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THE DOPAMINERGIC INNERVATION OF THE AVIAN TELENCEPHALON

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Abstract—The present review provides an overview of the distribution of dopaminergic fibers and dopaminoceptive elements within the avian telencephalon, the possible interactions of dopamine (DA) with other biochemically identified systems as revealed by immunocytochemistry, and the involvement of DA in behavioral processes in birds.

Primary sensory structures are largely devoid of dopaminergic fibers, DA receptors and the D1-related phosphoprotein DARPP-32, while all these dopaminergic markers gradually increase in density from the secondary sensory to the multimodal association and the limbic and motor output areas. Structures of the avian basal ganglia are most densely innervated but, in contrast to mammals, show a higher D2 than D1 receptor density. In most of the remaining telencephalon D1 receptors clearly outnumber D2 receptors. Dopaminergic fibers in the avian telencephalon often show a peculiar arrangement where fibers coil around the somata and proximal dendrites of neurons like baskets, probably providing them with a massive dopaminergic input. Basket-like innervation of DARPP-32-positive neurons seems to be most prominent in the multimodal association areas.

Taken together, these anatomical findings indicate a specific role of DA in higher order learning and sensory-motor processes, while primary sensory processes are less affected. This conclusion is supported by behavioral findings which show that in birds, as in mammals, DA is specifically involved in sensory-motor integration, attention and arousal, learning and working memory. Thus, despite considerable differences in the anatomical organization of the avian and mammalian forebrain, the organization of the dopaminergic system and its behavioral functions are very similar in birds and mammals.

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ABBREVIATIONS

6-OHDA	6-Hydroxydopamine
Acc	Nucleus accumbens
Ai	Archistriatum intermedium, pars centrale
Aid	Archistriatum intermedium, pars dorsale
Am	Archistriatum mediale
Ap	Archistriatum posterior
APH	Area parahippocampalis
Av	Archistriatum intermedium, pars ventrale
AVT	Area ventralis tegmentalis
Bas	Nucleus basalis
BNST	Bed nucleus of the stria terminalis
CDL	Corticoidea dorsolateralis
DA	Dopamine
DARPP-32	Dopamine- and cAMP-regulated phosphoprotein, MW 32 000
DBH	Dopamine-beta-hydroxylase
E	Ectostriatum
Ep	Ectostriatal belt
GABA	γ-Aminobutyric acid
GAD	Glutamate decarboxylase
HA	Hyperstriatum accessorium
HD	Hyperstriatum dorsale
HIS	Hyperstriatum intercalatus superior
Hp	Hippocampus
HV	Hyperstriatum ventrale
HVdv	Hyperstriatum ventrale dorso-ventrale
HVvv	Hyperstriatum ventrale ventroventrale
IHA	Nucleus intercalatus of the hyperstriatum accessorium
IMHV	Intermediate and medial part of the hyperstriatum ventrale
INP	Nucleus intrapeduncularis
ir	Immunoreactive
L1	Field L1
L2	Field L2
L3	Field L3
LFS	Lamina frontalis superior
LPO	Lobus parolfactorius
MNH	Mediorostral neostriatum/hyperstriatum ventrale
n.	Nucleus
NA	Noradrenaline
NC	Neostriatum caudale
NCL	Neostriatum caudolaterale
NF	Neostriatum frontale
NFL	Neostriatum frontolaterale
NIL	Neostriatum intermedium laterale
NIM	Neostriatum intermedium mediale
PA	Paleostriatum augmentatum
PFC	Prefrontal cortex
PNMT	Phenylethanolamine-*N*-methyl transferase
PP	Paleostriatum primitivum
SNC	Substantia nigra, pars compacta
SNR	Substantia nigra, pars reticulata
TH	Tyrosine hydroxylase
Tn	Nucleus taeniae
TO	Olfactory tubercle
TPO	Area temporo-parieto-occcipitalis
VP	Ventral pallidum

1. INTRODUCTION

The neuromodulatory dopaminergic system of mammals and birds is critically involved in numerous cognitive and behavioral functions, including appetitive and aversive behaviors (Balthazart *et al.*, 1997; Bertolucci-D'Angio *et al.*, 1990b; Deviche, 1984; Salamone, 1992, 1994; Sokolowski *et al.*, 1994), states of arousal and wakefulness (Ferrari and Giuliani, 1993; Ongini, 1993), motor control (Goodman *et al.*, 1983; Rieke, 1981, 1982; Salamone, 1992; Sokolowski and Salamone, 1994; Waddington and Daly, 1993), learning and memory (Beninger, 1993; Gruss and Braun, 1997; McDougall *et al.*, 1987; Schultz *et al.*, 1995), as well as working memory and attention (Güntürkün and Durstewitz, in press; Montaron *et al.*, 1982; Roberts *et al.*, 1994; Sawaguchi and Goldman-Rakic, 1991, 1994; Schultz *et al.*, 1993; Seamans *et al.*, 1998; Zahrt *et al.*, 1997). Since structure and function are tightly coupled in neural systems, information about

the neuroanatomical organization of the dopaminergic system is required to unravel the functional role of dopamine (DA) in these various cognitive and behavioral processes. A large body of evidence indicates that the principal function of DA is very similar in mammals and birds. Since members of these two classes of vertebrates have highly developed cognitive skills (e.g. Epstein *et al*., 1984; von Fersen *et al*., 1990; Lanza *et al*., 1982; Lubow, 1974) but radically different forebrain organizations, comparative studies may uncover the invariant structural features which enable the dopaminergic system to exert its specific functions.

The present article provides an overview over the structural organization of the dopaminergic system in avian species, compares it to mammals, and discusses behavioral findings and possible functional implications. However, this review will be restricted in two ways: First, almost all studies that dealt specifically with markers of the dopaminergic system in the avian brain (i.e. DA, DA receptors, DARPP-32) have been conducted within the last decade, and the present review will focus mainly on these studies. Older literature on the general distribution of markers of the monoaminergic or catecholaminergic systems are covered in the excellent review by Reiner *et al*. (1994). Second, most of our knowledge on the dopaminergic innervation of the bird brain derives from studies in pigeons and chicks. However, the few available studies from other avian species make it likely that the results obtained in these avian species generalize to other birds as well.

2. OVERVIEW OVER THE NEUROANATOMY OF THE AVIAN TELENCEPHALON

The avian telencephalon consists of nuclear structures, and mostly lacks the layered organization that is characteristic of mammalian isocortex (Fig. 1). This lack of lamination led early investigators to assume that most of the avian telencephalon consists merely of a hypertrophied striatum. Accordingly most forebrain areas were termed with the suffix '-striatum', and this nomenclature remains still in use

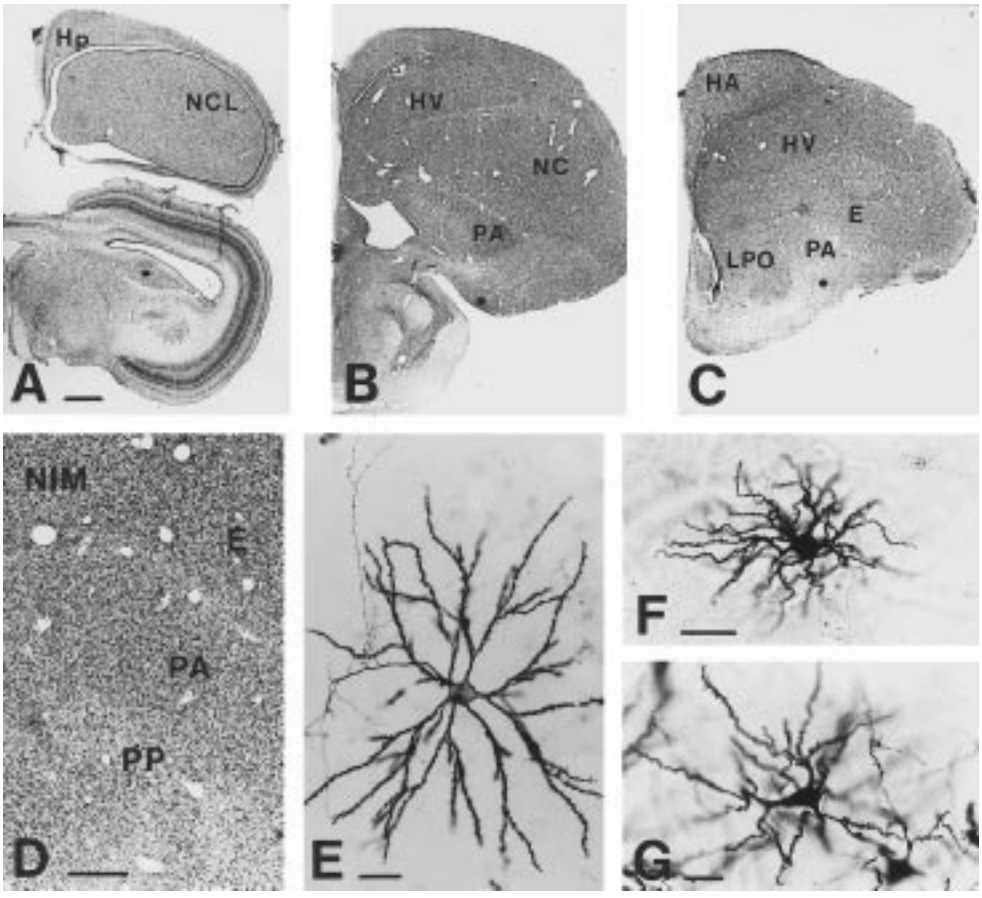

Fig. 1. Morphology of the avian telencephalon (brain of a pigeon, *Columba livia*). (A–C) A series of hemispheres stained for Cresyl Violet, indicating the location of several major structures. Rostro-caudal positions of the slices shown are approximately A 4.25 (A), A 7.25 (B) and A 10.00 (C) according to the pigeon brain atlas of Karten and Hodos (1967). (D) Detail from (C), showing part of the basal ganglia (PA, PP), the primary recipient area of the visual tectofugal pathway (ectostriatum), and a presumed multimodal area (NIM). (E–G) Prototypical examples of cells from the pigeon telencephalon that were labeled by intracellular filling (E) or Golgi impregnation (F and G). All cells display multipolar dendritic fields, a feature that seems to be associated with the organization of the avian forebrain in nuclei rather than layers. Scale bars represent 1 mm (A–C), 50 μm (D), 25 μm (E–G). See list for abbreviations.

(Ariëns-Kappers *et al.*, 1936; Edinger, 1903). On the basis of embryological (Källén 1953, 1962; Kuhlenbeck 1938; see also Striedter *et al.* 1998) cytoarchitectonic (Rehkämper *et al.*, 1984, 1985; Rehkämper and Zilles, 1991), hodological (Karten, 1969; Karten and Dubbeldam, 1973; Veenman *et al.*, 1995) and histochemical (Juorio and Vogt, 1967) criteria, however, it became clear that large parts of the telencephalon could be regarded as pallial, and as such might constitute possible cortex equivalents.

The flow of sensory information in the avian telencephalon follows a common pattern for all modalities: the primary sensory areas which receive subtelencephalic input, relay their information to adjacent secondary sensory structures, which in turn project in parallel to presumed multimodal areas as well as to motor and limbic structures, including the basal ganglia (Fig. 2).

As in all amniotes, two main visual pathways convey visual information from the retina to the telencephalon in birds. These are the thalamofugal and the tectofugal pathway. The tectofugal pathway may correspond to the mammalian colliculo-thalamo-extrastriate pathway, whereas the thalamofugal pathway is comparable to the mammalian geniculostriate pathway (review by Güntürkün 1991). The ectostriatum (E) is the primary sensory structure of the tectofugal pathway (Benowitz and Karten, 1976; Kondo, 1933). From there intratelencephalic projections lead to the surrounding ectostriatal belt (Ep) (Karten and Hodos, 1970; Ritchie, 1979). The thalamofugal visual pathway consists of a bilateral projection from a retinorecipient nucleus in the dorsal thalamus onto a thin band of granule cells, the intercalated nucleus of the hyperstriatum accessorium (IHA), as well as to the lateral part of the hyperstriatum dorsale (HD), which together constitute the primary sensory areas within the so-called Wulst. The IHA and HDl in turn project to secondary sensory structures within the Wulst, mainly to the hyperstriatum accessorium (HA) (Karten *et al.*, 1973; Shimizu *et al.*, 1995).

The same organization applies to a part of the somatosensory system which occupies the rostral extent of the Wulst, and that seems to be comparable to the mammalian primary somatosensory cortex (Karten, 1971; Medina *et al.*, 1997). Somatosensory fibers from the dorsal thalamus ter-

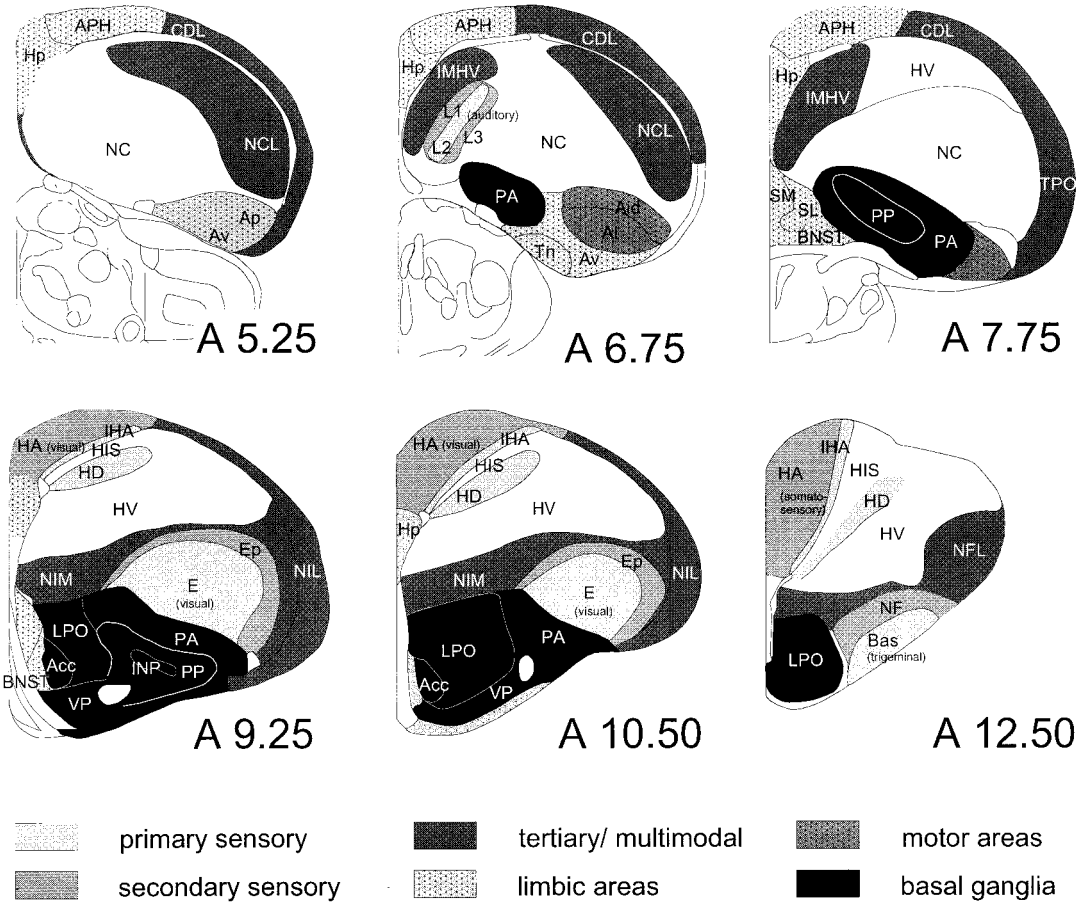

Fig. 2. Schematic overview of the functional anatomy of the pigeon telencephalon as described in Section 2. Brain areas that are still poorly understood with regards to their connections and functions were left blank. It should be noted, however, that the hyperstriatum intercalatus superior (HIS) probably receives secondary and, to a limited extent, possibly also primary visual input. The hyperstriatum ventrale (HV) is a highly heterogeneous region which probably encompasses multiple polysensory subdivisions.

minate in the HD and the IHA (Delius and Bennetto, 1972; Funke, 1989; Wild, 1997) which in turn project to the rostral HA (Wild, 1987). Another primary somatosensory telencephalic area is located within the nucleus basalis (Bas). The Bas mainly processes trigeminal information (Schall *et al*., 1986), but also receives additional somatosensory and auditory input (Arends and Zeigler, 1986; Wild and Farabaugh, 1996; Wild *et al*., 1997). It relays this information to the overlying frontal neostriatum (NF) (Wild and Farabaugh, 1996; Wild *et al*. 1985).

The main telencephalic area reached by auditory input from the thalamus is the so-called Field L complex in the caudomedial neostriatum (Karten, 1968). Field L2 is the primary sensory structure of the auditory system, which projects to adjacent fields L1 and L3 (Bonke *et al*., 1979; Karten, 1968; Wild *et al*., 1993).

The secondary sensory areas of all modalities are reciprocally connected with a region in the caudolateral neostriatum, which in the pigeon is referred to as NCL (Kröner and Güntürkün, in press; Leutgeb *et al*., 1996; Metzger *et al*., 1998). Other multimodal areas probably exist in the intermediate aspect of the hyperstriatum ventrale (IMHV) and the intermediate neostriatum (NIM; or mediorostral neostriatum/hyperstriatum ventrale, MNH, in chicks). Both these areas have been studied extensively in chicks in the context of imprinting (Bradley *et al*., 1985; Bredenkötter and Braun 1997; Metzger *et al*. 1996; reviews: Horn 1998; Scheich 1987). In addition, a system of 'cortico'-striatal projection neurons which occupies the most dorsal and lateral extent of the external pallium (PE) (Brauth *et al*., 1978; Veenman *et al.,* 1995) includes, from rostral to caudal, the lateral frontal neostriatum (NFL), the lateral intermediate neostriatum (NIL), the area temporo-parieto-occcipitalis (TPO) and the area corticoidea dorsolateralis (CDL).

At the next level of information processing in the avian brain, sensory information is funneled in parallel from both, the tertiary as well as the secondary sensory areas to the basal ganglia and, in addition, to the ventrolaterally located archistriatum (e.g. Bradley *et al*., 1985; Csillag *et al*., 1994; Kröner and Güntürkün, in press; Leutgeb *et al*., 1996; Metzger *et al*., 1998; Phillips, 1966; Shimizu *et al*., 1995; Wild *et al*., 1985, 1993). Functionally, the avian archistriatum has been divided into two main subdivisions (Davies *et al*., 1997; Dubbeldam *et al*., 1997; Zeier and Karten, 1971). These are a somatic sensorimotor part and a viscerolimbic division that is considered to be equivalent to the mammalian amygdala (Davies *et al*., 1997; Dubbeldam *et al*., 1997; Zeier and Karten, 1971).

