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Chapter 13 The accessory optic system: basic organization with an update on connectivity, neurochemistry, and function

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Abstract

The accessory optic system (AOS) is formed by a series of terminal nuclei receiving direct visual information from the retina via one or more accessory optic tracts. In addition to the retinal input, derived from ganglion cells that characteristically have large receptive fields, are direction-selective, and have a preference for slow moving stimuli, there are now well-characterized afferent connections with a key pretectal nucleus (nucleus of the optic tract) and the ventral lateral geniculate nucleus. The efferent connections of the AOS are robust, targeting brainstem and other structures in support of visual-oculomotor events such as optokinetic nystagmus and visual–vestibular interaction. This chapter reviews the newer experimental findings while including older data concerning the structural and functional organization of the AOS. We then consider the ontogeny and phylogeny of the AOS and include a discussion of similarities and differences in the anatomical organization of the AOS in nonmammalian and mammalian species. This is followed by sections dealing with retinal and cerebral cortical afferents to the AOS nuclei, interneuronal connections of AOS neurons, and the efferents of the AOS nuclei. We conclude with a section on Functional Considerations dealing with the issues of the response properties of AOS neurons, lesion and metabolic studies, and the AOS and spatial cognition.

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Abstract:

The accessory optic system (AOS) is formed by a series of terminal nuclei receiving direct visual information from the retina via one or more accessory optic tracts. In addition to the retinal input, derived from ganglion cells that characteristically have large receptive fields, are direction-selective and have a preference for slow moving stimuli, there are now well characterized afferent connections with a key pretectal nucleus (nucleus of the optic tract) and the ventral lateral geniculate nucleus. The efferent connections of the AOS are robust, targeting brainstem and other structures in support of visual-oculomotor events such as optokinetic nystagmus and visual-vestibular interaction. The present chapter reviews the newer experimental findings while including older data concerning the structural and functional organization of the AOS. We then consider the ontogeny and phylogeny of the AOS and include a discussion of similarities and differences in the anatomical organization of the AOS in nonmammalian and mammalian species. This is followed by sections dealing with retinal and cerebral cortical afferents to the AOS nuclei, interneuronal connections of AOS neurons, and the efferents of the AOS nuclei. We conclude with a section on Functional Considerations dealing with the issues of the response properties of AOS neurons, lesion and metabolic studies, and the AOS and spatial cognition.

1. Introduction Research over the past 20 years has resulted in great strides toward understanding the organization of the accessory optic system (AOS). In particular, there have been breakthroughs in at least four major areas. *First*, van der Want and co-workers demonstrated the ultramicroscopic architecture of connections within the AOS and of the AOS with the retina and pretectum. They showed that a prominent system of neurons of the medial terminal nucleus (MTN) that are GABAergic contacts the somata and dendrites of nonGABAergic neurons of the nucleus of the optic tract (NOT) via F-terminals (van der Togt et al., 1991; also van der Togt and Schmidt, 1994; Schmidt et al., 1994, 1998). They further discovered that MTN neurons are contacted by R-terminals from retinofugal axons (see also Lenn, 1972), that some MTN neurons display F-terminals on NOT neurons, and that a significant number of MTN somata represent local circuit neurons interconnecting the dorsal (MTN_d) and ventral (MTN_v) parts of the nucleus (van der Togt et al., 1993).

A *second* important contribution toward an understanding of the AOS has resulted from functional works, for instance electrophysiological studies (e.g., Mustari and Fuchs, 1989) and metabolic studies (e.g., Biral et al., 1987; Benassi et al., 1989; Lui et al., 1990). These researchers investigated the functional properties of AOS neurons, mainly related to slowly moving visual stimuli (optokinetic stimulation) and eye movements in the awake, behaving animal.

A *third* area providing important information concerned research on neurotransmitters and receptors in the AOS. It was demonstrated that most, if not all, of the MTN-NOT neurons are GABAergic (van der Togt et al., 1991; Giolli et al., 1992). Related to this, pharmacological studies by Schmidt et al. (1994, 1998) revealed that bicuculline, a $GABA_A$ receptor antagonist, increases the spontaneous activity of NOT/DTN neurons without any inhibitory action by GABAergic, MTN projection neurons on NOT neurons (van der Togt and Schmidt, 1994). From this, Schmidt and van der Togt linked $GABA_B$, and not $GABA_A$, receptors with the control of gaze stabilization involving AOS neurons.

The *fourth* major breakthrough is represented by studies that have improved our understanding of the AOS in relation to poorly differentiated areas of the ventral midbrain tegmentum, and these areas in relation to secondary AOS pathways to cortical and mesolimbic structures as well as olivocerebellar pathways. In this regard, Wylie et al. (1999) have shown a pathway in pigeon that arises both directly from the nucleus of the basal optic root (nBOR), and secondarily through synaptic relay in the ventral tegmental area (VTA), and terminates in the hippocampal cortex. A comparable mesotelencephalic path was described in rat by Gasbarri et al. (1994) who postulated that this pathway is concerned with spatial memory (Gasbarri et al., 1996). Other data show that the central region of the pigeon VTA/substantia nigra (Wylie et al., 1999) appears to correspond to the mammalian visual

tegmental relay zone (VTRZ), a region known to connect the AOS nuclei and adjacent VTA with the inferior olive (Maekawa and Takeda, 1979; Giolli et al., 1984, rabbit and rat; Blanks et al., 1995, marmoset; Wylie, 2001, pigeon). Other tract-tracing studies on rat (Fallon et al., 1984; Giolli et al., 1985c) suggested a bisynaptic retino-mesotelencephalic pathway in which retinofugal axons terminate on VTA neurons that, in turn, project to the caudate nucleus, putamen, and anterior cingulate and prefrontal cortices.

2. Features of the Accessory Optic Pathways and Nuclei

2.1 Topography and nomenclature (Figs. 1A-C)

The earliest definitive papers dealing with the accessory optic pathways were by Gudden (1870, 1881) who provided an amazingly accurate description, given that time, of his tractus peduncularis transversus in the rabbit. Gudden (1881) also reported that the tractus peduncularis transversus degenerated after contralateral eye enucleation in young animals. It was Bechterew (1894) who first described the main terminus for the AOS fibers, the nucleus tractus peduncularis transversus. Subsequently, the terms tractus peduncularis transversus and nucleus tractus peduncularis transversus (Anglicized to transpeduncular tract and nucleus of the transpeduncular tract) remained in common usage up until the 1960's, although several different names were applied to this tract and nucleus over the years, e.g., posterior accessory optic tract and nucleus of the posterior accessory optic tract, basal optic root and nucleus of the basal optic root, tractus opticus basalis and nucleus tractus opticus basalis, and tractus opticus tegmenti and nucleus tractus opticus tegmenti (the interested reader should consult papers dealing with the period 1881-1960, e.g., Gillilan, 1941; Le Gros Clark, 1942; Giolli, 1961, 1963; Giolli et al.,1968; and Mai, 1978). Beginning in the 1960's, researches quickly adopted a new, readily understandable, and standardized topographical- nomenclatural scheme, which currently serves as the template for descriptions of the topographical scheme for the mammalian AOS. This scheme was introduced by Hayhow and colleagues (see Hayhow, 1959, 1966; Hayhow et al., 1960). Figures 1A, B illustrate the topography and nomenclature for the mammalian AOS according to this scheme. Hayhow et al. recognized the inferior and superior fasciculi (IF and SF respectively) and subdivided the SF into anterior, medial and posterior fiber groups (SFa, SFm and SFp, respectively) (not labeled in Figs. 1A-B). They further demonstrated that retinofugal fibers terminate in three terminal AOS nuclei lying along the course of the SFp: the dorsal terminal nucleus (DTN), lateral terminal nucleus (LTN) and medial terminal nucleus (MTN) (Figs. 1A-C).

Among non-mammalian species, the retinofugal fibers to the nBOR were described in amphibians, reptiles and birds as arising from a distinct set of retinal ganglion cells, *the displaced ganglion cells* (Karten et al., 1977; Reiner et al., 1979; Fite et al., 1981; McKenna and Wallman, 1985). These fibers project via the basal optic root (BOR) to the nucleus of the basal optic root (nBOR) located in the midbrain tegmentum. Although certain interspecies differences exist, the nBOR of nonmammalian species and the mammalian AOS nuclei should be viewed as homologous structures, anatomically, functionally and in terms of most, though possibly not all, basic nerve connections.

2.2 Ontogeny

The development of the retinal projections to the nuclei of the AOS has been studied in a variety of mammalian species. The specificity of retinofugal projections to the AOS nuclei appears to be determined during the embryonic stage by the presence, both in retinal cells and in the neurons and neuropile of these nuclei, of a specific subset of cadherins (adhesion molecules), namely, cadherin-6B and cadherin-7 (Wohrn et al., 1998). There seems to be a common developmental pattern, in which retinal fibers first reach these nuclei, and then undergo a remodeling through terminal retraction and/or fiber degeneration. In rat, for instance, retinal afferents reach the AOS nuclei early, i.e., by embryonic day (E) 17 in the MTN and E20 in the DTN and LTN (Bunt et al., 1983). However, the development continues well after birth. Between postnatal day (P) 1 through P3, complex growth cones prevail, whereas at P6 through P12 axons start to collateralize. At still later stages (P16), growth cones and collaterals disappear, and varicosities and terminal arborizations appear as the animal develops the adult-like patterns (Bai et al.,

2001). These same authors have found that retinal afferents are much more widespread at birth, involving the AOS nuclei and the adjacent ventral tegmental area, whereas they are strictly confined to the AOS in adults. In both pigmented and albino rabbits, the AOS nuclei receive retinal afferents by E24; the ipsilateral projections are most conspicuous at E 26, then degenerate almost completely, so that at birth the retinal projections show an adult-like distribution, i.e., within the AOS nuclei and almost exclusively contralateral (Gayer et al., 1989). In grey squirrels the AOS nuclei are already innervated at birth (Cusick and Kaas, 1982), although these retinal projections undergo redistribution during postnatal development. Studies in the marsupial fat-tailed dunnart (Dunlop et al., 1997) have shown that the development of visual pathways in general and of accessory optic projections in particular, occurs entirely postnatally in this species: retinal projections don't reach the accessory optic nuclei until P15. This makes the dunnart a suitable species for studies on the development of the visual system.

A postnatal developmental pattern is also present in birds. Metabolic studies on the avian nBOR, homologous to the mammalian AOS, revealed late development of the physiologic responses (direction selectivity) in the different portions of the nucleus (McKenna and Wallman, 1985).

Manipulation during development (either enucleation or dark rearing) dramatically alters the retino-AOS projections, mainly increasing the ipsilateral contingent that is usually either very small or totally absent (rabbit: Collewijn and Holstege, 1984; wallaby: Marotte et al., 1989). It also changes the AOS functional properties (e.g., directional selectivity, velocity preference and ocular dominance) (Collewijn and Holstege, 1984; Grasse and Cynader, 1986). It is worth noting that a certain degree of plasticity is retained, even in the adult, following enucleation (Collewijn and Holstege, 1984).

Yan and Johnson (1988) found nerve growth factor (NGF) receptor immunoreactivity in the MTN of developing rats, both before and after birth. NGF immunoreactivity was also found in other visual nuclei, including the pretectal olivary nucleus, but, interestingly, not in the pretectal nucleus of the optic tract, which is a functional ally of the AOS in the optokinetic response.

2.3 Phylogeny

An AOS has been identified in all vertebrate species in which it has been sought. What follows is a summary of the AOS in a variety of species, revealing similarities and differences in the morphology of the AOS of nonmammalian and mammalian species. The data are summarized in Table 1.

Nonmammalian species: These exhibit an AOS composed of a basal optic root (BOR) and one or more terminal accessory optic nuclei lying in the ventral midbrain tegmentum (but see Wicht and Northcutt, 1990, hagfish). In fishes, early descriptions of the AOS were at times incomplete because of small brain size or the unique features of the brains. However, through careful tract-tracing experiments on catfish and goldfish, Finger and Karten (1978) demonstrated a nonmammalian AOS consisting of a BOR and two terminal nuclei (P1 and P2). The same pattern for the AOS was recognized in elasmobranchs (Northcutt, 1979) and several species of bony fishes (e.g., Finger and Karten, 1978; Northcutt, 1977; Northcutt and Butler, 1993).

Studies also showed the presence of a basic accessory optic system in amphibians (frog: Montgomery et al., 1981; Lazar, et al., 1983; salamanders: Riss et al., 1963; Jakway and Riss, 1972; Gruberg, 1973) and reptiles (turtles: Bass and Northcutt, 1981, Martin et al., 2003; lizards: Butler and Northcutt, 1971; snakes: Rio et al., 1983). Among birds, the pigeon AOS is well developed and consists of a BOR whose fibers terminate in principal (nBORp), dorsal (nBORd) and lateral divisions (nBORl) of the nBOR all found in the ventral midbrain tegmentum (VTA). For details about the nonmammalian AOS, the interested reader should consult articles by, e.g., Karten et al., 1977; Mai, 1978; Reiner et al., 1979; Brecha et al., 1980; Wallman et al., 1981; Fite et al., 1981; Fite, 1985.

Mammalian species: Data pertaining to the AOS tracts and terminal nuclei of nontherian mammals (monotremes) are important in an evolutionary sense. The egg-laying, monotremes, echidna and duckbilled platypus, are the sole surviving

representatives of nontherian mammals and are highly specialized for their mode of life. Echidna and the duckbilled platypus show considerably more features resembling reptiles than either marsupials or eutherian mammals (Hopson, 1969; Campbell and Hayhow, 1971, 1972). Campbell and Hayhow (1971) found that echidna has an AOS consisting solely of the inferior fasciculus (IF) and the MTN. In the duckbilled platypus, Campbell and Hayhow (1972) identified the MTN but were able to see only diffuse fibers representing an IF. Campbell and Hayhow (1971) described an AOS in echidna (Table 1) modeled after the basic nonmammalian pattern.

Among marsupials, *Didelphis* (the opossum) has a worldwide distribution. Its AOS exhibits a well developed IF, and like many mammalian species, a typical SF divisible into SFa, SFm and SFp tracts (Lent et al., 1976; Royce et al., 1976). Examining the AOS of the marsupial phalanger, Hayhow (1966) noted that it conformed to the mammalian pattern but had quite small SFp and LTN. In both opossum and phalanger, the DTN, LTN and MTN lie in the same relative positions of the brainstem as in eutherian mammalian.

Like marsupials, the AOS of eutherian mammals displays a departure from the nonmammalian plan. The AOS nuclei are not grouped closely together as in nonmammals. Rather, they are distributed along the AOS tracts as distinct dorsal, lateral and medial terminal nuclei (DTN, LTN and MTN)(Figs. 1A-C) with the MTN alone occupying the “pre-mammalian” location in the ventral midbrain tegmentum. Additionally, in mammals, neurons are scattered among the fibers of the SFp forming an interstitial nucleus of the superior fasciculus (inSFp)(Simpson et al., 1988).

