

Pathways for emotions and memory

I. Input and output zones linking the anterior thalamic nuclei with prefrontal cortices in the rhesus monkey

D. Xiao^b, H. Barbas^{a,b,c,*}

^a Department of Health Sciences, Boston University, 635 Commonwealth Avenue, Room 431, Boston, MA, USA

^b Program in Neuroscience, Boston University, Boston, MA, USA

^c New England Regional Primate Research Center, Harvard Medical School, Boston, MA, USA

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Abstract

The anterior thalamic nuclei occupy a central position in pathways associated with emotions and memory [AMA Arch. Neurol. Psychiatry 38 (1937) 725]. The goal of this study was to determine the anatomic interaction of the anterior nuclei with distinct prefrontal cortices that have been implicated in emotion and specific aspects of memory. To address this issue, we investigated the relationship of input and output zones in the anterior thalamic nuclei linking them with functionally distinct orbitofrontal, medial, and lateral prefrontal cortices. We identified input zones by mapping the pattern and topography of terminations of prefrontal axons, and the output zones by mapping projection neurons in the anterior nuclei, after injection of anterograde and bidirectional tracers in distinct prefrontal cortices.

The results showed that the anterior nuclei were preferentially connected with some orbitofrontal and medial prefrontal areas. In contrast, the anterior nuclei had comparatively sparse connections with most lateral prefrontal cortices, with the notable exception of frontal polar cortex, which had moderate but consistent connections with the anterior nuclei. Prefrontal cortices were connected mostly with the anterior medial nucleus, though medial areas 32 and 25 as well as the frontal polar cortex were also connected with the anterior ventral nucleus. The zones of axonal terminations were more expansive than the sites with projection neurons in the anterior nuclei, suggesting extensive influence of feedback projections from prefrontal cortices. The results suggest that the anterior thalamic nuclei may act in concert with orbitofrontal and medial prefrontal cortices in processes underlying emotions and long-term memory, and with the frontal polar cortex in prospective aspects of working memory.

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1. Introduction

The anterior thalamic complex includes the anterior medial (AM), anterior ventral (AV) and anterior dorsal (AD) nuclei, and occupies a central position in the classic Papez circuit for emotions (Papez, 1937). The involvement of the anterior nuclei in emotion has been demonstrated in humans by observing the effects of pathology (Mark et al., 1970;

Young et al., 2000; Ghika-Schmid and Bogousslavsky, 2000; George et al., 2001), and in animals by using fear conditioning paradigms, or inferred through connections with the amygdala (Martinez-Garcia et al., 1993; Poremba and Gabriel, 1997; Celerier et al., 2000). The cortical component of the Papez circuit for emotions classically included the cingulate gyrus (Le Gros Clark and Boggon, 1933; Kaitz and Robertson, 1981; Robertson and Kaitz, 1981), and prefrontal and infralimbic cortices in rats, cats, and monkeys (Vogt et al., 1979; Musil and Olson, 1991; Chiba et al., 2001; for review see Kolb, 1984). In addition, there is evidence that the anterior nuclei are connected with other prefrontal areas in rhesus monkeys (Jacobson et al., 1978; Kunzle, 1978; Goldman-Rakic and Porrino, 1985; Preuss and Goldman-Rakic, 1987; Yeterian and Pandya, 1988; Barbas et al., 1991; Morecraft et al., 1992; Dermon and Barbas, 1994).

Abbreviations: AD, anterior dorsal nucleus; AM, anterior medial nucleus; AV, anterior ventral nucleus; BDA, biotinylated dextran amine; Cdc, central denso-cellular nucleus; HRP-WGA, horseradish peroxidase-wheat germ agglutinin; MPAll, medial periallocortex (agranular cortex); OLF, olfactory cortex; olfactory tubercle, anterior olfactory nucleus; OPAll, orbital periallocortex (agranular cortex); OPro, orbital proisocortex (dysgranular cortex); Pcn, paracentral nucleus; Sm, stria medullaris

* Corresponding author. Tel.: +1-617-353-5036; fax: +1-617-353-7567.
E-mail address: barbas@bu.edu (H. Barbas).

Since the publication of the above studies, a considerable amount of evidence has been amassed on the functional heterogeneity of the prefrontal cortex as well as thalamic systems in distinct aspects of cognition, emotion and memory (for reviews see Goldman-Rakic, 1995; Steriade et al., 1997; Jones, 1998; Petrides, 2000; Fuster, 2001; Barbas et al., 2002). For example, orbitofrontal and medial prefrontal cortices are robustly linked with the amygdala and medial temporal structures, associated with emotions and long-term memory (for review see Barbas et al., 2002). In contrast, lateral prefrontal cortices appear to have a key role in cognitive tasks and distinct aspects of working memory (for review see Goldman-Rakic, 1988; Fuster, 1995; Petrides, 2000). In view of new evidence, it has become necessary to determine the extent of interaction of the anterior nuclei with functionally distinct prefrontal cortices. Here, we focused on this issue by investigating the extent and pattern of termination of axons in the anterior nuclei from functionally distinct orbitofrontal, medial, and lateral prefrontal cortices with the aid of anterograde tracers. In addition, with the aid of bidirectional tracers, we sought to compare the relationship of prefrontal axonal terminations to projection neurons directed to functionally distinct prefrontal cortices, with a goal to map pathways associated with emotions and specific aspects of memory.

2. Methods and techniques

2.1. Surgical procedures

Experiments were conducted on 21 adult rhesus monkeys (*Macaca mulatta*) under sterile procedure, according to the NIH Guide for the Care and Use of Laboratory Animals (DHEW Publication no. [NIH] 80-22, revised 1987, Office of Science and Health Reports, DRR/NIH, Bethesda, MD). All procedures used were designed to minimize animal suffering and reduce their number. To inject neural tracers, monkeys were anesthetized with ketamine hydrochloride (10 mg/kg, intramuscularly), followed either by sodium pentobarbital administered intravenously through a femoral catheter, or gas anesthetic (isoflurane) after intubation, until a surgical level of anesthesia was achieved. Overall physiological condition was monitored, including heart rate and temperature. A craniotomy was made, the dura was retracted to expose the cortex and the needle was lowered to the desired location under microscopic guidance.

