SEROTONIN 5-HT$_{1A}$ RECEPTOR BINDING SITES IN THE BRAIN OF THE PIGEON (*COLUMBA LIVIA*)

C. HEROLD,[a]* N. PALOMERO-GALLAGHER,[b]
O. GÜNTÜRKÜN[c] AND K. ZILLES[a,b]

[a]*C. & O. Vogt-Institute for Brain Research, Heinrich-Heine-University, 40225 Düsseldorf, Germany*

[b]*Institute of Neuroscience and Medicine (INM-2), Research Center Jülich, 52425 Jülich, Germany*

[c]*Institute for Cognitive Neuroscience, Faculty of Psychology, Ruhr-University, Bochum, 44780 Bochum, Germany*

Abstract—Present knowledge about the serotonergic system in birdbrains is very limited, although the pigeon was used as an animal model in various studies focused on the behavioral effects of serotonergic transmission. In the mammalian brain the 5-HT$_{1A}$ receptor is the most widespread serotonin receptor type, and is involved in various functions. Less is known about the distribution of 5-HT$_{1A}$ receptors in the avian species. Therefore, we analyzed serotonin 5-HT$_{1A}$ receptor binding sites in the pigeon brain using quantitative *in vitro* receptor autoradiography with the selective radioligand [^{3}H]-8-hydroxy-2-(di-n-propylamino)tetralin ([^{3}H]-8-OH-DPAT). The receptor is differentially distributed throughout the pigeon brain. High levels of 5-HT$_{1A}$ receptors are found in the nucleus pretectalis (PT). Moderate densities were detected in the tectum, as well as in the telencephalic nidopallium and hyperpallium. Very low levels were found in the hippocampal formation, the amygdaloid complex, the basal ganglia, and several thalamic nuclei. Furthermore, local variations in 5-HT$_{1A}$ receptor densities support the concept of further subdivisions of the entopallium. The regional distribution patterns of 5-HT$_{1A}$ receptors mostly display a similar distribution as found in homologue brain structures of mammals. © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: 5-HT$_{1A}$ receptor, [^{3}H]-8-OH-DPAT, avian, nucleus pretectalis, entopallium, MVL.

Serotonin (5-HT) is a modulatory neurotransmitter that is involved in a variety of physiological and behavioral functions. In mammals, dysfunction of the serotonergic system has been linked to various diseases such as depression, schizophrenia, Alzheimer's disease, and eating disorders (Müller et al., 2007; Michelsen et al., 2008; Remington, 2008; Terry et al., 2008; Akimova et al., 2009; Polter and

Li, 2010). In addition, growing evidence found in many species indicates that 5-HT modulates learning and memory (Jacobs and Azmitia, 1992; Winsauer et al., 1996; Meneses, 1999; Clarke et al., 2004; Meneses and Perez-Garcia, 2007; Müller et al., 2007; Bert et al., 2008; Gasbarri et al., 2008; González-Burgos and Feria-Velasco, 2008; Sitaraman et al., 2008; Sambeth et al., 2009; Bari et al., 2010).

Serotonin binds to multiple receptors (Hoyer et al., 2002; Green, 2006), which are widely distributed throughout the brain (Chalmers and Watson, 1991; Baumgarten and Grozdanovic, 1995; Barnes and Sharp, 1999; Riad et al., 2000). One of the most prominent is the 5-HT$_{1A}$ receptor, which was first cloned and described by Fargin et al. (1988). The 5-HT$_{1A}$ receptor belongs to the G protein coupled receptor superfamily and binds to a Gi/o protein (Innis and Aghajanian, 1987; Polter and Li, 2010). It displays a high affinity for 5-HT and occurs both pre- and postsynaptically (Hall et al., 1985; van Wijngaarden et al., 1990; Riad et al., 2000). As somatodendritic autoreceptors, 5-HT$_{1A}$ receptors modulate the activity of 5-HT neurons, whereas they modify neuronal activity in terminal areas as postsynaptic receptors (Müller et al., 2007).

The distribution of 5-HT$_{1A}$ receptors in the brain has been investigated by several methods in rodents, non-human primates, and humans. Thereby, a high correlation between receptor binding with [3H]-8-hydroxy-2-(di-n-propylamino)tetralin ([^{3}H]-8-OH-DPAT) and 5-HT$_{1A}$ mRNA densities has been shown (Chalmers and Watson, 1991; Pompeiano et al., 1992). High 5-HT$_{1A}$ receptor densities were detected in the dorsal and median raphe nuclei and in areas of the limbic system such as the hippocampus, the lateral septum, the amygdala, as well as the entorhinal and cingulate cortices (Glaser et al., 1985; Zilles et al., 1985, 2000; Palacios et al., 1990; Yilmazer-Hanke et al., 2003). Moderate binding was detected in the olfactory bulb, the thalamus, hypothalamus, and several brain stem nuclei as well as neocortical areas. Low levels, or no binding, were reported in the basal ganglia and cerebellum (Gozlan et al., 1983; Marcinkiewicz et al., 1984; Zilles et al., 1985, 2000; Hall et al., 1997; Vergé et al., 1986; Albert et al., 1990; Palacios et al., 1990; Pompeiano et al., 1992; Khawaja, 1995; Kia et al., 1996a,b; Farde et al., 1997; Raurich et al., 1999; Hume et al., 2001; Maeda et al., 2001; Geyer et al., 2005; Palchaudhuri and Flügge, 2005; Eickhoff et al., 2007; Topic et al., 2007). 5-HT$_{1A}$ receptors play a role in executive functions, anxiety related behavior, learning and reinforcement, feeding behavior, and locomotor activity (Zilles et al., 2000; Yilmazer-Hanke et al., 2003; Müller

et al., 2007; Sumiyoshi et al., 2007; Topic et al., 2007; Borg, 2008; Perez-Garcia and Meneses, 2009).

In pigeons, immunohistochemical studies revealed serotonin fibers and terminals to be broadly distributed throughout the brain. They were particularly prominent in several structures of the telencephalon (arcopallium pars dorsalis, nucleus taeniae, area parahippocampalis, septum), diencephalon (nuclei preopticus medianus, magnocellularis, nucleus geniculatus lateralis pars ventralis, nucleus triangularis, nucleus pretectalis), mesencephalon-rhombencephalon (superficial layers of the optic tectum, nucleus of the basal optic root, nucleus isthmo-opticus), and in most of the cranial nerve nuclei (Krebs et al., 1991; Challet et al., 1996). To date, detailed information about the distribution of 5-HT receptors in the avian brain is very sparse. One study described binding sites for [3H]-8-OH-DPAT in the basal ganglia (Dietl and Palacios, 1988), and a second study used [3H]-5-HT binding in the telencephalon of pigeons, which is non-selective for the different receptor types (Waeber et al., 1989). In addition, the role of 5-HT$_{1A}$ receptor signaling in behavioral outcome and cognitive functions is less investigated in the avian brain compared with mammals. Only a few studies suggest a role for this receptor type in ingestive behavior, circadian rhythm, sleep (Tejada et al., 2011; Fuchs et al., 2006; Garau et al., 2006; Da Silva et al., 2007; Campanella et al., 2009; Dos Santos et al., 2009), and impulsive reactions (Wolff and Leander, 2000). It was demonstrated that 5-HT modulates executive function during working memory in pigeons (Karakuyu et al., 2007) and possibly plays a role in visual attention switching (Miceli et al., 1999, 2002) and ingestive behavior (Güntürkün et al., 1989). Hence, comprehensive information about the regional distribution of 5-HT$_{1A}$ receptor densities is needed to constitute a relevant fundament for behavioral and pharmacological studies in birds. Furthermore, since the avian and mammalian pallia are partly homologous but differ in their morphological organization (Jarvis et al., 2005), 5-HT$_{1A}$ receptor densities could be relevant to compare homologue and analogue structures in birds and mammals. Therefore, we analyzed the distributions of the 5-HT$_{1A}$ receptor with the selective radioligand [3H]-8-OH-DPAT in the pigeon's CNS.

EXPERIMENTAL PROCEDURES

We examined a total of six pigeons (*Columba livia*) of unknown sex. Animals were decapitated and the brains removed from the skull, frozen immediately in isopentane at -40 °C and stored at -70 °C. Serial coronal 10 μm sections were cut with a cryostat microtome (2800 Frigocut E, Reichert-Jung, Vienna, Austria). Sections were thaw-mounted on gelatinized slides and freeze-dried before use for receptor autoradiography or histological staining for the visualization of cell bodies (Merker, 1983).