Among insectivores, the hedgehog AOS consists of IF, SF, DTN, LTN and MTN (Campbell et al., 1967; Tigges and Tigges, 1969; Dinopoulos et al., 1987). In the European *mole (Talpa europaea),* Lund and Lund (1965) reported that the AOS was poorly developed and consisted of barely discernible fiber bundles. The tree shrew (*Tupaia)* has variously been placed in the orders *Insectivora* or *Scandentia* (family *Tapaiidae*), the latter representing a group not distant from the ancestral line that gave rise to modern mammals. *Tupaia* is diurnal and possesses a well-developed visual system reflecting an active life swinging in trees of the rain forest. Its oculomotor system also includes an extraordinarily well developed AOS including all the fiber tracts and nuclear components described by Hayhow et al. (see Campbell et al., 1967; Laemle, 1968).

The rodents AOS was studied extensively in rat (e.g., Hayhow et al., 1960; Kostovic, 1971; Terubayashi and Fujisawa, 1984) hamster (Lin et al., 1976; Terubayashi and Fujisawa, 1984; Eichler and Moore, 1974), mouse (De Renzi et al., 1959; Terubayashi and Fujisawa, 1984; Pak et al., 1987), and squirrel (Tigges, 1970). In rat, the IF and SFp are fairly well developed, whereas the SFm consists of only a slender bundle of fibers when compared with the mouse. In all four rodents studied, the MTN is prominent and the LTN is of moderate size. Regarding the guinea pig, Graur et al. (1991) placed the guinea pig in the order *Caviomorpha* rather than *Rodentia* based on their analysis of amino-acid sequencing. Anatomically, Benassi et al. (1989) noted that the guinea pig SFp is especially well developed compared to rodents and that the AOS resembles more closely that of opossum than that of rodents.

Lagomorphs, along with *Tupaia*, have the best developed AOS of all the vertebrates studied to date. In rabbit, the tracts are well differentiated and the terminal nuclei are proportionately the largest among vertebrates (Giolli, 1961). Additionally, the IF, SFp, and MTN of the rabbit are the most prominent across species. In fact, the SFp is so large as to be visible macroscopically coursing on the surface of the lateral pretectum and inferomedially onto the surface of the cerebral peduncle. The rabbit SFp contains a prominent neuronal population scattered among its fibers (Giolli, 1961) which are considered a distinct nucleus, the inSFp (cf. Simpson et al., 1988).

Among carnivores, Hayhow (1959) and Zhang and Hoffmann (1993) reported, respectively, that the AOS in cat and ferret consists of the SFp, DTN, LTN and MTN. Hayhow emphasized that the LTN is the best developed of the AOS nuclei in cat. By contrast, Thorpe and Herbert (1976) recognized this organization in the ferret but failed to identify a DTN, whereas Lin and

Ingram (1972) reported that in the cat the IF was also identifiable. In the dog, Holbrook and Schapiro (1974) described the IF, SF, DTN and MTN; however, surprisingly, they did not find the LTN, regarded by Hayhow (1959) as the best developed of the AOS nuclei in cat.

Karamanlidis et al. (1972, 1974) described the AOS in two species of Artiodactyls (sheep and pig) and two species of Perissodactyls (horse and ox). In all four species they noted the SFp as the sole tract, which terminated on neurons of the inSFp, and they could not detect any accessory optic axons traceable to a MTN in sheep, pig and ox; however a MTN was found in the horse. Earlier reports by Nichterlein and Goldby (1944; sheep) and Cummings and de Lahunta (1969; sheep and horse) are in basic agreement with Karamanlidis and co-workers.

From fiber degeneration studies on primates, the SFp had once been viewed as the only accessory optic pathway, which terminated in the DTN, LTN, inSFp, with no MTN having been identified (see Giolli, 1963; Campos-Oretga and Glees., 1967; Campos-Ortega and Cluver, 1968; Hendrickson et al., 1970; Tigges and O'Steen, 1974; Lin and Giolli, 1979; Fredericks et al., 1988; review: Giolli and Tigges, 1970). However, anterograde transport studies subsequently uncovered a small component of AOS fibers of the SF issuing ventromedially to terminate in a typical MTN_v in prosimians (Itaya and Van Hoesen, 1983; Cooper, 1986; Weber and Giolli, 1986), Old World monkeys (Nakagawa et al., 1998), and New World monkeys (Weber and Giolli, 1986). Additionally, an MTN_d and an interstitial nucleus of the superior fasciculus, medial fibers (inSFm) were recognized as the AOS fiber termination sites in a *Microcebus murinus,* Old World monkeys and apes (Cooper and Magnin, 1987; Baleydier et al., 1990; Cooper et al., 1990), These latter nuclei in primates also have been designated as medial extensions of the LTN (Tigges et al., 1977; chimpanzee) or part of the midbrain reticular formation (Nakagawa et al., 1988, macaque monkey). Reinvestigation by Nakagawa et al. (1998) showed that the Japanese macaque had both MTN_v and MTN_d, connected by a slender strand of axons. Further, the MTN_v and MTN_d received accessory optic input via both a classical SF and small slips of fibers leaving the SF and passing through the cerebral peduncle and adjacent substantia nigra, to end in the MTN.

3. Afferents of the Accessory Optic Nuclei

3.1 Retinal afferents (Figs. 1 and 2)

Retinal afferents are the most conspicuous input to the AOS nuclei. They originate from the so-called displaced ganglion cells of Dogiel in birds (pigeons: Karten et al, 1977; chick: Mey and Johann, 2001) and amphibians (chameleon: Bellintani-Guardia and Ott, 2002), but not in mammals (Oyster et al., 1980; Farmer and Rodieck, 1982; Buhl and Peichl, 1986; Dann and Buhl., 1987). Retinal ganglion cells projecting to the AON belong to the direction-selective class (Oyster et al., 1980; Britto, 1983; Rosenberg and Ariel, 1991; Kogo et al., 1998). It has been suggested that they project exclusively to the accessory optic nuclei and do not collateralize to the superior colliculus as do, for example, the axons of ganglion cells projecting to the lateral geniculate (Buhl and Peichl, 1986). This is supported by the fact that AOS projecting ganglion cells appear to have a distinctive morphology (medium-sized, with a densely branching and stratified dendritic tree) (Buhl and Peichl, 1986; Dann and Buhl. 1987). Also, in contrast to retinal ganglion cell projections to other visual nuclei, those to the AOS nuclei apparently do not show a well-ordered mosaic distribution. However, their distribution is complex and appears to be determined by at least two different overlapping mosaics (Cook and Podugolnikova, 2001). The double-mosaic theory appears to be in agreement with the proposed subdivision of the MTN in two separate functional classes (and morphologically indistinguishable) according to their preferred direction (Simpson et al., 1988; Soodak and Simpson, 1988; see also below in this chapter).

Although some researchers have suggested a totally contralateral retino-AOS projection (Hayhow et al., 1960; Gayer et al., 1989), most studies support the presence of a small ipsilateral contingent of fibers. The ipsilateral contingent is more conspicuous in pigmented than in albino or mutant animals (Erickson and Cotter, 1983; Wree and Zilles, 1983; Pak et al., 1987). The AOS

fibers are of fine caliber and contain small varicosities; a few appear to collateralize to at least two of the AOS nuclei (Ling et al., 1998).

From the ultrastructural viewpoint, retinal terminals (defined as R-type) are identifiable by the presence of rounded vesicles and electron-lucent mitochondria (Nunes Cardozo and van der Want, 1987; van der Togt et al., 1993). They are located mainly on distal dendrites of AOS neurons, less frequently on soma or proximal dendrites (Lenn, 1972). They form asymmetrical synapses (therefore, excitatory) and contain glutamate (with glutamate transporter of the VGluT2 type: Fujiyama et al., 2003), and not GABA (Nunes Cardozo et al., 1991). Also, some neurons in the AOS are positive for N-acetylaspartylglutamate (NAAG), which disappears after optic nerve transection (Moffet et al., 1991). In pigeon, tyrosine-hydroxylase (TH) immunoreactivity has been found in the displaced retinal ganglion cells projecting to the AOS (Britto et al., 1988).

The AOS nuclei also contain high levels of mu-opioid receptors, in both albino and pigmented rat (Giolli et al., 1990; German et al., 1993) but not in guinea pig (Giardino et al., 1990; see below in this chapter). These opioid receptors disappear after monocular enucleation or eye-patching, which suggest that they are located on retinal terminals (Giolli et al., 1990; Ding et al., 1996).

3.2 Cerebral cortical afferents (Figs. 2 and 3)

The visual cortex projects to the AOS in some species but not in others (see reviews by Simpson et al., 1988; Lui, 1996; Blanks et al., 2000). In cat, direct cortico-AON projections have been found from the ipsilateral visual cortex, namely, from the secondary areas 21a, 21b, anteromedial and posteromedial lateral suprasylvian, whereas only the MTN receives an input from the primary visual cortex (Berson and Graybiel, 1980; Marcotte and Updyke, 1982).

There is some controversy surrounding the cortical projections to the primate AOS; this probably arises from: i) difficulty in defining the AOS nuclei in primates (e.g., see above in this chapter, the controversy about the presence of a MTN), ii) difficulty in defining cortical areas, or presence of subregions within a single area, and iii) technical problems interpreting and comparing data from studies employing different anatomical techniques and resulting varying sensitivities. The latter is of paramount importance in dealing with weak projections to small structures such as the AOS. The primary visual cortex (V1) was found to project to the LTN (the most conspicuous AOS nucleus in primates) in some studies (Campos-Ortega and Hayhow, 1972), but not in others (Maioli et al., 1989; Lui et al., 1995). These inconsistencies suggest the possibility that only specific retinotopic regions of V1 (corresponding to the representation of the vertical meridian) may be responsible for this connection (Lui et al., 1995).

Among secondary visual areas, the regions surrounding the superior temporal sulcus, namely, the middle temporal area (MT) and the medial superior temporal area (MTS), are known to be involved with visual motion detection and eye movements (e.g., Van Essen et al., 1981; Desimone and Ungerleider, 1986; Newsome et al., 1988; Dursteler and Wurtz, 1988; Salzman and Newsome, 1994; Andersen et al., 2000). Projections to the LTN appear to arise selectively from these visual areas (Spatz and Tigges., 1973; Maioli et al., 1989; Lui et al., 1995). Other authors (Boussaoud et al., 1992) found projections to the LTN in one case with a tracer injection involving area FST (fundus of the superior temporal sulcus), which is also involved in visual motion detection (see, e.g., Vanduffel et al., 2001). Area MST also sends direct projections to the other nuclei of the AOS, namely, MTN_d, inSFp and inSFm (Lui et al., 1995). This pattern of projections suggests that the AOS shows a more specific input from areas surrounding the superior temporal sulcus, than does the NOT, whose cortical inputs originate also from medial prestriate cortex, area V3 and V3a, V4 and VIP (Lui et al., 1995).

Lesions of the visual telencephalic/cortical areas in various species produce changes in the directional selectivity of AOS neurons (pigeon: Hamassaki et al., 1988; rat: Natal and Britto, 1988; cat: Grasse et al., 1984), thus suggesting a functional cortical-AOS input. However, connection studies have not revealed a direct projection in rabbits and guinea pigs (Giolli et al., 1978, 1988a; Hollander et al., 1979; Lui et al., 1994). Apparently, the same may be true for rats (Nauta and Bucher, 1954; Benzinger

and Massopust, 1983), although the AOS is not explicitly mentioned in these papers. Some confusion arises about the DTN because it lies in close proximity to the nucleus of the optic tract (NOT) of which it is a close functional ally. In fact, some studies deal with these two nuclei as a single complex (e.g., Schmidt et al., 1993). However, when the two structures have been distinguished histologically, a visual cortical input is found only on the NOT, and not the DTN (Lui et al., 1994).

3.3 AOS/NOT nuclear interconnections and other afferents (Fig. 2)

The AOS nuclei are extensively interconnected with the NOT (reviews by Simpson et al., 1988; Grasse and Cynader, 1991; van der Want et al., 1992; Blanks et al., 2000) and the efferent projectional system of the AOS nuclei (section 4). The pretectal nucleus lentiformis mesencephali (the nonmammalian equivalent of the mammalian NOT) and the NOT provide extensive input to the nBOR nuclei in pigeon (Brecha et al., 1980; Azevedo et al., 1983) and variously to the MTN, LTN, DTN, inSFp and inSFm of opossum (Vargas et al., 1997), rodents and lagomorphs (Terasawa et al., 1979; Holstege and Collewijn, 1982; Blanks et al., 1982; Giolli et al., 1984, 1985a, 1988a,b, 1992; van der Togt et al., 1991, 1993), carnivores (cat: Berson and Graybiel, 1980), *Tupaia* (Weber and Harting, 1980) and primates (macaque monkey: Carpenter and Pierson, 1973; Baleydier et al., 1990; marmoset: Blanks et al., 1995). AOS-AOS, Golgi type II interconnections form a prominent network in mammals (Carpenter and Pierson, 1973; Itoh, 1977; Terasawa et al., 1979; Berson and Graybiel, 1980; Holstege and Collewijn, 1982; Blanks et al., 1982; Giolli et al., 1984, 1985a, 1988b; van der Togt et al., 1991, 1993), and it is reported that most (Giolli et al., 1992) or all (van der Togt, 1991) of these internuclear neurons are GABAergic, that some of these GABA neurons are CGRP-immunoreactive (Zhou et al., 1999), and that a percentage of these GABAergic neurons are GABA/CGRP neurons making synapses with the somata, dendritic shafts and spines of nonGABA/nonCGRP neurons via symmetric synapses (Zhou et al., 1999). We can assume that this extensive network of internuclear neurons functions to fine tune information required for precise eye movements.

Nonretinal afferents from the lateral division of the ventral lateral geniculate nucleus target the MTN but not the other AOS nuclei. This has been reported in tract-tracing studies on rat, rabbit (Swanson et al., 1974; Giolli et al., 1988a) and cat (Edwards et al., 1974; Graybiel, 1974; Swanson et al., 1974). The lateral division of the ventral geniculate nucleus is interconnected with the NOT (e.g., Edwards et al., 1974; Graybiel, 1974; Swanson et al., 1974), contrasted with the MTN does not project to the ventral lateral geniculate nucleus (e.g., Giolli et al., 1988a). Other afferents to the rat and rabbit MTN were found to arise from the mesencephalic reticular formation, pars medialis, supraoculomotor-periaqueductal gray, and nucleus reticularis pontis, pars oralis (Giolli et al., 1988a)(Fig.2). Similarly, afferents from these three brainstem regions in mammals could not be traced to the DTN, LTN or inSFp in either rat or rabbit (Giolli et al., 1988a). The one exception is an apparently uniquely primate feature of a pathway from the olivary pretectal nucleus and terminating in the contralateral LTN in the macaque (Baleydier et al., 1990; and marmoset monkeys (Blanks et al., 1995; Clarke et al., 2003). Further, studies have failed to show afferents to any AOS nuclei from the midbrain reticular formation (Ruda, 1975; Eberhart et al., 1985).