Cortical injections were made 1.5 mm below the pial surface with a microsyringe (5 or 10 μ l; Hamilton) mounted on a microdrive. We injected the prefrontal cortex with three different tracers: the bidirectional tracers horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA, Sigma, St. Louis, MO; 8% solution, volume of 0.05–0.1 μ l); biotinylated dextran amine (BDA, MW 3000, Molecular Probes; 10% solution, volume of 6–8 μ l); or the anterograde tracer [3 H] leucine and [3 H] proline (New England

Nuclear, Boston, MA, now Perkin-Elmer, specific activity 40–80 μ Ci, volume of 0.4–1.0 μ l). After injection of tracers the wound was closed in anatomic layers and the skin sutured. The animals were monitored until recovery from anesthesia, they were given antibiotics and analgesic (Buprenex, intramuscularly) every 12 h, or as needed.

2.2. Perfusion and tissue processing

Animals were given an overdose of anesthetic (sodium pentobarbital, >50 mg/kg, to effect) and perfused through the heart with a fixative. In experiments with injection of HRP-WGA, animals were perfused 2 days after injection (40–48 h) with 2 l of fixative (1.25% glutaraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffered saline (PBS), pH 7.4), followed by 2 l of phosphate buffer (0.1 M, pH 7.4). The brain was then removed from the skull, photographed, and cryoprotected in glycerol phosphate buffer (10% glycerol, Sigma; 2% dimethyl sulfoxide, Sigma, in 0.1 M phosphate buffer, pH 7.4) for 1 day, and then in 20% glycerol phosphate buffer for two additional days.

In experiments with injection of BDA, animals were perfused 18 days after injection with 2–4 l of fixative (4% paraformaldehyde in 0.1 M sodium phosphate buffer, pH 7.4). The brain was then removed, photographed, and placed in graded series of sucrose solutions for cryoprotection (10, 15, 20, 25 and 30% in 0.1 M PBS with 0.05% azide). For both HRP-WGA and BDA cases, after cryoprotection the brain was frozen in -75°C isopentane and cut on a freezing microtome coronally at 40 or 50 μ m in 10 matched series.

In experiments with injection of [3 H]-labeled amino acids, after a 10-day survival period animals were perfused with saline followed by 10% paraformaldehyde. The brain was removed, dehydrated in 50% ethanol, embedded in paraffin and cut into 10 μ m thick coronal sections. The autoradiographic procedure was based on the method of Cowan et al. (Cowan et al., 1972). Tissue sections were counterstained with thionin and coverslipped.

2.3. Immunocytochemical and histochemical procedures

One series of sections was treated to visualize HRP (Mesulam et al., 1980) or BDA. In experiments with BDA injection, tissue sections were washed in 0.1 M PBS and placed in avidin–biotin complex solution (Vector Labs, cat. #PK 6100, Burlingame, CA) overnight. The sections were then washed and processed for immunoperoxidase reaction (3,3'-diaminobenzidine tetrahydrochloride (DAB, plus kit), Zymed lab, cat. #00-2020) to visualize the transported dextran. The tissue was mounted, dried, and counterstained with neutral red (for HRP) or thionin (for BDA). In all cases, adjacent series of sections were stained for Nissl, and myelin or AChE to aid in delineating architectonic borders in thalamic nuclei and the prefrontal cortex (Olszewski, 1952; Olivier et al., 1969; Jones, 1985; Barbas and Pandya, 1989).

2.4. Data analysis

2.4.1. Mapping anterograde label and retrogradely labeled neurons in the anterior nuclei

After prefrontal cortical injections of the bidirectional tracer HRP-WGA we mapped the distribution of terminals and labeled neurons in the anterior nuclei using a commercial tracing system (NeuroLucida, MicroBrightfield Inc., Colchester, VT). After cortical injections of anterograde tracers ($[^3\text{H}]$ amino acids or BDA), we mapped the distribution of terminals in the anterior nuclei. We used two methods to evaluate the density of anterograde label. The first was by visual inspection, under darkfield illumination at $100\times$, where anterograde label was rated as absent (0), light (+), moderate (++) or dense (+++). The second was by optical density analysis of terminals in the anterior nuclei using an image analysis system (MetaMorph, Universal Imaging Corp., West Chester, PA). The system includes a CCD camera mounted on the microscope to capture images directly from brain sections. Measurements of the density of anterograde label were made at $100\times$ magnification under darkfield illumination, using a fiber optic illuminator to ensure even lighting conditions (Optical Analysis Corp., Nashua, NH). Density measurements were obtained from 5 to 6 square shaped samples of identical size. To determine labeling above background level measurements were taken from adjacent areas with no labeled terminals, and the values were subtracted from the density scores. The range of numerical density scores was converted into a scale of (0) to (+++), corresponding to no label (0), light (bottom third, +), moderate (middle third, ++) and dense (top third, +++) label. The final scores from the visual and optical density analysis methods were highly correlated ($r = 0.98$, $P < 0.01$).

2.4.2. Photography

Photographs through the thalamus were captured with a CCD camera using a software system (NeuroLucida, Virtual slice, Colchester, VT). Images were transferred into Adobe Photoshop (Adobe Systems Inc., San Jose, CA) for arrangement and adjusting of contrast and overall brightness, but were not retouched.

3. Results

3.1. Injection sites in prefrontal cortices

Injection sites and types of neural tracers in prefrontal cortices are shown in Fig. 1 and Table 1. Injections of neural tracers were made in orbitofrontal areas in seven cases, medial prefrontal areas in four cases, and lateral prefrontal areas in 10 cases. The injection sites for cortical injections were reconstructed as described previously (e.g. Barbas, 1988). Most cases were used in studies of the connections of prefrontal cortices with other cortical areas (Barbas,