RECEPTOR AUTORADIOGRAPHY

Binding sites for serotonergic 5-HT$_{1A}$ receptors were labeled with [3H]8-OH-DPAT (Arvidsson et al., 1981; Hjorth and Carlsson, 1982) according to a previously published standardized protocol (Zilles et al., 2002a,b), which consists of three steps: (1) A preincubation step of 30 min at room temperature in buffer (170 mM Tris–HCl buffer with 4 mM CaCl$_2$ and 0.01% ascorbic acid, pH 7.6) removed endogenous ligand from the tissue. (2) During the main incubation step, binding sites were labeled with 1 nM [3H]8-OH-DPAT in buffer for 60 min at room temperature either in the presence of 1 μm 5-hydroxy tryptamine as a displacer (non-specific binding), or without the displacer (total binding). Specific binding is the difference between total and non-specific binding. Since non-specific binding sites amounted to less than 10% of total binding sites, total binding was considered equivalent to specific binding. (3) A final rinsing step of 5 min at 4 °C in buffer eliminated unbound radioactive ligand from the sections.

Sections were air-dried overnight and subsequently coexposed for 8 weeks against a tritium-sensitive film (Hyperfilm, Amersham, Braunschweig, Germany) with plastic [3H]-standards (Microscales, Amersham) of known concentrations of radioactivity. Adjacent sections were stained with a Nissl staining for cytoarchitectonic analysis.

IMAGE ANALYSIS

Autoradiographs were digitized (Schleicher et al., 2005; Zilles et al., 2002a) by means of a KS-400 image analyzing system (Kontron, Germany) connected to a CCD camera (Sony, Tokyo) equipped with an S-Orthoplanar 60-mm macro lens (Zeiss, Germany). The images were stored with a resolution of 512×512 pixels and 8-bit gray value. Images of coexposed microscales were used to compute a calibration curve by nonlinear, least squares fitting, which defined the relationship between gray values in the autoradiographs and concentrations of radioactivity. This enabled the pixel-wise conversion of the gray values of an autoradiograph into the corresponding concentrations of radioactivity. These concentrations of binding sites occupied by the ligand under incubation conditions are transformed into receptor binding site densities at saturation conditions by means of the equation: $(K_D+L)/A_S \times L$, where K_D is the equilibrium dissociation constant of ligand-binding kinetics, L is the incubation concentration of ligand, and A_S the specific activity of the ligand.

ANATOMICAL IDENTIFICATION

The borders of the structures as defined by the atlas of Karten and Hodos (1967) were microscopically identified in the sections processed for the visualization of cell bodies and traced on prints of the digitized autoradiographs. The mean gray values in anatomically identified brain regions (one to five sections per animal and region) are transformed into binding site concentrations (fmol/mg protein). The 5-HT$_{1A}$ receptor densities measured in numerous anatomical structures are summarized in Table 1.

STATISTICAL ANALYSIS

To investigate the binding site density differences between the subdivisions in the entopallium a Friedman ANOVA was conducted. For post hoc analysis, pair-wise comparisons were run with Wilcoxon rank test. All analysis was

Table 1. [³H]8-OH-DPAT binding in the pigeon brain

Brain area	Binding density			
	fmol/mg protein	±SD	Relative density compared with MBV (%)	
Hyperpallium accesorium (HA)	494	115	41	++
Hyperpallium densocellulare (HD)	378	71	31	++
Hyperpallium intercalatum (HI)	688	146	57	+++
Mesopallium (M)	300	49	25	++
Mesopallium dorsale (MD)	313	59	26	++
Mesopallium ventrale (MV)	286	58	24	+
Nucleus MVL	425	50	35	++
Nidopallium (N)	587	90	49	++
Nidopallium caudolaterale (NCL)	374	67	31	++
Nidopallium intermedium laterale (NIL)	629	86	52	+++
Entopallial belt (Ep)	338	70	28	++
Entopallium externum (Ee)	208	54	17	+
Entopallium internum pars externale (Eie)	99	33	8	+
Entopallium internum pars internale (Eii)	n.d.	n.d.	n.d.	n.d.
Nucleus commissuralis septi (CoS)	269	116	22	+
Nucleus sepatalis lateralis (SL)	378	54	31	++
Nucleus septalis medialis (SM)	408	96	34	++
Nucleus diagonalis Brocae (NDB)	342	63	28	++
Nucleus basorostralis pallii (Bas)	121	15	10	+
Arcopallium anterius (AA)	175	13	14	+
Arcopallium intermedium (AI)	229	28	19	+
Arcopallium dorsale (AD)	194	21	16	+
Arcopallium mediale (AM)	n.d.	n.d.	n.d.	n.d.
Nucleus posterioris amygdalopallii (PoA)	175	20	14	+
Hippocampus (Hp)	136	12	11	+
Area parahippocampalis (APH)	156	25	13	+
Area corticoidea dorsolateralis (CDL)	236	101	20	+
Area temporo-parieto-occipitalis (TPO)	252.	115.	21	+
Field L2 (L2)	296	75	24	+
Medial striatum (MSt)	136	14	11	+
Lateral striatum (LSt)	116	13	10	+
Globus pallidus (GP)	94	14	8	+
Nucleus intrapeduncularis (INP)	120	12	10	+
Olfactory tubercle (Otu)	194	74	16	+
Bed nucleus of the stria terminalis, (BST)	164	24	14	+
Nucleus taeniae amygdalae (TnA)	133	15	11	+
Ventral pallidum (VP)	134	6	11	+
Nucleus dorsolateralis anterior thalami, pars lateralis dorsolateralis (DLLdl)	164	100	14	+
Nucleus dorsolateralis anterior thalami, pars lateralis dorsomedialis (DLLdm)	127	37	10	+
Nucleus dorsolateralis anterior thalami, pars lateralis ventrolateralis (DLLvl)	160	95	13	+
Nucleus dorsolateralis anterior thalami, pars lateralis ventromedialis (DLLvm)	126	71	10	+
Nucleus rotundus (Rt)	59	27	5	+
Nucleus subrotundus (SRt)	n.d.	n.d.	n.d.	n.d.
Nucleus ovoidalis (Ov)	76	3	6	+
Nucleus superficialis parvocellularis (SPC)	120	16	10	+
Nucleus triangularis (T)	71	11	6	+
Nucleus pretectalis (PT)	1210	160	100	MBV++++
Nucleus spiriformis medialis (SpM)	n.d.	n.d.	n.d.	n.d.
Nucleus spiriformis lateralis (SpL)	n.d.	n.d.	n.d.	n.d.
Nucleus principalis precommisuralis (PPC)	259	50	21	+
Nucleus geniculatus lateralis. Pars ventralis (Glv)	370	72	31	++
Nucleus subpretectalis/nucleus interstitio-pretecto-subpretectalis (Sp/IPS)	40	3	3	+
Tectum opticum lamina 1	132	22	11	+
Tectum opticum laminae 2–4	597	104	49	++
Tectum opticum lamina 5	620	116	51	+++
Tectum opticum laminae 6–7	545	87	45	++
Tectum opticum laminae 8–13	200	28	17	+

Table 1. Continued

Brain area	Binding density			
	fmol/mg protein	±SD	Relative density compared with MBV (%)	
Tectum opticum lamina 14	66	10	5	+
Nucleus interpeduncularis (IP)	550	138	45	++
Nucleus intercollicularis (ICo)	408	116	34	++
Molecular layer	23	6	2	+
Purkinje+granular cell layer	33	12	3	+

[3H]8-OH-DPAT binding values are shown in fmol/mg protein. Data is presented as mean±SD. The percentage binding values for each structure and the qualitative classification are compared with the structure with the maximal binding (MBV). ++++, very high; +++, high; ++, moderate; +, low; n.d., non detectable.

performed using Statistica 9.0 (StatSoft, Europe GmbH, Hamburg, Germany).

RESULTS

Quantitative receptor autoradiography

Telencephalon. Autoradiographic analysis revealed a widespread, but heterogeneous distribution of 5-HT$_{1A}$ receptors in the pigeon's telencephalon (Table 1). In the following, we will provide a detailed account of our findings.

Pallial structures. High 5-HT$_{1A}$ receptor densities were seen in the hyperpallium intercalatum (HI), one of the pseudolayers of the avian Wulst. In contrast, the most dorsal layer of the Wulst, the hyperpallium apicale (HA) and the hyperpallium densocellulare (HD) showed moderate densities (Fig. 1A–D; Table 1). The second area with a high 5-HT$_{1A}$ receptor concentration was the nidopallium. Therein, the nidopallium intermedium laterale (NIL) showed the highest binding values. The area temporo-parieto-ocipitalis (TPO) could be easily discriminated from the nidopallium because TPO showed only low densities. In contrast to the nidopallium, the overall labeling in the entopallium was relatively low with the notable exception of its belt subregion, which showed comparable densities to those of the nidopallium caudolaterale (NCL) (Fig. 1B–H; Table 1). Different subdivisions of the entopallium were visible (Fig. 2). A comparison of binding site densities between the entopallial belt (Ep), the entopallium externum (Ee), and the entopallium internum pars externale (Eie) using a Friedman ANOVA showed a significant overall effect [chi square ($n=6$, $df=2$)$=12$, $P<0.01$]. Binding site densities decreased from Ep to Ee to Eie (all $P<0.05$; Wilcoxon). 5-HT$_{1A}$ receptors were not detectable in the entopallium internum pars internale (Eii). Within the mesopallium, the mesopallium ventrolaterale (MVL) showed a high binding site density (Fig. 1A–C; Table 1). All septal nuclei showed moderate binding site densities (Fig. 1D–F; Table 1). Only low 5-HT$_{1A}$ receptor concentrations were detected in the arcopallium, with lowest values in the nucleus taenia amygdalae (TnA) (Fig. 1G–L; Table 1). Additionally, low densities of 5-HT$_{1A}$ receptors were found in the dorsolateral corticoid area (CDL), area parahippocampalis (APH) and hippocampus (Hp) (Fig. 1D–L; Table 1).