3.4 Is the nucleus of the optic tract (NOT) an accessory optic nucleus?

Given the large number of functional, connectional and neuropharmacological similarities between the NOT and AOS nuclei and, in particular, the close physical proximity of the NOT and DTN, one might wonder whether it is appropriate to consider the NOT as part of the AOS. Clearly, the nucleus of the optic tract and the accessory optic nuclei are extensively interconnected by GABAergic and Non-GABAergic neurons (e.g., Giolli et al., 1984; van der Togt et al., 1991), and both are shown to functionally contribute to nystagmus and the fine tuning of eye movements (see Simpson et al., 1988; Biral et al., 1987; Benassi et al., 1889; Lui et al., 1990; Grasse and Cynader, 1982, 1984b). The AOS and NOT nuclei also share similar efferent projections to many of the same brainstem nuclei (e.g., rabbit: Holstege and Collewijn, 1982; Giolli et al., 1984) and, neuropharmocologically, both contain high concentrations of mu opioid receptors (Giolli et al., 1990) and GABA receptors (Bowery et al., 1987; Chu et al., 1990) within neurons and axon terminals. But, NOT and AOS nuclei do differ in important ways.

They have different cytoarchitecture (Gregory, 1985) and they do not jointly target certain oculomotor-related brainstem nuclei (rabbit: NOT: Holstege and Collewijn, 1982; AOS nuclei: Giolli et al., 1984). Further, in rodents and lagomorphs there is no visual cortical projection to the AOS nuclei whereas there is to the NOT (e.g., rabbit: Giolli and Guthrie, 1971; rat: Lui et al., 1994). It is true that in primates, the accessory optic nuclei and NOT both receive input from visual and oculomotor-related areas of cortex (Lui et al., 1995; Distler and Hoffmann, 2001), *viz.*, from the cortex lining the superior temporal sulcus in macaque monkey; but it is the NOT alone that is targeted by cortical neurons arising from certain other visual areas (VIP, V3, V3a and V4 and dorsomedial area 19: see Lui et al., 1995). Moreover, the AOS nuclei contain large numbers of CGRP immunoreactive somata and axons terminals compared to the NOT, which contains neither CGRP- positive cells or terminals (Ribak et al., 1997). The functional association, and often the technical difficulties in separating the NOT from the DTN in lesion or anatomical tract-tracing studies, has caused many authors to adopt the combined term NOT/DTN (Giolli et al., 1984; Simpson et al., 1988; van der Want et al., 1992; Distler and Hoffmann, 2001; van der Togt et al., 1991, 1994; Blanks et al., 2000). Until new data emerge, we prefer to continue with the designation NOT/DTN to acknowledge the largely functional and connectional similarities between the two nuclear populations, while at the same time respecting the important differences that exist.

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4. Efferents of the AOS nuclei

4.1 Efferents to the Inferior Olive (Figs. 2, 4-7):

The inferior olive receives substantial numbers of important projections, both direct and indirect, from neurons of the AOS nuclei. The direct projections arise from AOS neurons and travel within the medial longitudinal fasciculus (MLF), are almost entirely ipsilateral, are derived from the non-GABAergic neurons in the rat, rabbit, cat and monkey AOS and are distributed to the rostral parts of the dorsal cap (Horn and Hoffmann, 1987; Maekawa and Kimura, 1981; Wada et al., 1989; Schmidt et al., 1998). Retrograde tracer studies indicate that these direct AOS-inferior olivary projections in rat and rabbit arise from neurons of the MTN and LTN (Giolli et al., 1984, 1988b). In monkey, where the MTN is attenuated in size or non-existent, the AOS-inferior olivary projections is shown to arise from neurons of the LTN (Mustari et al., 1994; Blanks et al., 1995). In addition to the rostral dorsal cap, there are also LTN projections to the medial accessory olive in primate (Blanks et al., 1995). The indirect AOS-inferior olivary projections utilizing the poorly differentiated regions of ventral midbrain tegmentum were delineated in several mammalian species (cf. Blanks et al., 2000) by systematically mapping the tegmental neurons following injections of retrogradely label into the inferior olive, and mappings of the tegmental terminal fields following injections of anterograde tracers into the AOS nuclei. Giolli and colleagues (Giolli et al., 1984) termed this region of overlap the Ventral Tegmental Relay Zone (VTRZ) to designate this possible indirect, disynaptic pathway from the AOS to the IO. No direct physiological evidence exists to support this pathway nor its possible terminations or synaptic effects (excitation/inhibition) in the inferior olive, but their anatomical existence is overwhelming. Future studies are needed to examine these questions before the functional role of the AOS-VTRZ-IO can be better determined.

An important point that emerges from these anatomical studies is the crossed versus uncrossed nature of these two AOS-olivary pathways. As stated above, the direct AOS-olivary pathway is almost entirely uncrossed with only a minor decussation at the level of the IO (Blanks et al., 1995). In contrast, the AOS-VTRZ-IO pathway is contralateral with the AOS neurons crossing in the ventral tegmental decussation and the tegmento-olivary fibers synapsing in the inferior olive on the same side. The implications of both an uncrossed (direct AOS-olivary) and crossed (AOS-VTRZ-olivary) AOS connection with the olivocerebellar system were discussed earlier (Blanks et al., 1995; Blanks et al., 2000), in which it was argued that bilateral projections may assist in supporting the symmetry of optokinetic eye movements.

Earlier physiological studies in the rabbit MTN first demonstrated that this direct AOS-olivary pathway conveys

visual/optokinetic signals from the MTN via the rostral parts of the dorsal cap of the inferior olive to the Purkinje cells of the cerebellar flocculus (Maekawa and Takeda, 1977, 1979; Simpson et al., 1979, 1981). Similarly, the neurons of the NOT/DTN employ the same MLF-inferior-olivary-flocculus pathway, but unlike the MTN that projections to the rostral dorsal cap, those from the NOT/DTN are relayed through neurons in the caudal parts of the dorsal cap. Interestingly, this distinct rostro-caudal segregation of the pretectal- IO and AOS-IO fibers within the dorsal cap is very consistent across species, e.g., rabbit (Takeda and Maekawa, 1976; Simpson et al., 1988), rat (Giolli et al., 1985a), cat (Hoffmann et al., 1976), and primate (Sekiya and Kawamura, 1985, Hoffmann et al., 1988; Baleydier et al., 1990; Watanabe et al., 1991; Mustari et al., 1994; Blanks et al., 1995). Further, this rostrocaudal segregation of the AOS- and NOT- afferents to the dorsal cap have been demonstrated in functional labeling studies employing optokinetic stimulation in the horizontal plane activating the neurons of the NOT (Barmack and Young, 1990; Lui et al., 1999; Barmack, Chapter 8 on inferior olive).

The topography of the AOS- and NOT- inferior olivary projection in rabbit has been studied in great detail by Simpson and colleagues. These authors demonstrate that the direction-selectivity of the AOS neurons is remarkably similar to neurons innervating the vestibular semicircular canals, and Purkinje cells in the cerebellar flocculus. These finding led Simpson (1984) to conclude that the AOS is a visual system organized in vestibular coordinates, i.e., a matching of the receptive field properties of the semicircular canals, with that of AOS, inferior olivary and floccular Purkinje cells. Beginning with the original proposal of Ito and colleagues (Marr, 1969; Ito, 1982) and followed by a number of subsequent studies, this functional (learning hypothesis) role of the visual and vestibulo-olivo-cerebellar pathway is proposed to be involved with adaptation of the vestibulo-ocular reflex.

4.2 Other efferents (Figs. 2, 4-7, 8):

Whereas the afferents to the AOS nuclei are relatively limited in number (i.e., mainly from the retina, visual cortex, NOT and other AOS and pretectal nuclei, see section 3.3), their efferents are considerably more varied. In addition to the reciprocal connections between the NOT and the AOS nuclei, and those to the inferior olive, there are others that fall into the categories: preoculomotor, precerebellar and reticular structures.

***Preoculomotor projections of the AOS*:** In nonmammalian species it is reported that the AOS projects to the oculomotor nuclei in the pigeon (Brecha and Karten, 1979; Brecha et al, 1980), but not the turtle (Weber et al., 2003). Among the mammals studied to date, the AOS nuclei do not project directly to the oculomotor nuclei, but do target the accessory oculomotor nuclei: nucleus of Cajal and nucleus of the posterior commissure. Furthermore, there are projections to the nucleus of Bechterew, nucleus of Darkschewitsch and region of the periaqueductal gray above the oculomotor nucleus, designated as the “supra-oculomotor periaqueductal grey” (rat and rabbit: Giolli et al., 1984, 1985; marmoset monkey: Blanks et al., 1995). These efferents could provide a multisynaptic projection from the AOS to the ocular motor neurons. An unexpected finding is the presence of an AOS pathway to the pretectal olivary (Giolli et al., 1985a) and the Edinger-Westphal nuclei (Clarke et al., 2003), both involved in the pupillary light reflex and ocular accommodation through activation of the smooth muscles controlling the pupil and lens. The reason why the AOS nuclei are reciprocally connected with nuclei associated with the pupillary light reflex (see also above, section 3.3), which is part of the ‘near response’, is presently unknown. It could be suggested that this connection is linked to the functional role of the AOS in generating responses to the movement of the visual background, which implies the recognition of backgroung from foreground.

Other efferents which are extremely relevant for the oculomotor control are those to the vestibular nuclei (superior and lateral in rat and rabbit: Giolli et al., 1984; 1988; superior and medial in marmoset: Blanks et al., 1995), which represent part of the “indirect” pathway for the optokinetic nystagmus (see below) . It is known that all vestibular nuclei neurons respond not only to vestibular, but to optokinetic stimulation as well (Waespe and Henn, 1977). This property is functionally very important for the coordination of the optokinetic and vestibular systems in the control of compensatory eye movements. The optokinetic signal may

reach the vestibular nuclei both via the above mentioned direct projections, and via indirect connections , for instance through the nucleus prepositus hypoglossy (Buttner-Ennever et al., 1996).

***Precerebellar projections of the AOS*:** The other, so-called "direct" pathway for the optokinetic nystagmus could involve the AOS efferents to pre-cerebellar structures such as the basal pontine nuclei. Such a projection was found in various species, although small and limited to the dorsolateral portion of the pons (rabbit and rat: Giolli et al., 1984; Wells et al., 1989; marmoset: Blanks et al., 1995). On the contrary, the nucleus reticularis tegmenti pontis (NRTP) appears to receive direct input from the LTN in primates (Blanks et al., 1995), but not from the MTN of other mammals, where, however, the ventral tegmental relay zone (VTRZ: see below) likely acts as an intermediate relay station (Torigoe et al., 1986).

Regarding a possible direct connection from the AOS to the cerebellar cortex, this has been described in several nonmammals (fish: Finger and Karten, 1978; turtle: Reiner and Karten, 1978; Weber et al., 2003; pigeon: Brauth and Karten, 1977; Wylie and Linkenhoker, 1996; Wylie et al. 1997; but see Montgomery et al., 1981, frog), but its presence in mammals is controversial. Thus, whereas a direct AOS-cerebellar connection was described in chinchilla (Winfield et al., 1978) and tree shrew (Haines and Sowa, 1985), none was found in rat, rabbit, cat and marmoset monkey (Kawasaki and Sato, 1980; Feran and Grasse, 1982; Giolli et al., 1984, 1985a, 1988b; Blanks et al., 1995). This discrepancy may either reflect a real species difference, or result from differences inherent in the techniques used, for instance, anterograde vs. retrograde axonal transport. In those studies in which an AOS-cerebellar pathway was recognized, the direct AOS input is reported to target folium IX (uvula) (pigeon: Brauth and Karten, 1977; Brecha and Karten, 1980; Wylie and Linkenhoker, 1996; Wylie et al. 1997; tree shrew: Haines and Sowa, 1985), paraflocculus (pigeon: Brauth and Karten, 1977; Brecha and Karten, 1980), flocculus (chinchilla: Winfield et al., 1978) and also the cerebellar nuclei (Wylie and Linkenhoker, 1996; Wylie et al. 1997). While this discrepancy in the AOS-cerebellar pathway across mammals may reflect real species differences, it is more likely that it results from differences in the techniques used. A major point of concern in interpreting such data is the close proximity of the flocculus to the vestibular nuclei and the fiber bundles conveying the AOS-superior vestibular nucleus projection documented in the rat, rabbit and monkey (Giolli et al., 1988a; Blanks et al., 1995). It is possible that injections of retrograde tracers into the cerebellum, as employed by some of the investigators mentioned above that found a direct AOS-cerebellar connection, could have labeled the AOS-vestibular nucleus bundle as fibers of passage coursing with the superior cerebellar peduncle. This fiber of passage uptake thus would have labeled neurons in the AOS that could have been mistakenly interpreted as terminating in the cerebellum instead of the vestibular nucleus (cf. Giolli et al., 1988a; Blanks et al., 1995).

***Reticular formation projections of the AOS*:** In rodents and lagomorphs, MTN neurons target the nucleus parabrachialis pigmentosus and adjacent deep mesencephalic area, this latter a part of the ventral mesencephalic tegmental area of Tsai (VTA) (Giolli et al., 1984; 1985a). Giolli and colleagues named this portion of the VTA the "ventral tegmental relay zone" (VTRZ), and they defined it operatively as the relay region of the ventral tegmentum that receives fibers from the MTN and projects heavily to the inferior olive (Figs. 3-7). The VTRZ projects to several of the same nuclei that receive MTN efferents. In non-human primates, a tegmental region having the same connectional features as the VTRZ (afferent projections from the LTN and efferent projections to the IO) has been described (Blanks et al., 1995), but it overlaps in part with the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and the authors chose not to adopt the term VTRZ as used in other mammals. A region homologous to VTRZ is also present in the pigeon (Wylie et al., 1999; Wylie, 2001)(Fig. 8). The AOS and VTRZ have been found jointly to project to the caudate-putamen and prefrontal/anterior cingulate cortices in rat (Giolli et al., 1985c), to the hippocampus/parahippocampal area in pigeon and rat (Gasbarri et al., 1994; Wylie et al., 1999)(Fig. 8), and certain nuclei of the dorsolateral thalamus in pigeon (Wylie et al., 1998). As discussed in detail below, these nuclei appear to be involved in various cognitive aspects related to self-motion, such as spatial memory and distinction between self-motion and object-motion (see Wylie

et al., 1998; 1999). These findings suggest that the AOS-VTRZ might have a more complex role than the purely oculomotor aspects of the response to self-motion, i.e. optokinetic reflex, possibly providing part of the visual input needed for spatial cognition.