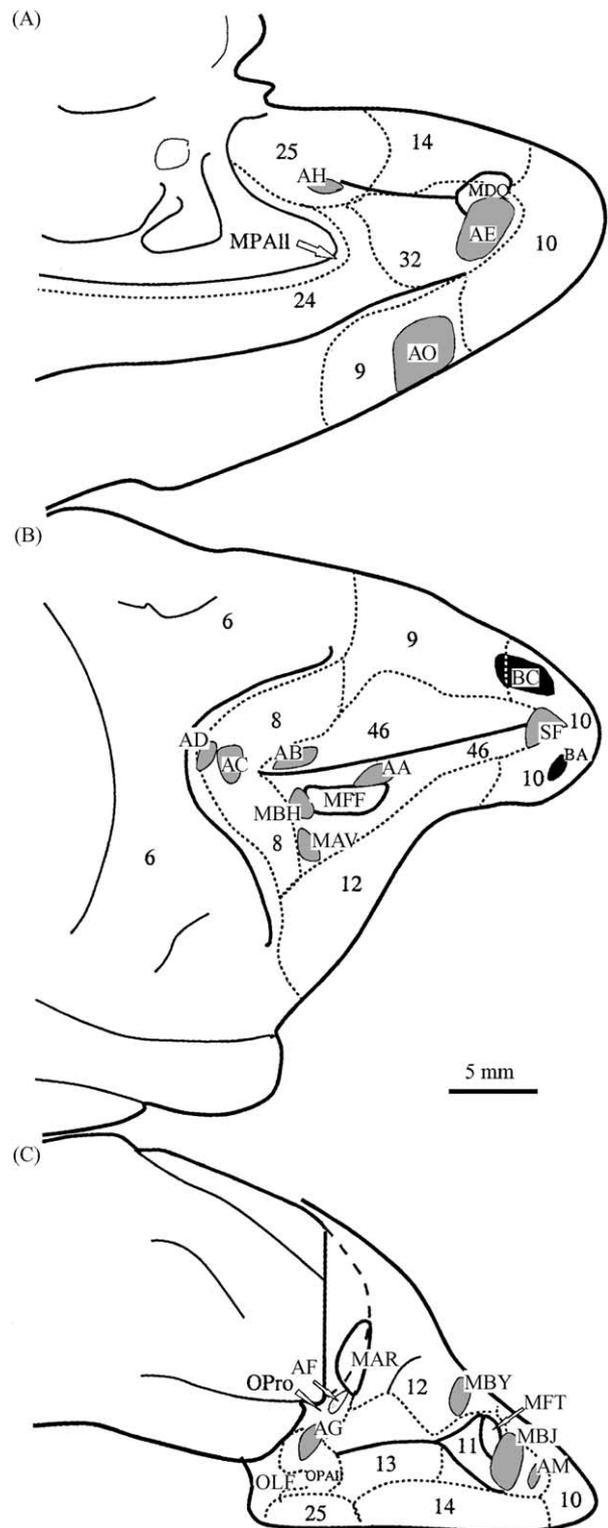


Fig. 1. Composite of injection sites shown on the medial (A), lateral (B) and orbital (C) surfaces of the prefrontal cortex in the rhesus monkey. The temporal pole is depicted transparent on the orbital view (C, large dashed line) to show the posterior part of the orbitofrontal cortex. Small dashed lines delineate areas indicated by numbers based on an architectonic map of the prefrontal cortex (Barbas and Pandya, 1989). MPAII, OPAl, OPro and OLF refer to architectonic areas. Other letter combinations refer to cases (see Table 1). The injection site patterns refer to the type of tracer used: gray, HRP-WGA; black area, BDA; black outline, $[^3\text{H}]$ amino acids.

Table 1
Injection sites, cases, tracer types and types of analysis

Injection site	Case	Tracer type and injection side
Orbitofrontal		
11	AM	HRP-WGA (L) ^a
11	MBJ	HRP-WGA (R) ^a
11	MFT	[³ H] amino acids (L) ^b
12	MBY	HRP-WGA (R) ^a
OPro	AF	HRP-WGA (L) ^a
OPro	MAR	[³ H] amino acids (L) ^b
OPro	AG	HRP-WGA (R) ^a
Medial		
9	AO	HRP-WGA (L) ^a
32	AE	HRP-WGA (L) ^a
32/M14	MDQ	[³ H] amino acids (L) ^b
M25	AH	HRP-WGA (R) ^a
Lateral		
D46	AB	HRP-WGA (R) ^a
V46	AA	HRP-WGA (R) ^a
V46	MBH	HRP-WGA (R) ^a
V46	MAV	HRP-WGA (R) ^a
V46	MFF	[³ H] amino acids (R) ^b
D8	AC	HRP-WGA (R) ^a
D8	AD	HRP-WGA (R) ^a
10	BA	BDA-WGA (R) ^b
10/9	BC	BDA-WGA (L) ^b
10/R46	SF	HRP-WGA (R) ^a

L: left side; R: right side.

^a Anterograde and retrograde analysis.

^b Anterograde analysis.

1988; Barbas, 1993; Barbas and Rempel-Clower, 1997; Barbas et al., 1999; Rempel-Clower and Barbas, 2000), the amygdala (Barbas and De Olmos, 1990), the hippocampal formation (Barbas and Blatt, 1995), the hypothalamus (Rempel-Clower and Barbas, 1998), the basal forebrain (Ghashghaei and Barbas, 2001) and the thalamus (Barbas et al., 1991; Dermon and Barbas, 1994). The analysis of thalamic connections in previous studies was restricted to retrogradely labeled neurons in thalamic nuclei projecting to prefrontal cortices. In two cases, with BDA injection not previously described, the injection occupied a small ventral and anterior part of area 10 (case BA; Fig. 1). In another case, the BDA injection was in the caudal part of dorsal area 10, and extended into a small part of the adjacent part of lateral area 9 (case BC; Fig. 1). In both cases, the injection site included all cortical layers and was confined to the cortical mantle.

3.2. Input–output zones linking prefrontal areas with the anterior nuclei

We first investigated the bidirectional connections between the anterior nuclei and prefrontal cortices after injection of anterograde or bidirectional tracers in prefrontal cortices. Axonal terminations from most prefrontal areas were noted in the anterior medial (AM) nucleus. Overall, orbitofrontal, medial prefrontal, and frontal polar areas

had moderate to robust connections with the anterior nuclei. In contrast, most dorsolateral prefrontal cortices had comparatively weaker connections with the anterior nuclei. Moreover, axons from prefrontal cortices terminated on both sides of the anterior nuclei, particularly in the AM nucleus, though the ipsilateral terminations were denser. The density and pattern of terminations from the prefrontal areas in AM varied, as described for each case later, and shown in Fig. 2. The descriptions below will be limited to the side ipsilateral to the injection side.

3.2.1. Orbitofrontal cases

Rostral (areas 11, O12¹) and caudal (area OPro) orbitofrontal areas were connected with the AM, but had few, if any, connections with the AV nucleus. Projections from area OPro to the AM were studied in three cases. Significant connections with the anterior nuclei were seen in only one case (case AF), consistent with the restricted projections from AM to area OPro described previously (Dermon and Barbas, 1994). In case AF, anterograde label in AM was seen at the dorsomedial part at the central and caudal extent of the nucleus (Fig. 3, top, A–D, case AF). The labeled axonal terminals were clustered in several patches. Projections from the cortex were more widely distributed than the labeled thalamocortical projection neurons.

Likewise, projections from orbital area 12 terminated in a large and dense patch in the dorsomedial part of AM (Fig. 3, bottom, A–D, case MBY). Several clusters of projection neurons were surrounded by axonal terminations, and small patches of lightly labeled axonal terminals were noted at the ventral and lateral part of AM bordering the mammillothalamic tract. The axonal terminations were more widely distributed than the projection neurons, suggesting at least partial segregation of input and output zones linking the AM with orbital area 12. Like in case AF (area OPro), label was denser at the caudal part of AM than at rostral sites (Fig. 2).