Subpallial structures. The basal ganglia showed relatively low 5-HT$_{1A}$ receptor concentrations when compared with those of the Wulst or the nidopallium. Densities were similar in all subpallial areas, with highest values in the olfactory tubercle (Otu) and the bed nucleus of the stria terminalis (BST), and with lowest concentrations in the globus pallidus (GP) (Fig. 1A–H; Table 1).

Diencephalon. In the thalamic nuclei overall densities were low. Highest 5-HT$_{1A}$ receptor densities were found in the nucleus geniculatus lateralis, pars ventralis (Glv), and lowest in the nucleus subrotundus (SRt). All parts of the nucleus dorsolateralis anterior thalami, pars lateralis (DLL) were labeled, with higher densities in the lateral regions than in the medial ones. Low receptor densities were also detected in the nucleus rotundus (Rt) and in the nucleus ovoidalis (Ov) (Fig. 1H–L, Table 1).

The highest 5-HT$_{1A}$ receptor densities in the pigeon's brain were detected in the nucleus pretectalis (PT). They were two-fold higher than those in the visual Wulst or the nidopallium, and almost 12-fold higher when compared with other diencephalic nuclei.

The nucleus principalis precommisuralis (PPC) contained moderate densities, whereas binding densities in the nucleus subpretectalis/nucleus interstitio-pretecto-subpretectalis (Sp/IPS) were close to zero (Fig. 1H–L; Table 1).

Mesencephalon-rhombencephalon. The nucleus interpeduncularis (IP) showed quite high 5-HT$_{1A}$ receptor densities. The nucleus intercollicularis (ICo) was moderately labeled. In the optic tectum a stepwise increase of 5-HT$_{1A}$ receptor densities was found from layer 1 to layer 5, with a peak in layer 5 and a stepwise decrease until layer 14, which presented the lowest densities in this structure. For comparison, 5-HT$_{1A}$ receptor densities in layer 5 of the optic tectum were comparable with those measured in the Wulst or the nidopallium (Fig. 1I–L, Table 1).

Cerebellum. 5-HT$_{1A}$ receptors occurred at very low densities in the cerebellar cortex with higher concentration in the Purkinje cell layer and in the granule cell layer than in the molecular layer (Table 1).
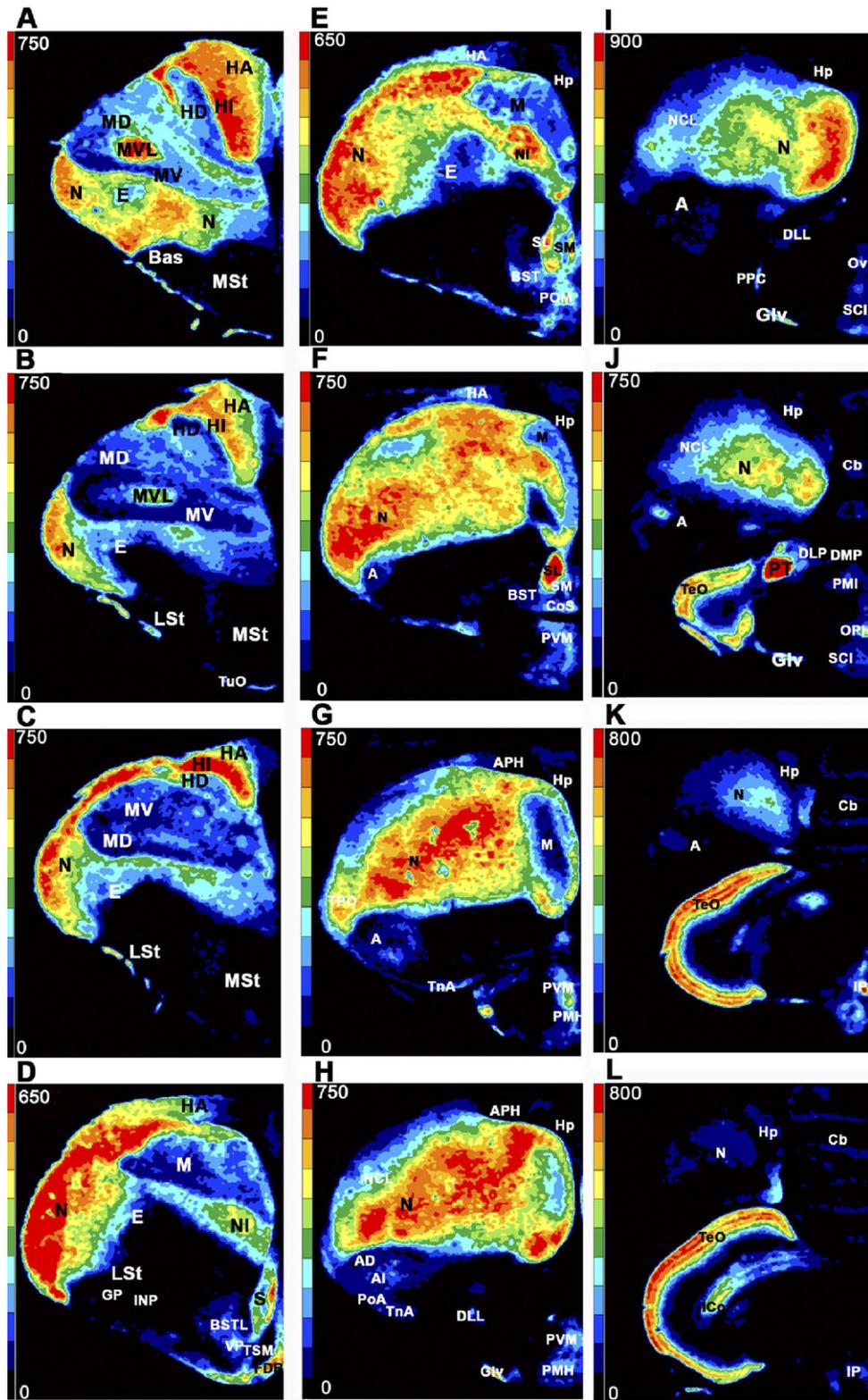
Fig. 1. Color-coded autoradiographs of [³H]8-OH-DPAT binding in the pigeon's CNS. For each sectioning level in a series of coronal sections the color-coded autoradiograph is shown (A–L). Images were arranged in rostro-caudal sequence (left, middle, and right column). Color coding indicates density of 5-HT$_{1A}$ receptor binding sites in fmol/mg protein. Note that color-coding of each image is optimized to the overall density. The maximum binding level is not included in the color graphs but is shown in the table (Table 1). Abbreviations used are defined in the autoradiography binding data table (Table 1). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.
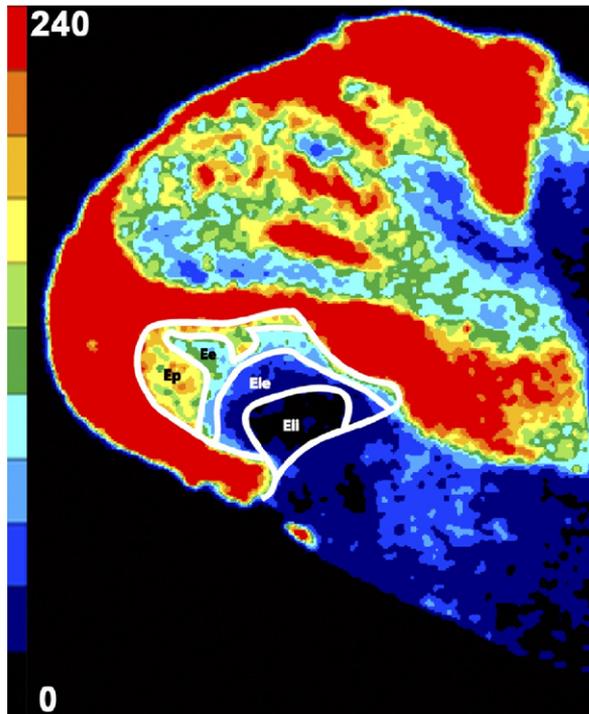
Fig. 2. Color-coded autoradiograph showing the heterogenous 5-HT$_{1A}$ receptor distribution in the pigeon's entopallium. Contrast enhancement is optimized to the density of 5-HT$_{1A}$ receptors in the entopallium. The 5-HT$_{1A}$ receptors showed a lamina-type allocation in the entopallium. Densities increased from the ventromedial area to the belt region. Ep, Entopallial belt; Ee, Entopallium externum; Eie, Entopallium internum pars externale; Eii, Entopallium internum pars internale. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

DISCUSSION

5-HT$_{1A}$ receptors were widely and heterogeneously distributed throughout the pigeon's brain. The highest density was found in the PT. This is in line with the dense innervation of the avian PT by serotonergic fibers (Cozzi et al., 1991; Challet et al., 1996; Metzger et al., 2002). Since PT is the source of visual and nonvisual input to the superficial layers of the optic tectum, it may modulate the inhibitory control of retinotectal transmission (Gamlin and Cohen, 1988; Gamlin et al., 1996) through 5-HT$_{1A}$ receptors. Lesions of PT as well as of the nucleus spiriformis lateralis (SpL) result in impairment of behavior involving tracking and pecking moving targets (Bugbee, 1979). Further, PT has reciprocal connections with the subpretectal nucleus SP and therefore, PT may control attention shift from one eye to the other (Theiss et al., 2003). The PT receives further input from the basal ganglia that underlines its function in visuomotor processing (Reiner et al., 1982). Like in birds, a prominent innervation of the area pretectalis with serotonergic fibers was reported for rats, turtles, and fish (Ueda et al., 1983; Lüth and Seidel, 1987; Cuadrado et al., 1993).