5 Neurotransmitters and Modulators

5.1. GABA (Fig. 9):

GABA is the major inhibitory neurotransmitter in the brain and plays a prominent role in the NOT and AOS pathways mediating optokinetic nystagmus and visual-vestibular interaction as GABAergic neurons are numerous in somata and axon terminals of the AOS nuclei (e.g., Ottersen and Storm-Mathisen, 1984; Penny et al., 1984; Giolli et al., 1985b; Magnaini et al., 1985) Double-label retrograde and GABA immunocytochemistry in rat and rabbit show that these nuclei are extensively interconnected by GABAergic projection neurons forming the NOT-MTN and NOT-MTN pathways. Similar pathways have been demonstrated in non-human primate in which the main interconnections are between the NOT and LTN (Mustari et al., 1994; Blanks et al., 1995). It has not been determined whether most of these interconnections in nonhuman primate also are GABAergic projection neurons as in other species.

The first evidence for the inhibitory nature of the AOS-NOT interconnections came from microelectrode studies in the rabbit. Maekawa and Simpson (1972) showed that electrical stimulation of the MTN and adjacent VTRZ in rabbit inhibited the transmission of visual impulses from the optic chiasm through the NOT to the inferior olive and cerebellar flocculus. Similarly, neurons in the NOT of rat are strongly inhibited by electrical stimulation of the MTN (Van der Togt and Schmidt, 1994; Schmidt et al., 1998). Iontophoretic application of bicuculline, a $GABA_A$ receptor antagonist, increases the spontaneous discharge of NOT/DTN neurons, but had no effect on the inhibition invoked by electrical stimulation of the MTN. One explanation proposed to explain these observations was that the MTN inhibition of NOT neurons may be $GABA_B$ mediated (Van der Togt and Schmidt, 1994). Given the possible functional importance of $GABA_A$ and $GABA_B$ receptors in the MTN-NOT pathway, it is important to establish that the NOT in rat contains an abundance of both $GABA_A$ and $GABA_B$ receptors (Bowery et al., 1987; Chu et al., 1990). The MTN of rat can be subdivided morphologically and pharmacologically into dorsal (MTN_d) and ventral (MTN_v) parts. Up to 98% of the MTN neurons projecting to the NOT in rat are GABAergic and they arise predominantly from the MTN_v. By contrast, those projecting to the inferior olive (IO) are nonGABAergic and arise from the MTN_d. Double-label studies reveal that no MTN neurons projected to both the NOT and IO (e.g., Schmidt et al., 1998). Moreover, it was found that the directionally selective neurons in the NOT prefer horizontal stimuli and receive the inhibitory input from the MTN_v-NOT neurons that predominantly (88%) prefer downwards vertical stimulus movement. Interestingly, the great majority of the MTN_d-IO neurons prefer upwards vertical movement. Given that peak AOS-NOT inhibition occurs during downward visual motion, it is likely that these inputs sharpen the tuning curves (i.e., response properties) of NOT neurons thereby favoring the upward vertical stimulus movement.

Single unit studies in pigeon (Hamassaki et al., 1988, turtle (Ariel and Kogo, 2001), and rat (Natal and Britto, 1987) show that lesions of the pretectal complex modify the directional selectivity of neurons in the AOS nuclei, presumably by disruption of the inhibitory, GABAergic, pretectal-AOS interconnections. Experiments by Schmidt et al. (1994) demonstrated that not only was spontaneous rate increased with application of the $GABA_A$ agonist, bicuculine, but visual evoked activity was increased as well. Direction-selectivity of NOT/DTN neurons to whole-field, moving stimuli was reduced for most neurons but not abolished. However, the difference between firing rates during stimulation in the preferred vs. non-preferred direction did not change systematically with drug application. This was interpreted as GABAergic inputs being responsible for shaping the response properties of direction-selective NOT/DTN neurons instead of generating it (Schmidt et al., 1994). In an earlier study, van der Togt and Schmidt (1994) reported that application of bicuculline to the NOT concomitant with electrical stimulation of the ipsilateral MTN did not reduce the inhibition of NOT neurons produced by MTN-NOT neurons stimulation. Van der Togt and Schmidt

(1994) concluded that the neuronal inhibition of NOT neurons may well be mediated by $GABA_B$ receptors, which are abundant in the rat NOT (Bowery et al., 1987; Chu et al., 1990).

Recent studies in the turtle examined the balance of excitatory and inhibitory sensory information converging on the AOS neuron. In this species, the retina sends an excitatory projection to the equivalent of the mammalian NOT (nucleus lentiformis mesencephali, NLM) and AOS nuclei (basal optic nucleus, nBOR) and, in turn, there is a strong GABAergic inhibitory NOT-AOS projection in this species mediated via $GABA_A$ receptors on the AOS neurons (Ariel and Kogo, 2001). The excitatory and inhibitory postsynaptic potentials in the AOS neurons have similar preferred directions, indicating that both synaptic inputs are maximally active onto the same cell under the same stimulus conditions. Given these general finding, these authors concluded that there must be a complex interaction of inhibitory and excitatory direction-selective inputs to nBON cells (Kogo et al., 1998). The importance of such an arrangement is that it allows 1) enhanced spatial coding (enhanced receptive fields) by convergence many retinal ganglion cells directly on the AOS neuron and indirectly through retino-NLM-nBON projections, 2) gain enhancement on the AOS neurons, and/or 3) sensory processing or tuning through a convergence of excitatory and inhibitory inputs (Ariel and Kogo, 2001). Further pharmacological studies on the turtle AOS revealed that of the converging, direction-selective, inhibitory/excitatory inputs to the nBOR, the inhibitory inputs are blocked by bicuculline mediated by the retinal-pretectal connections acting upon GABA (A) receptors located on the nBOR neurons, whereas the excitatory input is from retinal glutaminergic retinal afferents, given that retinal excitation of the nBOR was blocked by an antagonist of the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptor subtype (Kogo and Ariel, 2002). The likely source of direction-selectivity of NOT/DTN neurons remains their retinal input from excitatory, on-center, direction-selective retinal ganglion cells (Oyster et al., 1972; Hoffmann and Stone, 1985.

5.2 Opioid peptides:

Opioid peptides have profound sensory effects (Atweh and Kuhar, 1983) and are known to cause severe disruption of visual and oculomotor behavior in man, such as reduced visual sensitivity (Rothenberg et al., 1979), diminished gain of smooth pursuit, and hypometric saccades with reduced velocities (Rothenberg et al., 1980a, b; McLean et al., 1985). The four primary AOS nuclei(MTN, LTN, DTN, inSFp) contain high concentrations of the mu opioid receptor (rat, Fukushima et al., 1992; German et al., 1993; pigeon, Reiner et al., 1989), a sparse to moderate concentration of delta opioid receptors (Fallon and Loughlin, 1995; but see Fukushima et al., 1992), and a sparse concentration of kappa opioid receptors (Fukushima et al., 1992; Fallon and Loughlin, 1995; but see Speciale et al. 1993), whereas these nuclei show only low concentrations of opiates (Herkenham and Pert, 1982; Fallon and Loughlin, 1995; Fallon and Leslie, 1986; Mansour et al., 1987; Loughlin et al., 1995). Interestingly, the finding that about 89% of all mu receptors disappear within 7 days after monocular enucleation (Giolli et al., 1990) suggests that these receptors are located presynaptically on retinofugal axon terminals and not postsynaptic on AOS neurons. In agreement with this interpretation, Loughlin and Fallon (1995) report that while the rat MTN reveals high binding for mu-opioid receptors, very little mRNA is expressed for these receptors, suggesting that the receptors are produced outside the MTN and reside on afferent terminals.

The functional relationship between opioid receptors and putative neurotransmitters in the AOS has yet to be determined. Pharmacological data suggest that opioids exert their excitatory action in the brain indirectly by inhibiting the release of GABA (Kalyuzhny et al., 2000). GABAergic and opioidergic systems are closely linked and activity of the same neuron may be regulated directly by both GABA and opioids. It is known that opioids interact at GABAergic neurons and axon terminals and that such interactions produces neuronal inhibition comparable, perhaps, to that reported in the striatonigral and nigrostriatal systems of rat (Iwatsubo and Kondo, 1978; Turski et al., 1982; Abou-Khalil et al., 1984; Starr, 1985). The extraordinarily high levels of mu opioid receptors in the rat AOS nuclei, and the opioid effects on visual sensitivity (Rothenberg et al., 1979) diminished gain of

smooth pursuit and saccadic velocities (Rothenberg et al., 1980a,b), suggests that endogenous opiates may play a role in regulating visual transmission through the AOS nuclei, and through connections with the vestibular nuclei and precerebellar pathways, may account, in part, for such phenomena as the fluctuating gain of optokinetic nystagmus and other visuomotor reflexes.

5.3 Calcitonin Gene-Related Peptide (CGRP), Neuropeptide Y (NPY) & Vasoactive Intestinal Peptide (VIP):

The 37 amino acid neuropeptide encoded and generated by the gene for calcitonin and called calcitonin gene-related peptide (CGRP) has defied functional description. It is found in high concentration in neurons and fibers of sensory systems (Rosenfeld et al., 1983; Kawai et al., 1985; Skofitsch and Jacobowitz, 1985a; Kruger et al., 1988). It is also present in high concentrations in the AOS nuclei, but, surprisingly, is absent from the other primary visual nuclei (Ribak et al. (1997). Even the NOT, with its functional alliance to the AOS, lacks CGRP-ir neurons and fibers (Ribak et al., 1997; Zhou et al., 1999). Borostyanki (personal communication, R.A. Giolli) indicated a comparable distribution of CGRP-positive cells and fibers in rat to that described by Ribak et al. (1997) and Zhou et al. (1999). However, Borostyanki reported a minimal number of CGRP-positive neurons in cat AOS nuclei, and virtually no CGRP-positive neurons in the human AOS nuclei.

CGRP-positive neurons and fibers were investigated in the rat brain with light- (Ribak et al., 1997) and electron-microscopy (Zhou et al., 1999). It was learned that in the pretectum and lateral midbrain tegmentum, CGRP-positive neurons were confined almost entirely to the DTN, LTN and inSFp (Ribak et al., 1997). Electron microscopic analysis revealed that CRRP-ir somata are postsynaptic to axon terminals that make asymmetric synapses with retinal axon terminals (Zhou et al., 1999). These studies also showed that the axons of CGRP-ir neurons make axodendritic synapses of the symmetric type with nonCGRP somata, small distal dendrites, and dendritic spines wiithin the DTN, LTN and MTNv.

After unilateral ocular enucleation, degenerating retinofugal fibers are observed in the AOS nuclei (Zhou et al., 1999), and supplementary to this, electron microscopically revealed that these degenerating axons formed asymmetric synapses with CGRP-positive, small-caliber dendrites and dendritic spines (Zhou et al. (1999). These finding highlight the fact that at least some of the CGRP-positive neurons of the AOS nuclei receive direct retinal input. Furthermore, Zhou et al. (1999) estimated that greater than 90% of CGRP-ir neurons of AOS nuclei are GAD-positive. The function of CGRP in GABAergic-AOS neurons is unknown but could be involved in sequestering calcium, a claim made by Kruger et al. (1988) for the brain in general.

The hippocampus contains large numbers of GABAergic neurons which co-localize the calcium binding proteins, calretinin, calbindin and parvalbumin (Freund and Buzsaki, 1996). Relative to the AOS nuclei of rat, Zhou et al. (1999) found that 40% of the CGRP-ir neurons are immunoreactive to calretinin and 5% are immunolabeled with calbindin. It is possible that the presence of calretinin and calbindin in CGRP/GAD-ir neurons of AOS nuclei may relate to metabolizing large quantities of calcium required for high levels of nerve activity. The calretinin found in nearly half of the CGRP neurons may have a neuroprotective function, a function proposed for hippocampal neurons by Freund and Buzsaki (1996).

Borostyankoi et al. (1999) found high densities of NPY- and VIP-ir neurons and axon terminals in cat MTN, LTN and DTN, and Borostyankoi-Baldauf and Herczeg (2002) described a similar distribution of NPY and VIP immunoreactivity in the DTN and LTN of the human brain. However, while identifying both NPY and VIP immunoreactive neurons in the LTN, these authors only identified NPY in DTN neurons. Borostyankoi reported that the AOS nuclei in cat are the only primary visual nuclei to contain VIP-positive somata and terminals.

6. Functional Considerations

6.1. Response properties of AOS neurons:

The first electrophysiological recordings in the AOS nuclei were performed in the rabbit MTN (then called "nucleus of the transpeduncular tract") and revealed responses to photic stimulation (Hamasaki and Marg, 1960; 1962). Later it was Walley (1967) who discovered that most neurons in the MTN respond to moving visual stimuli, mainly upward vertical. The seminal works of Simpson and co-workers (also performed on rabbit) elucidated the response features of the AOS nuclei (Simpson et al., 1979; Soodak and Simpson, 1988; Simpson et al., 1988). They were characterized as having very large receptive fields and responding to large moving textured patterns (ideal optokinetic stimuli), with optimal speed ranging between 0.1 and 1.0 °/s. Preferred directions were usually "off-vertical" in MTN and LTN (either upward or downward, and somewhat posterior), whereas the DTN, both anatomically and physiologically connected to the pretectal nucleus of the optic tract (NOT), showed a horizontal, temporo-nasal preferred direction, similar to that of the NOT itself. It is important to note that these studies also revealed that whereas visual stimuli moving in the preferred direction increase the discharge rate of the neuron, motion in an anti-preferred direction (sometimes misleadingly referred to in the literature as "null" direction) inhibit the background discharge of AOS neurons. The anti-preferred direction is not necessarily opposite (i.e., 180 degrees) to the preferred directions. These results suggest that the AOS nuclei are the first post-retinal relay station in the pathway mediating the horizontal and vertical optokinetic reflex (OKR), a class of compensatory eye movements that serve the functional purpose of stabilizing images on the retina during self-motion and/or motion of the visual surround. The low optimal speed of AOS neurons, and their preferred directions, which basically overlap with the orientations in space of the vestibular semicircular canals, suggest that this neurons complement the vestibular system in detecting self-motion, and provide the substrate for the coordination of OKR with the vestibulo-ocular response (Soodak and Simpson, 1988; Simpson et al., 1979).