In cases with injections in area 11 ($n = 3$), labeled terminals were somewhat less dense in comparison with orbital area 12, and were distributed in both rostral and caudal parts of the AM (Figs. 2 and 4). Retrogradely labeled neurons were intermingled with anterograde label. In one case (MFT), the axonal terminals were widely distributed in rostral AM, but were focally clustered ventromedially at the caudal part of AM (Fig. 4, center, A–C). In cases with more rostrally located injections in area 11 (cases MBJ, AM), the density of labeled terminals was somewhat lower (Fig. 4, top, A–D; bottom, A and B).

3.2.2. Medial cases

As in the orbitofrontal cases, anterogradely labeled terminals originating from medial prefrontal cortices formed patches in the AM nucleus (Fig. 5). Unlike the orbitofrontal cases, however, significant anterograde label was noted in

Letters preceding numbers designating prefrontal architectonic areas refer to: D, dorsal; M, medial; O, orbital; R, rostral; V, ventral.

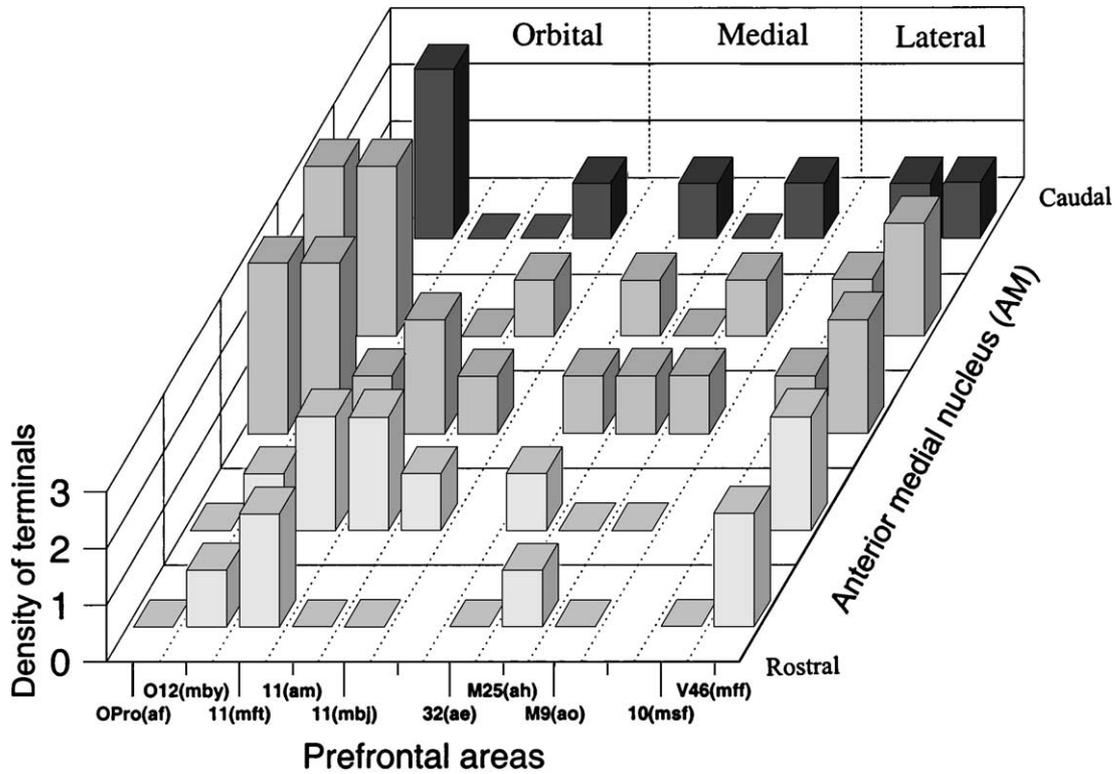


Fig. 2. Density of axonal terminations from prefrontal areas to the AM nucleus. (X-axis) Origin of projections in different prefrontal areas (cases in parentheses). (Y-axis) The termination of axons in rostral to caudal AM. (Z, vertical axis) Density of terminals measured by optical analysis (0, no label, to 3, dense label).