In the optic tectum 5-HT$_{1A}$ receptors showed a laminar specific distribution. The major retino-recipient layer 5 displays the highest density of 5-HT$_{1A}$ receptors in the optic tectum, and is also densely innervated by serotonergic fibers (Metzger et al., 2006). Layer 5b of the optic tectum, which is a major retino-recipient layer, receives further input from PT (Gamlin et al., 1996). Since the optic tectum and PT showed a high density of 5-HT$_{1A}$ receptors, the receptors may play a substantial role of 5-HT$_{1A}$ receptors in controlling the output of these regions.

A nucleus in the brain stem, the IP, also showed a quite high density of 5-HT$_{1A}$ receptors. This finding matches with the presence of a high density of 5-HT fibers and terminals in IP (Challet et al., 1996), and is in line with other autoradiography studies in human and rats that also showed high binding sites for 5-HT receptors in IP (Palacios et al., 1983; Kaulen et al., 1986). In birds IP has been implicated in appetitive and consummatory male sexual behavior (Dermon et al., 1999). Further, a lesion study in rats showed that IP is enclosed in a network of controlling avoidance behavior (Hammer and Klingberg, 1990). Rats with IP lesions were hypoactive and showed diminished exploratory behavior. Because behavioral drug tests in mammals have shown that 5-HT$_{1A}$ receptors are also involved in appetitive and avoidance behavior, the same may be true for the avian species. Indeed, it was detected in ringdoves that systemic injections of 8-OH-DPAT increased locomotor activity (Tejada et al., 2011).

In the thalamic nuclei 5-HT$_{1A}$ receptors are found to occur at moderate densities. The relatively highest density was detected in the ventral part of the lateral geniculate nucleus (Glv), which receives a strong serotonergic innervation, though to a lesser extent than PT (Cozzi et al., 1991; Challet et al., 1996). Furthermore, the Glv receives direct input from the retina and afferents from the visual Wulst, has reciprocal connections with the optic tectum, and projects to the pretectal nuclei (Guiloff et al., 1987; Güntürkün and Karten, 1991). Lesions of the Glv had shown that this area is involved in visuomotor function (Guiloff et al., 1987). The dorsal part of the lateral geniculate nucleus (Gld), contains relatively low 5-HT$_{1A}$ receptor densities. The Gld is also a retinorecipient optic center in the thalamus, projects to the Wulst, and is part of one of the two ascending visual pathways in birds, the thalamofugal pathway (Karten et al., 1973). In addition, the Rt, which is the thalamic in- and output structure of the second visual pathway, the tectofugal pathway (Rogers and Deng, 1999; Hellmann and Güntürkün, 2001; Schmidt and Bischof, 2001; Folta et al., 2004), also contained very low 5-HT$_{1A}$ receptor densities.

The overall 5-HT$_{1A}$ receptor density in the pigeon Wulst was high. This implicates that 5-HT$_{1A}$ receptors are critically involved in the function of the avian Wulst, which is in part comparable with the function of primary visual, somatosensory and motor cortices in mammals (Keary et al., 2010; Ng et al., 2010; Reiner et al., 2005; Iwaniuk and Wylie, 2006). The avian Wulst is also a part of the thalamofugal pathway in birds (Hodos et al., 1973; Karten et al., 1973; Shimizu and Bowers, 1999). It was suggested that the processing of visual information in the thalamofugal tract is associated with the performance of more complex visual tasks that include a more detailed analysis of infor-

mation, like during migration behavior (Budzynski et al., 2002). The thalamofugal pathway corresponds to the mammalian geniculostriate pathway (Shimizu and Karten, 1990). The Gld, the thalamic relay station of the thalamofugal projection receives input from the central area of the pigeon's retina, and thus, from the lateral visual field (Remy and Güntürkün, 1991). Consequently, lesions of the thalamofugal system affect discrimination tasks in the lateral but not in the frontal field of view (Güntürkün and Hahmann, 1999; Budzynski and Bingman, 2004). The highest 5-HT$_{1A}$ receptor density was detected in the HI, which is one of the pseudolayers of the avian Wulst. Pseudolayers are nuclear structures that do not display the laminar organization of the mammalian cerebral cortex where columns have an orthogonal position to laminae (Medina and Reiner, 2000; Butler et al., 2005). HI receives visual input from the Gld and is also part of the thalamofugal system (Güntürkün and Hahmann, 1999). In addition, HI is the output layer that gives rise to projections to the dorsocaudal telencephalon like the area parahippocampalis and the area corticoidea dorsolateralis (Shimizu et al., 1995). In most avian species the Wulst contains three further pseudolayers (Medina and Reiner, 2000). The intermediate layer is a thin band of granule cells, the interstitial part of the hyperpallium apicale (IHA), which is a major recipient for sensory thalamic input (Watanabe et al., 1983; Wild, 1987; Shimizu et al., 1995). The HD receives only visual thalamic input and mainly projects to subpallial and pallial parts. The most superficial layer, the HA, is the main output layer and projects to the striatum, the thalamus and the brainstem, as well as to other pallial structures (Reiner and Karten, 1982; Veenman et al., 1995; Shimizu et al., 1995; Medina and Reiner, 2000). In addition, HA receives afferents from all other layers of the Wulst (Shimizu et al., 1995). 5-HT$_{1A}$ receptor had lower densities in HA and HD than in HI. HI/HD showed comparable concentrations of 5-HT$_{1A}$ receptors to those measured in layers II-III of human V1 (Eickhoff et al., 2007). Taken together, 5-HT$_{1A}$ receptors can play a crucial role in controlling Gld output to the Wulst and hence to higher associative structures.

The nidopallium was also enriched in 5-HT$_{1A}$ receptors, with higher amounts in the NIL than in its medial parts. In addition, the associative (Güntürkün, 2005) forebrain structure NCL was also densely labeled, and could be subdivided into a medial and a lateral part (Herold et al., 2011). The dense receptor labeling is in contrast to the few serotonergic terminals within NCL (Challet et al., 1996). However, our findings are in accordance with the results of Karakuyu et al. (2007), who examined serotonin efflux during a working memory paradigm in pigeons. They observed serotonin release in the NCL, but not in the striatum during working memory tasks. Since the serotonin release was independent of a short term memory component, the authors concluded that serotonin within NCL could control executive functions like attention switching without being involved in the process of memorization of stimulus information. Because of the relatively high 5-HT$_{1A}$ receptor densities measured in the NCL, future studies should con-

firm a specific role of this receptors type for executive functions. For example, in rats, 5-HT$_{1A}$ receptor modulations in the mPFC have been shown to be very important for optimal attention functioning (Carli et al., 2006). 5-HT$_{1A}$ receptor densities in the nidopallium are comparable with those found in frontal areas of humans and monkeys (Herold et al., 2011; Goldman-Rakic et al., 1990) but are different from the findings in rats (Herold et al., 2011; Pazos and Palacios, 1985).