The connectivity, neurotransmitter content, and cytoarchitecture of the avian basal ganglia are highly similar to that in mammals (Anderson and Reiner, 1991b; Karten and Dubbeldam, 1973; Reiner and Anderson, 1990; Reiner *et al*., 1983, 1984a; Veenman and Reiner, 1994; Veenman *et al*., 1995). Based on the palliostriatal connections, a functional segregation of the avian striatum into associative, sensorimotor and limbic territories has recently been suggested (Veenman *et al*., 1995), similar to the situation in mammals (Parent, 1990). The paleostriatum augmentatum (PA) and lobus parolfactorius (LPO) make up the dorsal (somatomotor) striatum. Ventral striatal structures include the nucleus accumbens (Acc), the bed nucleus of the stria terminalis (BNST), and the olfactory tubercle (TO) which constitute the 'visceral-limbic' parts of the avian striatum. The pallidal parts of the avian basal ganglia consist of the paleostriatum primitivum (PP), which is homologous to the globus pallidus of mammals, and the ventral pallidum (VP) which is comparable to the 'limbic' VP of mammals (Karten and Dubbeldam, 1973; Medina and Reiner, 1997).

The description of the dopaminergic innervation of the avian telencephalon given in Section 5 will follow the functional classification outlined above. It will turn out that the distribution of DA and DA receptors is closely related to these functional subdivisions. However, certain exceptions exist, as, for example, components of the song system of songbirds subserve sensory as well as motor functions.

3. ORIGIN OF DOPAMINERGIC FIBERS IN THE AVIAN TELENCEPHALON: MESENCEPHALIC A8–A10 CELL GROUPS

Comparable to the situation in mammals, the dopaminergic innervation of the avian telencephalon arises mainly from three mesencephalic dopaminergic cell populations located in the n. tegmenti pedunculopontinus pars lateralis and the area ventralis tegmentalis of Tsai (AVT) (Fig. 3; Kitt and Brauth, 1986; Metzger *et al*., 1996; Waldmann and Güntürkün, 1993). The former nucleus is homologeous to the mammalian substantia nigra pars compacta (SNC) (Brauth *et al*., 1978; Karten and Dubbeldam, 1973; Kitt and Brauth, 1986; Reiner *et al*., 1983; Rieke, 1981, 1982), where according to Reiner *et al*. (1994) the rostro-ventral part comprises the A9 group and the caudo-dorsal part the A8 group. The medial part of the n. tegmenti pedunculopontinus is considered to be equivalent to the mammalian substantia nigra, pars reticulata (SNR) (Kitt and Brauth, 1981; Reiner *et al*., 1983). The avian AVT is homologeous to the ventral tegmental area of mammals (A10 group) (Kitt and Brauth, 1981, 1986; Reiner *et al*., 1983, 1994; Waldmann and Güntürkün, 1993). In the AVT and SNC, intense perikaryal immunoreactivity (ir) for tyrosine hydroxylase (TH) and DA (Fig. 3A–C) but not for dopamine-beta-hydroxylase (DBH), noradrenaline (NA) or phenylethanolamine-*N*-methyl transferase (PNMT) can be observed (Bailhache and Balthazart, 1993; Moons *et al*., 1995; Reiner *et al*., 1994; Waldmann and Güntürkün, 1993; Wynne and Güntürkün, 1995). TH is the rate-limiting enzyme in the synthesis of all catecholamines and, with a few exceptions (Smeets and Gonzales, 1990), must be present in dopaminergic neurons. The presence of DBH which converts DA to noradrenaline, or of PNMT which converts noradrenaline to adrenaline, would indicate non-dopaminergic catecholaminergic neurons and fibers. An A8–A10 group has been recognized in many avian species, including zebra

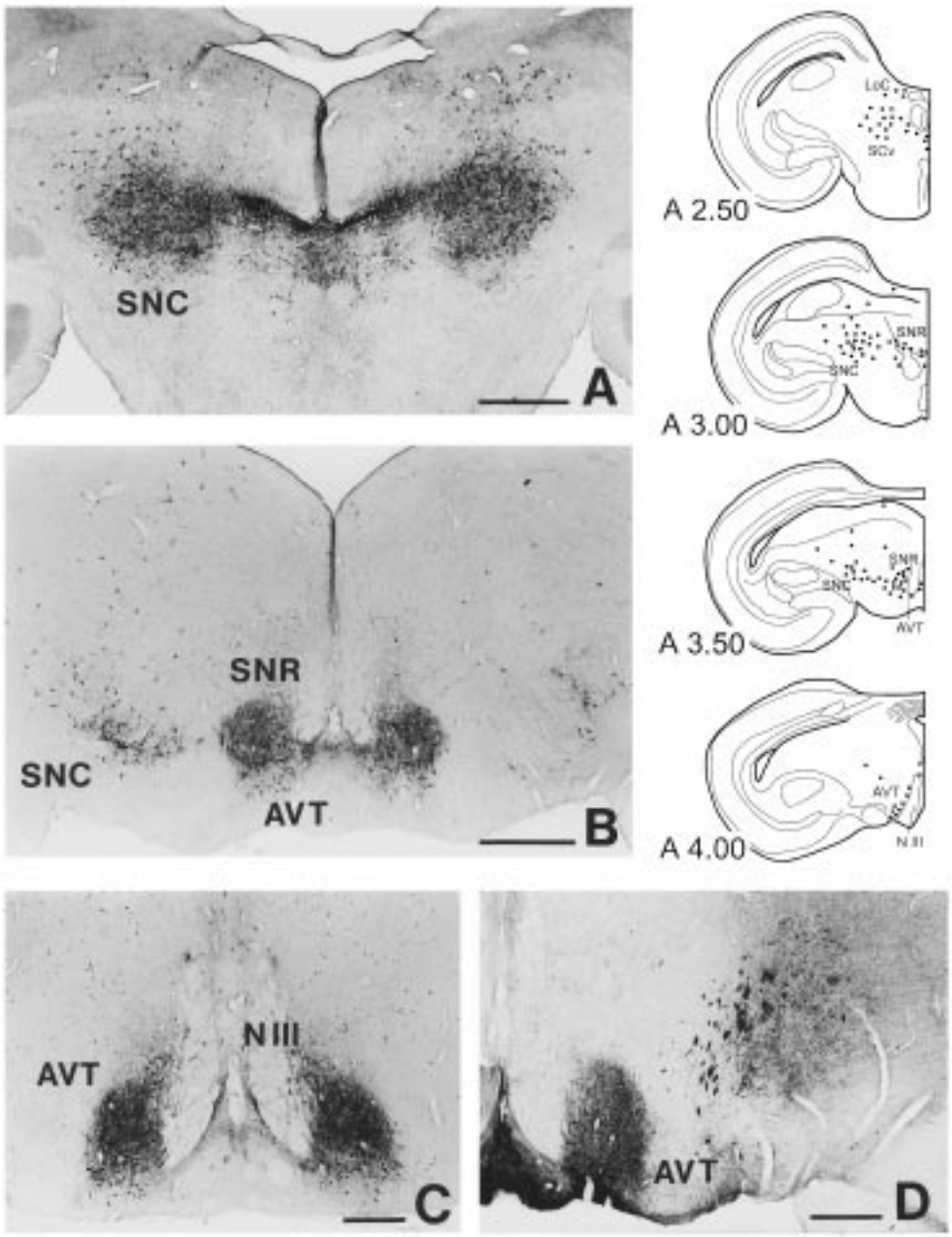

Fig. 3. Dopaminergic neurons in the avian midbrain. (A–C and inset) Cells in the nucleus tegmenti pedunculopontinus and the area ventralis tegmentalis of Tsai constitute the avian homologues of the substantia nigra, pars compacta (SNC) and reticulata (SNR), and the ventral tegmental area (AVT), respectively. (D) Similar view as seen in the right part of (C) labeled for DARPP-32. In contrast to dopamine-immunoreactivity as shown in (C), only fibers are labeled with DARPP-32ir. Scale bars represent 1 mm (A and B) and 500 μm (C and D).

finches (Bottjer, 1993; Lewis *et al*., 1981), quail (Bailhache and Balthazart, 1993; Bons and Oliver, 1986), warbling grass parakeet (Takatsuki *et al*., 1981), chicks (Metzger *et al*., 1996; Moons *et al*., 1994), and pigeons (Kitt and Brauth, 1981, 1986; Waldmann and Güntürkün, 1993; Wynne and Güntürkün, 1995). The SNR, on the other hand, exhibits comparatively little perikaryal but high neuropil labeling for DA (Waldmann and Güntürkün, 1993; Wynne and Güntürkün, 1995), as it is the case in mammals where the SNR mainly contains GABAergic neurons (Fallon and Loughlin, 1995).

From the AVT and SNC, fibers ascend mainly ipsilaterally within two tracts of the mediolateral part of the lateral forebrain bundle (Karten and Dubbeldam, 1973; Kitt and Brauth, 1986; Metzger *et al*., 1996; Wynne and Güntürkün, 1995). In general, there is substantial overlap in the telencephalic projection zones of the SNC and AVT (Kitt and Brauth, 1986; Metzger *et al*., 1996; Waldmann and Güntürkün, 1993), although some degree of special-

ization and topographical organization seems also to be present (see, for example, Section 5.4.1).

Vice versa, the A8–A10 group receives pallidal inputs from the PP and striatal inputs from the LPO, PA and Acc (Karten and Dubbeldam, 1973; Kitt and Brauth, 1981; Reiner *et al*., 1994). By far most of the striatonigral projection neurons co-contain substance P and dynorphin, while the remainder contain enkephalin (Anderson and Reiner, 1990, 1991b; Reiner *et al*., 1983, 1984b; Reiner and Anderson, 1990). These two apparently disjunctive groups of neurons project to different populations of dopaminergic and overlapping populations of non-dopaminergic tegmental and nigral neurons (Reiner *et al*., 1994; Smeets, 1991), where substance P-ir fibers make symmetric synaptic contacts predominantly on thin dendrites and spines (Anderson *et al*., 1991), whereas enkephalinergic fibers contact dopaminergic somata as well (Medina *et al*., 1995).

Both, D1 and D2 receptor densities seem to be quite low in the pigeon SNC compared to the 'striatal' parts of the avian basal ganglia (Dietl and Palacios, 1988; Richfield *et al*., 1987). Thus, D2 receptors seem not to play such a prominent role as autoreceptors in avian dopaminergic midbrain neurons (at least not within the local SNC/VTA circuit) as they do in mammals (Brock *et al*., 1992; Bunney *et al*., 1987; Cooper *et al*., 1996; Yung *et al*., 1995). Furthermore, DARPP-32 neuropil labeling (indicating the presence of D1 receptors, see Section 4.3) but no soma labeling could be detected in the VTA, SNC and SNR (Fig. 3D). This observation agrees well with the mammalian situation (Ouimet *et al*., 1984, 1992).

Within the telencephalon, the bulbus olfactorius seems to be the only structure containing a small number of dopaminergic neurons around and below the glomeruli (Wynne and Güntürkün, 1995), which probably correspond to the mammalian A16 group described by Björklund and Lindvall (1984).

4. GENERAL FEATURES OF THE DOPAMINERGIC INNERVATION OF THE AVIAN TELENCEPHALON

Before getting into a detailed description of the distribution of dopaminergic fibers and dopaminoceptive elements in the avian telencephalon, some general remarks on specific features of the dopaminergic innervation of the avian brain, and on markers of the dopaminergic system seem to be in place.

4.1. 'Basket'- and 'En Passant'-Type of Dopaminergic Innervation

The dopaminergic innervation in the avian telencephalon takes two different, and possibly discrete, forms. The first form, which is found also in the mammalian cortex (Oades and Halliday, 1987; Williams and Goldman-Rakic, 1993), is characterized by dopaminergic fibers contacting the somata and dendrites of neurons 'en-passant' while passing through their target region. These dopaminergic axons often travel in close vicinity along the somata and dendrites of target-neurons while forming a large number of bouton-like axonal swellings. The second one, called the 'basket'-type, is a very peculiar arrangement of dopaminergic fibers in the avian telencephalon. In this case, single fibers densely coil around the somata and initial dendrites of postsynaptic targets, enwrapping them in basket-like structures (Fig. 4). In some telencephalic regions, this type of innervation can be so dense that unlabeled postsynaptic neurons and their initial dendrites can virtually be seen by labeling of catecholaminergic fibers alone (Fig. 4A and B). These fibers exhibit many varicosities in the vicinity of the soma and proximal dendrites, which have been shown to contain large numbers of round clear vesicles and also a few dense core vesicles (Metzger *et al*., 1996; Karle *et al*., 1992, 1994; see Section 4.4). Baskets seem to contact predominantly bigger neurons, whereas smaller neurons are more likely innervated en-passant (Wynne and Güntürkün, 1995). However, basket-type structures are not a speciality of the dopaminergic system, as they can also be demonstrated with antibodies against NA and DBH (Moons *et al*., 1995).

4.2. Tyrosine Hydroxylase as a Marker of Dopaminergic Fibers in the Avian Telencephalon

Many studies have been carried out using THir as a marker of dopaminergic fibers in the avian telencephalon. As noted already, TH is the rate-limiting enzyme in the synthesis of all catecholamines and, with few exceptions (Smeets and Gonzales, 1990), must be present in dopaminergic neurons. In general, the distribution of THir fibers closely follows that of DAir fibers and might be a better indicator for the distribution of dopaminergic fibers than for the much sparser noradrenergic innervation in the avian telencephalon, which predominantly distributes along the VP, septum, HA and the hippocampal region (Bailhache and Balthazart, 1993; Karle *et al*., 1996; Moons *et al*., 1994, 1995; Reiner *et al*., 1994; Wynne and Güntürkün, 1995). However, there are also some exceptions like the area parahippocampalis (APH) or the n. taeniae (Tn) which are quite high in THir but low in DAir fibers (Wynne and Güntürkün, 1995). Hence, THir might be a good marker of dopaminergic fibers in most but not all telencephalic areas.

4.3. DARPP-32 as a Marker of D1-Receptors and Dopaminoceptive Neurons

DARPP-32 is a dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 000 that plays a role as a 'third messenger' in the intracellular cascade induced by D1-receptor stimulation (Hemmings *et al*., 1987a,b, 1995). Via activation of the adenylyl cyclase, D1-receptor action stimulates cAMP synthesis, which through protein kinase A leads to phosphorylation of DARPP-32. Phosphorylated DARPP-32 in turn inhibits protein phosphatase-1, and thus affects the state of various target proteins. In rat striatal neurons for instance, DA affects via phosphorylation of DARPP-32 the gating of Na^+ and various high-voltaged-activated Ca^{2+} channels (Hemmings *et al*., 1987a, 1995).

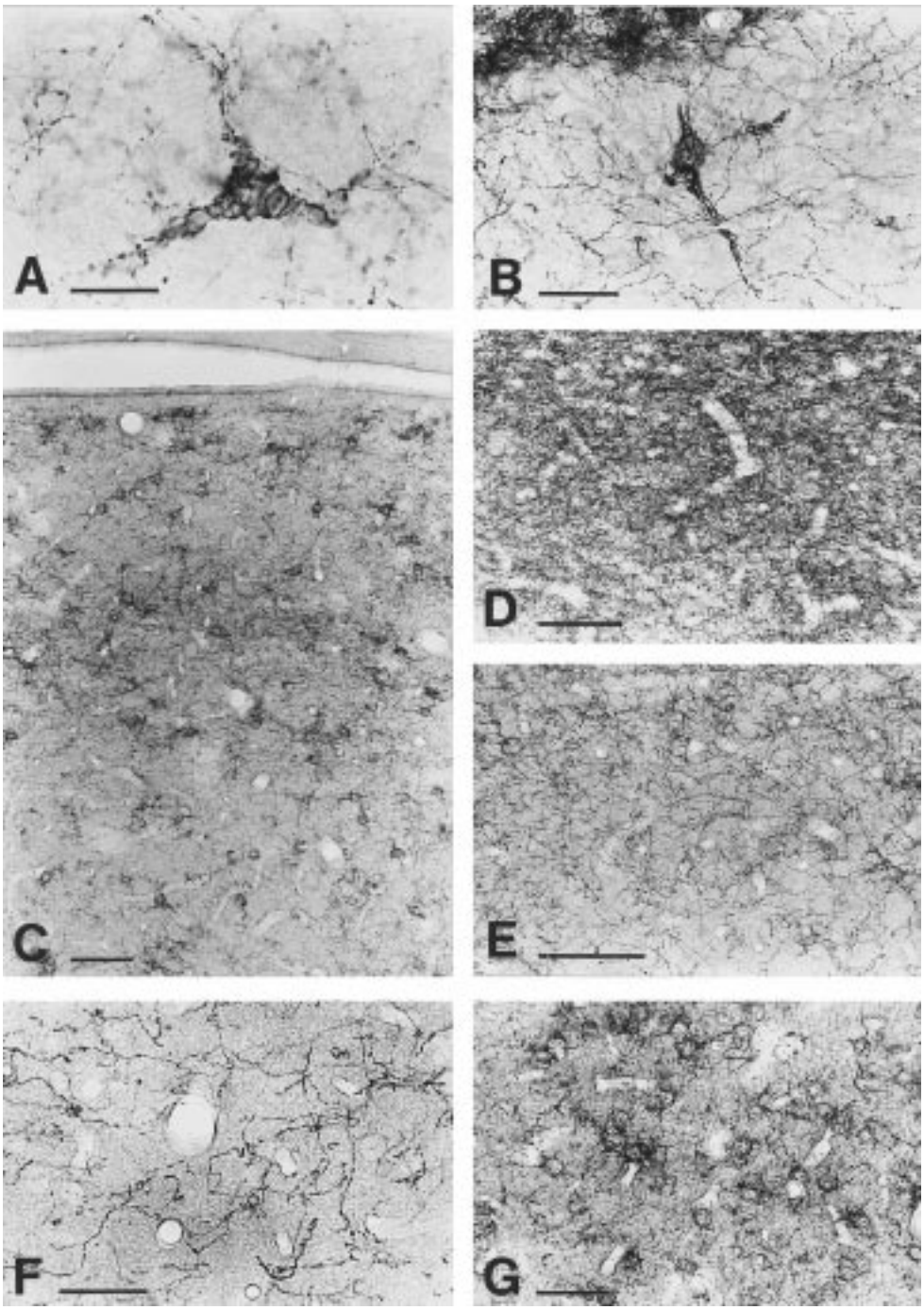

Fig. 4. Modes of dopaminergic innervation in the avian telencephalon. (A and B) Examples of the 'basket-type' of dopaminergic innervation. (C–G) Examples illustrating various densities and relative contributions of en-passant and basket-type innervations. Photomicrographs were taken from the NCL (A and C), PP (B), Aid (D), Ai (E), NIM (F) and Av (G). Scale bars represent 100 μm (C–E), 50 μm (F and G) and 25 μm (A and B).

DARPP-32 is itself dephosphorylated by Ca^{2+}/calmodulin-dependent protein phosphotase 2B (calcineurin), thus opening possibilities for the interaction of glutamatergic transmission and Ca^{2+} influx with DA-induced effects (Hemmings *et al*., 1987a, 1995; Nishi *et al*., 1997). In mammals the distribution of DARPP-32 has been shown to be closely related to that of D1-receptors (Berger *et al*., 1990; Hemmings and Greengard, 1986; Ouimet *et al*., 1984; Walaas and Greengard, 1984). In general, this is also the case in the pigeon (Durstewitz *et al*., 1998) and chick (Schnabel *et al*., 1997) brain.