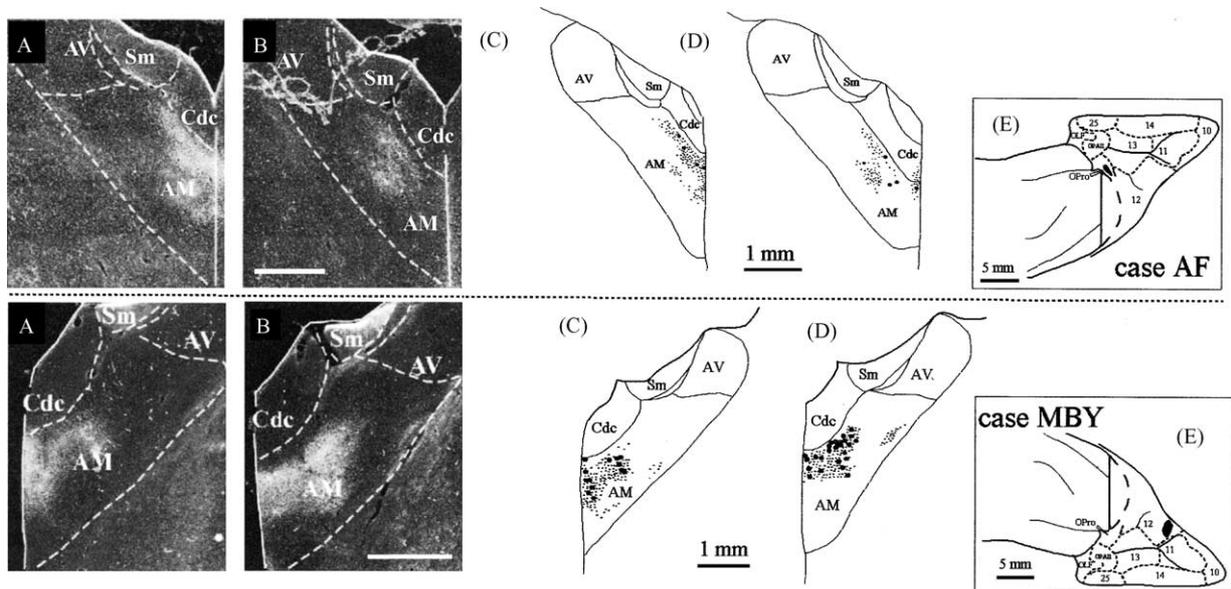


Fig. 3. Connections of posterior orbitofrontal areas with the anterior nuclei. (Top: A and B) Darkfield photomicrographs taken from representative coronal sections from rostral to caudal extent of the thalamic anterior nuclei showing anterograde label in AM (white grain) after injection of HRP-WGA in area OPro (case AF). (C and D) Maps of coronal sections through the anterior nuclei in case AF showing the distribution of labeled projection neurons (big dots) directed to area OPro and anterograde label of axonal terminations (small dots) originating in area OPro. (E) Injection site in area OPro (black area) on the basal surface. (Bottom: A and B) Darkfield photomicrographs from representative coronal sections through the anterior nuclei showing anterograde label in AM (white grain) after injection of HRP-WGA in area O12 (case MBY). (C and D) Maps of coronal sections through the anterior nuclei in case MBY showing the distribution of projection neurons (big dots) directed to area O12 and anterograde label of axonal terminations (small dots) in AM originating in area O12. (E) Injection site in orbital area 12 (black area) on the basal surface. Scale bar in A and B (top and bottom) = 1 mm. Scale bar in E (top and bottom) = 5 mm.

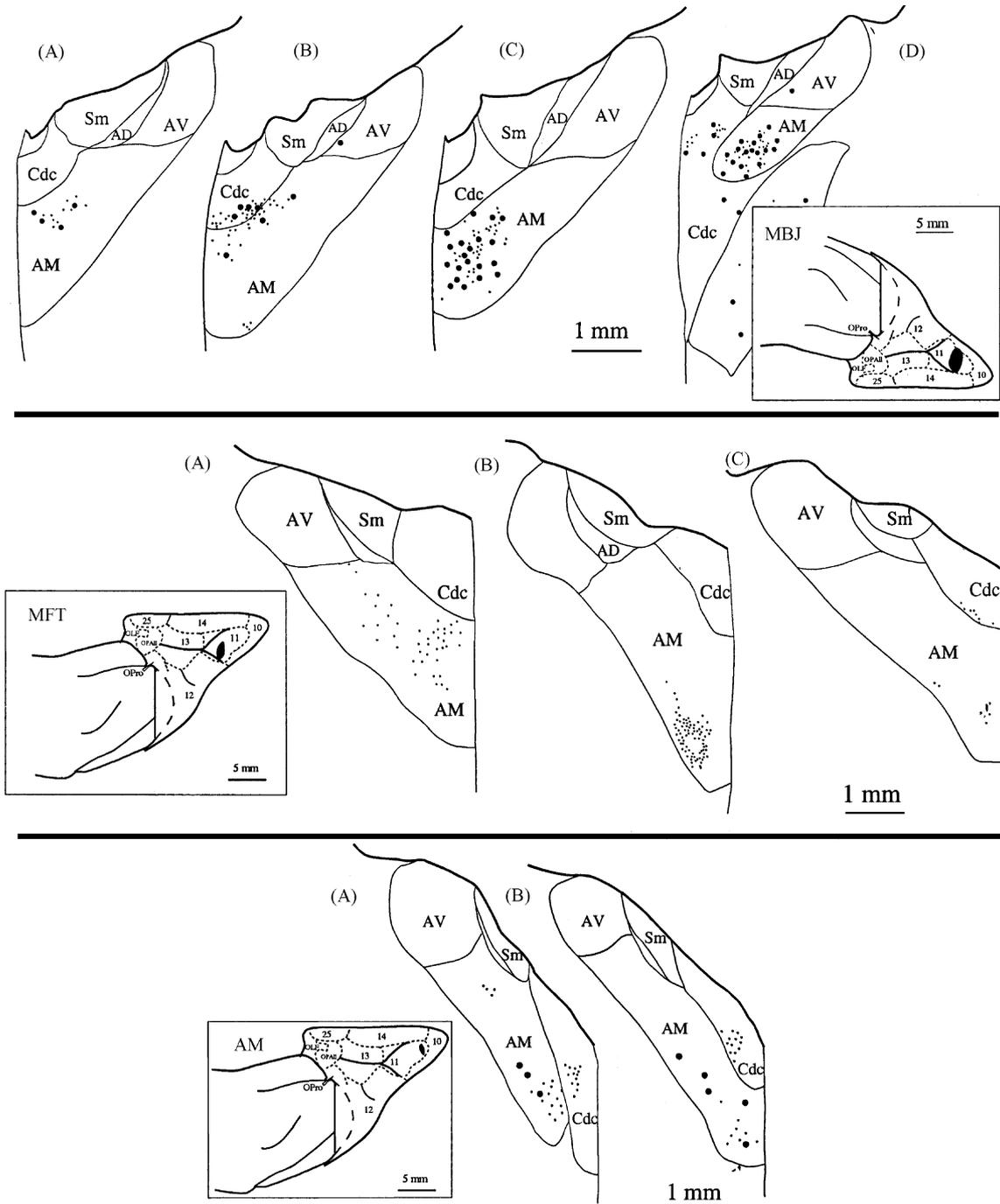


Fig. 4. Connections of anterior orbitofrontal area 11 with the anterior nuclei in three cases. Distribution of labeled neurons (big dots) and terminals (small dots) shown in a series of coronal sections in rostral (left) to caudal (right) thalamic anterior nuclei after tracer injection in area 11. (Top: A–D) Bidirectional connections mapped in the anterior nuclei after injection of HRP-WGA in case MBJ. (Centre: A–C) Distribution of axonal terminals in the anterior nuclei after injection of [3 H] amino acids in case MFT. (Bottom: A and B) Bidirectional connections mapped in the anterior nuclei after injection of HRP-WGA in case AM. Insets: injection site on the orbital surface in each case (black area).

the AV nucleus as well, in cases with injections in medial areas 25 and 32. In addition, very few labeled neurons were noted in the anterior nuclei, suggesting a dominant feedback system from medial prefrontal cortices to the anterior nuclei.