In birds the former archistriatum has been subdivided into a somatosensory arcopallium and a complex of structures that are comparable with the mammalian amygdaloid complex (Reiner et al., 2004; Saint-Dizier et al., 2009). In birds, the amygdaloid complex includes the nucleus posterior amygdalopallialis (PoA), the TnA, and the area subpallialis amygdalae (SpA), and has been linked to visceral and limbic functions because of its connections with the hypothalamus and caudal brain stem nuclei. A dense 5-HT innervation was found for limbic structures like the TnA, the parahippocampal area (APH), hippocampus (HP), and area septalis in pigeons, chicken, and quails (Yamada et al., 1985; Cozzi et al., 1991; Challet et al., 1996). Recently it was shown that injections of the 5-HT$_{1/2/7}$ receptor antagonist Metergoline and the 5-HT$_{1B/1D}$ agonist GR46611 into TnA induced hypophagic responses, whereas the same treatment in the arcopallium intermedium (AI) resulted in a selective increase in water intake (Campanella et al., 2009). These effects seemed to be regionally specific because Metergoline and GR46611 injections into the arcopallium mediale (AM) failed to affect those behaviors. In line with this, we found only low 5-HT$_{1A}$ densities in TnA and AI, supporting the view that transmission through 5-HT$_{1A}$ receptors in those regions plays no, or only a minor role in ingestive behavior (Campanella et al., 2009). However, our findings are in contrast to those of the mammalian amygdaloid nuclei, which contain high or intermediate 5-HT$_{1A}$ receptor concentrations (Hall et al., 1997; Yilmazer-Hanke et al., 2003; Palchaudhuri and Flügge, 2005; Perez-Garcia and Meneses, 2008). Further, a strong serotonergic innervation of the hippocampus and the parahippocampal area has been reported, however the 5-HT$_{1A}$ receptor density observed in the present study is low. This is not a contradictory finding, since 5-HT binds to a variety of further 5-HT receptors. Moreover, the boundaries of the avian hippocampal formation are still not completely determined. Krebs et al. (1991) detected dense 5-HT termination fields in the dorsomedial hippocampus. In our data, we could identify this field in the hippocampus by the highest concentration of 5-HT$_{1A}$ receptors at the dorsomedial hippocampus, and a further field at the caudal and ventromedial site of the hippocampus. Future studies are clearly needed to clarify the exact boundaries of different areas in the hippocampal formation of the avian species. The low overall density of 5-HT$_{1A}$ receptors in the avian hippocampus is in contrast to that in rats and other mammals (Topic et al., 2007; Pazos and Palacios, 1985; Zilles et al., 1985, 2000; Wree et al., 1987; Zilles, 1989; Kraemer et al., 1995; Aznavour et al., 2009).

Thus, low 5-HT$_{1A}$ receptor densities in the pigeon's hippocampal formation may demonstrate an avian-specific situation and implicate that this receptor type might have a different role in the avian hippocampal formation than in mammals. In contrast, all septal nuclei showed dense labeling that is in line with a strong serotonergic innervation in pigeons (Challet et al., 1996) and published 5-HT$_{1A}$ receptor densities for cats, rats, non-human primates, and humans (Aznavour et al., 2009; Aznavour and Zimmer, 2007; Khawaja, 1995; Pazos and Palacios, 1985).

Within the telencephalon, the entopallium is the end station of the tectofugal pathway (Hodos and Karten, 1970; Manns et al., 2007; Valencia-Alfonso et al., 2009). Because of the projections and connectivity of the entopallium, this structure was compared with the human extrastriate cortex (Veenman et al., 1995). Only a few serotonergic terminals were found in the entopallium of pigeons (Challet et al., 1996). In line with this, labeling of 5-HT$_{1A}$ receptors in the entopallium was low, except for the entopallial belt (perientopallium; Ep), which showed comparable densities to those of the NCL. The Ep serves as an intermediary between the core components of the entopallium and the subsequent projections to the nidopallium and the arcopallium, although the Ep is also reached by a minute thalamic projection (Krützfeldt and Wild, 2004, 2005). Some authors compare the neurons of the Ep to layers II and III neurons of the mammalian neocortex (Shimizu and Karten, 1990; Shimizu et al., 1995; Veenman et al., 1995). Herein, our results support this suggestion, because layers II and III of the human extrastriate cortex also contain the highest numbers of 5-HT$_{1A}$ receptors when compared with the other neocortical layers (Zilles et al., 2004; Eickhoff et al., 2007). The input region of the entopallium is the entopallial core, which can be further subdivided into an entopallium externum (Ee) and internum (Ei) (Hellmann et al., 1995; Krützfeldt and Wild, 2005). Our results in principle support such a subdivision. We found a heterogeneous 5-HT$_{1A}$ receptor distribution within the entopallial core, with higher densities in the Ee than in the Eie, and no labeling in the Eii. This could imply that these subdivisions have functional implications, which have to be analyzed in further studies determining the role of the entopallium within the tectofugal pathway. To date, it is not clear whether neurons of the core components are comparable with layer IV neurons in the neocortex of mammals, or whether they are a mixture composed of layer IV and V neurons (Krützfeldt and Wild, 2005). Our results show a low concentration for 5-HT$_{1A}$ receptors in Eie and Eii. This was also found in layers IV and V of the human extrastriate cortex (Eickhoff et al., 2007). In line with the finding of a laminar and columnar organization in the avian auditory cortex (Wang et al., 2010), our results support the idea that the entopallium may have a similar laminar-type organization (Wild and Krützfeldt, 2010).

In pigeons, the medial entopallium has strong reciprocal connections to an area of the ventrolateral mesopallium dorsal to the entopallium (Krützfeldt and Wild, 2005). This area is distinct in Nissl-stained sections and was described in the former hyperstriatum ventrale as hyperstriatum ventrale ventrolaterale (HVvl) (Husband and Shimizu, 1999). This area may be compared with the nucleus MVL in the zebra finch (Krützfeldt and Wild, 2004), and could be also observed in sparrows, canaries, and chicken (Huber and Crosby, 1929; Stokes et al., 1974; Alpár and Tömböl, 2000). In our study, this area showed a dense labeling for 5-HT$_{1A}$ receptors that differed clearly from the rest of the mesopallium confirming a nuclear structure. Therefore, our findings support the idea of Krützfeldt and Wild (2005) that this area is comparable with the nucleus MVL in the zebra finch.

In the basal ganglia low 5-HT$_{1A}$ receptor densities were detected. These findings are in line with one of the few studies that determined the distributions of serotonin 5-HT$_{1A}$ receptors in the avian brain (Dietl and Palacios, 1988). Low densities were also found in the basal ganglia of mammals (Dietl and Palacios, 1988; Palomero-Gallagher et al., 2009). Thus, this result underlines the conservation of receptor distribution patterns in the basal ganglia of different species over a long span of separate evolution.

CONCLUSION

In conclusion, 5-HT$_{1A}$ receptors were prominent in regions that process visual information and higher cognitive functions. In contrast to mammals, low binding sites were detected in limbic structures such as the hippocampus or the amygdala. Future functional studies should address these differences and similarities between the serotonergic systems in avian and mammalian brains. We detected comparable densities of 5-HT$_{1A}$ receptors in pallial structures that have been compared with different layers of specific structures in the mammalian neocortex. Herein, our results support the idea of a nucleus to lamina homology between avian and mammalian brain structures. However, it seems to be necessary to delineate some structures more precisely because as in case of the entopallium it is indicated that the entopallium itself has a laminar-type organization.

REFERENCES

Akimova E, Lanzenberger R, Kasper S (2009) The serotonin-1A receptor in anxiety disorders. Biol Psychiatry 66:627–635.

Albert PR, Zhou QY, Van Tol HH, Bunzow JR, Civelli O (1990) Cloning, functional expression, and mRNA tissue distribution of the rat 5-hydroxytryptamine1A receptor gene. J Biol Chem 265:5825–5832.

Alpár A, Tömböl T (2000) Efferent connections of the ectostriatal core. An anterograde tracer study. Ann Anat 182:101–110.

Arvidsson LE, Hacksell U, Nilsson JL, Hjorth S, Carlsson A, Lindberg P, Sanchez D, Wikstrom H (1981) 8-Hydroxy-2-(di-n-propylamino-)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. J Med Chem 24:921–923.

Aznavour N, Benkelfat C, Gravel P, Aliaga A, Rosa-Neto P, Bedell B, Zimmer L, Descarries L (2009) MicroPET imaging of 5-HT 1A receptors in rat brain: a test-retest [18F]MPPF study. Eur J Nucl Med Mol Imaging 36:53–62.

Aznavour N, Zimmer L (2007) [18F]MPPF as a tool for the *in vivo* imaging of 5-HT1A receptors in animal and human brain. Neuropharmacology 52:695–707.

Bari A, Theobald DE, Caprioli D, Mar AC, Aidoo-Micah A, Dalley JW, Robbins TW (2010) Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. Neuropsychopharmacology 35:1290–1301.

Barnes NM, Sharp T (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38:1083–1152.

Baumgarten HG, Grozdanovic Z (1995) Psychopharmacology of central serotonergic systems. Pharmacopsychiatry 28 (Suppl 2):73–79.

Bert B, Fink H, Rothe J, Walstab J, Bönisch H (2008) Learning and memory in 5-HT(1A)-receptor mutant mice. Behav Brain Res 195:78–85.

Borg J (2008) Molecular imaging of the 5-HT(1A) receptor in relation to human cognition. Behav Brain Res 195:103–111.

Budzynski CA, Bingman VP (2004) Participation of the thalamofugal visual pathway in a coarse pattern discrimination task in an open arena. Behav Brain Res 153:543–556.

Budzynski CA, Gagliardo A, Ioalé P, Bingman VP (2002) Participation of the homing pigeon thalamofugal visual pathway in sun-compass associative learning. Eur J Neurosci 15:197–210.

Bugbee N (1979) The effect of bilateral lesions in the nucleus spiriformis lateralis on visually guided behavior in the pigeon. Ph.D. Thesis, University of Maryland, College Park, MD.