The use of antibodies against DARPP-32 as a marker of dopaminoceptive structures has the advantage that postsynaptic neural targets of dopaminergic fibers are often labeled to a large extent

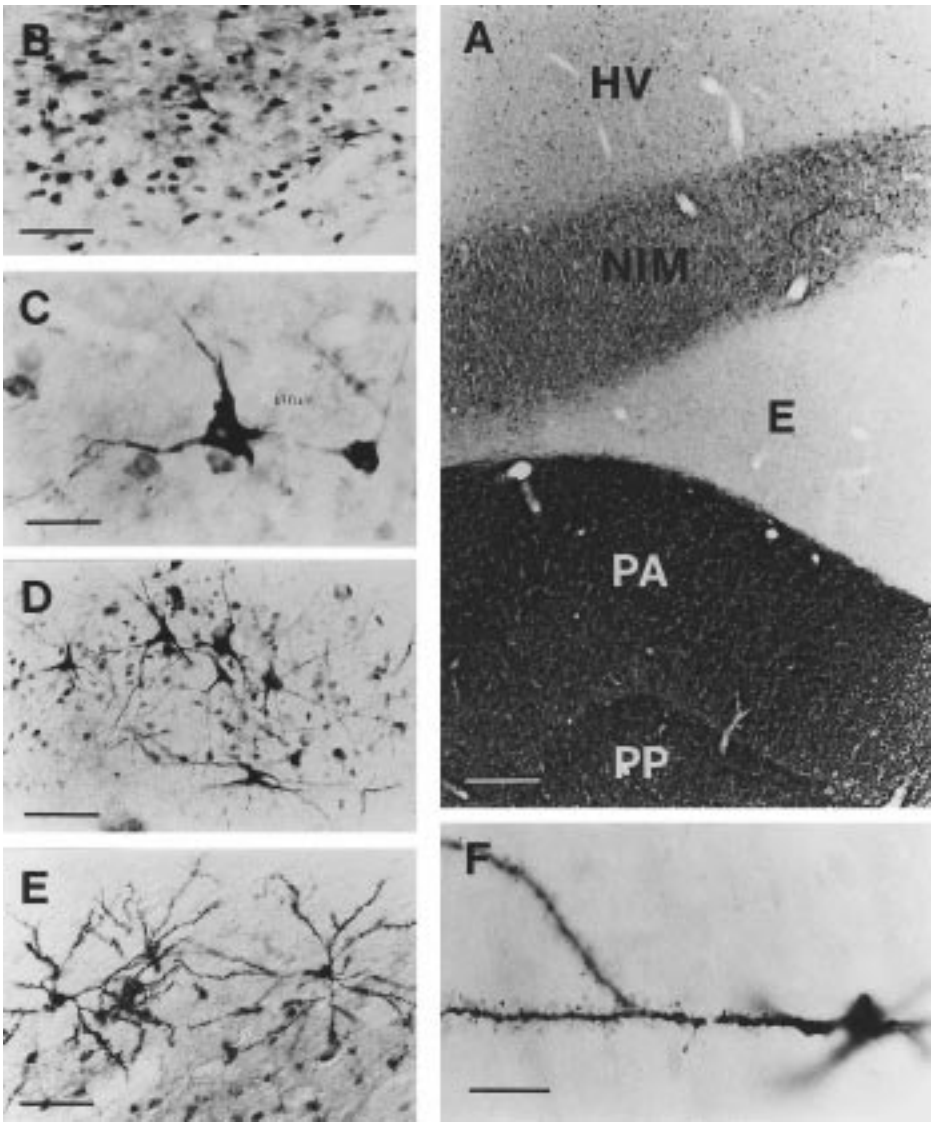

Fig. 5. DARPP-32 immuno-labeling in the pigeon forebrain. (A) Frontal section at level A 9.00, illustrating the different intensities of DARPP-32-positive neuropil staining. (B and C) Most DARPP-32-positive cells displayed only labeling of the soma and initial dendritic segments. (D–F) In some neurons also fine dendritic processes and spines are visible. Photomicrographs were taken from the n. basalis (B), neostriatum frontolaterale (C), ventromedial hippocampus (D), border of ectostriatum and ectostriatal belt (E) and medial septum (F). Scale bars represent 250 μm (A), 50 μm (B, D, E), 20 μm (C), 15 μm (F). Scale bars represent 250 μm (A), 50 μm (B, D, E), 20 μm (C), 15 μm (F). Taken from Durstewitz *et al*. (1998).

(Fig. 5). In some cases even fine dendritic branches and spines are clearly visible at the light-microscopic level (Fig. 5D–F), revealing additional information about the morphological properties of dopaminergic targets which are not apparent using D1 receptor-ir (see Schnabel *et al*., 1997). The clear perikaryal labeling obtained with DARPP-32-ir also enables morphometric approaches since cell counts can easily be performed.

4.4. Ultrastructural Features of the Dopaminergic Innervation and of Dopaminoceptive Neurons

At the ultrastructural level, dopaminergic and THir fibers in the avian basal ganglia and in the neostriatum form many varicosities which often exhibit multiple active zones and contain many round clear small to medium-sized vesicles together with some large dense core vesicles (Karle *et al*., 1992, 1994, 1996; Metzger *et al*., 1996), indicating the co-release of DA and neuropeptides as it is the case in mammalian dopaminergic neurons (Cooper *et al*., 1996; Seroogy *et al*., 1988a,b). Some of these varicosities (*ca* 50% in the avian basal ganglia according to Karle *et al*. 1996) show small and flat synaptic specializations, most often of the symmetrical type, but occasionally also asymmetrical ones (Karle *et al*., 1996; Metzger *et al*., 1996). Dopaminergic synapses within the neostriatum, LPO and PA are most

often found on thin dendritic shafts (*ca* 50% in the basal ganglia), less frequently on dendritic spines, and occasionally (< 20% in the basal ganglia) on thick dendritic shafts or perikarya (Karle *et al.*, 1996; Metzger *et al.*, 1996). Thus, in the vicinity of the soma, unspecialized varicosities seem to prevail. On dendritic spines, dopaminergic synapses are sometimes engaged in 'triadic complexes' with other unlabeled symmetric or asymmetric synapses terminating on the same spine, or where they make axo-axonic contacts on these unlabeled synapses (Metzger *et al.*, 1996). Thus, in the avian brain as in mammals (Calabresi *et al.*, 1987; Hernández-López *et al.*, 1997; Law-Tho *et al.*, 1994; Pralong and Jones, 1993; Yang and Seamans, 1996), DA might control both, synaptic transmission via pre- and/or postsynaptic mechanisms as well as postsynaptic somatic and dendritic membrane properties. Furthermore, both these aspects of neural functioning may be modulated via D1 receptors, as D1 receptor-ir and DARPP-32ir have been observed not only within the dendrites but occasionally also in axons and axon terminals (Schnabel *et al.*, 1997).

5. DISTRIBUTION OF DOPAMINERGIC FIBERS AND DOPAMINOCEPTIVE ELEMENTS IN THE AVIAN TELENCEPHALON

The distribution of dopaminergic fibers is closely related to functional subdivisions of the avian telencephalon. Most prominently, structures of the avian basal ganglia receive by far the densest dopaminergic input, whereas all primary sensory structures seem to be devoid of DA, L-DOPA, DA receptors and DARPP-32 (Dietl and Palacios, 1988; Durstewitz *et al.*, 1998; Juorio, 1983; Juorio and Vogt, 1967; Metzger *et al.*, 1996; Moons *et al.*, 1994; Schnabel and Braun, 1996; Wynne and Güntürkün, 1995). All other telencephalic areas fall somewhere in between, however, with clear regional differences. In the following, we will describe the distribution of dopaminergic fibers and dopaminoceptive elements according to functional subdivisions, following the pathway of sensory information from the primary sensory to the motor output structures as outlined in Section 2. Figures 6–9 give an overview over the distribution of dopaminergic fibers, D1 receptors,

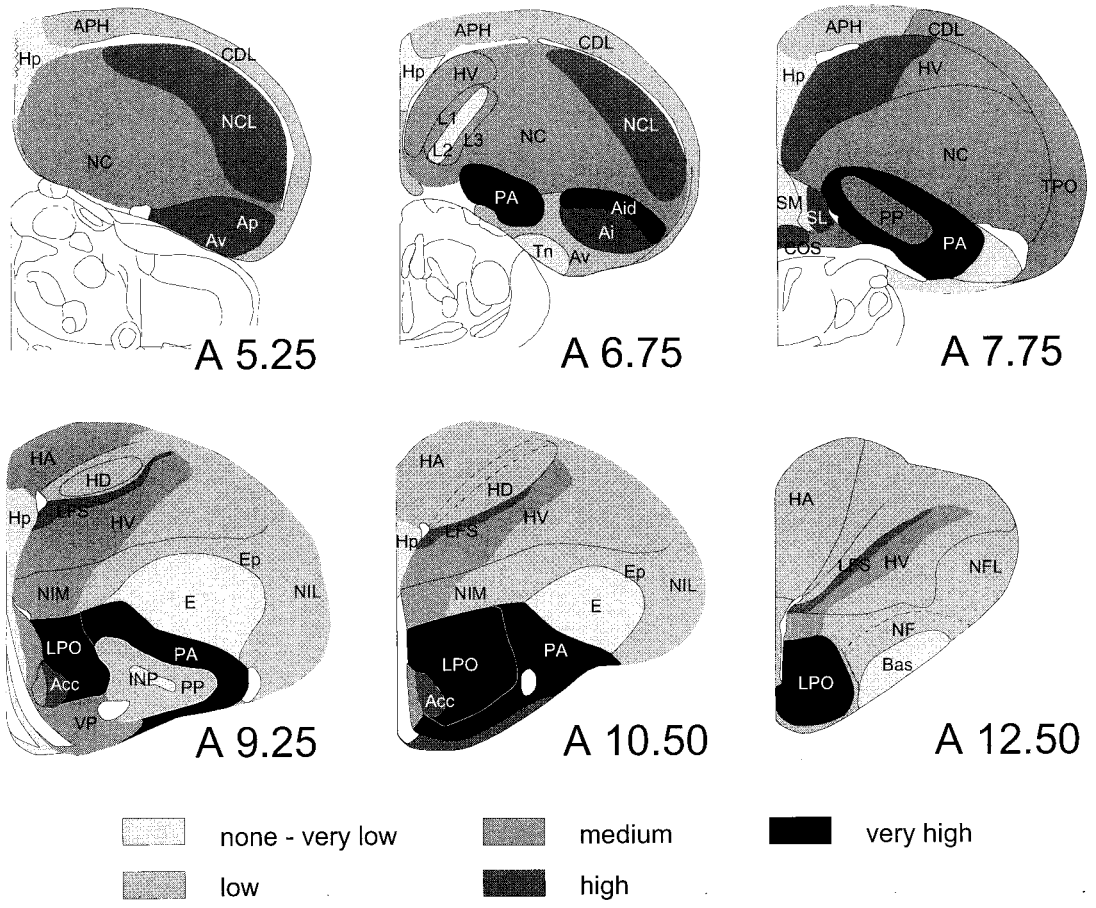

Fig. 6. Schematic illustration of the distribution of dopaminergic fibers in the avian telencephalon.

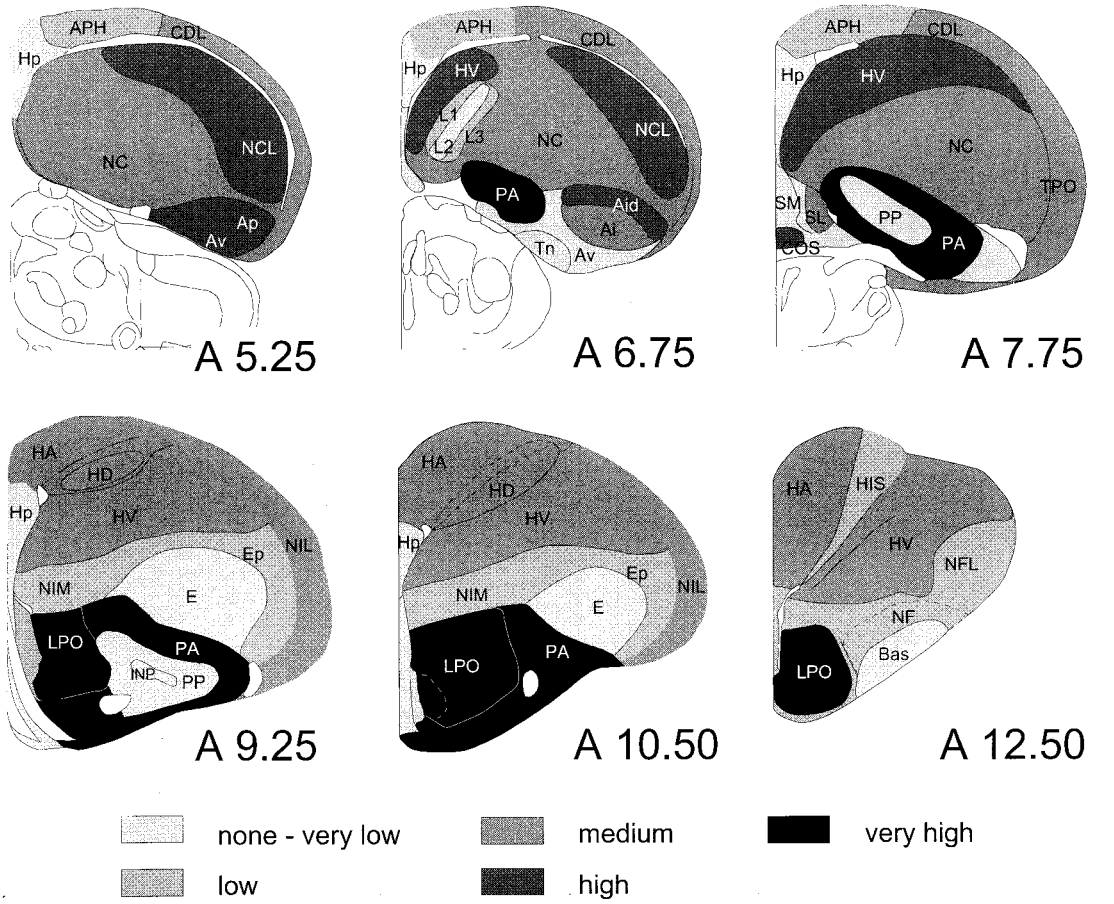

Fig. 7. Schematic illustration of the distribution of D1 receptors in the avian telencephalon.

D2 receptors and DARPP-32 neuropil and soma labeling throughout the avian telencephalon. In addition, findings on colocalizations of markers of the dopaminergic system with other biochemically identified systems will be discussed.

However, before going into details, it should be mentioned that although the general pattern may be the same across avian species, some strain and species differences exist. Thus, Divac *et al.* (1988) observed an about two-fold higher DA concentration in the posterior telencephalon of mixed breed than of white Carneaux pigeons, while in the anterior telencephalon the DA concentration was only slightly higher. Nevertheless, the relative DA concentration in six telencephalic regions examined remained qualitatively the same in both strains. Similarly, telencephalic DA concentrations were noted to vary by factors of up to five between chicks, ducks, finches, pigeons, fowls and quails (Juorio and Vogt, 1967; Juorio, 1983).

5.1. Primary Sensory Areas

5.1.1. *Dopaminergic Fibers and Projections*

Primary sensory areas of the pigeon and chick telencephalon display by far the lowest DAir and L-DOPAir (Fig. 10A; Metzger *et al.*, 1996; Wynne and Güntürkün, 1995; Moons *et al.*, 1994) and no projections from the VTA or SNC to these areas have been demonstrated, except for a restricted input to the HD (Kitt and Brauth, 1986). Whereas the E (visual tectofugal), Field L2 (auditory) and the Bas (trigeminal) are devoid of dopaminergic fibers, some DAir fibers are present in the rostral (somatosensory) and caudal (visual thalamofugal) IHA and lateral HD, the two input laminae of the Wulst. Interestingly, the specific sensory nuclei of the thalamus (e.g. the n. rotundus which projects to the E) also contain little or no THir (Reiner *et al.*, 1994). Thus, primary sensory processes do not seem to be modulated, at least not to a significant extent, by DA in the adult avian brain.

5.1.2. *D1 Receptors*

Given the virtual absence of a dopaminergic innervation, it comes with no surprise that the D1 receptor density in the primary sensory structures is very low, with the E exhibiting the lowest D1-specific binding in the whole telencephalon (Dietl and Palacios, 1988; Schnabel *et al.*, 1997; Schnabel and Braun, 1996; Stewart *et al.*, 1996). However, as it is the case for DAir labeling, the IHA and HD are higher in D1-specific binding, although still significantly lower than the respective secondary projection zones in the HA and most of the neostriatum (Schnabel *et al.*, 1997).

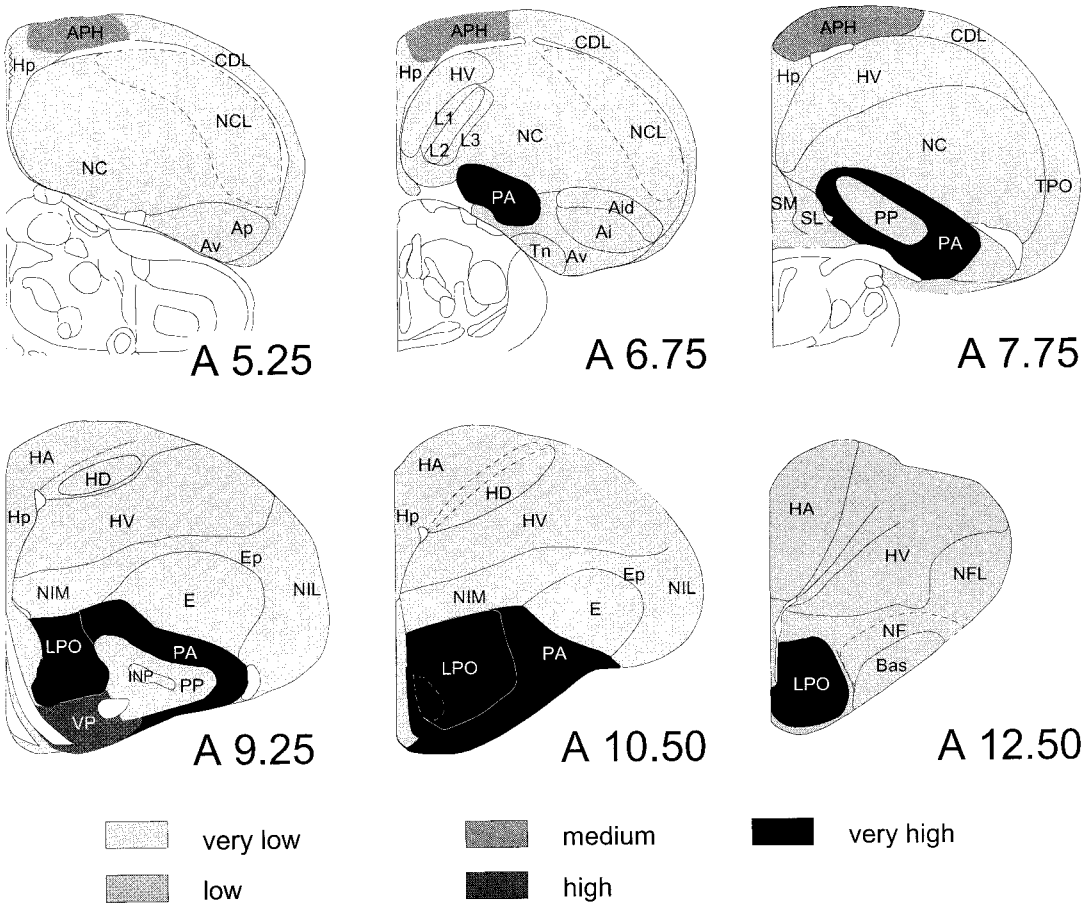

Fig. 8. Schematic illustration of the distribution of D2 receptors in the avian telencephalon.