Several electrophysiological studies performed in other species (frog: Cochran et al., 1984; turtle: Rosenberg and Ariel., 1998; chicken: Burns and Wallman, 1981; pigeon: Morgan and Frost, 1981; Gioanni et al., 1984; Crowder and Wylie, 2001; rat: van der Togt et al., 1993; cat: Grasse and Cynader, 1982, 1984b) confirmed the qualitative response properties of AOS neurons in rabbits, with some species differences in the distribution of cells with different directional preferences and in the range of the most effective stimulus speed (for instance, see Crowder et al., 2003a). Slightly different results were obtained in turtle, where both excitation and inhibition can be present, for any given stimulus direction, in the same cell of the nBOR (Ariel and Kogo, 2001), and in the rainbow trout, where both horizontal and vertical preferred directions were found both in AOS and pretectal nuclei (Klar and Hoffmann, 2002). A very important feature of LTN in non-human primates (Mustari and Fuchs, 1989) is that monkey LTN neurons are still direction- and speed-selective, but they respond to either pure visual (optokinetic) stimuli, to eye movements (smooth pursuit) or both. Thus, in non-human primates, eye movement-related activity differentiates AOS neurons from the NOT neurons, which are purely visual (Mustari and Fuchs, 1990).

6.2. Metabolic and lesion studies (Fig. 10):

The functional role of the AOS in mediating the optokinetic nystagmus is further supported by metabolic studies using the ^{14}C-2deoxyglucose technique (2DG). A selective functional activation in the rat MTN is present during optokinetic stimulation, but neither during vision of a stationary optokinetic pattern nor during constant, diffuse illumination. Furthermore, 2DG consumption, mainly localized within the ventral MTN, is significantly higher during vertical compared to horizontal optokinetic stimulation (Biral et al., 1987). A selective activation of the MTN during vertical optokinetic nystagmus also is present in the guinea pig, where, however, it is higher in the MTN_d than the MTN_v (Lui et al., 1990)(see Fig. 10, this chapter). Additionally, in guinea pig, another AOS nucleus, the inSFp, shows substantial increased metabolic activity during vertical OKN (Benassi et al.,

1989). In chicken, the dorsal portion of the nBOR is mainly activated for upward vertical stimulation and the ventral portion for downward stimulation (McKenna and Wallman, 1985).

Lesion studies reveal a complex pattern of interactions within different parts of the optokinetic system, and between the optokinetic and vestibular systems. Lesions of the nBOR lead to the disruption of vertical OKN (frog: Làzar, 1983). However, the destruction of the LTN and deafferentation of MTN in cat (Clèment and Magnin, 1984) also cause a spontaneous nystagmus in the horizontal plane, whose slow phase is directed ipsilaterally to the lesioned side, and a reduction in the gain of the vestibulo-ocular reflex, irrespective of the direction. In pigeon, the reversible inactivation of the nBOR by means of either tetrodotoxin or lidocaine alters the visual responses of neurons of the nucleus lentiformis mesencephali, homologous of the mammalian NOT (Gu et al., 2001, Crowder et al., 2003b), although some discrepancies exist between these studies regarding the changes that occur. The rat MTN modulates the activity in the NOT (Schmidt et al., 1998); conversely, the pretectum can modulate the directional tuning of AOS neurons both in pigeons (Wang et al., 2001) and rat (Natal and Britto, 1987). All these results can be accounted for by the important reciprocal connections between the AOS and the pretectum, and between the AOS and the vestibular nuclei (see above in this Chapter).

To the best of our knowledge, there are no reports available on the *clinical effects* of a lesion of the AOS nuclei in humans. It is likely that these very small structures are never damaged in isolation, therefore the clinical picture may fall within the wider picture of brainstem (namely mesencephalic) lesions. Furthermore, it is quite possible that in humans the smooth pursuit system may partially or totally override the defective AOS.

Although the involvement of the AOS in the optokinetic pathway has been definitely established, some connectional findings might seem at odds with its purely optokinetic role, and may suggest new lines for future research. For instance, quite unexpected is the finding that the LTN has reciprocal connections with the pretectal olivary nucleus (PON) and projects to the Edinger-Westphal nucleus (Blanks et al., 1995; Buttner-Ennever et al., 1996; Clarke et al., 2003), nuclei known for their involvement in the pupillary light reflex and ocular accommodation. A possible functional role of the AOS in this reflex will need to be reconsidered, however, it is also possible (see also above, section 4.2), that this connection may subserve the recognition of backgroung from foreground, which is necessary for compensatory eye movements.

6.3 AOS and spatial cognition: Recent anatomical and electrophysiological experiments by Wylie and coinvestigators (1999) showed that pigeon nBOR neurons project to the hippocampal formation, both directly and through synapse in the ventral tegmental nuclei of Tsai (see Fig. 8 ATV: VTA).Previously, Gasbarri et al. (1994) had noted that injections of a retrograde tracer into the rat septal hippocampal CA1 and the dorsal CA1 region of temporal hippocampal formation resulted in labeling of dopaminergic neurons in the VTA, this suggesting that an AOS/VTA-hippocampal projection also is present in the rat.

Behavioral studies in rat revealed that the hippocampal formation is involved in a form of navigation or “path integration” (e.g., Foster et al., 1989, McNaughton et al., 1995, 1996) in which an animal can determine spatial orientation re: starting position, destination, and present location based upon information from self-motion, even in the absence of external cues (e.g., Mittelsteadt and Mittelsteadt, 1980; Whishaw et al., 1997). Path integration is disrupted after lesions of the fimbria-fornix (Whishaw and Maaswinkel, 1998) and activity of hippocampal neurons can depend on self-motion cues (Foster et al., 1989). Clearly, the source of information on self-motion is conveyed by many sensory systems, somatosensory, vestibular, visual and in particular analysis of optic flow fields by the speed- and direction-selective neurons of the AOS (cf. Simpson 1984, Simpson et al., 1988). These neurons encoding optic flow fields are monocular or in some instances binocular and are activated either by surround motion, self motion or a combination of the two (e.g., Graf et al., 1988, Wylie and Frost 1990, 1991, 1999; Wylie at al., 1998). Based upon this information, Wylie and coworkers postulated that the visual (optic flow field) information conveyed by the AOS is used by the animal for path integration.

Quite intriguing is the presence of AOS connections with diencephalon and basal ganglia (e.g., Wylie et al., 1998; 1999; see also section 4.2). Fallon et al. (1984) and Giolli et al. (1985c) have demonstrated a disynaptic pathway in rat connecting retinal ganglion cells with the anteromedial striatum (caudate-putamen) and the prefrontal and anterior cingulate cortex. This retino-mesotelencephalic pathway was first described by Giolli et al. (1985c). The relay neurons containing double label were located in two mesencephalic areas: medial pars compacta of the substantia nigra and lateral nucleus paranigralis of the ventral tegmental area (VTA).). Parallel to this, direct electrical stimulation of the prefrontal and anterior cingulate cortex targeted by this retino-mesotelencephalic pathway elicits eye and eyelid movements (Hall and Lindholm, 1974); Torigoe et al. (1986) argued that these cortical regions targeted by the retinorecipient population of the VTA in rat -e.g., prefrontal (area 32) and anterior cingulum (area 24b)- may, in general, function as the rodent equivalent of the frontal eye field of non-human primates. These findings suggest that structures like the AOS, thus far have been considered involved only in the oculomotor response to self-motion, may actually play a role in more cognitive functions, such as spatial memory and attention. This hypothesis may be supported by data from recent studies (which, however, consider only the horizontal branch of the OKR) by suggesting that attention may be directed according to the OKN beating field, i.e., the mean position of gaze during the nystagmus (Watanabe, 2001). Moreover, there is clinical evidence that the optokinetic response causes an improvement in the spatial neglect of stroke patients (Keller, 2004).

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Abbreviations

4n	Trochlear nerve
6n	Abducens nerve
ALH	Anterolateral hypothalamus
AOS	Accessory optic system
AOT-IF	Accessory optic tract, inferior fasciculus
AOT-SF	Accessory optic tract, superior fasciculus
apn	Anterior pretectal nucleus
AVT(also VTA)	Ventral tegmental area of Tsai
B	Nucleus of Bechterew
BOR,	Basal optic root
Br. IC	Brachium, inferior colliculus
BSC	Brachium of superior colliculus
ce	Central sulcus

cP	cerebral peduncle
CP	posterior commissure
CTG	Central gray of mesencephalon
D,	Nucleus of Darkschewitsch
DC	Dorsal cap
DLPN	Dorsolateral pontine nucleus, basal pontine complex
DMNm	Deep mesencephalic nucleus, pars medialis
DTN, dtn	Dorsal terminal nucleus, accessory optic system
ec	external calcarine sulcus
EW, E-W	Nucleus of Edinger-Westphal
FL	Cerebellar flocculus
GABA	gamma-aminobutyric acid
$GABA_{A,B}$	GABA, alpha and beta receptors
FR	Fasciculus retroflexus
HRP	Horseradish peroxidase
Hy	Hypothalamus
IC	Inferior colliculus
ICN	Interstitial nucleus of Cajal
IF	Inferior fasciculus, accessory optic system
III	Oculomotor nerve and oculomotor nucleus
inSFm	Interstitial nucleus of the superior fasciculus, medial fibers
inSFp	Interstitial nucleus of the superior fasciculus, posterior fibers
Iop, IOP	Principal nucleus, inferior olivary complex
ip	Intraparietal sulcus, interpeduncular nucleus
IPN	Interpeduncular nucleus
IV	Trochlear nucleus
la	Lateral sulcus
LG	Lateral geniculate nucleus
LGNd	Lateral geniculate nucleus, pars dorsalis
LGNv	Lateral geniculate nucleus, pars ventralis
Li	Nucleus limitans
LTN, ltn	Lateral terminal Nucleus, accessory optic system
lu	Lunate sulcus
LVN	Lateral vestibular nucleus
MAO	Medial accessory nucleus, inferior olivary complex
MB	Mammillary body
MCM	Nucleus medialis corporis mammillaris
MD	Dorsomedial thalamic nucleus
MG	Medial geniculate nucleus
MGB	Medial geniculate body

MGN	Medial geniculate nucleus
ML	Medial lemniscus
MLF	Medial longitudinal fasciculus
MPv	Deep mesencephalic nucleus, pars ventralis
MRF	Midbrain reticular formation
MST	Medial superior cortical area
MT	Middle temporal cortical area
MTN, mtn	Medial terminal nucleus, accessory optic system
$MTN_{d,v}$	Medial terminal nucleus, (dorsal and ventral divisions), accessory optic system
MVN	Medial vestibular nucleus
N3	Oculomotor nerve
NB	Nucleus of Bechterew
nBORd	Basal optic nucleus, pars dorsalis
nBORl	Basal optic nucleus, pars lateralis
nBORp	Basal optic nucleus, pars principalis
ND	Nucleus of Darkschewitsch
NOT	Nucleus of the optic tract
NPC	Nucleus of posterior commissure
NRPO	Nucleus reticularis pontis oralis
NRTP	Nucleus reticularis tegmenti pontis
oi	Inferior occipital sulcus
OPN	Pretectal olivary nucleus
OT	Optic tract
PA	Anterior pretectal nucleus
PAG	Periaqueductal gray
PAGm	Periaqueductal gray, medial part
Pbp	Nucleus parabrachalis pigmentosus
pC	Cerebral peduncle
pdl	Dorsolateral division, basal pontine complex
pM	Mammillary peduncle
pm	Medial division, basal pontine complex
pn	Nucleus paranigralis of ventral tegmental area
PN	Basal pontine nuclei
PN	Basal pontine nuclei
PO	Pretectal olivary nucleus
pp	Posterior pretectal nucleus
PP	Posterior pretectal nucleus
ppn	Posterior pretectal nucleus
PRF	Pontine reticular formation
Pul, m, l, i	Pulvinar, medial, lateral & inferior divisions

pv	Ventral division, basal pontine complex
PVG	Periventricular gray
R	Thalamic reticular nucleus
RF	Mesencephalic reticular formation
riMLF,	Rostral nucleus, medial longitudinal fasciculus
RN	Red nucleus
rpc	Pontine reticular nucleus, pars caudalis
rpo	Pontine reticular nucleus, pars oralis
Ru	Red nucleus
SC	Superior colliculus
SCE	Stratum cellulare externum
SCI	Stratum cellulare internum
SFa, SFm, SFp	Superior fasciculus, anterior, middle and posterior fibers, accessory optic system
Sg	Suprageniculate nucleus
SGI	Stratum griseum intermediale, superior colliculus
SGP	Stratum griseum profundus, superior colliculus
SGS	Stratum griseum superficiale, superior colliculus
SN	Substantia nigra
SNc	Substantia nigra, pars compacta
SNr	Substantia nigra, pars reticularis
Sop	Stratum opticum, optic tectum
Sp V	Spinal nucleus of trigeminal nerve
SpL	Nucleus subpretectalis, pars lateralis
SpM	Nucleus subpretectalis, pars medialis
StN	Subthalamic nucleus
sts	Superior temporal sulcus
SVN	Superior vestibular nucleus
V3, V4	Visual areas 3 and 4
V3a	Posterior intraparietal area
VI	Abducens nerve
VIP	ventral intraparietal area
VL	Nucleus ventralis lateralis
vl	Lateral vestibular nucleus
VLO	Ventrolateral outgrowth, inferior olivary complex
vm	Medial vestibular nucleus
VN	Vestibular nuclei
VPI	Nucleus ventralis posterior inferior of thalamus
VPL	Nucleus ventralis posterior lateralis of thalamus
VPM	Nucleus ventralis posterior medialis of thalamus
vs	Superior vestibular nucleus

vsp	Spinal vestibular nucleus
VTA	Ventral tegmental area of Tsai
VTRZ	Visual tegmental relay zone
ZI	Zona incerta

Figure Legends

Figs. 1A-C (A) and (B) are lateral and ventral views, respectively, of the rat brain depicting the main optic pathway and its relationship to the fiber components and terminal nuclei of the accessory optic system (taken from Fig. 2, Hayhow et al., 1960). The fibers of the inferior fasciculus are labeled as AOT-IF, while those of the superior fasciculus are labeled as AOS-SF. The medial, lateral and dorsal terminal nuclei are denoted as MTN, LTN and DTN, respectively. (C) shows coronal sections through the posterior diencephalon and rostral midbrain of rabbit in which WGA/HRP had been injected into the contralateral eye and the tracer transported centrally through the optic tract to the superior colliculus, pretectal nuclei, and AOS nuclei. The fascicles of the AOS are not labeled, but the four AOS nuclei, are labeled on the right side on the brainstem (mtn, ltn, dtn and inSFp). (Reproduced from Fig. 1 of van der Want et al., 1992).