After HRP injection in the rostral part of area 32 (Fig. 5, top inset), light anterograde label was seen in small clusters at the dorsal and ventromedial part of the AM nucleus (Fig. 5, top, A–D, case AE). The ventrally situated patch of label was found only in rostral sections. Labeled axonal

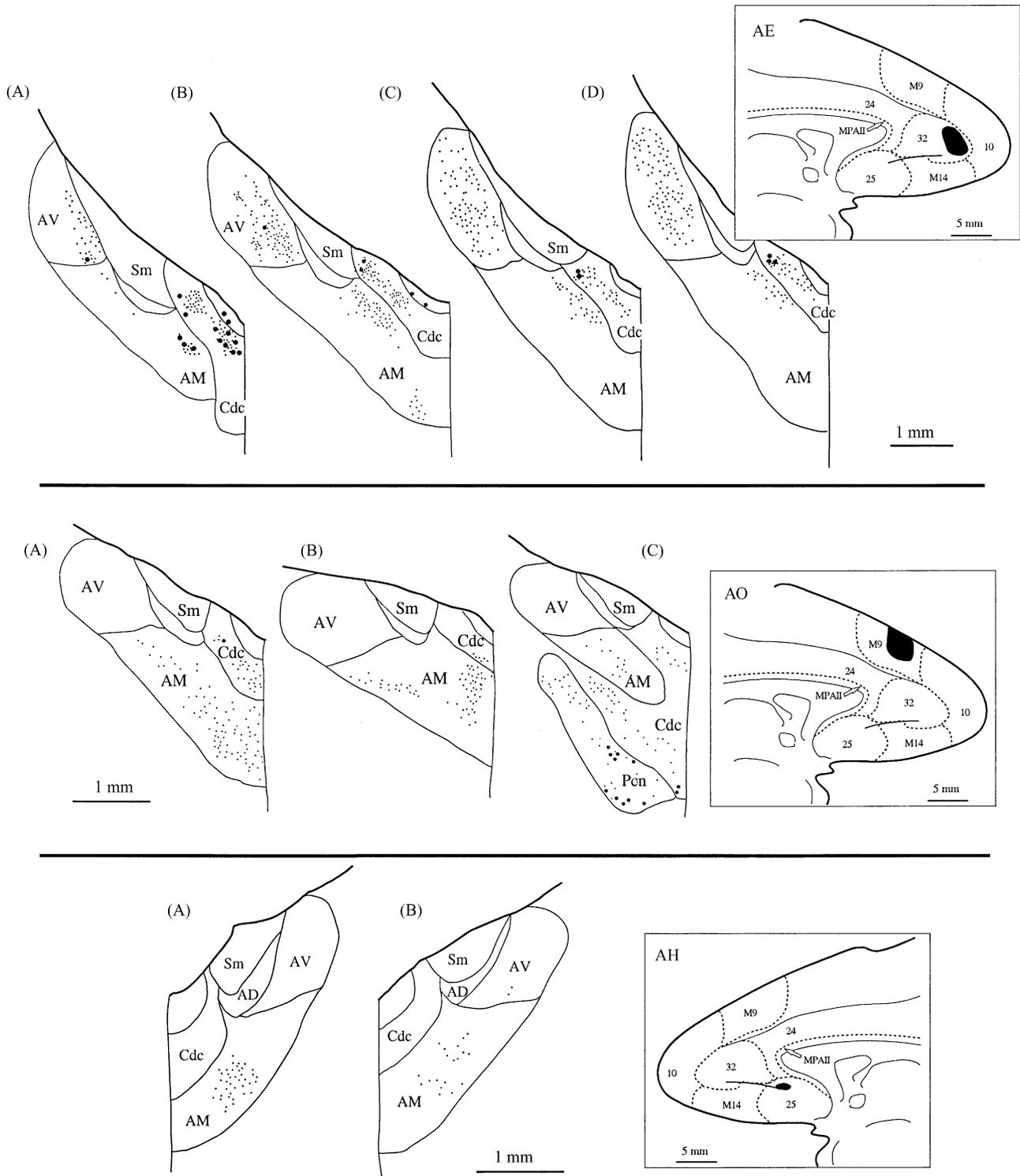


Fig. 5. Connections of medial prefrontal cortices with the anterior thalamic nuclei. Distribution of labeled neurons (big dots) and axonal terminals (small dots) shown in a series of coronal sections in rostral (left) to caudal (right) thalamic nuclei after injection of HRP-WGA. (Top: A–D) Bidirectional connections mapped in the anterior nuclei after injection of HRP-WGA in area 32, case AE. (Center: A–C) Anterograde label mapped in the anterior nuclei after injection of HRP-WGA in area M9, case AO. (Bottom: A and B) Anterograde label mapped in the anterior nuclei after injection of HRP-WGA in medial area 25, case AH. Insets: injection site on the medial surface in each case (black area).

terminals surrounded projection neurons rostrally. At caudal levels of the nucleus there was anterograde label but no labeled neurons (Fig. 5, top, B–D). Moderate anterograde label was also seen in AV (Fig. 5, top, A–D, case AE). In another case, with [³H] amino acid injection in the ventral part of area 32 and the dorsal part of area 14 (case MDQ), there was no evidence of labeling in the anterior nuclei (not shown).

After injection of HRP in medial area 9 (Fig. 5, center, inset), there was no evidence of labeled neurons, but light to moderate anterograde label was clustered in distinct patches at the caudal part of AM, occupying both medial and lateral aspects of the nucleus (Fig. 5, center, A–C, case AO). At rostral levels of the nucleus axonal terminals were more diffusely distributed than in caudal sections.

After a very small injection of HRP in medial area 25 (Fig. 5, bottom inset, case AH), labeled axonal terminals were seen at the center of the AM nucleus, which were diffuse rostrally and in two patches caudally. There was no evidence of labeled neurons (Fig. 5, bottom, A and B, case AH).

3.2.3. Dorsolateral cases

Among lateral areas, area 10 had the strongest connections with AM ($n = 3$). In a case with BDA injection in ventral area 10 moderate terminal label was seen in patches at the ventrolateral part of AM (Fig. 6, top, A–D, case BA). In this case, some anterograde label was found in the AV nucleus as well. In a case with injection in the caudal part of dorsal area 10, which extended somewhat into area 9 (Fig. 1, case BC), moderate terminal label was noted in distinct clusters in the ventromedial and central parts of AM (not shown). Significant axonal label was also noted in AV. In another case with injection of HRP in dorsal area 10 which impinged on the rostral part of area 46, only light label was seen in AM (Fig. 6, bottom, A–C, case SF).

Projections from other lateral prefrontal cortices were comparatively sparse. After injections of HRP-WGA or [³H] amino acids in area 46 ($n = 5$, cases AB, AA, MBH, MAV, MFF), we noted moderate anterograde label at the medial and ventral portion of the AM nucleus in only one case (case MFF, not shown). There was no evidence of label in AM after injections in dorsal area 8 ($n = 2$, cases AC and AD).