5.1.3. *D2 Receptors*

In general, D2 receptor densities as measured by [^{3}H]spiperone and [^{3}H]CV205-502 are low and homogeneously distributed throughout the whole avian telencephalon, except for the basal ganglia and the hippocampal complex as discussed below (Dietl and Palacios, 1988; Schnabel and Braun, 1996; Stewart *et al.*, 1996).

5.1.4. *DARPP-32*

The distribution of DARPP-32ir confirms the extremely low or absent dopaminergic input to the primary sensory structures. The E and Field L2 are largely devoid of DARPP-32ir (Fig. 10B; Durstewitz *et al.* 1998; Schnabel *et al.* 1997). The IHA and HD display low levels of neuropil labeling and a low percentage of labeled neurons, while, however, scoring in both respects again much lower than the respective secondary sensory zones in the HA and most of the neostriatum (Durstewitz *et al.*, 1998; Schnabel *et al.*, 1997). Hence, primary sensory regions in the avian forebrain could be sharply delineated and differentiated from bordering areas by virtue of their low DARPP-32ir (Fig. 5A; Fig. 10B).

The only primary sensory forebrain area that might deviate from this general pattern, at least in pigeons, is the trigeminal Bas. Although it is very low in terms of DARPP-32ir neuropil labeling, the pigeon's Bas contains a high proportion of labeled perikarya, many of them exhibiting clear neuronal properties (Fig. 5B; Durstewitz *et al.* 1998; but see Schnabel *et al.* 1997) for chicks. This finding might be related to other peculiarities of the Bas and to the specific demands imposed on the neural circuit controlling pecking behavior, in which the Bas is critically involved (Schall, 1987; Wild *et al.*, 1985). The Bas is the only avian forebrain structure with direct sensory inputs bypassing the thalamus (Schall *et al.*, 1986). Moreover, within the trigeminal neural circuit controlling pecking, sensory signals possibly must be integrated very fast and relayed rather directly to motor outputs. As the dopaminergic system probably plays a central role in sensory-motor integration and learning (see Section 7), the dopaminergic modulation might start earlier in this trigeminal somatosensory circuit than within other forebrain systems. This notion is furthermore underpinned by the fact that the Bas receives auditory and possibly also vestibular input, in addition to trigeminal information (Schall *et al.*, 1986; Schall and Delius, 1986; Wild *et al.*, 1997), and might thus actually be regarded as a multimodal structure. Furthermore, behavioral evidence supports the hypothesis of a dopaminergic modulation within the pigeon Bas: Lindenblatt and Delius (1988) showed that local apomorphine-injections into the Bas induce pecking bouts, while Wynne and Delius

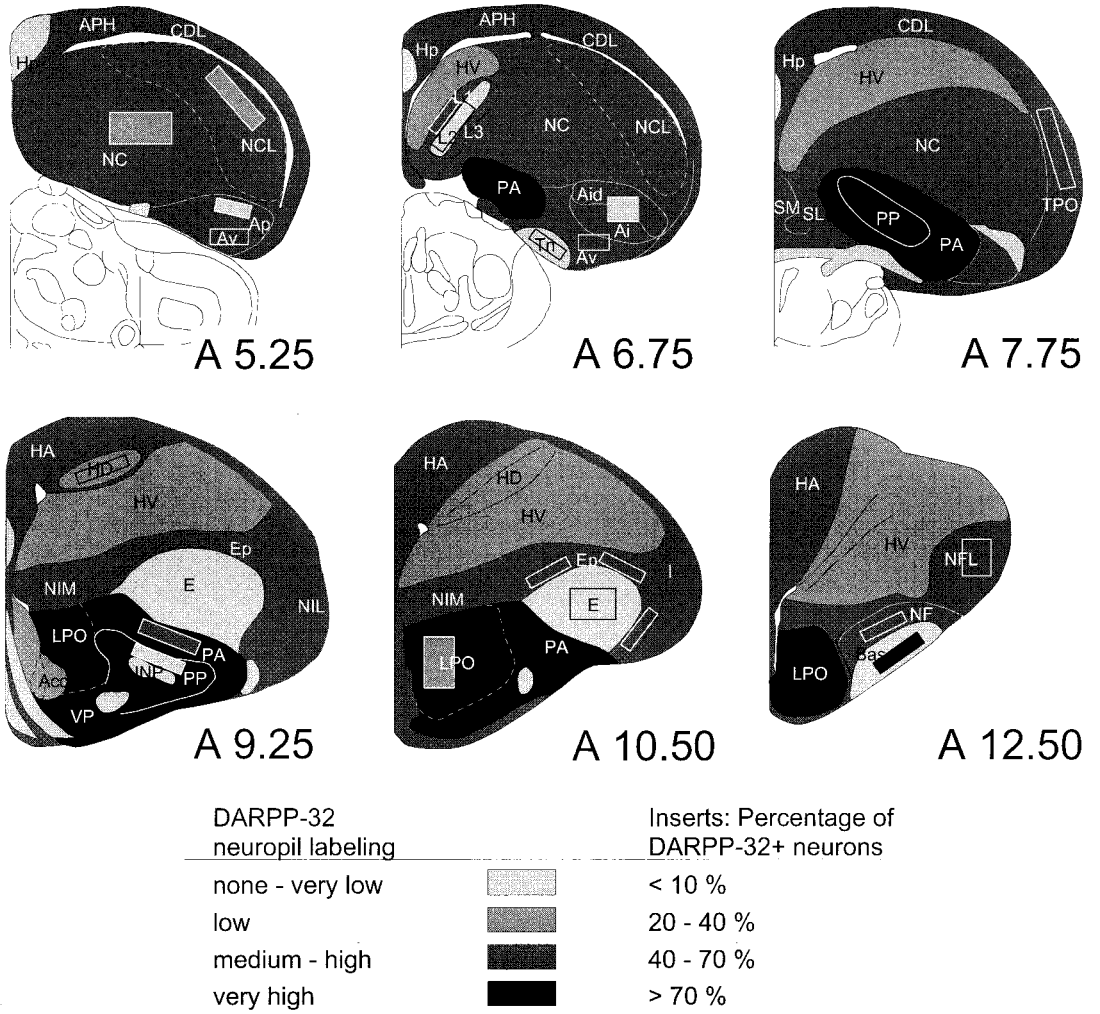

Fig. 9. Schematic illustration of the distribution of the D1-receptor related phosphoprotein DARPP-32 in the avian telencephalon.

(1996) made it likely that Bas lesions decrease pecking fits induced by peripheral apomorphine-injections.

However, the high number of DARPP-32ir neurons in the pigeon Bas is clearly at odds with the lack of D1-receptors and dopaminergic fibers reported so far, as well as with the lack of DARPP-32 in the chick Bas (Schnabel *et al.*, 1997). In this context, it should be pointed out that DARPP-32 is not exclusively involved in the D1-induced cascade but is regulated by other neuromodulator/neurotransmitter pathways as well, for example, by D2- or NMDA-receptor stimulation via Ca^{2+} influx (Hemmings *et al.*, 1995; Nishi *et al.*, 1997). Thus, DARPP-32 in the Bas might be linked to intracellular pathways other than the one coupled to the D1 receptor, and differences between pigeons and chicks might exist in this respect.

5.1.5. *Colocalizations*

Durstewitz *et al.* (1998) found that glutamate decarboxylase (GAD)-ir neurons were never colocalized with DARPP-32 or located in THir baskets throughout the whole pigeon telencephalon, including the primary sensory areas.

5.2. Secondary Sensory and Multimodal Areas

5.2.1. *Dopaminergic Fibers and Projections*

In general, the dopaminergic innervation of both, the secondary sensory and tertiary association areas is clearly higher than that of the primary areas (Figs 10 and 11). In addition, most of the multimodal areas score higher than the secondary sensory areas due to an increasing rostrocaudal and mediolateral gradient of DAir structures (Fig. 6; Metzger *et al.*, 1996; Wynne and Güntürkün, 1995). Thus, in the secondary visual Ep and the trigeminal NF, DA concentration is very low. The HA which includes the secondary projection fields of the thalamofugal visual and the somatosensory system receives a moderate dopaminergic input (Metzger *et al.*, 1996; Moons *et al.*, 1994; Wynne and Güntürkün, 1995).

Among the presumed multimodal forebrain structures, the rostrally located NFL is only moderate and thus lowest in its DA content (Metzger *et al.*, 1996; Moons *et al.*, 1994; Wynne and Güntürkün,

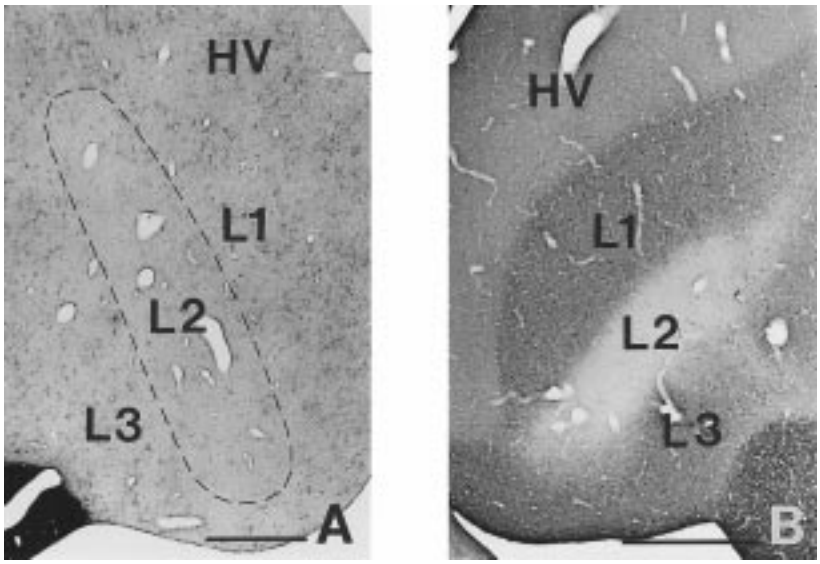

Fig. 10. Distribution of dopaminergic fibers and dopaminoceptive elements in primary and secondary sensory areas as exemplified for the auditory Field L complex. (A) The primary sensory area L2 is almost devoid of dopaminergic fibers and (B) of DARPP-32 immunoreactivity, while the surrounding secondary sensory 'belt' regions L1 and L3 show considerably more labeling for DA and DARPP-32. Scale bars represent 500 μm.

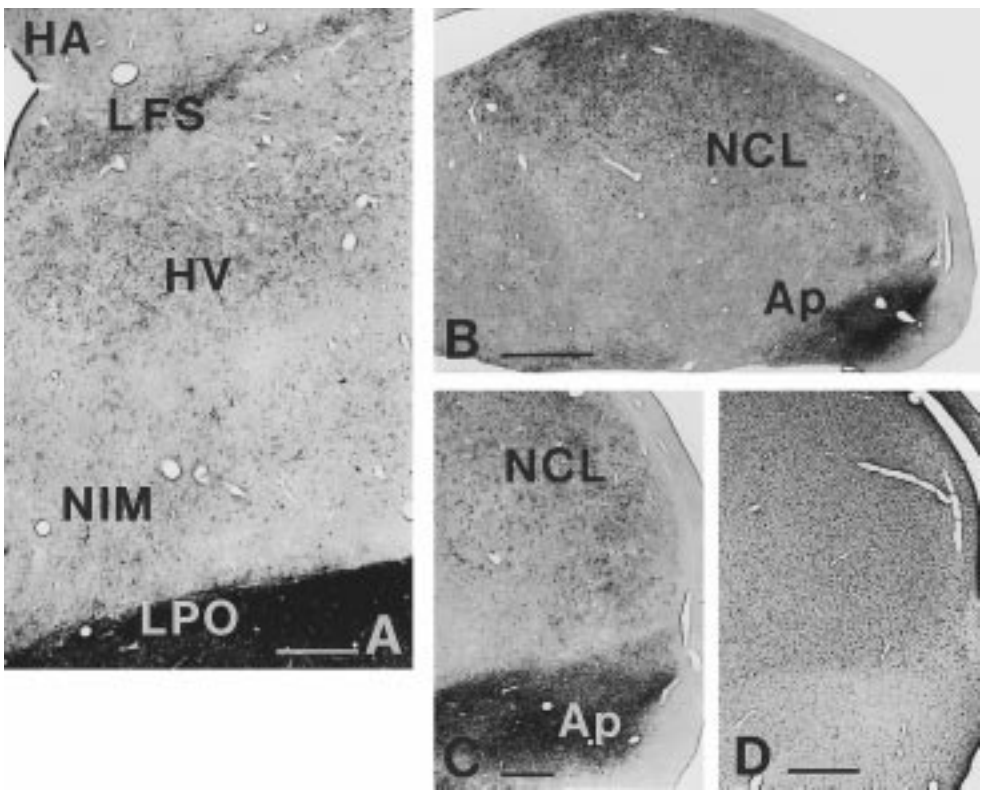

Fig. 11. Dopaminergic innervation and DARPP-32 immunoreactivity in higher order sensory and multimodal structures. (A) Distribution of dopaminergic fibers in the rostromedial forebrain. The neostriatum intermedium (NIM) and hyperstriatum ventrale (HV) and possibly also the lamina frontalis superior (LFS), constitute multimodal areas. Note that in the NIM and HV the density of dopaminergic fibers increases slightly from lateral to medial. (B) Localization of the neostriatum caudolaterale (NCL), the presumed prefrontal cortex of birds, in the caudal telencephalon. (C) Detail of the dopaminergic innervation of the NCL and the posterior archistriatum. (D) DARPP-32 immunoreactivity in the caudal neostriatum is evenly distributed at medium levels, but is low in the archistriatum. Scale bars represent 1 mm (B) and 50 μm (A, C, D).

1995), while the medial portion of the lamina frontalis superior seems to be most densely innervated by dopaminergic fibers (Fig. 11A), with the fibers arising mainly from the SNC (Bottjer, 1993; Kitt and Brauth, 1986; Wynne and Güntürkün, 1995). High DAir and basket-like structures are also present in the MNH (Fig. 11A; Metzger *et al*., 1996; Moons *et al*., 1994; Wynne and Güntürkün, 1995), an area that has been implicated in filial imprinting (Gruss and Braun, 1996, 1997). Metzger *et al*. (1996) also demonstrated a prominent input to these areas from VTA by retrograde tracing, and to a lesser extent from SNC.

Considerable numbers of basket-like structures and dopaminergic fibers are also present in multimodal areas comprising the pallium externum, especially in the TPO, which receives its major input from SNC (Kitt and Brauth, 1986). Within the caudal neostriatum which is generally very high in DA input, the NCL has received special attention because of its presumed equivalency to the prefrontal cortex (PFC) of mammals. This assumption was first derived from behavioral, radioenzymatical and histofluorescence studies conducted by Divac, Mogensen and Björklund (Divac *et al*., 1985; Divac and Mogensen, 1985; Mogensen and Divac, 1982). These authors demonstrated that the NCL contains a high DA-to-NA-ratio and an especially high number of catecholaminergic fibers of presumed dopaminergic origin, as it is characteristic for the PFC of mammals (Berger *et al*., 1988, 1991; Björklund *et al*., 1978; Divac *et al*., 1978; Glowinski *et al*., 1984; Van Eden *et al*., 1987). Using immunocytochemical methods, Waldmann and Güntürkün (1993) and Wynne and Güntürkün (1995) confirmed that the NCL could be differentiated from the surrounding caudal neostriatum by its denser dopaminergic innervation and by the higher number of DAir fibers which constitute a basket, while the number of baskets *per se* does not increase in the NCL (Fig. 11B and C; see also Divac *et al*., 1994). The dopaminergic input to the NCL arises from the dopaminergic midbrain nuclei AVT and SNC (Waldmann and Güntürkün, 1993).

In chicks, a region in the dorsocaudal neostriatum shares the location, connections and dense dopaminergic innervation with the pigeon's NCL (Metzger *et al*., 1996, 1998). This tertiary area has also been studied in the context of imprinting (Bock *et al*., 1997; Schnabel and Braun, 1996). Its dopaminergic innervation is also characterized by a higher occurrence of basket-like structures and by a dopaminergic input from AVT and SNC (Metzger *et al*., 1996). However, it appears that the area of densest DAir and THir is shifted somewhat ventromedially from the ventricle compared to pigeons (Metzger *et al*., 1996; own unpublished observations).

5.2.2. *D1 Receptors*

In general, the distribution of D1 receptors closely mimics that of dopaminergic fibers, although D1 receptors seem to be more homogeneously distributed throughout the entire neostriatum and hyperstriatum than dopaminergic fibers, which seem to be more locally restricted (Fig. 7). The HA, HD, HV and neostriatum contain comparable, medium concentrations of D1 receptors, with the hyperstriatal areas scoring a bit higher than at least the rostral and intermediate neostriatum (Ball *et al*., 1995; Dietl and Palacios, 1988; Schnabel and Braun, 1996; Schnabel *et al*., 1997; Stewart *et al*., 1996). In addition, two obvious tendencies in distribution are apparent (Schnabel and Braun, 1996; Schnabel *et al*., 1997): First, the number of D1 receptors increases from rostral to caudal in both, hyperstriatal and neostriatal areas. Second, in the neostriatum, the number of D1 receptors increases from medial to lateral. Thus, the NCL and the caudal HV are the telencephalic areas highest in D1-specific binding outside the basal ganglia. This finding also implies that secondary sensory structures in the frontal neostriatum, like the Ep and the NFL, but also the secondary auditory fields L1 and L3, are less dense in D1 receptors than most tertiary telencephalic regions. Hence, in general, and possibly with some species differences (Ball *et al*., 1995), there is an increase of D1-receptor density proceeding from primary sensory to tertiary multimodal structures. This pattern might be related to an increase in sensorymotor integration and complex learning processes that take place primarily in higher-order structures

5.2.3. *D2 Receptors*

D2 receptor densities in the neostriatum and hyperstriatum are low and homogeneously distributed (Fig. 8; Dietl and Palacios, 1988; Schnabel and Braun, 1996; Stewart *et al*., 1996). For example, Schnabel and Braun (1996) found the density of D2 receptors to be about one-third or less (< 25 fmol mg^{-1}) of that of D1 receptors in these areas. Hence, outside the basal ganglia, dopaminoceptive neurons in the avian telencephalon seem to be modulated predominantly via receptors of the D1 class, although it should be kept in mind that even low densities of D2 receptors might play an important physiological role.