Fig. 2 Neuron flow diagram showing the afferent and efferent connections of the AOS nuclei in mammals. Solid arrows denote efferents of the AOS nuclei, whereas broke arrows depict afferents to the AOS nuclei. The projection of AOS nuclei to the cerebellar flocculus, as marked by an asterisk, indicates that this AOS projections has yet to be demonstrated convincingly in mammals.(modified from Fig. 5, Lui, 1996).

Figs. 3A-C (A) Illustrates the site of injection of ^{3}H-leucine into cortical area MST in a macaque. In (B) the location and dimension of the tracer injection is seen in three serially arranged coronal sections oriented from rostral (section 290) to caudal (section 350). (C) shows four coronal sections through the rostral-lateral brainstem after the axonal tracer was transported to axon terminals in the DTN, LTN, MTN_d and inSFp. Other projections of area MST are seen in thalamic and pretectal nuclei and in the superior colliculus. (Modified from Fig. 5, Lui et al., 1995).

Fig. 4 The efferent projections of the MTN are depicted semi-diagrammatically according to experimental findings in the rat and rabbit. The plane of this figure is nearly horizontal with the nuclei revealed in the coronal plane. Arrows depict projections of the MTN while the relative thick nesses of arrows denote their relative sizes of the various projections of the MTN. (taken from Fig. 12, Giolli et al., 1984).

Fig. 5 Semi-diagrammatic depiction of the projections of the LTN of the marmoset. The illustration is in a horizontal plane with the nuclei seen in the coronal plane. Arrows depict the LTN projections and arrow thickness reveals the relative sizes of fiber projections. (Modified from Fig. 14.2, Blanks et al., 2000).

Fig. 6 Summary of mesodiencephalic areas (filled areas) in the marmoset receiving input from the ipsilateral LTN and, in turn, projecting to the inferior olive. The LTN and its efferents are its projections are displayed as black areas and arrows. (Taken from Fig. 9, Blanks et al., 1995).

Fig. 7A,B Bright- (A) and dark-field (B) photomicrographs of a coronal section showing terminal axon labeling in the visual tegmental relay zone (VTRZ, nucleus parabrachialis pigmentosus) after tracer injection of contralateral MTN in a rabbit. In (B), note that a patchy field of terminals is encircled by a broken line. A second broken line (ventrally) outlines the MTN. Other labeling is seen of axons in passage within the VTA. The scale bar indicates 500 um in B. (Reproduced from Figs. 7A, B of Giolli et al., 1984).

Fig. 8 The results of a double labeling experiment performed on pigeon in which chartings A-F are of coronal sections in rostrocaudal sequence are shown. Attention is directed to the ventral tegmental area of Tsai (AVT) as seen in each section. *Small dots* indicate axon terminals labeled anterogradely from injection of biotinylated dextran amine into the left nBOR whereas *larger dots* represent somata retrogradely labeled from bilateral injections into the hippocampal formation. The overlap of terminal axonal labeling with retrograde neuronal labeling within the VTA is evident. (From Fig. 6, Wylie et al., 1999).

Fig. 9 GAD-immunoreactive somata and axon terminals are seen in the MTN_v, MTN_d and inSFp of the gerbil AOS. The upper photomicrograph shows the continuity between the inSFp at the base of the midbrain and the MTN_v and MTN_d extending into the midbrain tegmentum between the substantia nigra and VTA (n. parabrachialis pigmentosus and n. paranigralis). The two boxed zones show regions of the MTN and inSF containing GAD immunopositive somata and axon terminal. Clusters of GAD-immunoreactive terminals are evident in the MTN. GAD-positive neurons are also present in the pars compacta and pars reticularis of the substantia nigra. The scale bars show that the upper photomicrograph is 5X larger than the two lower micrographs. (taken from Fig. 3, Giolli et al. 1985b).

Fig. 10 Autoradiograms of coronal sections of the midbrain tegmentum of a guinea pig after 2DG administration and vertical-visual field stimulation directed upward. The isotope reaches its maximum level in the MTN_d with the isotope showing elevated levels also in the contiguous inSFp. High uptake of isotope dorsal and medial to the MTN is present in the periaqueductal gray and probably also the nucleus of Darkschewitsch. Dorsal and lateral to the MTN, high uptake is seen in the thalamus. The sections are ~300 um part with the more rostral section shown below. (Taken from Fig. 7, Lui et al., 1990).

Table 1: Topography of Accessory Optic Pathways and Terminal Nuclei in Mammals Studied[1]

Orders	Species	IF[2]	SF-af[2]	SF-mf[2]	SF-pf[2]	MTN[3]	LTN	DTN	inSFp
Monotremes	Echidna	●	-	-	-	●	-	-	-
	Platypus	●	-	-	-	●	-	-	-
Marsupials	*Didelphis*	●	•	•	•	●	•	•	?
	Phalanger	●	●	●	•	●	•	•	?
Insectivores	Hedgehog	-	•	•	●	●	●	●	?
Caviomorpha	Guinea pig	●	●	●	•	●	●	•	●
Scandentia	*Tupaia*	●	●	●	●	●	●	●	?
Rodents	Rat	●	●	•	●	●	●	●	●
	Hamster	●	•	•	•	●	●	●	?
	Mouse	●	●	●	●	●	●	●	●
Lagomorphs	Rabbit	●	●	-	●	●	●	●	●
Ungulates	Sheep. Pig, Ox	-	-	-	●	-	●	●	?
	Horse	-	-	-	●	●	●	●	?
Carnivores	Cat, Ferret	-	-	-	●	●	●	●	?
Primates (Prosimians)	Lemur	-	-	-	●	●	●	●	?
	Galago	-	-	-	●	●	●		
	Microcebus	•	-	-	●	●	●	●	?
Primates (Simians)	Macaque	-	-	-	●	•	●	●	●
	Marmoset	-	-	-	●	•	●	●	●
	Gibbon	-	-	-	●	•	●	●	?

[1] The relative size and differentiation of the AOS fiber bundles and terminal nuclei in each species is indicated by the size of the filled circle as follows:

- small
- medium
- large

Reports dealing with this ratings scale are discussed in the body of the chapter. (-)indicate that fiber bundles or terminal nuclei were not found in a species, whereas (?) indicates insufficient evidence for the existence of bundles or nuclei in different species.

[2] IF, inferior fasciculus, SF-af, superior fasciculus, anterior fibers, SF-mf, superior fasciculus, middle fibers, SF-pf, superior fasciculus, posterior fibers.

[3] The MTNd, but not the MTNv, has been identified in macaque monkeys and gibbon ape. Whether a MTNv is present in the marmoset has not been resolved.

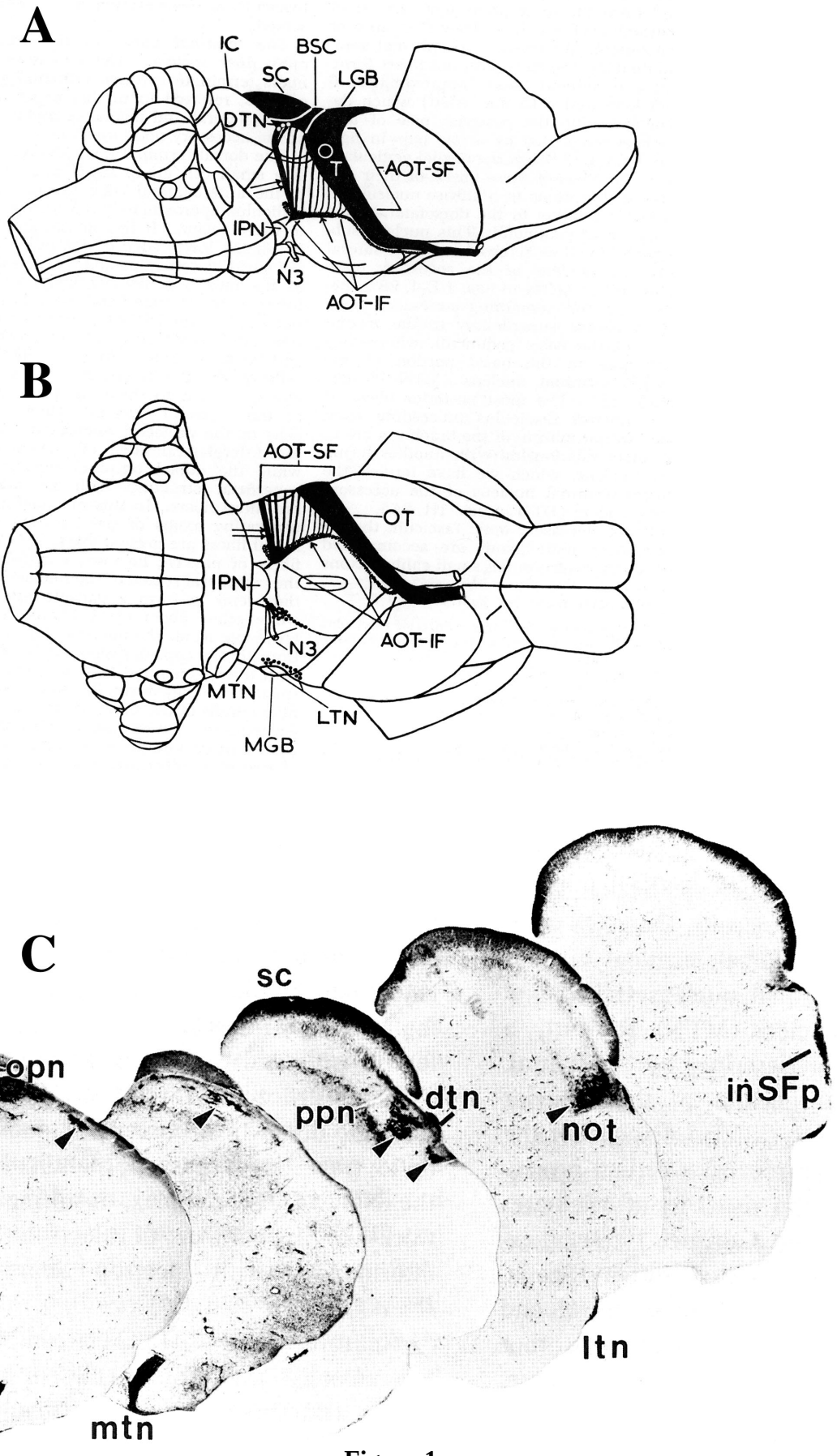
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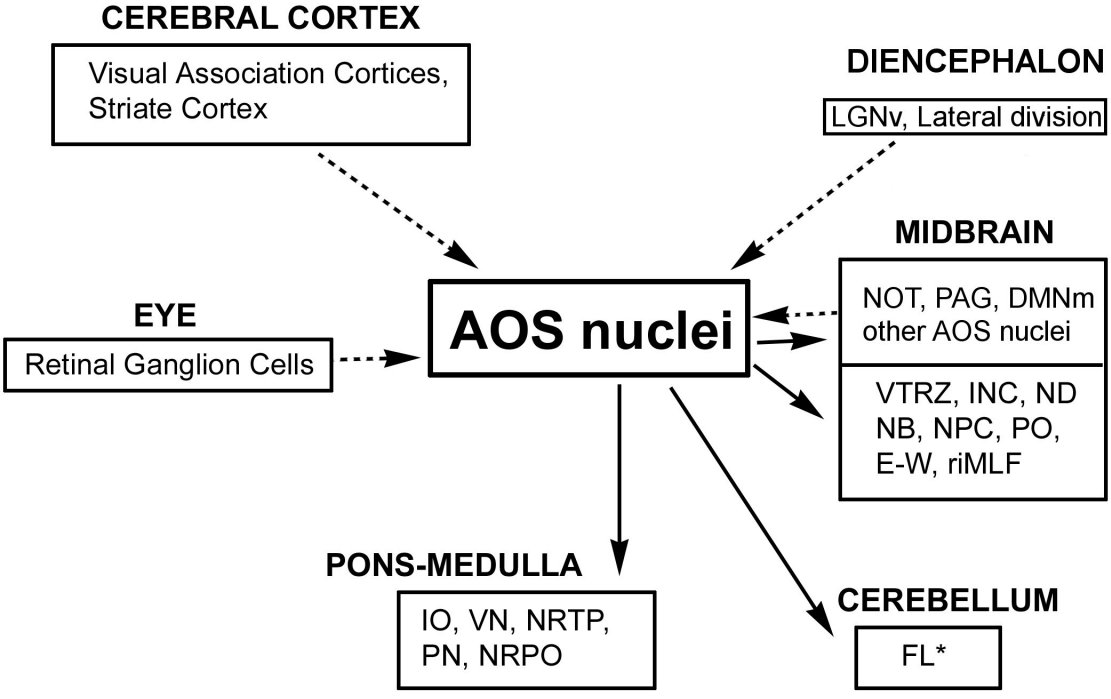
Figure 1

Figure 2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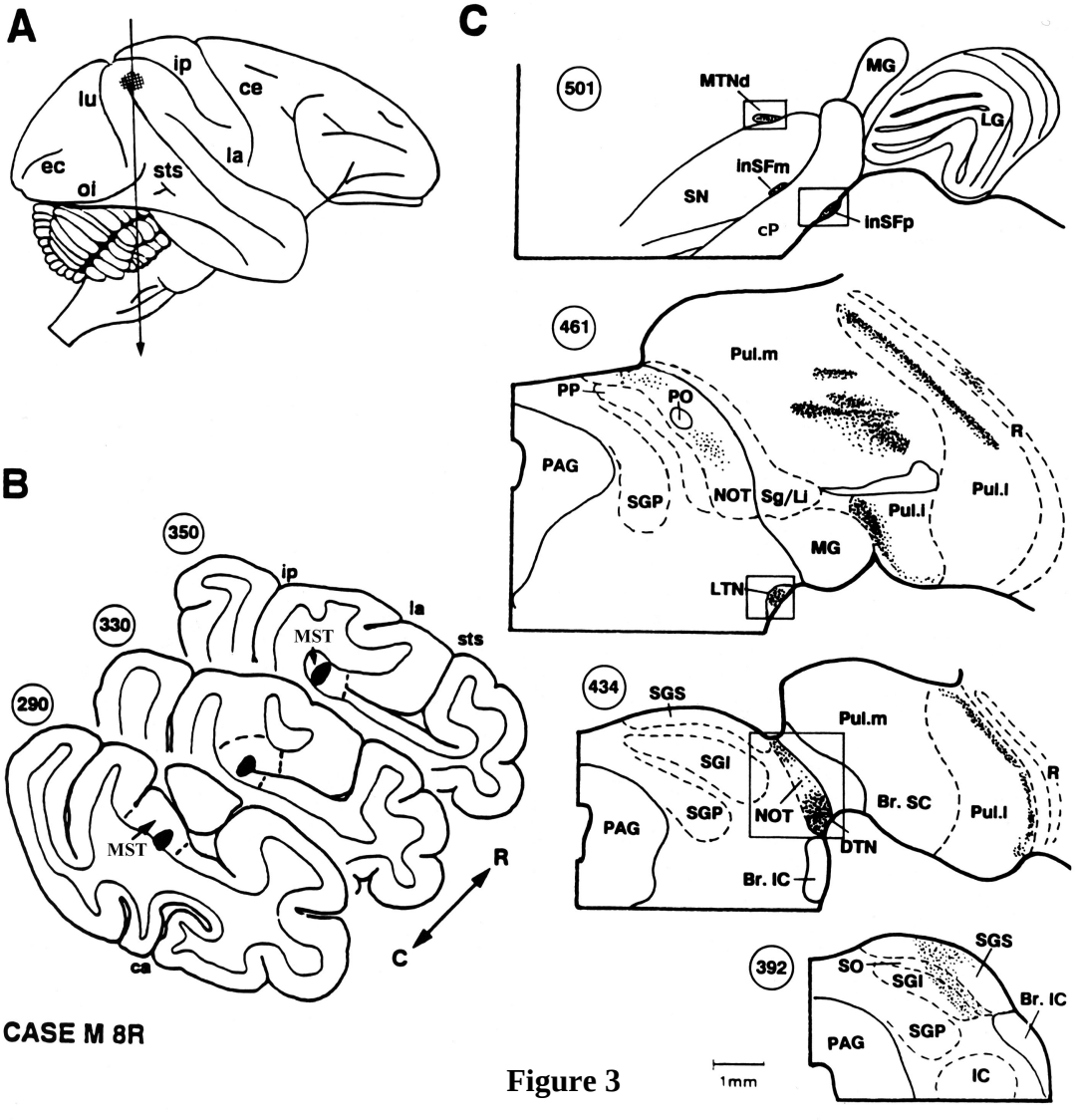
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1mm