Butler AB, Manger PR, Lindahl BI, Arhem P (2005) Evolution of the neural basis of consciousness: a bird-mammal comparison. Bioessays 2005(27):923–936.

Campanella LC, da Silva AA, Gellert DS, Parreira C, Ramos MC, Paschoalini MA, Marino-Neto J (2009) Tonic serotonergic control of ingestive behaviours in the pigeon (*Columba livia*): the role of the arcopallium. Behav Brain Res 205:396–405.

Carli M, Baviera M, Invernizzi RW, Balducci C (2006) Dissociable contribution of 5-HT1A and 5-HT2A receptors in the medial prefrontal cortex to different aspects of executive control such as impulsivity and compulsive perseveration in rats. Neuropsychopharmacology 31:757–767.

Challet E, Miceli D, Pierre J, Repérant J, Masicotte G, Herbin M, Vesselkin NP (1996) Distribution of serotonin-immunoreactivity in the brain of the pigeon (*Columba livia*). Anat Embryol (Berl) 193:209–227.

Chalmers DT, Watson SJ (1991) Comparative anatomical distribution of 5-HT1A receptor mRNA and 5-HT1A binding in rat brain—a combined *in situ* hybridisation/*in vitro* receptor autoradiographic study. Brain Res 561:51–60.

Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC (2004) Cognitive inflexibility after prefrontal serotonin depletion. Science 304:878–880.

Cozzi B, Viglietti-Panzica C, Aste N, Panzica GC (1991) The serotoninergic system in the brain of the Japanese quail. An immunohistochemical study. Cell Tissue Res 263:271–284.

Cuadrado MI, Coveñas R, Tramu G (1993) Neuropeptides and monoamines in the carp (*Cyprinus carpio*) pretectum: an immunocytochemical study. Tissue Cell 25:549–561.

Da Silva RA, Da Silva AS, Poffo MJ, Ribas DC, Faria MS, Marino-Neto J, Paschoalini MA (2007) Feeding behavior after metergoline or GR-46611 injections into the paraventricular nucleus of the hypothalamus in the pigeon. Behav Brain Res 179:248–257.

Dermon CR, Stamatakis A, Tlemçani O, Balthazart J (1999) Performance of appetitive or consummatory components of male sexual behavior is mediated by different brain areas: a 2-deoxyglucose autoradiographic study. Neuroscience 94:1261–1277.

Dietl M, Palacios JM (1988) Receptor autoradiography as a tool for the study of the phylogeny of the basal ganglia. J Recept Res 8:521–532.

Dos Santos MM, Hoeller AA, dos Santos TS, Felisbino MB, Herdt MA, da Silva ES, Paschoalini MA, Marino-Neto J (2009) Behavioural

and electroencephalographic effects of systemic injections of 8-OH-DPAT in the pigeon (*Columba livia*). Behav Brain Res 201:244–256.

Eickhoff SB, Rottschy C, Zilles K (2007) Laminar distribution and co-distribution of neurotransmitter receptors in early human visual cortex. Brain Struct Funct 212:255–267.

Farde L, Ginovart N, Ito H, Lundkvist C, Pike VW, McCarron JA, Halldin C (1997) PET-characterization of [carbonyl-11C]WAY-100635 binding to 5-HT1A receptors in the primate brain. Psychopharmacology (Berl) 133:196–202.

Fargin A, Raymond JR, Lohse MJ, Kobilka BK, Caron MG, Lefkowitz RJ (1988) The genomic clone G-21 which resembles a beta-adrenergic receptor sequence encodes the 5-HT1A receptor. Nature 335:358–360.

Folta K, Diekamp B, Güntürkün O (2004) Asymmetrical modes of visual bottom-up and top-down integration in the thalamic nucleus rotundus of pigeons. J Neurosci 24:9475–9485.

Fuchs T, Siegel JJ, Burgdorf J, Bingman VP (2006) A selective serotonin reuptake inhibitor reduces REM sleep in the homing pigeon. Physiol Behav 87:575–581.

Gamlin PD, Cohen DH (1988) Projections of the retinorecipient pretectal nuclei in the pigeon (*Columba livia*). J Comp Neurol 269:18–46.

Gamlin PD, Reiner A, Keyser KT, Brecha N, Karten HJ (1996) Projection of the nucleus pretectalis to a retinorecipient tectal layer in the pigeon (*Columba livia*). J Comp Neurol 368:424–438.

Garau C, Aparicio S, Rial RV, Nicolau MC, Esteban S (2006) Age-related changes in circadian rhythm of serotonin synthesis in ring doves: effects of increased tryptophan ingestion. Exp Gerontol 41:40–48.

Gasbarri A, Cifariello A, Pompili A, Meneses A (2008) Effect of 5-HT(7) antagonist SB-269970 in the modulation of working and reference memory in the rat. Behav Brain Res 195:164–170.

Geyer S, Luppino G, Ekamp H, Zilles K (2005) The macaque inferior parietal lobule: cytoarchitecture and distribution pattern of serotonin 5-HT1A binding sites. Anat Embryol (Berl) 210:353–362.

Glaser T, Rath M, Traber J, Zilles K, Schleicher A (1985) Autoradiographic identification and topographical analysis of high affinity serotonin receptor subtypes as a target for the novel putative anxiolytic TVX Q 7821. Brain Res 358:129–136.

Goldman-Rakic PS, Lidow MS, Gallager DW (1990) Overlap of dopaminergic, adrenergic, and serotoninergic receptors and complementarity of their subtypes in primate prefrontal cortex. J Neurosci 10:2125–2138.

González-Burgos I, Feria-Velasco A (2008) Serotonin/dopamine interaction in memory formation. Prog Brain Res 172:603–623.

Gozlan H, El Mestikawy S, Pichat L, Glowinski J, Hamon M (1983) Identification of presynaptic serotonin autoreceptors using a new ligand: 3H-PAT. Nature 305:140–142.

Green AR (2006) Neuropharmacology of 5-hydroxytryptamine. Br J Pharmacol 147 (Suppl 1):S145–S152.

Guiloff GD, Maturana HR, Varela FJ (1987) Cytoarchitecture of the avian ventral lateral geniculate nucleus. J Comp Neurol 264:509–526.

Güntürkün O (2005) The avian "prefrontal cortex" and cognition. Curr Opin Neurobiol 15:686–693.

Güntürkün O, Grothues A, Hautkappe A, Visé F, Wawrzyniak N, Zwilling U (1989) Serotonergic modulation of ingestive behavior in pigeons. Pharmacol Biochem Behav 32:415–421.

Güntürkün O, Hahmann U (1999) Functional subdivisions of the ascending visual pathways in the pigeon. Behav Brain Res 98:193–201.

Güntürkün O, Karten HJ (1991) An immunocytochemical analysis of the lateral geniculate complex in the pigeon (*Columba livia*). J Comp Neurol 314:721–749.

Hall H, Lundkvist C, Halldin C, Farde L, Pike VW, McCarron JA, Fletcher A, Cliffe IA, Barf T, Wikström H, Sedvall G (1997) Autoradiographic localization of 5-HT1A receptors in the post-mortem

human brain using [3H]WAY-100635 and [11C]WAY-100635. Brain Res 745:96–108.

Hall MD, El Mestikawy S, Emerit MB, Pichat L, Hamon M, Gozlan H (1985) [3H]8-hydroxy-2-(di-n-propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of the rat brain. J Neurochem 44:1685–1696.

Hammer KH, Klingberg F (1990) Active avoidance is permanently abolished after lesions of the nucleus interpeduncularis in rat. Biomed Biochim Acta 49:489–497.

Hellmann B, Güntürkün O (2001) Structural organization of parallel information processing within the tectofugal visual system of the pigeon. J Comp Neurol 429:94–112.

Hellmann B, Waldmann C, Güntürkün O (1995) Cytochrome oxidase activity reveals parcellations of the pigeon's ectostriatum. Neuroreport 6:881–885.

Herold C, Palomero-Gallagher N, Hellmann B, Kröner S, Theiss C, Güntürkün O, Zilles K (2011) The receptor architecture of the pigeons' nidopallium caudolaterale: an avian analogue to the mammalian prefrontal cortex. Brain Struct Funct 216:239–254.

Hjorth S, Carlsson A (1982) Buspirone: effects on central monoaminergic transmission—possible relevance to animal experimental and clinical findings. Eur J Pharmacol 83:299–303.

Hodos W, Karten HJ (1970) Visual intensity and pattern discrimination deficits after lesions of ectostriatum in pigeons. J Comp Neurol 140:53–68.

Hodos W, Karten HJ, Bonbright JC Jr (1973) Visual intensity and pattern discrimination after lesions of the thalamofugal visual pathway in pigeons. J Comp Neurol 148:447–467.

Hoyer D, Hannon JP, Martin GR (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 71:533–554.

Huber GC, Crosby EC (1929) The nuclei and fiber paths of the avian diencephalon, with consideration of telencephalic and certain mesencephalic centers and connections. J Comp Neurol 48:1–225.