5.2.4. *DARPP-32*

DARPP-32ir is distributed with medium to high densities throughout the entire neostriatum, HA, CDL and TPO (Fig. 9; Durstewitz *et al*., 1998; Schnabel *et al*., 1997). Thus, DARPP-32ir reaches much higher levels in the secondary and tertiary areas than in the primary sensory structures (Fig. 5A; Fig. 10B). In addition, Schnabel *et al*. (1997) reported a rostrocaudal and a mediolateral trend in the DARPP-32 distribution in the chick neostriatum as it has been described for D1 receptors. However, Durstewitz *et al*. (1998) were not able to discriminate between secondary sensory and multimodal pigeon forebrain structures based on DARPP-32ir neuropil labeling and cell countings, although a slight trend in neuropil labeling was also observed by these authors. Thus, differences between secondary sensory and multimodal areas with regards to their dopaminergic input may not be so apparent in DARPP-32ir as they are in D1 receptor and dopaminergic fiber density.

A relatively high percentage of neurons (up to *ca* 60%) exhibits DARPP-32ir in the secondary sensory

and multimodal areas, about the same as in structures of the basal ganglia and the ventral archistriatum, and significantly higher than in the HD (receiving primary visual input) and the dorsal archistriatum (Fig. 11D; Durstewitz *et al.*, 1998). The NCL has already been introduced as the possible avian equivalent of the mammalian PFC, and as such receives a prominent dopaminergic input. However, this structure cannot be differentiated from the surrounding neostriatal areas by DARPP-32 neuropil labeling or by its relative number of DARPP-32-positive neurons (Fig. 11D; Durstewitz *et al.*, 1998). In contrast, the percentage of DARPP-32-positive neurons seems even to decrease proceeding from rostral to caudal. Similar discrepancies in the distribution of dopaminergic fibers, D1 receptors and DARPP-32 have also been observed in the mammalian neocortex (Berger *et al.*, 1990; see Section 6.2).

One of the most obvious discrepancies between the distributions of DARPP-32ir and D1 receptors, however, is the significantly higher amount of DARPP-32 in the neostriatum than in the HV, while just the opposite is the case for the density of D1 receptors (Durstewitz *et al.*, 1998; Schnabel *et al.*, 1997). Another possible discrepancy is the considerable DARPP-32ir in the CDL where Ball *et al.* (1995) reported very low concentrations of D1 receptors. These discrepancies might be partly related to the fact that ligand-binding autoradiographic demonstrations of D1 receptors have different properties than the immunocytochemical demonstration of a receptor-related phosphoprotein. Thus, while receptorautoradiography might provide objective means to demonstrate receptor densities, immunocytochemistry reveals more about the morphology and possible colocalizations of the cells under study. However, it should be stressed that DARPP-32 generally is a good marker for the distribution of D1 receptors in avian species as it is in mammals (Berger *et al.*, 1990; Hemmings and Greengard, 1986; Ouimet *et al.*, 1992).

5.2.5. *Colocalizations*

Figure 12A presents examples from the caudal neostriatum of DARPP-32ir neurons which are located in TH-baskets. A quantitative examination of the number of DARPP-32ir neurons located in TH-baskets showed that this percentage differs considerably between various areas (Durstewitz *et al.*, 1998). The highest percentage (15–30%) of DARPP-32/TH-basket colocalizations was observed in the multimodal lateral and caudal aspects of the neostriatum, including the NCL, that is, exactly in those regions, which expressed the highest numbers of D1 receptors according to Schnabel *et al.* (1997). Less DARPP-32/TH-basket colocalizations were found in the rostral and intermediate neostriatum (5–15%), including most of the secondary sensory areas. The lowest percentage of DARPP-32/TH-basket colocalizations occurred in the hyperstriatal and hippocampal regions ($< 5\%$), although the HA is strongly innervated by dopaminergic fibers and exhibits a high concentration of D1 receptors. That some areas are dense in D1 receptors and dopaminergic input but display only few basket-like structures is a further hint to a functional dissociation between an 'en passant'-mode of dopaminergic innervation and the basket-like DA input. According to the functional considerations outlined in Section 6.3, one might speculate that the higher level lateral and caudal neostriatal areas have a special role in synchronizing and coordinating network activity.

In the male quail telencephalon, especially within the neostriatum, colocalizations of THir baskets and varicosities and aromatase-ir cells were observed (Balthazart *et al.*, 1998). The enzyme aromatase converts testosterone into 17β-estradiol which is involved in the activation of male sexual behavior. These colocalizations may thus represent an anatomical basis for the regulation of male sexual behavior by DA (see Section 7.3). DA probably stimulates aromatase activity and is, vice versa, possibly influenced itself by aromatase (Balthazart and Absil, 1997; Pasqualini *et al.*, 1995).

From a functional point of view, it is of great importance to identify the postsynaptic targets of the dopaminergic innervation. Baskets provide a clear and convenient morphological marker to do this. GABAergic inhibitory neurons constitute one of the prominent potential candidates which might be dopaminergically modulated via baskets. Veenman and Reiner (1994) estimate the fraction of GABAergic neurons to be *ca* 10–12%, homogenously distributed throughout most of the telencephalon. Antibodies directed against GAD, the enzyme which converts glutamate to GABA, labels approximately the same population of cells, and thus represents a useful indicator for GABAergic neurons (Veenman and Reiner, 1994). Like in other telencephalic structures, throughout the neostriatum and hyperstriatum no GADir neurons were observed that were located in THir baskets (Fig. 12B) or were colocalized with DARPP-32 (Fig. 12C; Durstewitz *et al.*, 1998). Thus, GABAergic neurons in the pigeon telencephalon might not express D1 receptors and might not receive a strong dopaminergic input. As in addition D2 receptors are very low in these areas, GABAergic neurons possibly do not receive a significant dopaminergic input at all. Hence, an interesting functional conclusion might be that mainly or solely excitatory neurons are the targets of the dopaminergic innervation in the pigeon telencephalon. However, it has to be emphasized that D2 receptors despite their low densities might nevertheless modulate the physiological activity of dopaminoceptice neurons in a significant manner. Thus, it still has to be investigated whether GABAergic neurons express D2 receptors.

5.3. Septum, Hippocampal Complex, Archistriatum

5.3.1. *Dopaminergic Fibers and Projections*

Prominent motor and limbic structures in the avian telencephalon include the septum, the hippocampal complex and the archistriatum. The lateral septum exhibits a high number of DAir, L-DOPAir and THir baskets and fibers (Bailhache and Balthazart, 1993; Balthazart *et al.*, 1998; Bottjer,

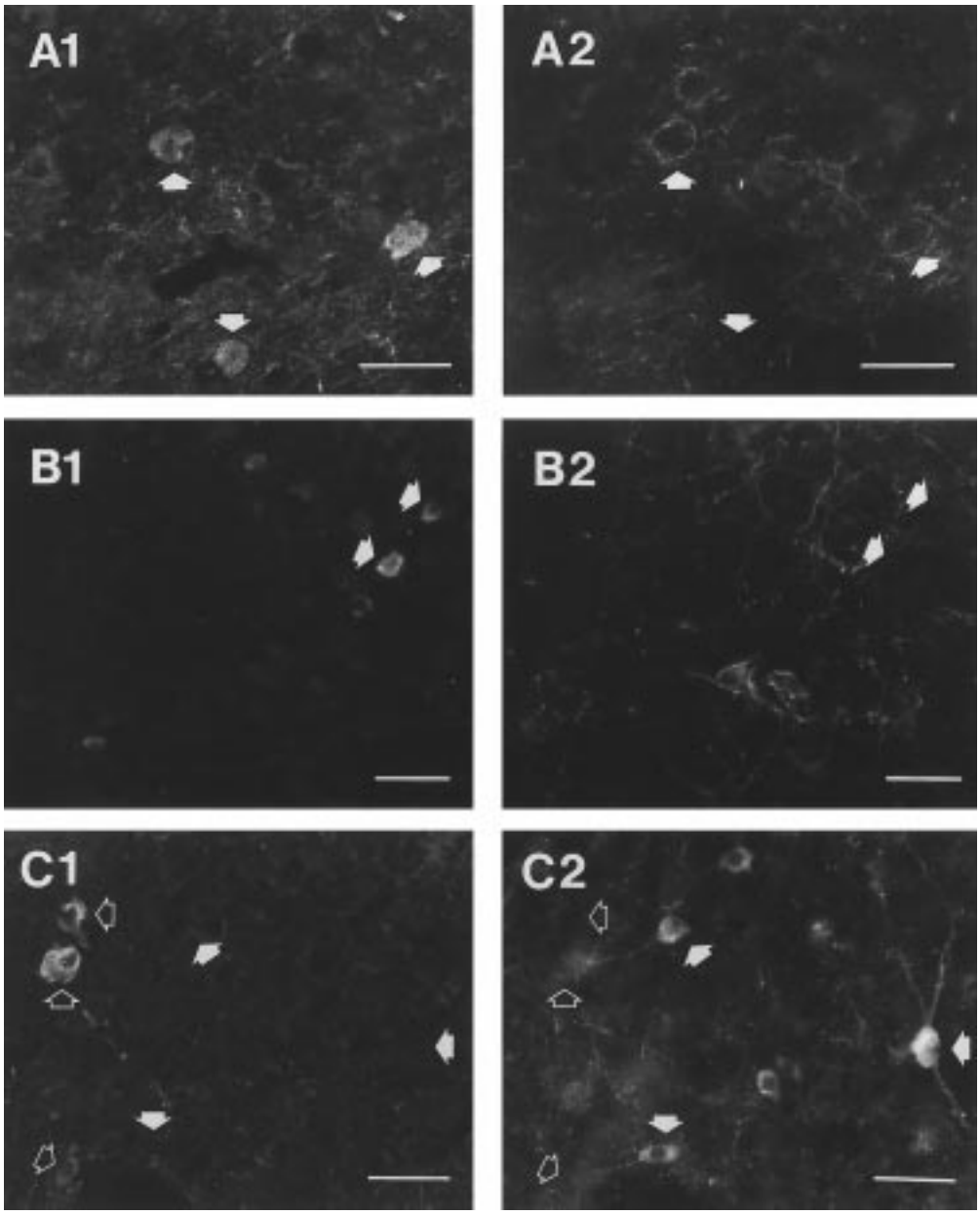

Fig. 12. Fluorescence double-labeling against (A) DARPP-32 and TH, (B) GAD and TH and (C) DARPP-32 and GAD. The photomicrographs of each pair were taken from the same site in caudal neostriatum of the pigeon telencephalon. Two of three DARPP-32ir neurons (A1) are surrounded by THir baskets (A2). GADir neurons (B1) do not receive input from THir baskets (B2). GADir neurons (C2) do not show DARPP-32 immunoreactivity (C1), although GADir and DARPP-32ir neurons may occur in close vicinity to each other. Arrows mark corresponding positions in each pair. In (C), open and filled arrows indicate positions of DARPP-32ir and some GADir cells, respectively. Scale bars represent 30 μm (A and B), 40 μm (C). Taken from Durstewitz *et al.* (1998).

1993; Moons *et al.*, 1994; Wynne and Güntürkün, 1995), whereas the medial septum displays a high density of THir and NAir fibers (Moons *et al.*, 1995) but only moderate to low amounts of DAir and L-DOPAir (Fig. 13A). The lateral septum, and especially the ventrolaterally located region, receives most of its dopaminergic input from the VTA, while the medial septum is more densely innervated by axons from the SNC (Kitt and Brauth, 1986).

In the hippocampus (Hp) and APH only a low number of DAir and L-DOPAir structures was detected (Metzger *et al.*, 1996; Moons *et al.*, 1994; Wynne and Güntürkün, 1995), which mainly stem from the SNC (Kitt and Brauth, 1986). Hence, the dense THir in these areas may be mainly due to a noradrenergic innervation, which has also been demonstrated by DBHir and NAir (Bailhache and

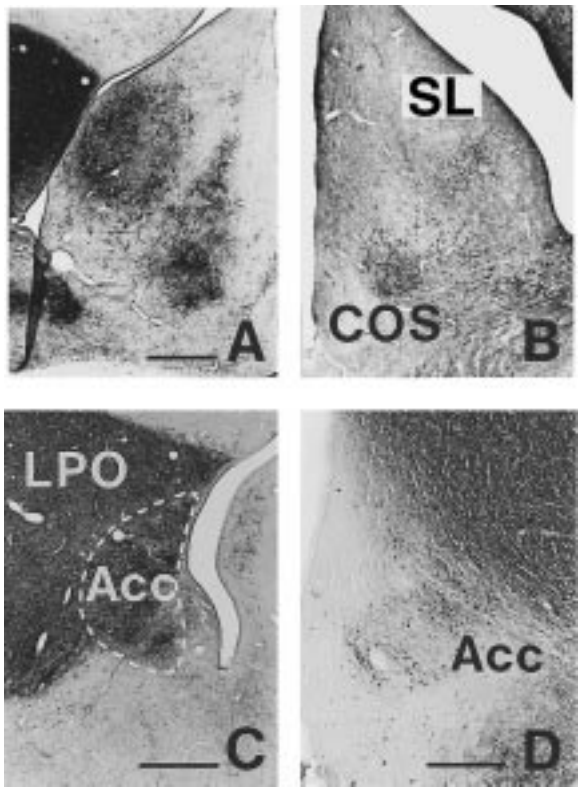

Fig. 13. (A) Dopamine- and (B) DARPP-32 immunoreactivity in the septum. (C) Dopamine- and (D) DARPP-32 immunoreactivity in the nucleus accumbens. Scale bars represent 50 μm (A–C) and 25 μm (D).

Balthazart, 1993; Moons *et al.*, 1995; Reiner *et al.*, 1994).

The archistriatum displays a very heterogenous innervation by dopaminergic fibers (Fig. 11C; Fig. 14A). A particular dense dopaminergic input, reaching levels as high as in the basal ganglia, was described for the most dorsal archistriatum intermedium (Aid), which constitutes part of the sensorimotor archistriatum, as well as for the posterior 'limbic-visceral' archistriatum (Ap) (Bailhache and Balthazart, 1993; Balthazart *et al.*, 1998; Metzger *et al.*, 1996; Wynne and Güntürkün, 1995). This input stems mainly from SNC, and to a lesser extent from VTA (Kitt and Brauth, 1986). However, whereas Metzger *et al.* (1996) reported the rest of the archistriatum in the chick to be low in dopaminergic structures, Wynne and Güntürkün (1995) demonstrated a relatively high number of dopaminergic structures throughout the whole pigeon archistriatum, with a decreasing gradient of dopaminergic fiber density from dorsal to ventral. The ventromedially located Tn is devoid of DAir, but is relatively high in THir, NAir and DBHir (Bailhache and Balthazart, 1993; Moons *et al.*, 1995). Interestingly, despite the very low DAir fiber density in the ventral archistriatum, there is nevertheless a high number of DAir baskets present in this structure, possibly surrounding the large projection cells which give rise to the descending tractus occipitomesencephalicus (Wynne and Güntürkün, 1995). Projections to the intermediate archistriatum from VTA and SNC have also been demonstrated by Kitt and Brauth (1986).

5.3.2. *D1 Receptors*

In general, the medial and lateral septum seem to be very low in D1 receptor binding, at least in the quail (Ball *et al.*, 1995). However, in accordance with its relatively dense input from SNC (Kitt and Brauth, 1986), the n. commissuralis of Baylé *et al.* (1974) within the medial septum is relatively high in D1 density (Ball *et al.*, 1995), and this seems also to be the case in the domestic chick as judged from Fig. 1 of Stewart *et al.* (1996). Both, the Hp and the APH are very low in D1-specific binding (Schnabel and Braun, 1996; Schnabel *et al.*, 1997; Stewart *et al.*, 1996).

The pattern of [^{3}H]SCH23390 labeling in the archistriatum in general follows that described for dopaminergic fibers. In particular, the dorsal archistriatum intermedium contains a very high number of D1 receptors, while the density strongly drops in the ventral archistriatum (Dietl and Palacios, 1988; Schnabel and Braun, 1996; Schnabel *et al.*, 1997; Stewart *et al.*, 1996).

5.3.3. *D2 Receptors*

The dorsal Hp and medial APH are the only telencephalic regions besides the basal ganglia (see below) which display considerable amounts of D2 receptors (Schnabel and Braun, 1996; Stewart *et al.*, 1996). As it is the case in the basal ganglia, D2

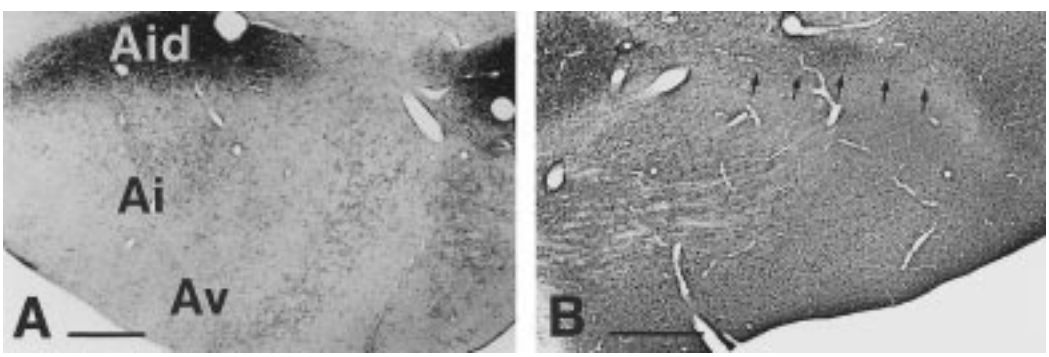

Fig. 14. (A) Dopaminergic fibers and (B) DARPP-32 immunoreactivity in the archistriatum. DARPP-32 immunoreactivity within the archistriatum is largely restricted to the Av and a small rim of the Aid (arrows). Scale bars represent 500 μm.

receptors even outnumber D1 receptors in the avian hippocampal areas.

5.3.4. *DARPP-32*

The septum is devoid of DARPP-32ir except for the n. commissuralis of Baylé *et al.* (1974) and a circumscribed region in the lateral septum (Fig. 13B), both of which contain DARPP-32ir somata as well as fibers (Durstewitz *et al.*, 1998).

DARPP-32ir neuropil labeling in the Hp is heterogenous, with the medial part being completely blank, while the ventromedial part and the lateral border show considerable neuropil labeling and a high number of DARPP-32ir somata (Durstewitz *et al.*, 1998). These regions probably correspond to the V-shaped region and area 7 of Krebs *et al.* (1991) and Erichsen *et al.* (1991), respectively. The APH displays moderate to high levels of DARPP-32ir neurons and neuropil labeling.