Figure 3

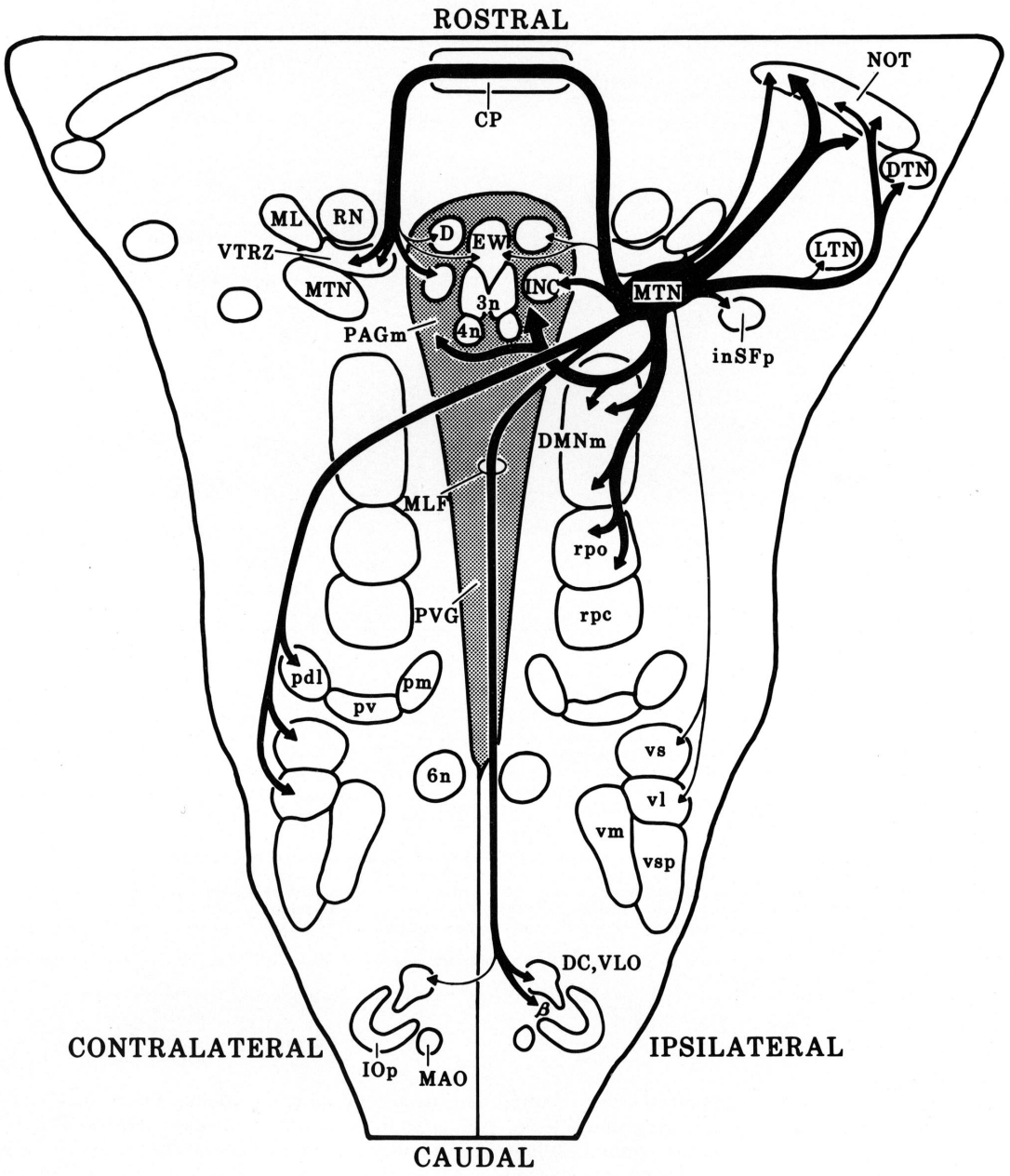

ROSTRAL
CP
NOT
DTN
ML
RN
VTRZ
D
EW
LTN
MTN
INC
MTN
3n
4n
PAGm
inSFp
DMNm
MLF
rpo
PVG
rpc
pdl
pm
pv
vs
6n
vl
vm
vsp
DC,VLO
CONTRALATERAL
IPSILATERAL
IOp
MAO
CAUDAL

Figure 4

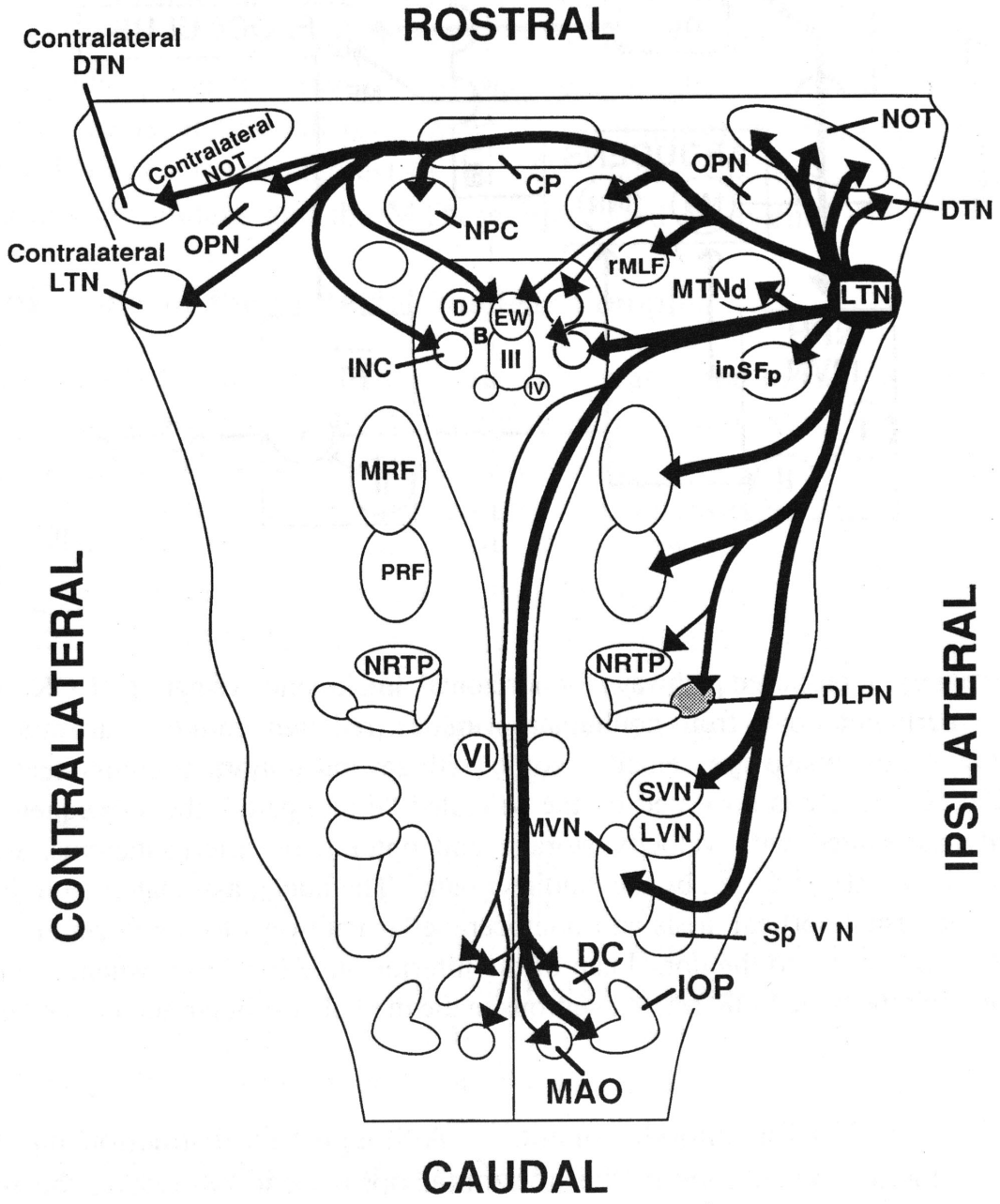

ROSTRAL
Contralateral DTN
Contralateral NOT
OPN
Contralateral LTN
CP
NPC
NOT
OPN
DTN
rMLF
MTNd
LTN
D
EW
B
III
IV
INC
inSFp
MRF
PRF
NRTP
NRTP
DLPN
VI
SVN
MVN
LVN
Sp V N
DC
IOP
MAO
CONTRALATERAL
IPSILATERAL
CAUDAL

Figure 5

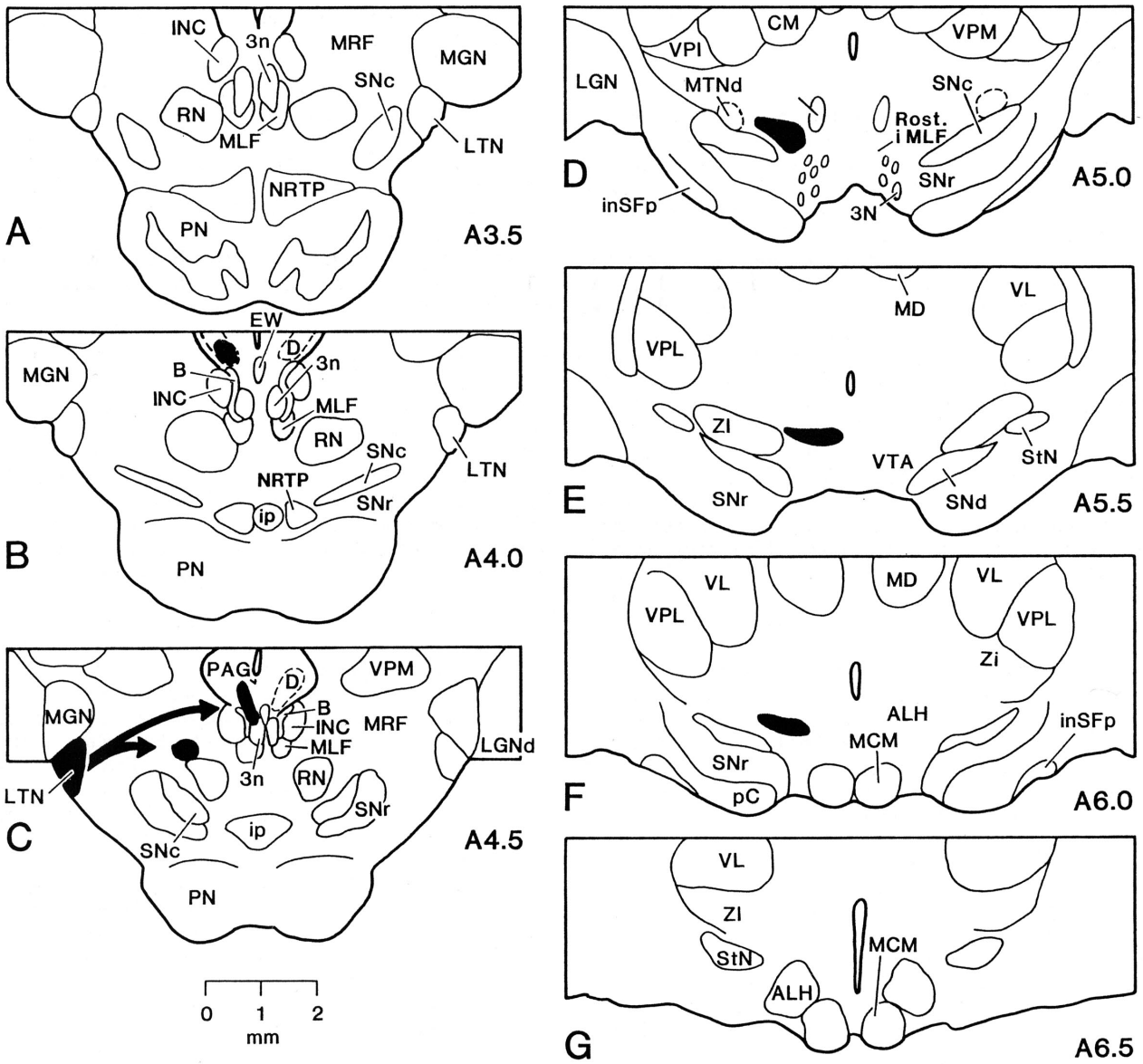

INC
3n
MRF
MGN
SNc
RN
MLF
LTN
NRTP
PN
A
A3.5
EW
D
MGN
B
3n
INC
MLF
RN
SNc
LTN
NRTP
SNr
ip
B
PN
A4.0
PAG
D
VPM
MGN
B
INC
MRF
MLF
LGNd
LTN
3n
RN
SNr
C
ip
SNc
A4.5
PN
0
1
2
mm
CM
VPM
VPl
LGN
MTNd
SNc
Rost.
i MLF
D
SNr
A5.0
inSFp
3N
MD
VL
VPL
ZI
VTA
StN
SNr
SNd
E
A5.5
VL
MD
VL
VPL
VPL
Zi
ALH
inSFp
MCM
SNr
pC
F
A6.0
VL
ZI
StN
MCM
ALH
G
A6.5