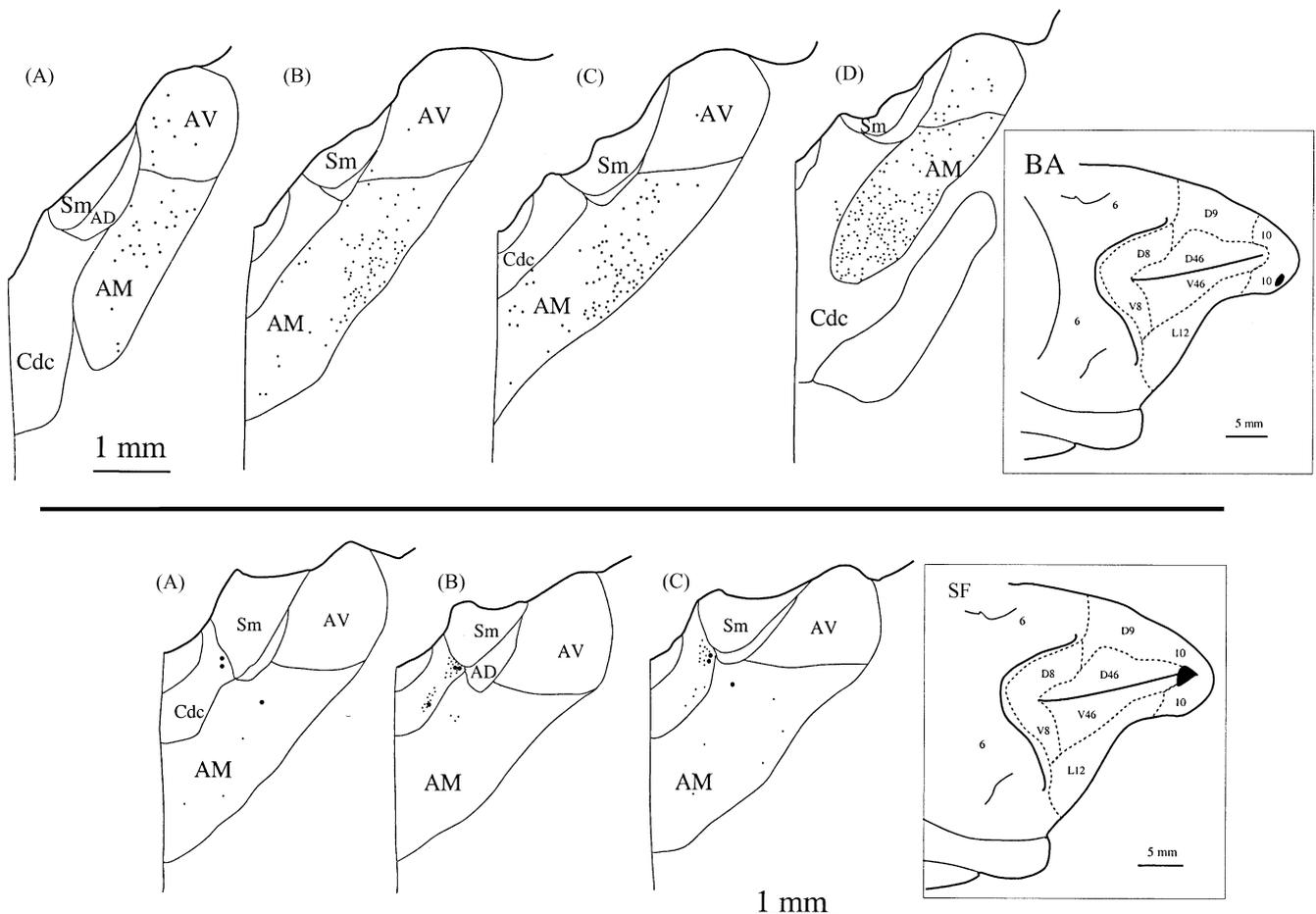


Fig. 6. Connections of prefrontal area 10 with the anterior nuclei in two cases. Distribution of labeled neurons (big dots) or terminals (small dots) shown in a series of coronal sections in rostral (left) to caudal (right) anterior thalamic nuclei after tracer injections in area 10. (Top: A–D) Distribution of axonal boutons mapped in the anterior nuclei after injection of BDA in ventral area 10, case BA. (Bottom: A–C) Bidirectional connections mapped in the anterior nuclei after injection of HRP-WGA in dorsal area 10, case SF. Insets: injection site on the lateral surface in each case (black area).

4. Discussion

The results provided evidence that the anterior thalamic nuclei are preferentially connected with some orbitofrontal and medial prefrontal cortices, and have moderate and consistent connections with frontal polar cortices. The prefrontal areas examined were preferentially connected with the anterior medial nucleus, even though medial areas 32 and 25 and the frontal polar cortex had more widespread connections that involved the anterior ventral nucleus as well. Moreover, in the anterior nuclei prefrontal axonal terminations were more expansive, in comparison with the restricted origin of projection neurons, and terminated bilaterally, suggesting that the prefrontal cortex may exert widespread influence on the anterior nuclei.

Connections linking the AM nucleus and the orbitofrontal cortex were suspected on the basis of early cortical ablation studies in monkeys, which resulted in retrograde degeneration in the AM nucleus (Walker, 1936). These results were later confirmed in neural tracing studies (Kievit and Kuypers, 1977; Preuss and Goldman-Rakic, 1987; Barbas et al., 1991; Morecraft et al., 1992; Dermon and Barbas, 1994; Bachevalier et al., 1997; Cavada et al., 2000). Large injections of the bidirectional tracer HRP encompassing rostral and central orbitofrontal areas (10, 11, 12, 13 and 14) showed dense labeling in the AM nucleus in macaque monkeys (Cavada et al., 2000). Similarly, large injections of retrograde tracers, which included the frontal pole (area 10) and other prefrontal areas (9, 46, 12, 11, 25 and 24), lateral and orbitofrontal cortices (areas 46, 11, and 13), area 12 and ventral area 46, labeled the AM nucleus in macaque monkeys (Ilinsky et al., 1985; Goldman-Rakic and Porrino, 1985; Preuss and Goldman-Rakic, 1987).

The other significant projection to AM arose from medial prefrontal areas, including medial prefrontal areas 32, 25, and 9, consistent with the classic view of connections of the AM nucleus with anterior (areas 24 and 32), as well as with posterior (area 23) cingulate areas (Le Gros Clark, 1932; Le Gros Clark and Boggan, 1933; Mettler, 1947; Domesick, 1969). This finding has been confirmed in modern tracing studies in rats, cats and monkeys (Krettek and Price, 1977; Niimi et al., 1978; Baleydier and Mauguier, 1980; Kaitz and Robertson, 1981; Robertson and Kaitz, 1981; Kolb, 1984; Seki and Zyo, 1984; Room et al., 1985; Yeterian and Pandya, 1988; Barbas et al., 1991; Musil and Olson, 1991; Dermon and Barbas, 1994; Velayos et al., 1998; Chiba et al., 2001).