Hume S, Hirani E, Opacka-Juffry J, Myers R, Townsend C, Pike V, Grasby P (2001) Effect of 5-HT on binding of [(11)C] WAY 100635 to 5-HT(IA) receptors in rat brain, assessed using in vivo microdialysis nd PET after fenfluramine. Synapse 41:150–159.

Husband SA, Shimizu T (1999) Efferent projections of the ectostriatum in the pigeon (Columba livia). J Comp Neurol 406:329–345.

Innis RB, Aghajanian GK (1987) Pertussis toxin blocks 5-HT1A and GABAB receptor-mediated inhibition of serotonergic neurons. Eur J Pharmacol 143:195–204.

Iwaniuk AN, Wylie DR (2006) The evolution of stereopsis and the Wulst in caprimulgiform birds: a comparative analysis. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 192:1313–1326.

Jacobs BL, Azmitia EC (1992) Structure and function of the brain serotonin system. Physiol Rev 72:165–229.

Jarvis ED, Güntürkün O, Bruce L, Csillag A, Karten H, Kuenzel W, Medina L, Paxinos G, Perkel DJ, Shimizu T, Striedter G, Wild JM, Ball GF, Dugas-Ford J, Durand SE, Hough GE, Husband S, Kubikova L, Lee DW, Mello CV, Powers A, Siang C, Smulders TV, Wada K, White SA, Yamamoto K, Yu J, Reiner A, Butler AB (2005) Avian brains and a new understanding of vertebrate brain evolution. Nat Rev Neurosci 6:151–159.

Karakuyu D, Herold C, Güntürkün O, Diekamp B (2007) Differential increase of extracellular dopamine and serotonin in the "prefrontal cortex" and striatum of pigeons during working memory. Eur J Neurosci 26:2293–2302.

Karten H, Hodos W (1967) A stereotaxic atlas of the brain of the pigeon (Columba livia). Baltimore, MD: The Johns Hopkins University Press.

Karten HJ, Hodos W, Nauta WJ, Revzin AM (1973) Neural connections of the "visual wulst" of the avian telencephalon. Experimental studies in the piegon (Columba livia) and owl (Speotyto cunicularia). J Comp Neurol 150:253–278.

Kaulen P, Brüning G, Rommelspacher H, Baumgarten HG (1986) Characterization and quantitative autoradiography of [3H]tryptamine binding sites in rat brain. Brain Res 366:72–88.

Keary N, Voss J, Lehmann K, Bischof HJ, Löwel S (2010) Optical imaging of retinotopic maps in a small songbird, the zebra finch. PLoS One 5(8):e11912.

Khawaja X (1995) Quantitative autoradiographic characterisation of the binding of [3H]WAY-100635, a selective 5-HT1A receptor antagonist. Brain Res 673:217–225.

Kia HK, Brisorgueil MJ, Hamon M, Calas A, Verge D (1996a) Ultra-structural localization of 5-hydroxytryptamine1A receptors in the rat brain. J Neurosci Res 46:697–708.

Kia HK, Miquel MC, Brisorgueil MJ, Daval G, Riad M, El Mestikawy S, Hamon M, Verge D (1996b) Immunocytochemical localization of serotonin1A receptors in the rat central nervous system. J Comp Neurol 365:289–305.

Kraemer M, Zilles K, Schleicher A, Gebhard R, Robbins TW, Everitt BJ, Divac I (1995) Quantitative receptor autoradiography of eight different transmitter-binding sites in the hippocampus of the common marmoset, Callithrix jacchus. Anat Embryol 191:213–225.

Krebs JR, Erichsen JT, Bingman VP (1991) The distribution of neurotransmitters and neurotransmitter-related enzymes in the dorsomedial telencephalon of the pigeon (Columba livia). J Comp Neurol 314:467–477.

Krützfeldt NO, Wild JM (2004) Definition and connections of the entopallium in the zebra finch (Taeniopygia guttata). J Comp Neurol 468:452–465.

Krützfeldt NO, Wild JM (2005) Definition and novel connections of the entopallium in the pigeon (Columba livia). J Comp Neurol 490:40–56.

Lüth HJ, Seidel I (1987) Immunohistochemical characterization of serotoninergic afferent pathways in the visual system of the rat. J Hirnforsch 28:591–600.

Maeda J, Suhara T, Ogawa M, Okauchi T, Kawabe K, Zhang MR, Semba J, Suzuki K (2001) In vivo binding properties of [carbonyl-11C]WAY-100635: effect of endogenous serotonin. Synapse 40:122–129.

Manns M, Freund N, Patzke N, Güntürkün O (2007) Organization of telencephalotectal projections in pigeons: impact for lateralized top-down control. Neuroscience 144:645–653.

Marcinkiewicz M, Vergé D, Gozlan H, Pichat L, Hamon M (1984) Autoradiographic evidence for the heterogeneity of 5-HT1 sites in the rat brain. Brain Res 291:159–163.

Medina L, Reiner A (2000) Do birds possess homologues of mammalian primary visual, somatosensory and motor cortices? Trends Neurosci 23:1–12.

Meneses A (1999) 5-HT system and cognition. Neurosci Biobehav Rev 23:1111–1125.

Meneses A, Perez-Garcia G (2007) 5-HT(1A) receptors and memory. Neurosci Biobehav Rev 31:705–727.

Merker B (1983) Silver staining of cell bodies by means of physical development. J Neurosci Methods 9:235–241.

Metzger M, Britto LR, Toledo CA (2006) Monoaminergic markers in the optic tectum of the domestic chick. Neuroscience 141:1747–1760.

Metzger M, Toledo C, Braun K (2002) Serotonergic innervation of the telencephalon in the domestic chick. Brain Res Bull 57:547–551.

Miceli D, Repérant J, Bertrand C, Rio JP (1999) Functional anatomy of the avian centrifugal visual system. Behav Brain Res 98:203–210.

Miceli D, Repérant J, Rio JP, Hains P, Medina M (2002) Serotonin immunoreactivity in the retinal projecting isthmo-optic nucleus and evidence of brainstem raphe connections in the pigeon. Brain Res 958:122–129.

Michelsen KA, Prickaerts J, Steinbusch HW (2008) The dorsal raphe nucleus and serotonin: implications for neuroplasticity linked to major depression and Alzheimer's disease. Prog Brain Res 172:233–264.

Müller CP, Carey RJ, Huston JP, De Souza Silva MA (2007) Serotonin and psychostimulant addiction: focus on 5-HT1A-receptors. Prog Neurobiol 81:133–178.

Ng BS, Grabska-Barwińska A, Güntürkün O, Jancke D (2010) Dominant vertical orientation processing without clustered maps: early visual brain dynamics imaged with voltage-sensitive dye in the pigeon visual Wulst. J Neurosci 30:6713–6725.

Palacios JM, Probst A, Cortes R (1983) The distribution of serotonin receptors in the human brain: high density of [3H]LSD binding sites in the raphe nuclei of the brainstem. Brain Res 274:150–155.

Palacios JM, Waeber C, Hoyer D, Mengod G (1990) Distribution of serotonin receptors. Ann N Y Acad Sci 600:36–52.

Palchaudhuri M, Flügge G (2005) 5-HT1A receptor expression in pyramidal neurons of cortical and limbic brain regions. Cell Tissue Res 321:159–172.

Palomero-Gallagher N, Bidmon HJ, Cremer M, Schleicher A, Kircheis G, Reifenberger G, Kostopoulos G, Häussinger D, Zilles K (2009) Neurotransmitter receptor imbalances in motor cortex and basal ganglia in hepatic encephalopathy. Cell Physiol Biochem 24:291–306.

Pazos A, Palacios JM (1985) Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res 346:205–230.

Perez-Garcia G, Meneses A (2008) Memory formation, amnesia, improved memory and reversed amnesia: 5-HT role. Behav Brain Res 195:17–29.

Perez-Garcia G, Meneses A (2009) Memory time-course: mRNA 5-HT1A and 5-HT7 receptors. Behav Brain Res 202:102–113.

Polter AM, Li X (2010) 5-HT1A receptor-regulated signal transduction pathways in brain. Cell Signal 22:1406–1412.

Pompeiano M, Palacios JM, Mengod G (1992) Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. J Neurosci 12:440–453.

Raurich A, Mengod G, Artigas F, Cortés R (1999) Displacement of the binding of 5-HT(1A) receptor ligands to pre- and postsynaptic receptors by (−)pindolol. A comparative study in rodent, primate and human brain. Synapse 34:68–76.

Reiner A, Brecha NC, Karten HJ (1982) Basal ganglia pathways to the tectum: the afferent and efferent connections of the lateral spiriform nucleus of pigeon. J Comp Neurol 208:16–36.

Reiner A, Karten HJ (1982) Laminar distribution of the cells of origin of the descending tectofugal pathways in the pigeon (Columba livia). J Comp Neurol 204:165–187.