With the exception of the Tn, which is virtually devoid of DARPP-32, the pigeon archistriatum is homogenously stained by DARPP-32ir with densities comparable to the neostriatum and the APH (Fig. 14B; Durstewitz *et al.*, 1998). Only the ventral but not the dorsal archistriatum in addition contains a high percentage of DARPP-32ir neurons, while just the opposite is the case for the distribution of DA fibers and receptors (Metzger *et al.*, 1996; Wynne and Güntürkün, 1995; see Section 5.3.1). However, the finding of many large DARPP-32ir neurons in the ventral archistriatum is consistent with the relatively high number of dopaminergic baskets in this region (Wynne and Güntürkün, 1995), and may thus further establish a functional dissociation between a 'basket'- and an 'en passant'-mode of dopaminergic innervation. In addition, a small, dense population of DARPP-32ir cells was observed at the dorsomedial border of the intermediate archistriatum (Fig. 14B; Durstewitz *et al.*, 1998), lying within the dorsal archistriatum intermedium dorsale which is also densely innervated by dopaminergic fibers and is dense in D1-receptor content (see Sections 5.3.1 and 5.3.2). As judged from Fig. 3 in Schnabel *et al.* (1997), the situation seems to be comparable in chicks, with quite high numbers of DARPP-32ir somata and fibers in the dorsal intermediate and most ventral archistriatum, but low staining in between.

5.3.5. *Colocalizations*

In the archistriatum, and especially in its ventral component, a large proportion of DARPP-32ir neurons are located within THir baskets (15–40%; Durstewitz *et al.*, 1998). Since axons which constitute baskets very likely exert a massive effect on their postsynaptic targets, it is conceivable that many D1-positive archistriatal cells are to an important extent under modulatory control of the dopaminergic system. Since in the quails archistriatum intermedium THir fibers have also been found to enwrap aromatase-ir neurons, it is possible that D1-positive archistriatal cells are jointly modulated by DA and steroids and thus play an important role in the motor control of sexual behavior (Balthazart *et al.*, 1998). In contrast, in the hippocampal complex, the percentage of DARPP-32ir neurons located in THir baskets is very low ($< 5\%$), further supporting the notion that most if not all THir baskets in this region may be of non-dopaminergic and thus probably noradrenergic origin (Moons *et al.*, 1995; Reiner *et al.*, 1994; Wynne and Güntürkün, 1995).

In the archistriatal and hippocampal regions GADir neurons were never observed to be located within TH baskets or to be colocalized with DARPP-32 (Durstewitz *et al.*, 1998). Thus, in these regions like in most other telencephalic areas the avian dopaminergic system might mainly modulate non-GABAergic and thus excitatory forebrain neurons. The situation may be different in the hippocampal region, however, where a higher density of D2 receptors has been observed (see Section 5.3.3). In the mammalian cortex, mainly GABAergic interneurons seem to be modulated via D2 receptors, while the activity of pyramidal cells seems to be mainly modulated via D1 receptors (Godbout *et al.*, 1991; Law-Tho *et al.*, 1994; Pirot *et al.*, 1992; Rétaux *et al.*, 1991; Yang and Seamans, 1996). If this would hold true also in the dorsal HP and medial APH, where D2 receptors are even more numerous than D1 receptors, then one might speculate that in the hippocampal areas mainly the network of inhibitory interneurons is modulated by DA, in contrast to the situation in other telencephalic areas.

5.4. Basal Ganglia

5.4.1. *Dopaminergic Fibers and Projections*

The avian basal ganglia can be subdivided into four major functional regions: 1 the LPO and the PA which together are comparable to the dorsal, somatomotor striatum; 2 the Acc, TO and BNST, which form the ventral, visceral-limbic striatum; 3 the PP; and 4 the VP, which constitute the dorsal and ventral pallidum, respectively (Karten and Dubbeldam, 1973; Reiner *et al.*, 1984a; Veenman *et al.*, 1995). Whereas the dorsal striatum contains small, densely packed cells, the PP mainly contains sparsely scattered large projection neurons.

Comparable to the mammalian situation, anterograde and retrograde tracing studies demonstrated that structures of the avian basal ganglia are the ones receiving the densest input from the dopaminergic midbrain nuclei SNC and VTA, with some degree of topographical organization (Bons and Oliver, 1986; Brauth *et al.*, 1978; Karten and Dubbeldam, 1973; Kitt and Brauth, 1986; Metzger *et al.*, 1996). Thus, the LPO and the rostromedial PA receive input from VTA and the central core of SNC (but see Metzger *et al.*, 1996 in chicks), the medial and caudal PA receive inputs mainly from the medial SNC, and the lateral PA from the lateral SNC (Bons and Oliver, 1986; Brauth *et al.*, 1978; Kitt and Brauth, 1986). Structures of the ventral striatum also receive projections from the SNC, and to a somewhat lesser degree from VTA (Balthazart and Absil, 1997; Kitt and Brauth, 1986). In contrast, notable mesencephalic projections to the PP and n. intrapeduncularis (INP), that is, pallidal parts of the avian basal ganglia, were not observed (Brauth *et*

al., 1978; Kitt and Brauth, 1986; Medina and Reiner, 1997).

The results from tracing studies have been confirmed by immunocytochemical investigations in several avian species using antibodies directed against DA, L-DOPA or TH (Fig. 15; Bailhache and Balthazart, 1993; Balthazart *et al*., 1998; Bottjer, 1993; Karle *et al*., 1996; Metzger *et al*., 1996; Moons *et al*., 1994; Wynne and Güntürkün, 1995). The 'striatal' parts of the avian basal ganglia are characterized by an extremely dense meshwork of dopaminergic fibers (Fig. 15A and C), which exhibit many bouton-like axonal swellings. Actually, this meshwork is so dense that basket- and non-basket-types of dopaminergic innervation can hardly be differentiated in these regions, except for the BNST and the Acc, where the innervation is less dense (Karle *et al*., 1996; Wynne and Güntürkün, 1995). In the Acc, a high number of DAir (but not THir) basket-like structures are observed in addition to DAir and THir fibers (Fig. 13C). In contrast, DA- and TH-positive labeling in the 'pallidal' parts of the avian basal ganglia is comparatively weak (Fig. 15A and C; Bailhache and Balthazart, 1993; Balthazart *et al*., 1998; Bottjer, 1993; Karle *et al*., 1996; Metzger *et al*., 1996; Moons *et al*., 1994; Wynne and Güntürkün, 1995). Moons *et al*. (1994) were not able to detect any DAir or L-DOPAir in the PP and INP in the chick brain at all. However, Wynne and Güntürkün (1995) observed that many unlabeled large neurons in the pigeon PP are enwrapped by basket-like DA-positive structures (cf Fig. 4B). The light labeling of the PP may thus in part be due to the sparse distribution of the large projection neurons in this area.

Considerable THir occurs in the VP, which must be largely due to labeling of noradrenergic fibers (Bailhache and Balthazart, 1993; Karle *et al*., 1996; Moons *et al*., 1995; Wynne and Güntürkün, 1995). In contrast, by far the most TH-positive elements in the PA and LPO seem to be of dopaminergic origin, as only little DBHir and NAir were observed in these regions (Karle *et al*., 1996; Moons *et al*., 1995). Furthermore, in the PA and LPO, DAir and THir terminals make up for about 15–20% of all synaptic terminals in these areas (Karle *et al*., 1996). A substantial decrease of DA concentration within the basal ganglia from rostral to caudal has been noted by Juorio and Vogt (1967).

5.4.2. *D1 Receptors*

Autoradiographic D1-receptor binding studies, all using [^{3}H]SCH23390 as ligand, in chicks (Schnabel *et al*., 1997; Stewart *et al*., 1996), pigeons (Dietl and Palacios, 1988; Richfield *et al*., 1987), Japanese quails (Ball *et al*., 1995), and European starlings (Casto and Ball, 1994) consistently demonstrated that D1 receptors are most abundant in structures of the avian basal ganglia (Fig. 7). However, the absolute binding of [^{3}H]SCH23390 varied by several orders of magnitude between studies, ranging in the LPO from 3.8 fmol mg^{-1} protein (Stewart *et al*., 1996) to 2800 fmol mg^{-1} (Ball *et al*., 1995). This might partly be due to species and strain differences (see Divac *et al*., 1988; Juorio and Vogt, 1967), but as large variations occur even within a given species (e.g. compare studies in chicks of Schnabel *et al*., 1997 and Stewart *et al*., 1996), differences in technical procedures are probably the main factor. Nevertheless, the consistent result of all of these stu-

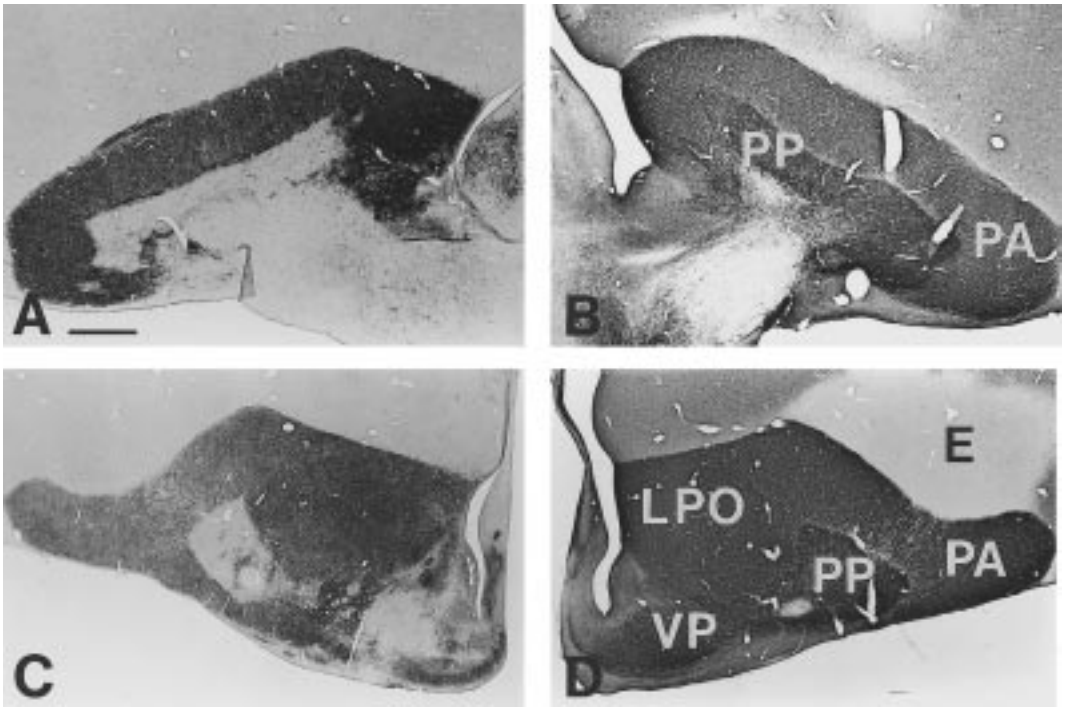

Fig. 15. (A and C) Dopamine-immunoreactive fibers and (B and D) DARPP-32 immunoreactivity in the basal ganglia. Scale bar represents 1 mm.

dies was an about five- to ten-fold lower concentration of D1 receptors in the pallidal parts (PP and VP) than in the striatal parts (LPO, PA, BNST, Acc, TO) of the avian basal ganglia.

With respect to the subdivisions within the avian striatum, some authors reported higher D1 concentrations in the LPO than in the PA (Ball *et al*., 1995; Schnabel *et al*., 1997), while others could not observe notable differences (Dietl and Palacios, 1988; Richfield *et al*., 1987; Stewart *et al*., 1996). In addition, Schnabel *et al*. (1997) reported a decreasing rostro-caudal gradient of D1 receptors in the LPO, in accordance with the rostro-caudally decreasing DA concentration noted earlier (Juorio and Vogt, 1967; Juorio, 1983). In a developmental study by Schnabel and Braun (1996) in chicks, D1 receptors showed a gradual but non-significant increase during the first post-hatch week. Thus, the D1 receptor system seems to be largely developed in chicks at the time of hatching, consistent with their precocial nature.

5.4.3. *D2 Receptors*

The density of D2 receptors (Fig. 8) in striatal parts of the avian basal ganglia (LPO, PA, BNST, TO, Acc) seems to be even higher (*ca* 1.5-fold) than that of D1 receptors (Dietl and Palacios, 1988; Richfield *et al*., 1987; Stewart *et al*., 1996), although this was not consistently found (Schnabel and Braun, 1996; Stewart *et al*., 1996). The lack of a higher D2 receptor density in the Schnabel and Braun (1996) study is possibly due to a significant developmental increase in the striatal parts of the basal ganglia during the first post-hatch week as reported by these authors. Stewart *et al*. (1996), on the other hand, found that the relation of D1:D2 receptor densities in the basal ganglia depended on the learning history of the animals, since after one-trial avoidance learning the density of D1- but not D2-receptors was highly increased in the LPO. The density of D2 receptors in the LPO is approximately the same as (Dietl and Palacios, 1988; Richfield *et al*., 1987; Schnabel and Braun, 1996) or slightly lower than in the PA (Stewart *et al*., 1996). In contrast, D2 densities are five- to ten-fold lower in the PP and INP than in the LPO/PA (Dietl and Palacios, 1988; Richfield *et al*., 1987; Stewart *et al*., 1996).

5.4.4. *DARPP-32*

In pigeons (Durstewitz *et al*., 1998) and chicks (Schnabel *et al*., 1997), the striatal parts of the basal ganglia exhibit very dense DARPP-32 labeling (Fig. 15B and D), consistent with the abundance of D1 receptors in these structures. In addition, and in contrast to the autoradiographic D1-receptor binding studies, the pallidal PP (but not the INP) is as dense in its DARPP-32 labeling as the striatal components (Fig. 15B and D). However, DARPP-32-positive labeling in the PP is almost exclusively constrained to fiber labeling, whereas a high number of DARPP-32ir somata shows up in the neighbouring PA and LPO. It is conceivable that the dense neuropil labeling in PP stems from descending D1-positive axons, as it is the case in the globus pallidus of rats. In these animals, D1- and DARPP-32- but not D2-positive fibers which probably belong to the striatonigral and striatoentopeduncular tracts have been described surrounding unlabeled somata and dendrites in the globus pallidus (Ouimet and Greengard, 1990; Yung *et al*., 1995). Finally, the avian Acc is relatively low in DARPP-32 content (Fig. 13D; Durstewitz *et al*., 1998; Schnabel *et al*., 1997), in contrast to the high densities of dopaminergic fibers (Wynne and Güntürkün, 1995) and D2 receptors (Dietl and Palacios, 1988), but consistent with the low density of D1 receptors in the quail Acc according to Ball *et al*. (1995).

5.4.5. *Colocalizations*

Anderson and Reiner described two major populations of striatonigral projection neurons, one that co-contains substance P and dynorphin and makes up for *ca* 85–95% of all projection neurons, and the other that contains enkephalin and makes up for only 1–4% of all projection neurons (Anderson and Reiner, 1990, 1991b; Reiner *et al*., 1984b; Reiner and Anderson, 1990). Projections from both of these neuronal populations in the medial striatum terminate on DAir and THir, but also—to an about equal degree—on unlabeled cells in the SNC (Anderson *et al*., 1991; Medina *et al*., 1995). Vice versa, both populations of striatonigral projection neurons receive input from THir fibers as demonstrated by EM, targeting perikarya, dendritic shafts and spines (Karle *et al*., 1992, 1994). Furthermore, a subpopulation of substance P-ir projection neurons (39%) also contained somatostatin, whereas neurons containing only somatostatin or neuropeptide Y were not observed to project to the SNC (Anderson and Reiner, 1990). These findings demonstrate that in the avian like in the mammalian basal ganglia (Song and Harlan, 1994; Takagi, 1986) subpopulations of striatal output neurons which interact with the dopaminergic midbrain neurons could be differentiated by means of the neuropeptides co-released by these neurons.

Reiner and Anderson (1990) and Reiner *et al*. (1994) supposed that both, substance P containing and enkephalin containing neurons are also colocalized with GABA. However, until now there is no convincing evidence confirming this hypothesis. According to immunocytochemical studies, the percentage of GADir and GABAir neurons in the avian basal ganglia seems to be low ($< 15\%$), even after pre-treatment with colchicine, and no significant regional variations could be observed throughout the entire telencephalon (Durstewitz *et al*., 1998; Veenman and Reiner, 1994). If this pattern should hold true in the light of other methods such as *in situ* hybridization, this would stand in striking contrast to what is known from the mammalian basal ganglia, where the vast majority of neurons are of the medium spiny type which utilizes GABA (Chesselet *et al*., 1987; Kita and Kitai, 1988; Surmeier *et al*., 1988). This apparent difference between the mammalian and avian basal ganglia might also explain why no colocalizations of GAD and DARPP-32 could be detected in the PA by Durstewitz *et al*. (1998). In contrast, in the mamma-

lian striatum, the very high percentages of GABAergic and DARPP-32ir neurons *per se* implicate a high degree of overlap (Anderson and Reiner, 1991a; Ouimet *et al.*, 1984, 1992).

However, it has to be pointed out that the extremely dense meshwork of THir and DAir fibers and the very high concentration of DARPP-32 in the avian basal ganglia make the study of possible colocalizations at the light-microscopic level extremely difficult if not impossible in this structure. For two other reasons the apparent lack of DARPP-32/GAD colocalizations in the paleostriatum does not exclude that GABAergic neurons in these regions are dopaminoceptive: First, Veenman and Reiner (1994) reported a subpopulation of small GABAergic neurons not detected by GAD immunochemistry. Second, as discussed already, D2 receptors are even more abundant than D1 receptors in the avian basal ganglia, so that the possibility remains that GABAergic cells in these regions are equipped with receptors of this class. Hence, the issue whether GABAergic neurons in the avian basal ganglia receive a significant dopaminergic input awaits further investigation.

In the VP and the BNST of the male quail brain, aromatase-ir cells were found to be located in THir baskets, and THir varicosities were found in close vicinity of almost all of these cells (Balthazart *et al.*, 1998). In fact, due to the particular high concentration of both of these markers in the VP and BNST, these structures might be major loci of interaction between catecholaminergic systems and forebrain steroid hormone activity.