Figure 6

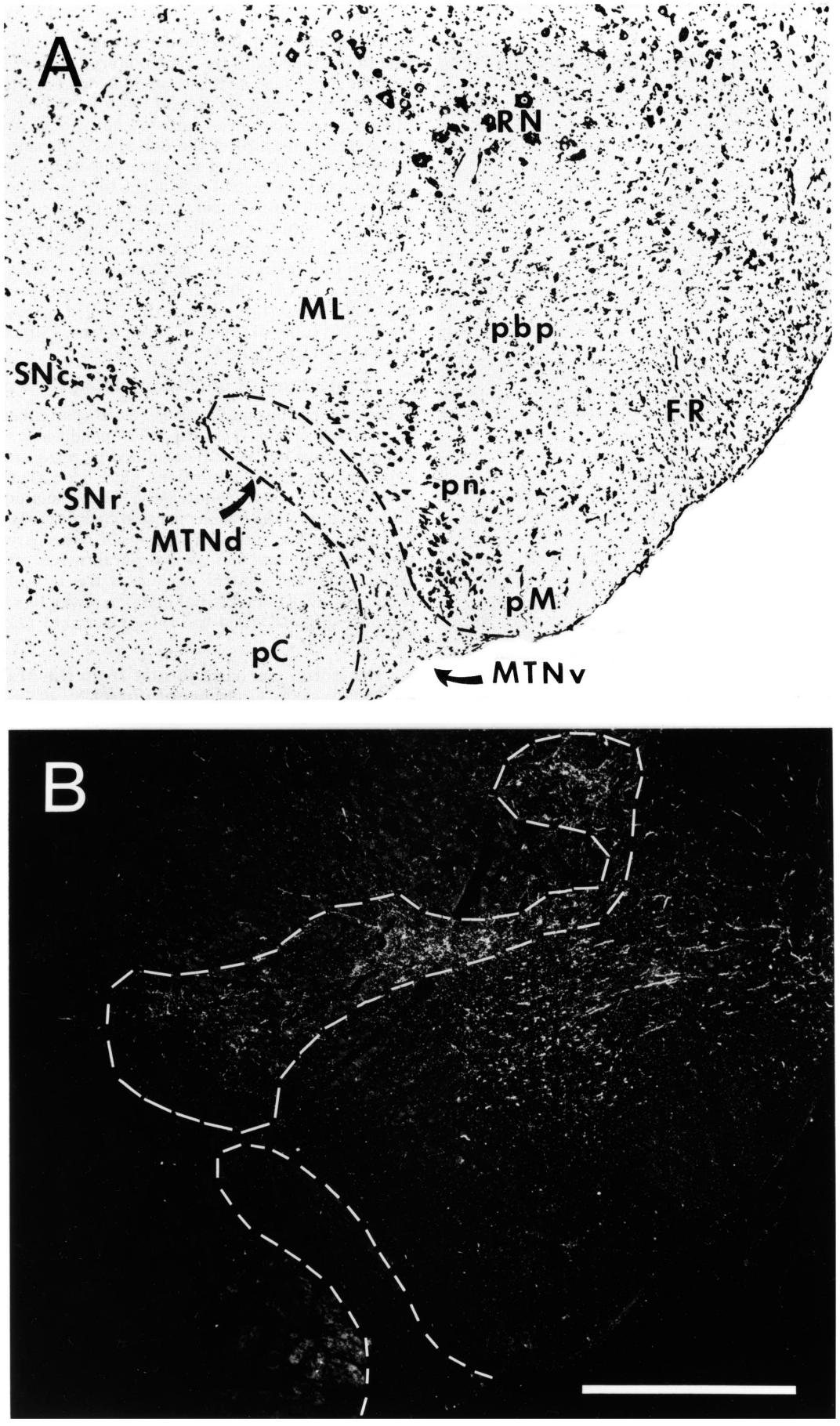


Figure 7

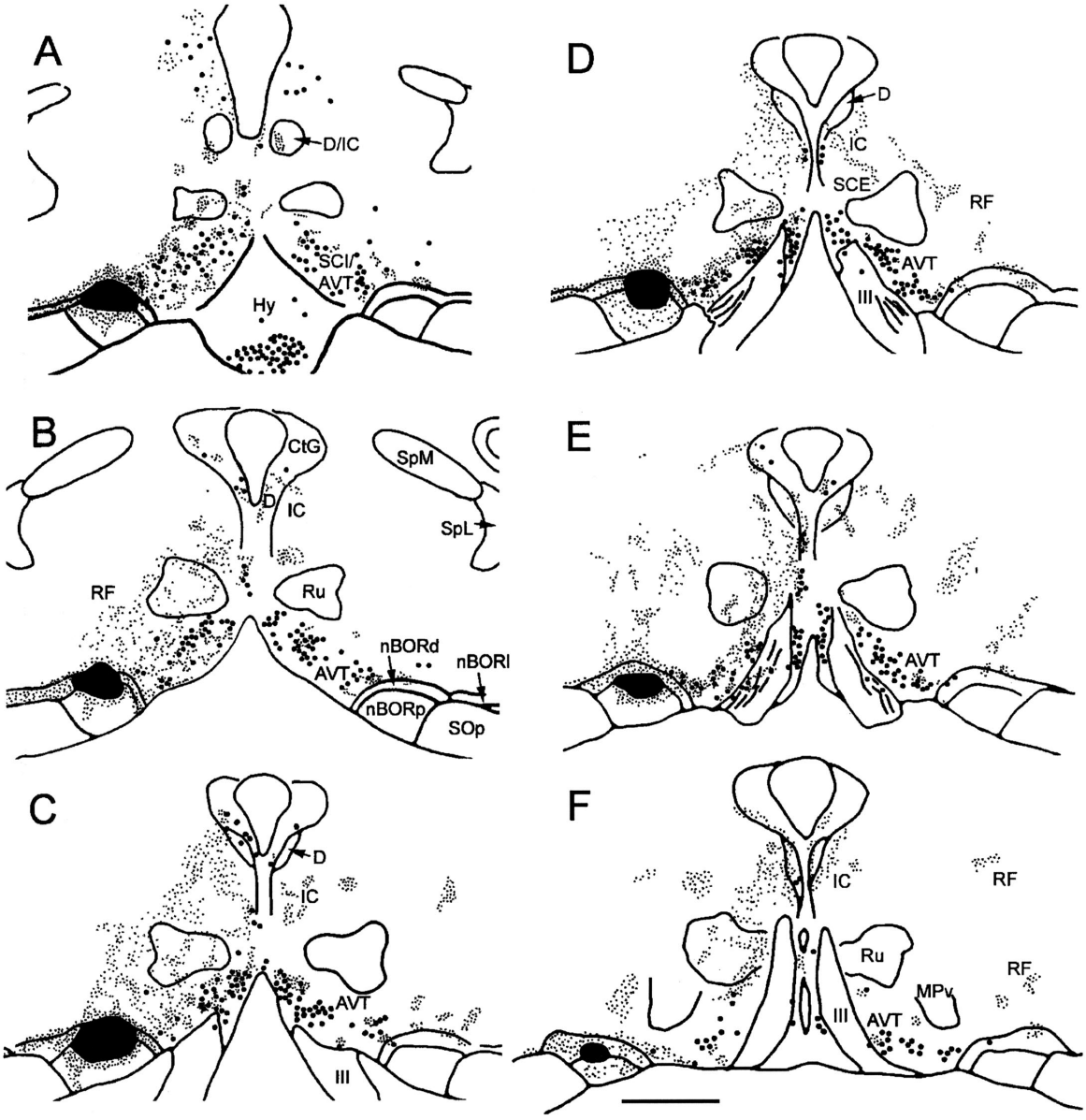
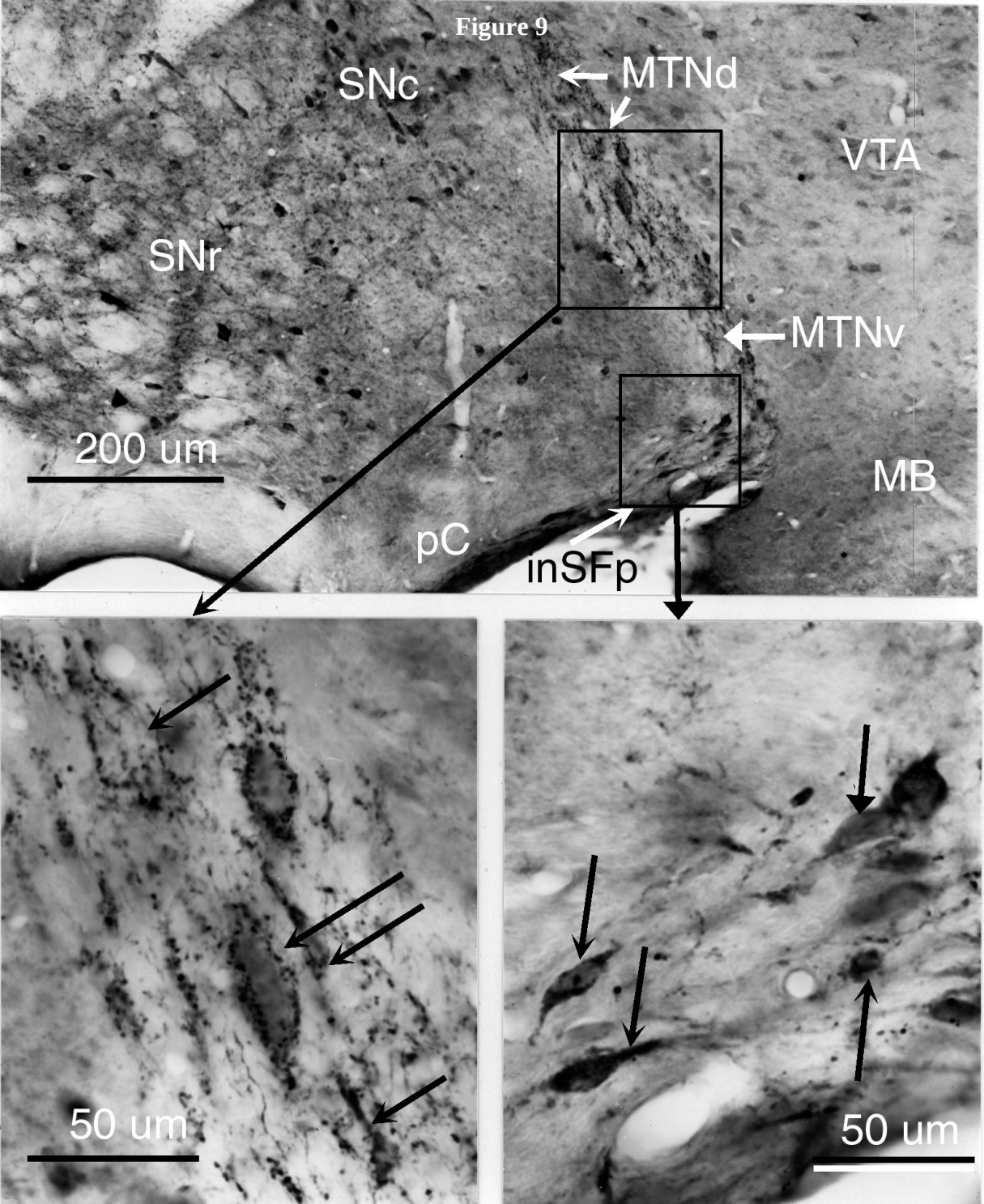

A
D/IC
SCl/
AVT
Hy
B
CtG
SpM
D
IC
SpL
RF
Ru
nBORd
nBORl
AVT
nBORp
SOp
C
D
IC
AVT
III
D
D
IC
SCE
RF
AVT
III
E
AVT
F
IC
RF
Ru
RF
MPv
III
AVT

Figure 8

Figure 9



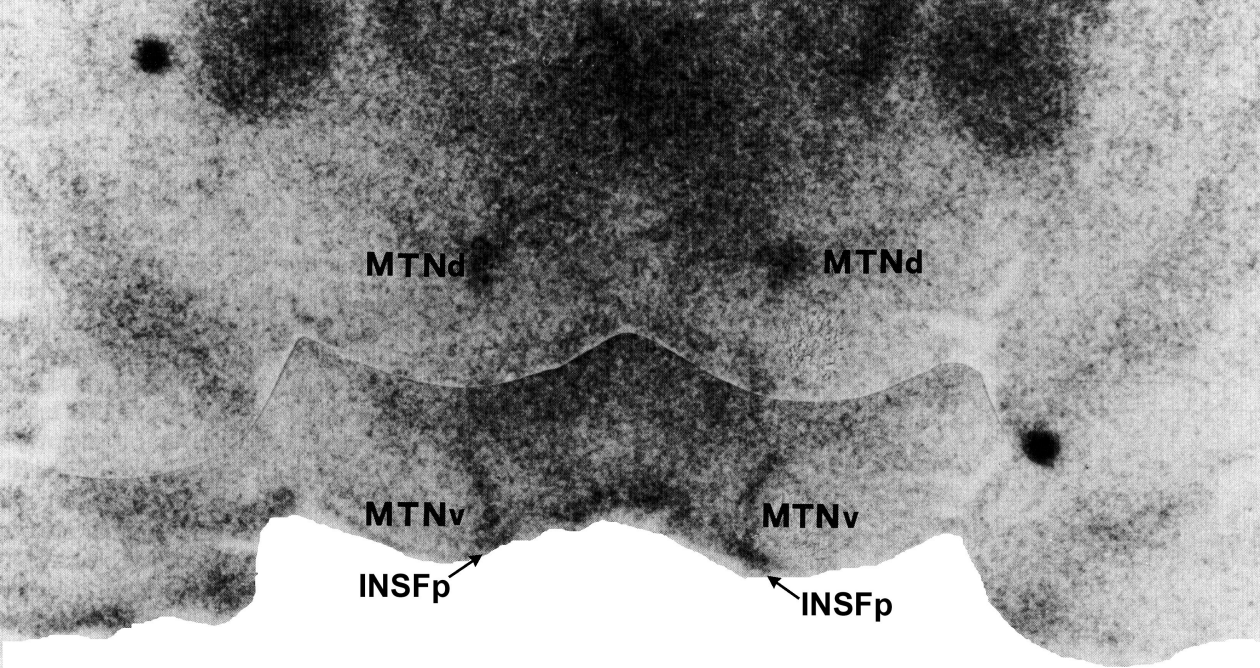


Figure 10