et al., 1997; Juliano and Eslin, 1991). Systemic atropine antagonized both the BF-mediated desynchronization of the cortical EEG and facilitation of the thalamocortical response in the rat auditory cortex (Metherate and Ashe, 1991; Bakin and Weinberger, 1996). It is suggested that the long-lasting (up to days) modifications in neuronal excitability induced by cholinergic activation is mediated via reduction of the Ca^{2+}-dependent potassium current, I_{AHP} (Saar et al., 2001), and may involve second-messenger systems, such as the protein kinase C and calcium–calmodulin kinase (Woody et al., 1986; Cox et al., 1994; Pineda et al., 1995).

In our experiments, the long-lasting facilitatory effect on stimulus-evoked sensory cortical responses was diminished or abolished by the muscarinic antagonist atropine, suggesting that the effect of both BF and PFC stimulations are mainly mediated by cholinergic mechanisms. Because the PFC does not contain cholinergic projection neurons to other cortical areas, the facilitatory effects observed are likely mediated by activation of specific cholinergic neurons in the BF. However, our experimental procedure cannot elucidate the mechanism(s) of cholinergic facilitation induced by BF activation. Cholinergic facilitation may be the consequence of postsynaptic activation of muscarinic receptors that result in an increase in the input resistance and thus an increase of the synaptic potentials (Krnjevic and Phillis, 1971; McCormick and Prince 1986; Metherate and Ashe, 1993).

When interpreting the effect of BF stimulation, one has to consider that roughly only one-third to one-half of all BF cortically projecting cells are cholinergic, and the rest use GABA or other transmitters (Gritti et al., 1997). Pharmacological studies have demonstrated a muscarinic-receptor-mediated inhibition of GABA release that disinhibits hippocampal pyramidal cells via a presynaptic action (Behrends and ten Bruggencate, 1993; Rouse et al., 2000). A similar mechanism may be operational in the neocortex. Indeed, the brief (about 200 ms) suppression of thalamocortical response after stimulation of the BF may involve cortically projecting GABAergic BF or intracortical inhibitory neurons (Metherate and Ashe, 1991). Finally, morphological (Aoki and Kabak, 1992; Mrzljak et al., 1993) and electrophysiological (Tremblay et al., 1990) studies suggest that cholinergic terminals in the cortex may interact with glutamatergic terminals to facilitate cortical plasticity. Also, it has been suggested that BF projections may modulate cortical LTP since BF stimulation will reduce cortical GABAergic inhibition, due to cortically projecting GABAergic BF neurons to cortical GABAergic neurons, and will evoke ACh-mediated reduction of potassium permeability, favoring the opening of NMDA channels (Verdier and Dykes, 2001).

Selective modulation of sensory processing via the PFC-BF

The PFC maintains connectivity with virtually all sensory neocortical and motor regions and a wide range of subcortical structures (for references see Groenewegen and Uylings, 2000). In the dorsomedial PFC ('shoulder' cortex of Leonard, 1969), two subregions have generally been distinguished: a medial, Cg1 (dorsal division) and a more lateral region, M2 (medial precentral or medial agranular cortex) in the rat atlas by Paxinos and Watson (1998). These two subregions can be differentiated from each other as well as from the rest of the PFC, including the prelimbic, infralimbic and orbitofrontal cortices based on connectivity and function (Conde et al., 1995; Groenewegen and Uylings, 2000). Connectional studies noted a medio-lateral and rostro-caudal difference in the distribution of somatic or visual inputs to the dorsomedial PFC in that motor and somatosensory areas project to more rostral and lateral parts of the dorsomedial PFC, whereas input from visual areas tends to be located more medially and caudally (Vogt and Miller, 1983; Miller and Vogt, 1984; Reep et al., 1990; Van Eden et al., 1992; Conde et al., 1995). Although our experiments do not permit to decide whether or not the PFC responses are due to monosynaptic or polysynaptic stimulations, they nevertheless strongly suggest, in agreement with above anatomical data, a segregation of somatosensory and visual inputs in distinct areas in the dorsomedial PFC. Also, antidromic responses were evoked in the somatosensory-responsive or visual-responsive PFCs by stimulation of the somatosensory or visual cortical areas, respectively, suggesting a feedback pathway specific for each sensory system.

Behavioral and neurophysiological studies suggest that the functions of the rat dorsomedial PFC area constitute an amalgam of premotor, supplementary motor areas and of frontal eye fields as observed in primates (for references see Conde et al., 1995). For example, a unilateral lesion of the dorsomedial PFC in the rat impairs the approach to contralateral visual cues and causes transient unilateral sensory neglect (Vargo et al., 1988) that is similar to that observed in monkeys and humans (Heilman et al., 1993). In contrast, the medial PFC, including the prelimbic area in rat, is critical in working-memory functions, such as using short-term spatial information stored in the hippocampus to guide subsequent foraging behavior (Seamans et al., 1998). Neurons in the rat medial PFC also become active before and during lever pressing for reward and in anticipation of reward delivery (Chang et al., 1997; Gill et al., 2000). Passingsham (1998) suggests that most tasks that are disrupted following PFC damage depend on acquiring conditional associations.