Reiner A, Perkel DJ, Bruce LL, Butler AB, Csillag A, Kuenzel W, Medina L, Paxinos G, Shimizu T, Striedter G, Wild M, Ball GF, Durand S, Güntürkün O, Lee DW, Mello CV, Powers A, White SA, Hough G, Kubikova L, Smulders TV, Wada K, Dugas-Ford J, Husband S, Yamamoto K, Yu J, Siang C, Jarvis ED (2004) Revised nomenclature for avian telencephalon and some related brainstem nuclei. J Comp Neurol 473:377–414.

Reiner A, Yamamoto K, Karten HJ (2005) Organization and evolution of the avian forebrain. Anat Rec A Discov Mol Cell Evol Biol 287:1080–1102.

Remington G (2008) Alterations of dopamine and serotonin transmission in schizophrenia. Prog Brain Res 172:117–140.

Remy M, Güntürkün O (1991) Retinal afferents to the tectum opticum and the nucleus opticus principalis thalami in the pigeon. J Comp Neurol 305:57–70.

Riad M, Garcia S, Watkins KC, Jodoin N, Doucet E, Langlois X, el Mestikawy S, Hamon M, Descarries L (2000) Somatodendritic localization of 5-HT1A and preterminal axonal localization of 5-HT1B serotonin receptors in adult rat brain. J Comp Neurol 417:181–194.

Rogers LJ, Deng C (1999) Light experience and lateralization of the two visual pathways in the chick. Behav Brain Res 98:277–287.

Saint-Dizier H, Constantin P, Davies DC, Leterrier C, Lévy F, Richard S (2009) Subdivisions of the arcopallium/posterior pallial amygdala complex are differentially involved in the control of fear behaviour in the Japanese quail. Brain Res Bull 79:288–295.

Sambeth A, Riedel WJ, Tillie DE, Blokland A, Postma A, Schmitt JA (2009) Memory impairments in humans after acute tryptophan depletion using a novel gelatin-based protein drink. J Psychopharmacol 23:56–64.

Schleicher A, Palomero-Gallagher N, Morosan P, Eickhoff SB, Kowalski T, de Vos K, Amunts K, Zilles K (2005) Quantitative architectural analysis: a new approach to cortical mapping. Anat Embryol (Berl) 210:373–386.

Schmidt A, Bischof HJ (2001) Integration of information from both eyes by single neurons of nucleus rotundus, ectostriatum and lateral neostriatum in the zebra finch (Taeniopygia guttata castanotis Gould). Brain Res 923:20–31.

Shimizu T, Bowers AN (1999) Visual circuits of the avian telencephalon: evolutionary implications. Behav Brain Res 98:183–191.

Shimizu T, Cox K, Karten HJ (1995) Intratelencephalic projections of the visual wulst in pigeons (Columba livia). J Comp Neurol 359:551–572.

Shimizu T, Karten HJ (1990) Immunohistochemical analysis of the visual wulst of the pigeon (Columba livia). J Comp Neurol 300:346–369.

Sitaraman D, Zars M, Laferriere H, Chen YC, Sable-Smith A, Kitamoto T, Rottinghaus GE, Zars T (2008) Serotonin is necessary for place memory in Drosophila. Proc Natl Acad Sci U S A 105:5579–5584.

Stokes TM, Leonard CM, Nottebohm F (1974) The telencephalon, diencephalon, and mesencephalon of the canary, Serinus canaria, in stereotaxic coordinates. J Comp Neurol 156:337–374.

Sumiyoshi T, Park S, Jayathilake K, Roy A, Ertugrul A, Meltzer HY (2007) Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res 95:158–168.

Tejada S, Rial RV, Gamundí A, Esteban S (2011) Effects of serotonergic drugs on locomotor activity and vigilance states in ring doves. Behav Brain Res 216:238–246.

Terry AV Jr, Buccafusco JJ, Wilson C (2008) Cognitive dysfunction in neuropsychiatric disorders: selected serotonin receptor subtypes as therapeutic targets. Behav Brain Res 195:30–38.

Theiss MP, Hellmann B, Güntürkün O (2003) The architecture of an inhibitory sidepath within the avian tectofugal system. Neuroreport 14:879–882.

Topic B, Willuhn I, Palomero-Gallagher N, Zilles K, Huston JP, Hasenöhrl RU (2007) Impaired maze performance in aged rats is accompanied by increased density of NMDA, 5-HT1A, and alpha-adrenoceptor binding in hippocampus. Hippocampus 17:68–77.

Ueda S, Takeuchi Y, Sano Y (1983) Immunohistochemical demonstration of serotonin neurons in the central nervous system of the turtle (Clemmys japonica). Anat Embryol (Berl) 168:1–19.

Valencia-Alfonso CE, Verhaal J, Güntürkün O (2009) Ascending and descending mechanisms of visual lateralization in pigeons. Philos Trans R Soc Lond B Biol Sci 364:955–963.

van Wijngaarden I, Tulp MT, Soudijn W (1990) The concept of selectivity in 5-HT receptor research. Eur J Pharmacol 188:301–312.

Veenman CL, Wild JM, Reiner A (1995) Organization of the avian "corticostriatal" projection system: a retrograde and anterograde pathway tracing study in pigeons. J Comp Neurol 354:87–126.

Vergé D, Daval G, Marcinkiewicz M, Patey A, el Mestikawy S, Gozlan H, Hamon M (1986) Quantitative autoradiography of multiple 5-HT1 receptor subtypes in the brain of control or 5,7-dihydroxytryptamine-treated rats. J Neurosci 6:3474–3482.

Waeber C, Dietl MM, Hoyer D, Palacios JM (1989) 5.HT1 receptors in the vertebrate brain. Regional distribution examined by autoradiography. Naunyn Schmiedebergs Arch Pharmacol 340:486–494.

Wang Y, Brzozowska-Prechtl A, Karten HJ (2010) Laminar and co-lumnar auditory cortex in avian brain. Proc Natl Acad Sci U S A 107:12676–12681.

Watanabe M, Ito H, Masai H (1983) Cytoarchitecture and visual receptive neurons in the Wulst of the Japanese quail (*Coturnix coturnix japonica*). J Comp Neurol 213:188–198.

Wild JM (1987) The avian somatosensory system: connections of regions of body representation in the forebrain of the pigeon. Brain Res 412:205–223.

Wild JM, Krützfeldt NO, Karten HJ (2010) Neocortical-like organization of avian auditory "cortex." Commentary on Wang Y, Brzozowska-Prechtl A, Karten HJ (2010): laminar and columnar auditory cortex in avian brain. Proc Natl Acad Sci USA 107:12676–12681. Brain Behav Evol 76:89–92.

Winsauer PJ, Bixler MA, Mele PC (1996) Comparison of the effects of typical and atypical anxiolytics on learning in monkeys and rats. J Pharmacol Exp Ther 276:1111–1127.

Wolff MC, Leander JD (2000) A comparison of the behavioural effects of 5-HT2A and 5-HT2C receptor agonists in the pigeon. Behav Pharmacol 11:355–364.

Wree A, Zilles K, Schleicher A, Horváth E, Traber J (1987) Effect of the 5-HT1A receptor agonist ipsapirone on the local cerebral glucose utilization of the rat hippocampus. Brain Res 436:283–290.

Yamada J, Kitamura N, Yamashita T (1985) The relative frequency and topographical distribution of somatostatin-, GRP-, APP⁻, glucagon-, 5-HT-, and neurotensin-immunoreactive cells in the proventriculus of seven species of birds. Arch Histol Jpn 48:305–314.

Yilmazer-Hanke DM, Roskoden T, Zilles K, Schwegler H (2003) Anxiety-related behavior and densities of glutamate, GABAA, acetylcholine and serotonin receptors in the amygdala of seven inbred mouse strains. Behav Brain Res 145:145–159.

Zilles K (1989) Codistribution of transmitter receptors in the human and rat hippocampus. In: Hippocampus: new vistas (Chan-Palay V, Köhler C, eds), pp 171–187. New York, NY: AR Liss.

Zilles K, Palomero-Gallagher N, Grefkes C, Scheperjans F, Boy C, Amunts K, Schleicher A (2002b) Architectonics of the human cerebral cortex and transmitter receptor fingerprints: reconciling functional neuroanatomy and neurochemistry. Eur Neuropsychopharmacol 12:587–599.

Zilles K, Palomero-Gallagher N, Schleicher A (2004) Transmitter receptors and functional anatomy of the cerebral cortex. J Anat 205:417–432.

Zilles K, Schleicher A, Glaser T, Traber J, Rath M (1985) The ontogenetic development of serotonin (5-HT1) receptors in various cortical regions of the rat brain. Anat Embryol 172:255–264.

Zilles K, Schleicher A, Palomero-Gallagher N, Amunts K (2002a) Quantitative analysis of cyto- and receptor architecture of the human brain. Brain mapping: the methods, 2nd ed., Vol. 21, pp 573–602. San Diego, CA: Academic Press.

Zilles K, Wu J, Crusio WE, Schwegler H (2000) Water maze and radial maze learning and the density of binding sites of glutamate, GABA, and serotonin receptors in the hippocampus of inbred mouse strains. Hippocampus 10:213–225.