5.5. Dopaminergic Innervation of Song Nuclei in Song Birds

The brain of song birds contains several sexually dimorphic nuclei involved in the song system (Nottebohm *et al.*, 1976, 1982) which are adapted to the specific sensorimotor requirements of song perception and production. In the context of the dopaminergic system, these specific nuclei deserve special discussion, because, interestingly, they receive a much denser dopaminergic input as measured by THir and catecholamine histofluorescence than the surrounding tissue (Bottjer, 1993; Lewis *et al.*, 1981; Sakaguchi and Saito, 1989; Soha *et al.*, 1996). Among these nuclei are a nucleus in the dorsolateral LPO, the so-called area X, the robust n. of the archistriatum, the lateral magnocellular n. of the anterior neostriatum, the n. interfacialis, and the high vocal center located in the caudal neostriatum. In addition to the higher THir exhibited by these nuclei compared to the surrounding areas, a higher density of D1-specific binding has been demonstrated in area X of male starlings compared to the surrounding LPO (Casto and Ball, 1994). Furthermore, a dense input to area X from VTA and SNC has been shown by retrograde tracing (Lewis *et al.*, 1981). In addition, the sexual dimorphism of the song nuclei is also reflected in their dopaminergic innervation as these nuclei in male birds which sing receive a much denser dopaminergic input than in the non-singing females. In contrast, sex differences with regards to DA receptor densities have not been observed in non-singing birds like quails (Ball *et al.*, 1995).

What makes these nuclei even more interesting in terms of their dopaminergic innervation is that the density of the dopaminergic input to these nuclei as well as DA levels and turnover rates are clearly correlated with the phases of song learning. Thus, in young zebra finches (< 30 days), THir in the song nuclei is even *less* dense than in the surrounding tissue (Sakaguchi and Saito, 1989; Soha *et al.*, 1996), while a strong developmental increase occurs with the onset of the sensorimotor phase of song learning around day 35. In accordance with these findings, Harding *et al.* (1998) observed highly significant increases in DA levels and turnover rates in the song nuclei within the LPO, the n. robustus of the archistriatum, the lateral magnocellular n. of the anterior neostriatum, and the n. interfacialis in the neostriatum in zebra finches between postnatal days 35–55, which strongly declined again at day 90. A similar peak around day 35 at least in DA turnover was observed in the auditory Field L. Thus, the dopaminergic system probably has a prominent role in song learning and production that might be related to the requirement that sensory and motor aspects have to be integrated over time during song learning and production (see Section 7.6).

6. COMPARATIVE ASPECTS OF THE DOPAMINERGIC SYSTEM IN MAMMALIAN AND AVIAN SPECIES

From the description given in Sections 4 and 5, readers familiar with the dopaminergic system of mammals may have recognized that the avian dopaminergic system shares many important organizational features with its mammalian counterpart. Like in mammals (Berger and Gaspar, 1994; Björklund and Lindvall, 1984; Fallon and Loughlin, 1995; Swanson, 1982), the dopaminergic innervation of the avian telencephalon arises mainly from a small population of dopaminergic midbrain nuclei in the VTA and SNC, where only a small percentage of fibers crosses into the contralateral hemisphere (Metzger *et al.*, 1996; Kitt and Brauth, 1986). The following description focuses on some very prominent and interesting similarities and differences in the dopaminergic innervation of the telencephalon of birds, rodents and primates.

6.1. Basal Ganglia

Like the avian 'striatum', the caudate-putamen in rats and primates receives the densest dopaminergic fiber input and displays the highest concentrations of D1- as well as D2-receptors (Ariano, 1997; Björklund and Lindvall, 1984; Brock *et al.*, 1992; Camps *et al.*, 1990; Joyce *et al.*, 1993; Ouimet *et al.*, 1984; Yung *et al.*, 1995). In addition, in mammals and birds the caudate-putamen, or dorsal striatum, is higher in its dopaminergic innervation, DARPP-32 content and DA receptor density (at least in D2-specific binding; Richfield *et al.*, 1987) than the n. accumbens/ventral striatum (Ball *et al.*, 1995; Brock *et al.*, 1992; Durstewitz *et al.*, 1998; Hemmings and

Greengard, 1986; Joyce *et al*., 1993; Karle *et al*., 1996; Yung *et al*., 1995; Wynne and Güntürkün, 1995). In contrast, 'pallidal' structures in both amniote classes are much weaker innervated. Furthermore, despite the lower D1 receptor densities in pallidal compared to striatal structures, a high amount of DARPP-32 is present in the mammalian globus pallidus (Hemmings and Greengard, 1986; Ouimet *et al*., 1984, 1992) and its avian equivalent PP (see Section 5.4.4). However, as discussed for the PP in Section 5.4.4, the high DARPP-32ir in the globus pallidus of rats is almost exclusively due to neuropil labeling, in contrast to the high number of DARPP-32ir neurons in the striatum (compare Fig. 5B in Durstewitz *et al*., 1998 to Fig. 8 in Ouimet *et al*., 1984), and may stem from intense staining of descending striatonigral and striatopallidal fibers. Finally, a rostro-caudal gradient in DA receptor densities and DA concentration as observed in birds (see Section 5.4) has also been noted in mammals (Bockaert *et al*., 1976; Boyson *et al*., 1986; Richfield *et al*., 1987; Tassin *et al*., 1976)

However, some differences between birds and mammals are also apparent. First, direct comparisons between pigeons, rats and cats revealed that the concentration of D1 receptors in the avian 'striatum' is about five- to ten-fold lower, and that in the avian 'pallidum' is about 20-fold lower than in the mammalian striatum (Dietl and Palacios, 1988; Richfield *et al*., 1987). In contrast, the density of D2 receptors in the pigeons 'striatum' is only about half of that in the mammalian striatum, while, however, this difference is larger for the pallidum (Dietl and Palacios, 1988; Richfield *et al*., 1987). Second, the first point implies that the ratio of D1:D2 receptors is different in the avian and the mammalian basal ganglia. Whereas in mammals D1 receptors are much more prevalent than D2 receptors (Joyce *et al*., 1993), the opposite seems to be the case in birds (see Section 5.4.3). As D1- and D2-receptors are linked to different G-proteins and influence adenylate cyclase activity in opposite ways (Hemmings *et al*., 1987b; Robinson and Caron, 1997), the different D1:D2 receptor ratios may imply important differences in basal ganglia function between birds and mammals.

The possible lack of DARPP-32/GAD colocalizations in the pigeon PA has already been discussed (Section 5.4.5), and has been related to other particularities of the avian basal ganglia, namely to the fact that the number of GAD- and GABA-positive neurons in the avian basal ganglia as assessed by immunocytochemical techniques (Durstewitz *et al*., 1998; Veenman and Reiner, 1994) seems to be much lower than in the mammalian basal ganglia (Kita and Kitai, 1988; Surmeier *et al*., 1988).

6.2. Cortex

As in birds, in rodents and primates the dopaminergic input to cortical areas is clearly weaker than that to the striatum, and the densities of dopaminergic receptors and of DARPP-32 sharply decline outside the basal ganglia (Ariano, 1997; Berger *et al*., 1988, 1990, 1991; Berger and Gaspar, 1994; Björklund and Lindvall, 1984; Brock *et al*., 1992; Hemmings and Greengard, 1986; Joyce *et al*., 1993; Ouimet *et al*., 1984, 1992). In the frontal cortices of rats and primates, the density of D1 receptors has been estimated to be *ca* five- to ten-fold higher than that of D2 receptors (Joyce *et al*., 1993; Lidow *et al*., 1991), whereas this ratio seems to be in the range of 3:1 throughout most of the bird telencephalon (Dietl and Palacios, 1988; Schnabel and Braun, 1996; Stewart *et al*., 1996). In contrast, in the avian Hp the density of D2 receptors outnumbers that of D1 receptors (Stewart *et al*., 1996). In the mammalian Hp, the D1:D2 ratio seems to be at least lower than in the neocortex although in general D1 receptors may still be more numerous (Dewar and Reader, 1989; Joyce *et al*., 1993). However, D1 and D2 receptors distribute differentially across hippocampal layers (Köhler *et al*., 1991).

With respect to the functional organization of the dopaminergic innervation of the avian and mammalian 'neocortex', strong equivalencies can be observed. Like in birds, the primary visual, auditory, and somatosensory cortices in mammals are only weakly innervated by dopaminergic fibers, at least much weaker than the respective secondary areas (Berger *et al*., 1988, 1991; Berger and Gaspar, 1994; Joyce *et al*., 1993). These areas also express lower levels of DARPP-32 (Berger *et al*., 1990). In addition, layer IV in the granular cortices in rats and primates, which is the major target zone of specific thalamic input, lacks a significant dopaminergic input (Berger *et al*., 1988, 1991; Berger and Gaspar, 1994; Joyce *et al*., 1993; Phillipson *et al*., 1987).

With respect to the 'higher order' neocortical areas, considerable differences between rodents and primates have been pointed out by Berger and coworkers (Berger *et al*., 1991; Berger and Gaspar, 1994). In general, the dopaminergic innervation of the primate neocortex is more widespread than that of the rat neocortex, and may thus compare better to the dopaminergic innervation of the avian neostriatal and hyperstriatal areas. In both, rodents and primates, the prefrontal areas and the anterior cingulate cortex are densely innervated (Berger *et al*., 1991; Berger and Gaspar, 1994; Joyce *et al*., 1993). Therefore, the dense dopaminergic innervation of the NCL in pigeons was taken as an indication that this multimodal area may be comparable to the mammalian PFC (Divac *et al*., 1985; Divac and Mogensen, 1985; Waldmann and Güntürkün, 1993; Wynne and Güntürkün, 1995). However, the PFC of mammals is not a homogeneous structure. In primates, only the orbitofrontal and ventrolateral portions receive a dense dopaminergic input, while the dorsolateral part is lower in this respect (Berger *et al*., 1988; Lewis *et al*., 1992; Williams and Goldman-Rakic, 1993), and is also very low in DARPP-32 content in adult animals (Berger *et al*., 1990). In rats, however, the medial prefrontal areas, in particular the pre- and infralimbic region, which are assumed to be equivalent to the primate dorsolateral PFC, are the neocortical areas highest in DA fiber density (Berger *et al*., 1991; Berger and Gaspar, 1994; Joyce *et al*., 1993). In fact, this was one of the reasons for Preuss (1995) to question the assumed equivalency between the rat pre- and infralimbic

cortex and the primate dorsolateral PFC. Similar subdivisions of the avian 'prefrontal cortex' were not identified yet. Given the dense dopaminergic input of the NCL, one would compare this area to the prelimbic/infralimbic area of rats, or to the orbitofrontal or ventrolateral PFC of primates. On the other hand, the percentage of DARPP-32ir neurons in the NCL was lower than in other, more rostrally located neostriatal structures, reminiscent of the relatively low DARPP-32ir in the adult primate dorsolateral PFC (Berger *et al.*, 1990). The NCL would also compare better to the primate dorsolateral PFC with respect to its functional characteristics, as both areas seem to be involved especially in spatial working memory (Funahashi and Kubota, 1994; Gagliardo and Divac, 1993; Gagliardo *et al.*, 1996; Goldman-Rakic, 1988; Güntürkün, 1997; Mogensen and Divac, 1982, 1993; Wilson *et al.*, 1993; but see Petrides, 1995).

Furthermore, in primates, in contrast to rats, the premotor and motor cortices are very densely innervated by the dopaminergic system (Berger *et al.*, 1991; Berger and Gaspar, 1994; Joyce *et al.*, 1993). Insofar, pigeons and chicks compare better to monkeys than to rats (see also Reiner *et al.*, 1994), as major parts of the avian 'motor cortex', in particular the dorsal archistriatum intermedium, also receive a rich dopaminergic input. The comparison holds also for the distribution of DARPP-32ir neurons: despite its exceptionally high dopaminergic input, the primate motor cortex displays only a sparse distribution of DARPP-32ir neurons (Berger *et al.*, 1990), similar to the very low number of DARPP-32ir neurons throughout most of the intermediate archistriatum (Durstewitz *et al.*, 1998). In addition, Berger *et al.* (1990) pointed out a mismatch between the distribution of D1 receptors and DARPP-32ir neurons in the primate motor cortex similar to that described for the dorsal archistriatum (Sections 5.3.2 and 5.3.4).

Finally, moderate to high numbers of dopaminergic fibers are present in the secondary sensory and association areas of the primate neocortex (Berger *et al.*, 1988, 1991; Berger and Gaspar, 1994). In this respect, the dopaminergic innervation of the avian telencephalon might also be more similar to that of primates than to that of rats.

6.3. Laminae-Specific Distribution of Dopaminergic Fibers

An additional feature of the dopaminergic innervation of the mammalian neocortex is its laminae-specific distribution. In the rat medial and orbital (lateral) prefrontal areas, the deep layers V–VI are the major targets of dopaminergic fibers (Berger *et al.*, 1991; Björklund and Lindvall, 1984; Joyce *et al.*, 1993). In the primate granular cortices, the superficial layers I–III are generally even more densely innervated than the deep layers V–VI, whereas in the motor and anterior cingulate (agranular) cortices all layers receive a dense dopaminergic input (Berger *et al.*, 1988, 1991; Berger and Gaspar, 1994; Goldman-Rakic *et al.*, 1992; Lewis *et al.*, 1992). As outlined in Section 2, a cortical lamination is absent in the avian brain. Nevertheless, based on hodological, histochemical and functional criteria, some authors have compared subdivisions of the avian telencephalon to specific laminae of the mammalian neocortex. It was argued that the primary sensory areas (E, IHA, Field L2, Bas) are equivalent to the thalamic input layer IV of the respective neocortical areas (extrastriate and striate visual, auditory, somatosensory) and the secondary sensory belts surrounding these primary areas and the HD to layers II–III (Karten and Shimuzu, 1989; Reiner and Karten, 1983; Veenman *et al.*, 1995). Furthermore, the sensorimotor archistriatum, the HA, structures of the PE and possibly the NCL, which either give rise to the major descending pathways or directly project onto the sensorimotor avian striatum, have been identified with the neocortical output layers V–VI. This conception would again render the dopaminergic innervation of the avian brain more similar to that of primates than to that of rats, as both, the 'deeper layers' and the 'superficial layers' of the avain 'neocortex' would be high in DA and DARPP-32.

From a functional perspective, another interesting parallel between birds and mammals might lie in the fact that DA-baskets seem to contact predominantly bigger neurons in the avian brain ($\phi > 15\ \mu$m), whereas smaller neurons are more likely innervated en-passant (Wynne and Güntürkün, 1995). Likewise, in the mammalian neocortex, the bigger pyramidal neurons reside in the deeper layers and are thus the ones probably most heavily innervated by DA fibers within their deep proximal and, in primates in addition, upper layer distal apical dendrites. Moreover, the bigger pyramidal cells are the ones which most likely exhibit repetitive oscillatory bursting-characteristics in the neocortex (Mason and Larkman, 1990; Yang *et al.*, 1996a), an electrophysiological feature that—theoretically—could be exclusively due to their bigger somata and dendrites (Mainen and Sejnowski, 1996). Thus, dopaminergic baskets may innervate neurons in the avian telencephalon with specific functional characteristics as dopaminergic fibers possibly do in the mammalian neocortex.

6.4. Ultrastructural Features and Postsynaptic Targets of the Dopaminergic Innervation

With respect to the postsynaptic targets of the dopaminergic input to the mammalian neocortex, pyramidal cells seem to be the predominant dopaminoceptive population, and most DARPP-32ir neurons are of the pyramidal type (Berger *et al.*, 1990; Goldman-Rakic *et al.*, 1989; Smiley and Goldman-Rakic, 1993). Thus, the finding that GADir neurons in the avian telencephalon do not express DARPP-32 and are never located in THir baskets (Durstewitz *et al.*, 1998), on a first glance, fits well into the mammalian schema. However, dopaminergic fibers in the PFC have also been observed to terminate on smooth, presumably GABAergic, stellate cells (Smiley and Goldman-Rakic, 1993), and the activity of GABAergic neurons in the mammalian PFC has been shown to be modulated by DA *in vivo* and *in vitro* (Penit-Soria *et al.*, 1987; Pirot *et al.*, 1992; Rétaux *et al.*, 1991; Yang *et al.*, 1997). The

dopaminergic effect on GABAergic activity can be antagonized by D2- but not by D1-receptor blockers (Godbout *et al*., 1991; Pirot *et al*., 1992; Rétaux *et al*., 1991 but see Yang *et al*., 1997), although D2 receptors are present in much lower densities in the mammalian neocortex than D1 receptors (see Section 6.2). Hence, GABAergic neurons may be affected mainly via D2 receptors, and this might also be the case in the avian brain. Thus, despite their low densities, D2 receptors might play an important functional role also in the avian telencephalon, and further investigation of this subject is certainly very important.

Dopaminergic fibers in the avian telencephalon also have most of their ultrastructural features in common with their mammalian counterparts. In both animal classes, dopaminergic synapses are relatively small, are mainly of the symmetric type, contact predominantly dendritic arbors and spines, and sometimes converge with other unlabeled synapses on the same spine (i.e. form triadic complexes) (Goldman-Rakic *et al*., 1989; Karle *et al*., 1996; Metzger *et al*., 1996; Séguéla *et al*., 1988; Smiley and Goldman-Rakic, 1993; Yung *et al*., 1995; see Section 4.4). In addition to a specialized synaptic release-mode, much of the neuromodulator seems to be released via unspecialized axonal varicosities in both amniote classes (Cooper *et al*., 1996).

In conclusion, the general pattern of the distribution of dopaminergic fibers and receptors in the avian telencephalon, as well as the laminar and biochemical characteristics of the dopaminergic target neurons, are quite similar to that of mammals. Some specific differences seem also to exist, but may partly be due to the fact that our knowledge about DA receptor subtypes in the avian brain is still incomplete. Finally, considerable differences in the cortical organization of the dopaminergic system have also been observed within the class of mammals.

7. BEHAVIORAL STUDIES AND FUNCTIONAL IMPLICATIONS

From the neuroanatomical features of the dopaminergic innervation in the avian brain, some functional clues could be derived. For example, the fact that primary sensory areas are devoid of DA, while higher sensory, associative and motor areas that have a direct link to structures of the avian basal ganglia receive a dense dopaminergic input and are high in DA receptors makes it likely that DA plays a special role in sensory-motor integration and associative learning.

In fact, the dopaminergic system in mammals is implicated especially in motor, associative and higher order functions like aversive and appetitive learning and working memory (Beninger, 1993; Salamone, 1992, 1994; Sawaguchi and Goldman-Rakic, 1991, 1994; Schultz *et al*., 1993, 1995; Seamans *et al*., 1998; Sokolowski *et al*., 1994; Zahrt *et al*., 1997). Although much less is known about the involvement of DA in behavioral and cognitive functions in birds, from the studies in avian species that do exist so far a similar functional involvement of the dopaminergic system as in mammals is apparent. The next sections will deal with these studies.

7.1. Dopaminergic Modulation of (Unconditioned) Motor Functions

Dopamine in the avian brain has been shown to be critically involved in motor functions. Rieke (1980, 1981) observed that unilateral kainic acid lesions of the paleostriatum, or its source of dopaminergic input, the SNC, in pigeons induced persistent turning in one direction, postural problems, arhythmic movements and head or whole body tremors. These behavioral dysfunctions were reproduced by unilateral injections of GABA agonists into the SNC (Rieke, 1982). Furthermore, the turning behavior elicited by unilateral GABA-agonistic injections into the SNC or 6-hydroxydopamine (6-OHDA) destruction of dopaminergic neurons in this area could be enhanced by apomorphine but was suppressed by haloperidol administration (Rieke, 1982; Yanai *et al*., 1995).