It is reasonable to assume that 'top-down' biasing signals that are produced in different parts of the PFC, and representing information about the organization and control of various goal-directed behaviors, could amplify behaviorally relevant sensory processing (Miller and Cohen, 2001). One possible route, by which the PFC regulates sensory processing, could lead via the topographically organized pathways from the PFC to the BF and hence back to posterior sensory cortical areas. Since the BF receives most of its input from more ventral (infralimbic-prelimbic) and orbital PFC regions (Sesack et al., 1989; Zaborszky et al., 1997), it remains to be established how the projection from the dorsomedial PFC to prelimbic-infralimbic areas (Fisk and Wyss, 1999) could be involved in the transfer of sensory-related information from the PFC to the BF.

Global or specific role of basalo-cortical cholinergic input in facilitating sensory processing?

As it is discussed above, cortical release of ACh from the BF appears to be essential for the enhancement of sensory-evoked responses and cortical reorganization of the body-surface representation (Juliano et al., 1991; Metherate and Ashe, 1991; Webster et al., 1991; Rasmusson, 2000). It is an important question whether the BF organization can support selective cortical processing or whether the release of ACh in any cortical area is only part of a general arousal reaction. If the BF contributes selectively to sensory processing in the cortex, cholinergic input from the BF should be activated spatially and temporally correlated to the ongoing sensory processes. For example, it is expected that if the rat is performing a visual task, ACh increases only in the visual cortex and not in the entire cortex simultaneously. On the other hand, a diffuse cholinergic projection to the entire cortical mantle would be more consistent with a global role of this system, such as in arousal (Sarter and Bruno, 1997). Experiments measuring ACh release are somewhat confusing due to the poor temporal and spatial resolutions afforded by dialysis or cortical cup techniques used for ACh collection (e.g. Rasmusson, 2000). However, a recent study suggests that BF stimulation sites that resulted in larger ACh release from the visual cortex compared with the somatosensory cortex are different from those BF sites which induced larger ACh efflux in the somatosensory cortex as opposed to the visual cortex (Jimenez-Capdeville et al., 1997).

Anatomical studies have shown segregation of cholinergic neurons within the BF projecting to somatosensory or visual areas. The majority of BF cholinergic neurons projecting to somatosensory cortex concentrate in a region ventro-lateral to and within the globus pallidus. The visual cortical projections arise mainly from the horizontal limb of the diagonal band (Rye et al., 1984). BF axons in the cortex have a restricted arborization with very little collateralization to adjacent subdivisions within primary or secondary somatosensory cortices (Baskerville et al., 1993). These studies would support the notion that the cholinergic input from the BF is capable of selectively modulating different sensory cortical areas. However, tracing studies (Saper, 1984; Price and Stern, 1985) also indicate that the segregation is not complete. BF neurons that project to the visual cortex are distributed throughout a considerable rostro-caudal extent in the BF and 20–30% of the neurons projecting to the primary somatosensory and visual cortical regions are segregated only by a narrow space of 50–200 μm from each other (Zaborszky and Raza, unpublished

observations). Thus they are likely to receive the same input from the PFC. Indeed, 25% of the BF units responded to stimulation of both somatosensory and visual PFC areas. At present, it is unclear whether or not the partial overlap of basalo-cortical neurons connected to different sensory modality representations are related to cross-modality integration or reflect some other unknown aspect of BF organization.

CONCLUSION

Many neurobehavioral studies have indicated the involvement of the PFC in higher cognitive functions such as planning, working memory, behavioral inhibition and attentional shifting (Goldman-Rakic, 1987; Muir, 1996; Robbins, 1998; Miller and Cohen, 2001). A classic sign of PFC damage is that subjects seem unable to focus on a task when other, irrelevant events compete for their attention (Duncan et al., 1996). Attention in different sensory modalities is characterized by a special pattern of regional cerebral blood flow which is compatible with the presence of partially segregated modality-specific sub-territories in the multimodal PFC areas of monkeys (Pandya and Yeterian, 1998). PET imaging studies in humans showed increased activations both in the PFC and BF in a sustained-attention task (Paus et al., 1997). After lesions in the BF in experimental animals, the attention-related P300 voltage deflections disappeared from scalp recording, and the decreased cortical ACh efflux is paralleled with impaired attentional function (Whisaw et al., 1985; Voytko et al., 1994; Wang et al., 1997; McGaughy et al., 2002). Together with our present results, these data suggest that the role played by the PFC in these cognitive operations could be due in part to its close relation with the BF in modulating sensory responses.

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