4.1. Circuits for emotion linking prefrontal areas with the anterior nuclei

The AM nucleus occupies a key position in Papez's circuit for emotions (Papez, 1937). Papez formulated his classic hypothesis on the basis of clinical observations and

lesion studies. Patients with tumors impinging on the anterior nuclei, or epileptic patients whose anterior nuclei were removed, showed abrupt changes in emotional expression. Subsequent studies substantiated Papez's theory by providing evidence that lesions or stimulation of the AM nucleus elicit mood swings, including sadness, agitation, emotional indifference and inability to interpret dramatic events within an emotional context (Spiegel and Wycis, 1962; Mark et al., 1963; Mark et al., 1970; Clarke et al., 1994; for review see Tasker and Kiss, 1995). In addition, perseveration, addictive behavior, and lack of motivation were reported after damage to the AM nucleus (Mark et al., 1970; Young et al., 2000; Ghika-Schmid and Bogousslavsky, 2000; George et al., 2001). Cell degeneration in the AM nucleus following cingulate lesions was positively correlated with lack of maternal behavior in mice, exhibited by disinterest in building nests and taking care of pups (Slotnick and Nigrosh, 1975). In addition, lesion of the AM nucleus reduced auditory fear conditioning responses in rats (Celerier et al., 2000).

One key region connected with the anterior medial nucleus was the orbitofrontal cortex, involving a small part of the posteriorly situated area OPro, orbital area 12 and area 11. The orbitofrontal cortex is known to be involved in reward and goal motivated behavior in primates (Tremblay and Schultz, 1999; Schultz et al., 2000). In humans, pathology in the orbitofrontal cortex has been described in several psychiatric and neurologic diseases where emotional behavior is affected. For example, hyperactivation of orbitofrontal cortex in humans is associated with obsessive compulsive disorder (Rapoport and Fiske, 1998), while its damage is associated with impairment in decision making and sociopathic personality disorder (Damasio et al., 1990; Saver and Damasio, 1991; Rapoport and Fiske, 1998; Bechara et al., 2000; Damasio, 2000).

Medial prefrontal cortices, which are also robustly connected with the AM nucleus, have been associated with aspects of emotional behavior that differ from the orbitofrontal cortices. For example, lesions of the anterior cingulate cortex result in impaired motivation and marked apathy in psychiatric patients (Mega and Cummings, 1994). Medial prefrontal areas at the anterior cingulate have been implicated in emotional communication through connections with auditory cortices (Barbas et al., 1999; for reviews see Vogt and Barbas, 1988; Devinsky et al., 1995; Barbas et al., 2002), a pathway which appears to be affected in schizophrenic patients who experience auditory hallucinations (for review see Barbas, 2000). Structural changes in the cingulate cortex and reduction of the total number of neurons in the AM nucleus have been noted in the brains of schizophrenic patients (Young et al., 2000; for review see Benes, 1993). Our findings of a strong linkage of the AM nucleus with both orbitofrontal and medial prefrontal areas may help explain why its damage results in deficits commonly associated with damage to orbitofrontal cortices, as well as with medial prefrontal cortices.

4.2. Circuits for distinct aspects of memory linking prefrontal areas with the anterior nuclei

In addition to a role in emotional processes, both medial and orbitofrontal cortices have been implicated in aspects of long-term memory. The involvement of posterior orbitofrontal areas in memory can be understood by their bidirectional connections with entorhinal and perirhinal cortices and the hippocampal formation (Barbas, 1993; Barbas and Blatt, 1995; Barbas et al., 1999; Cavada et al., 2000; Insausti and Munoz, 2001; for reviews see Wall and Messier, 2001; Barbas et al., 2002). However, among prefrontal cortices, it is the caudal medial areas in the anterior cingulate (areas 25, 24, and the caudal part of area 32) that stand out as the principal recipients of heavy projections from the hippocampal formation, originating from the subicular complex and CA₁ (Barbas and Blatt, 1995). In addition, caudal medial areas 32, 25 and 24 have bidirectional connections with anterior medial temporal cortices, including the entorhinal (area 28) and perirhinal (areas 35, 36) areas (Vogt and Pandya, 1987; Barbas, 1988; Carmichael and Price, 1995; Bachevalier et al., 1997; Barbas et al., 1999). Damage to these medial areas around the rostral part of the corpus callosum in humans, results in anterograde amnesia comparable to the classic amnesic syndrome described after hippocampal lesions (Talland et al., 1967; Alexander and Freedman, 1984; D'Esposito et al., 1996; for review see Barbas, 1997). Medial prefrontal cortices are also robustly connected with midline thalamic nuclei, the magnocellular sector of the mediodorsal nucleus (MDmc), and the caudal part of parvocellular MD (MDpc) (Baleyrier and Mauguier, 1980; Goldman-Rakic and Porrino, 1985; Barbas et al., 1991; Morecraft et al., 1992; Ray and Price, 1993; Dermon and Barbas, 1994), all of which have been implicated in long-term memory (for reviews see Markowitsch, 1982; Squire and Zola-Morgan, 1988; Amaral et al., 1990; Squire, 1992; Zola-Morgan and Squire, 1993).

Our findings further demonstrated a consistent connection between prefrontal polar cortex and the AM nucleus. This prefrontal area has been implicated in a special type of prospective working memory, where the subject must hold the main goal in mind while attending to concurrent secondary goals (Okuda et al., 1998; Burgess et al., 2000). Based on evidence from patients with circumscribed cerebral lesions and functional MRI studies on normal subjects, the frontal polar cortex appears to be involved in complex planning and strategy switch among planned and unexpected events, a circuit that may also involve the dorsolateral prefrontal cortex, the dorsolateral striatum, and parahippocampal regions (Okuda et al., 1998; Koechlin et al., 1999; Koechlin et al., 2000; Burgess et al., 2000). Suppression of the activity of the frontal polar region was found in manic patients who make poor decisions (Murphy et al., 1999).

The above evidence suggests that the frontal polar cortex and the anterior thalamic nuclei may have a common role in prospective aspects of working memory. In contrast, the

pathways linking orbitofrontal and medial prefrontal cortices with the anterior nuclei may be engaged in processes underlying emotion and long-term memory. Further physiologic and imaging studies are necessary to address this issue.

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