Apomorphine has also been shown to facilitate stereotypic pecking bouts in a dose-dependent manner, alone or induced by feeding stress, and the avian basal ganglia is a likely site for these dopaminergic effects (Cheng and Long, 1974; Deviche, 1985; Goodman *et al*., 1983; Nisticò and Stephenson, 1979; Rieke, 1982; Zarrindast and Amin, 1992). In contrast, DA antagonists like haloperidol, chlorpromazine or clozapine inhibit behavioral stereotypies (Cheng and Long, 1974; Goodman *et al*., 1983; Kostal and Savory, 1994), and could cause sedation and tonic immobility that could be reversed by paleostriatal but not by neostriatal lesions (Sanberg and Mark, 1983). The effects of apomorphine and amphetamine on pecking behavior can furthermore be antagonized by specific D1- (SCH23390) as well as by high doses of specific D2-receptor blockers (sulpiride), with a combination of both being most effective, while D1- or D2-specific agonists enhance apomorphine induced pecking (Dehpour *et al*., 1998; Zarrindast and Amin, 1992; Zarrindast *et al*., 1992; Zarrindast and Namdari, 1992). *Low* doses of sulpiride, however, enhanced pecking, presumably by blocking D2 autoreceptors, and *low* doses of apomorphine, on the other hand, might reduce pecking also via an autoreceptor mechanism (Deviche, 1985). It is important to point out that DA antagonists like haloperidol do not prevent all aspects of motor behavior although they reduce pecking bouts and turning, and may lead to sedation. Hence, even after haloperidol administration, Goodman *et al*. (1983) observed pigeons engaging in some normal behaviors like feeding, and Rieke (1982) was still able to elicit orienting and escape responses, including flying, by stressful stimuli.

Stereotypic motor behavior and hyperactivity on the one hand as induced by supranormal DA receptor stimulation or DA activity, and sedation on the other hand as induced by, for example, neuroleptic drugs, are also typically observed in mammals including humans (Bo *et al*., 1988; Clark and White, 1987; Gessa *et al*., 1985; Le Moal and Simon, 1991; Ridley, 1994; Sokolowski and Salamone, 1994;

Waddington and Daly, 1993; Wickens, 1990). However, like in birds, behavioral reactions to intense or significant stimuli may be left intact after DA depletion or subnormal DA receptor stimulation in the basal ganglia (Salamone, 1992). Thus, Salamone (1992) concluded that DA is not that much involved in motor processes *per se* but more in sensory-motor integration that requires novel motor sequences or in processes that extend significantly in time (see also Taylor and Saint-Cyr 1995). DA might also be especially important for motor behavior that is driven by internal states without being directly controlled by external stimuli.

Lindenblatt and Delius (1988) demonstrated that apomorphine-induced pecking bouts could also be elicited by local injections into the Bas, and could be reversed by 6-OHDA injections into this structure. However, since dopaminergic fibers and receptors seem to be lacking in the Bas, the behavioral effects of DA-agonistic drugs might also be attributed to ligand diffusion into the adjacent PA and PP. Consistent with this interpretation, apomorphine injections into the Bas also produced contralateral turning (Lindenblatt and Delius, 1988), a typical symptom of altered DA activity in the avian basal ganglia (Rieke, 1981, 1982). Wynne and Delius (1996) reported that apomorphine-induced pecking could be reduced by lesions of the Bas, thus demonstrating that the Bas is involved in apomorphine-induced stereotypies. However, this result does not necessarily imply that the Bas is in fact a site of apomorphine action. Apomorphine might increase pecking rates via actions in the basal ganglia, while Bas lesions could reduce pecking rates independently. On the other hand, the finding of Durstewitz *et al.* (1998) that the Bas had high number of DARPP-32ir neural cell bodies may hint to some anatomical basis for the apomorphine induced pecking bouts. Hence, the neuroanatomical site of the apomorphine-induced pecking bouts remains unclear.

7.2. Dopaminergic Involvement in Arousal and Wakefulness

Ferrari and Giuliani (1993) found that DA in the chick brain might also participate in the regulation of states of arousal and wakefulness. Selective D2 agonists induced hypomotility and sleep-like states. However, for some D2 agonists (like lisuride) or the mixed D1/D2 agonist apomorphine, this effect reversed at higher doses, leading to behavioral excitation and increased spontaneous pecking instead. Similar dose-dependent patterns were also observed in rodents, where the sedatory effects of the drugs were attributed to predominant stimulation of presynaptic D2 autoreceptors at lower doses (Ferrari and Giuliani, 1993; Ongini, 1993). In accordance with this interpretation, microinfusion of apomorphine into the rat VTA, but not into the Acc, caudate n. or PFC, induces behavioral and EEG signs of sleep, which could be antagonized by sulpiride (Bagetta *et al.*, 1988a,b). In general, in mammals dopaminergic drugs increase alertness, wakefulness and exploratory activity, with accompanying indications in the EEG, while lesions of the dopaminergic system, DA antagonists or subnormal DA activity after preferential D2 autoreceptor stimulation have the opposite effect (Bagetta *et al.*, 1988a,b; Gessa *et al.*, 1985; Montaron *et al.*, 1982; Ongini, 1993). Dopaminergic effects on arousal and wakefulness on the one hand, and on behavioral excitation and stereotypies (see Section 7.1) on the other, may in fact be mediated by the same neural mechanism (see Section 7.6).

7.3. Dopaminergic Modulation of Appetitive and Consummatory Behavior

DA in the mammalian brain is well known to regulate aspects of food and water intake (Bertolucci-D'Angio *et al.*, 1990a,b; Cooper and Al-Naser, 1993; Wilson *et al.*, 1995), and of sexual behavior (Pfaus and Phillips, 1989). Likewise, apomorphine and DA administration in pigeons reduces food consumption (Deviche, 1984; Ravazio and Paschoalini, 1992), possibly because apomorphine and DA could substitute for the rewarding value of food. Alternatively, the low doses of apomorphine used by Deviche (1984) might have reduced food intake by very much the same mechanism that has been proposed for apomorphine-induced sedation (see Section 7.2), that is, primarily via D2 autoreceptors. In fact, Deviche (1984) noted that the doses of apomorphine used in his study were too low to elicit pecking bouts, or even inhibited pecking.

Apomorphine also reduces appetitive and consummatory aspects of sexual behavior in the male quail (Absil *et al.*, 1994; Castagna *et al.*, 1997). These apomorphine-induced effects are probably due to D2-receptor stimulation as D2 agonists reduce both appetitive and consummatory sexual behavior, while D1 agonists do just the reverse, that is, increase both aspects of sexual behavior (Balthazart *et al.*, 1997). Again, these actions of the dopaminergic system may be related to a rewarding function of DA which has been proposed by several authors (Schultz *et al.*, 1993, 1995; see Beninger, 1993; see Salamone, 1992, 1994; Wickens, 1990; Wickens and Kötter, 1995). According to studies in rats, part of the dopaminergic effects on food consumption and sexual behavior might be regulated by dopaminoceptive hypothalamic nuclei (Cooper and Al-Naser, 1993). However, additional structures are probably also involved since increases of DA metabolites during food consumption or upon presentation of appetitive stimuli have also been observed in the Acc, medial PFC and in the amygdala in rats (Bertolucci-D'Angio *et al.*, 1990b; Wilson *et al.*, 1995).

The 'reward theory' of DA function partly derived from studies on intracranial self-stimulation and self-administration of dopaminergic drugs (Fibiger, 1978; Le Moal and Simon, 1991; Wise, 1978; Yokel and Wise, 1975). Self-administration of cocaine was also observed in pigeons, where it could be antagonized by haloperidol (Winsauer and Thompson, 1991), pointing to a similarly 'rewarding' action of DA in the avian as in the mammalian brain.

7.4. Dopaminergic Modulation of Learning and Conditioned Behavior

Dopamine in the avian telencephalon is involved in various forms of learning. Stewart *et al.* (1996) found that after a one-trial taste aversion avoidance learning, D1- but not D2-specific binding increased highly significantly in the LPO. A role for DA in parts of the striatum, namely in the Acc, in passive avoidance training (and, more generally, in aversive situations) is also well established in mammals (Beninger, 1993; Bertolucci-D'Angio *et al.*, 1990a,b; Salamone, 1994). In an *in vivo* microdialysis study, Gruss and Braun (1997) demonstrated decreased levels of the DA metabolite homovanillic acid in the MNH after auditory imprinting in young chicks, while significant increased levels were observed after exposing the chicks to handling stress. Stressful situations induce increases of DA metabolites also in rats in the Acc and medial PFC (Abercrombie *et al.*, 1989; Bertolucci-D'Angio *et al.*, 1990b). The studies by Soha *et al.* (1996) and Harding *et al.* (1998) reported in Section 5.5 suggest that DA is additionally involved in the sensorimotor stage of song learning in zebra finches as the postnatal development of the innervation of various forebrain song nuclei by THir fibers as well as DA levels and turnover in these nuclei are correlated with this period. A direct involvement of DA in learning mechanisms is made likely by a study by Lindenblatt and Delius (1987) who showed that apomorphine (and thus probably DA) might serve as a positive reinforcer when coupled with a conditioned stimulus. Furthermore, DA antagonists like haloperidol reduce the rate of conditioned responding without affecting discrimination performance (Tombaugh, 1981), while conditioned responding of young chicks for heat reinforcement was shown to be enhanced especially after combined D1- and D2-agonist injection (Dose and Zolman, 1994). Finally, following apomorphine administration, chicks were found to be unable to suppress formerly rewarded but now punished responses, while this can be reversed by haloperidol pretreatment (McDougall *et al.*, 1987).

Although these studies show that DA is somehow involved in various learning processes, the nature of the underlying mechanism is still far from clear. Thus, often it may not be easy to decide whether the DA-induced effects can be attributed to a specific role of DA in learning, to its motivational effect, to its role in motor behavior, or to its impact on attention and arousal (see Salamone 1992). This is especially true when DA agonists are administered systemically, thus acting on many structures. For example, McDougall *et al.* (1987) hinted to the fact that apomorphine in their experiments generally enhanced the response rate but that this effect may have been obscured due to a ceiling effect as long as the response was associated with reward only. Only when punishment was introduced, the behaviorally exciting effect of apomorphine might have become apparent. Thus, although it is interesting to note that increased pecking rates prevail even in the presence of punishment, the main effect of apomorphine may not be to inhibit response suppression learning but to induce behavioral excitation.

7.5. Dopaminergic Modulation of Working Memory

A failure to inhibit inadequate responses as demonstrated by McDougall *et al.* (1987) is also often observed after lesions of the rat and primate PFC, or lesions of its dopaminergic afferents (Dias *et al.*, 1997; Fuster, 1989; Sokolowski and Salamone, 1994). A failure to suppress irrelevant response options may also play a role in the inability of pigeons with NCL lesions—depending on the extent to which the NCL was destroyed—to perform a reversal learning (Hartmann and Güntürkün, 1998) or a go/no-go task (Güntürkün, 1997). In addition, lesions of the NCL or its main source of thalamic afferents, the n. dorsolateralis posterior thalami, lead to diminished delayed alternation performance (Gagliardo *et al.*, 1996; Güntürkün, 1997; Mogensen and Divac, 1982, 1993). Tasks which involve a delay are thought to be indicative of working memory functions, as in these tasks an animal has to actively hold information in memory for the guidance of responding in forthcoming situations (Fuster, 1989). Reduced delayed alternation performance is also a characteristic deficit observed after PFC lesions in mammals (Fuster, 1989). With regards to the transient nature of the spatial working memory deficits after NCL lesions, the NCL compares better to the pre-/infralimbic region of rats than to the dorsolateral PFC of primates, where lesions lead to more serious and longer-lasting working memory deficits (Preuss, 1995).

DA and D1 receptors within the PFC are well known to be involved in working memory functions in primates and rats (Brozoski *et al.*, 1979; Müller *et al.*, 1998; Sawaguchi and Goldman-Rakic, 1991, 1994; Seamans *et al.*, 1998; Simon *et al.*, 1980; Zahrt *et al.*, 1997). Also in pigeons, blockade of dopaminergic transmission or receptors by systemic administration of various neuroleptic drugs like chlorpromazine and clozapine has been shown to decrease delayed matching to sample performance in a dose-dependent fashion (Picker and Massie, 1988; Watson and Blampied, 1989). Interestingly, both these drugs *increased* accuracy when administered at *low* doses, possibly via predominant actions on D2 autoreceptors at these doses (Picker and Massie, 1988).

Only recently our laboratory has gathered evidence that D1 receptors specifically in the pigeon NCL might be involved in response inhibition and working memory. Thus, Diekamp *et al.* (1998) presented evidence that local D1 receptor blockade by SCH23390 in the NCL impairs go/no-go performance. After local SCH23390 application, pigeons tended to respond to all stimuli irrespective of their reward value. Güntürkün and Durstewitz (in press) trained pigeons in a labyrinth task which had a spatial working memory and a non-spatial reference memory component. At the beginning of a daily session pigeons were randomly placed at one of two starting positions in a labyrinth with 24 chambers, in which 12 arms contained red cups that were never baited, while the remaining 12 chambers contained white cups that were baited only at the onset of a session. Thus, as a reference memory component of

the task, pigeons had to learn to discriminate red from white cups as only the latter ones contained food pellets. Moreover, they had to learn never to return to an arm visited previously as each white cup only contained food once at the onset of a session. This was the working memory component of the task as pigeons mentally had to keep track of all arms already visited, or—complementary—had to keep in mind all arms still worth visiting. After local SCH23390 injections into the NCL, pigeons had no problems with their reference memory, but were significantly impaired compared to pigeons which received saline control injections in the working memory part. In addition to true working memory errors, which were defined as re-entrances into arms after the animal had already visited one or more other arms, there was also a significant increase in 'perseveration' errors. Perseveration in this task was defined as an immediate re-entrance into an arm, most often due to the fact that a pigeon stayed in an arm and tried to access the same food cup a couple of times in close temporal succession. Perseveration is also a well known phenomenon in prefrontal mammals and patients with prefrontal disorders or lesions (Dias *et al.*, 1997; Iversen and Mishkin, 1970; Fuster, 1989; Milner and Petrides, 1984).

7.6. The Possible Function of Dopamine in Sensory-Motor Processes

Summarizing Sections 7.1, 7.2, 7.3, 7.4 and 7.5, the dopaminergic system in birds—consistent with the anatomical data—plays a role in motor functions, in arousal, in learning and probably in working memory, while DA levels do not change with visual experience (Davies *et al.*, 1983) and DA receptor antagonists, in general, do not seem to affect sensory discrimination *per se*, although they might interfere with sensory-motor integration and instrumental responding (Güntürkün and Durstewitz, in press; Mogensen and Divac, 1993; Tombaugh, 1981). Thus, in the avian telencephalon the dopaminergic system is involved in very much the same motor and cognitive functions as it is in mammals, supporting the notion of a tight link between structure and function in the nervous system. That is, the similar structural/anatomical organization of the dopaminergic system in birds and mammals seems to give rise to a similar functional organization, despite the facts that the evolution of birds and mammals diverged >200 million years ago and that the organization of avian telencephalic areas is quite different from that of mammals.

As already noted in Section 7.4, some of the behavioral functions of DA might be difficult to discern. According to Salamone (1992), the apparent dopaminergic involvement in motor functions and in motivation might actually refer to common neural processes, related to sensory-motor integration evolving in time, and to instrumental or 'intentional' behavior. To unravel the possible function of DA in various motor and cognitive processes, and to explicate the detailed neural mechanisms by which DA achieves these functions, knowledge about DA-induced manipulations of neural and synaptic biophysical properties is essential. However, to our knowledge, until now nothing is known about dopaminergic modulation of electrophysiological and biophysical properties of neurons in avian forebrain regions, neither *in vivo* nor *in vitro*.

In the PFC of rats, DA enhances a persistent Na^+ current (Gorelova and Yang, 1997; Shi *et al.*, 1997; Yang and Seamans, 1996), reduces a slowly inactivating K^+ and a dendritic high-voltage-activated Ca^{2+} current (Seamans *et al.*, 1997; Yang and Seamans, 1996; Yang *et al.*, 1996b), reduces glutamate-induced excitatory synaptic currents (Law-Tho *et al.*, 1994; Pralong and Jones, 1993), and increases spontaneous activity of GABAergic interneurons (Godbout *et al.*, 1991; Penit-Soria *et al.*, 1987; Pirot *et al.*, 1992; Rétaux *et al.*, 1991; Yang *et al.*, 1997). It could be shown by computational modeling that DA by inducing these biophysical changes could act to stabilize active neural representations, and to protect them against interfering stimulation and noise (Durstewitz *et al.*, in press). That is, DA ensures that delay-activity of PFC neurons in working memory tasks, which is believed to represent the active holding of goal-related information (Funahashi and Kubota, 1994; Fuster, 1989; Goldman-Rakic, 1995), is sustained until the goal has been achieved. The finding that mainly or exclusively excitatory neurons are equipped with D1 receptors (see Section 5) fits well into this functional schema, as, at least in mammals, the D1 receptor-mediated effects on pyramidal cells are the ones contributing most to the stabilizing effect of DA (Durstewitz *et al.*, in press).

The proposed function of DA may not just be important in working memory situations, but in fact in any sensory-motor process, where a representation of the current goal-state of the movement has to be kept upright and to be compared with incoming sensory information. Indeed, sustained delay-activity has also been observed in the primate premotor and motor cortices (Di Pellegrino and Wise, 1991), the striatum (Apicella *et al.*, 1992), and the posterior parietal cortex (Constantinidis and Steinmetz, 1996), which all receive a dense dopaminergic input in primates. In addition, as pointed out by Salamone (1992), temporally extended sensory-motor processes and sequences are especially susceptible to interference with the dopaminergic system while brief responses are less easily disrupted. Sustained delay-activity may be furthermore important in various, especially operant, learning processes where a temporal gap between related stimuli has to be bridged in order to detect the relation. Thus, various forms of learning, selective attention, working memory and sensory-motor integration may all depend on the stability (and thus maintenance) of neural representations, which might be critically regulated by DA. Hence, some of the seemingly very different effects that DA exerts in different anatomical structures may in fact be related to the same basic neural mechanism. However, active maintenance of representations may be less important in primary sensory processes, and this could explain why primary sensory areas are not or only weakly innervated by DA in birds as well as in mammals.

The here proposed function of DA might also explain the peculiar finding that many DARPP-32ir neurons show up in the Bas, although it is a primary

sensory center. The Bas is the only region of the avian telencephalon that receives direct sensory inputs without thalamic relay, and it is involved in a forebrain circuit for the control of pecking where sensory and motor signals have to be integrated within extremely short time spans. Thus, the Bas might be directly involved in sensory-motor processes where sustained delay-activity plays an important role.

In conclusion, the structural and functional organization of the telencephalic dopaminergic system in birds and mammals suggests that DA might have a common function across animal classes and possibly within different telencephalic regions. DA seems to be particularly involved in sensory-motor and associative processes, where it might act to stabilize and sustain neural activity related to behavioral or motor goal states, or to linkage of temporal discontingent stimuli.

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