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Neuroscience Letters 432 (2008) 40–45
Neuroscience Letters
www.elsevier.com/locate/neulet

The orbital cortex in rats topographically projects to central parts of the caudate–putamen complex

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Received 17 September 2007; received in revised form 30 November 2007; accepted 1 December 2007

Abstract

Disturbances of the orbitofrontal–striatal pathways in humans have been associated with several psychopathologies including obsessive–compulsive disorder and drug addiction. In nonhuman primates, different subareas of the orbitofrontal cortex project topographically to central and ventromedial parts of the striatum. Relatively little is known about the anatomical organization of the rat orbital cortex while there is a growing interest in this cortical area from a functional and behavioral point of view. The aim of the present neuroanatomical tracing study was to determine in rats the striatal target area of the projections of the orbital cortex as well as the topographical organization within these projections. To this end, anterograde tracers were injected in the different cytoarchitectonically distinct subareas of the orbital cortex. The results show that the individual orbital areas, i.e. medial orbital area, ventral orbital area, ventrolateral orbital area and lateral orbital area, project to central parts of the caudate–putamen, exhibiting a mediolateral and, to a lesser degree, rostrocaudal topographical arrangement. Orbital projections avoid the most dorsal, as well as rostral and caudal parts of the caudate–putamen. Terminal fields from cytoarchitectonically different areas show a considerable overlap. Superficial cortical layers project preferentially to the striatal matrix, deep layers to the patch compartment. The projections from the ventrolateral orbital area are strongest and occupy the most extensive striatal area. In addition to projections to the caudate–putamen, the ventrolateral, lateral and dorsolateral orbital areas have a scarce projection to the most lateral part of the nucleus accumbens shell in the ventral striatum. In contrast to nonhuman primates, the remainder of the rat nucleus accumbens is virtually free of orbital projections.

Keywords: Corticostriatal projections; Prefrontal cortex; Neuroanatomical tracing; Rat; Basal ganglia; Orbitofrontal cortex

The orbitofrontal cortex forms an extensive part of the prefrontal cortex in humans and is thought to be specifically involved in our social and emotional behavior [19,27]. Several forms of psychopathology, including drug addiction and obsessive–compulsive disorder (OCD), have been associated with disturbances of the orbitofrontal cortex e.g. [18,26]. Apart from the orbitofrontal cortex, connectionally associated striatal areas, as part of basal ganglia–thalamocortical circuits, and the dopaminergic and serotonergic systems have also been implicated in these disorders [10,22,28,34]. Yet, the underlying mechanisms of these neuropsychiatric disturbances and the contribution of various cortical and subcortical structures are still far from understood.

In rats, cytoarchitectonic, hodological and behavioral studies suggest the existence of distinct prefrontal areas that are, at least to some degree, comparable to such areas in primates [8,23,29,33]. Thus, like in nonhuman primates, three main subdivisions of the rodent prefrontal cortex have been recognized: a dorsal (anterior cingulate and dorsal prelimbic areas) and a ventral subdivision (ventral prelimbic and infralimbic areas) in the medial prefrontal cortex and an orbital (in some studies indicated as orbitofrontal) subdivision in the ventral surface of the frontal lobe [8,15]. The medial prefrontal areas appear to be involved in behavioral processes such as response selection,

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doi:10.1016/j.neulet.2007.12.024

attentional set-shifting and behavioral flexibility, which are similar to the functions attributed to regions in the lateral prefrontal cortex in primates [8,9,20]. The ventrally located orbital cortex in rats has been much less characterized in functional-anatomical and behavioral terms than its medial prefrontal counterpart. However, similar to the orbitofrontal cortex in primates, this region has been implicated in stimulus-reward associated reversal learning and choice involving delayed reinforcement [8], and it has been shown to play a role, in conjunction with the striatum and the serotonergic system, in a rat model of OCD [16,17]. Thus, the orbital cortex in rats seems comparable to the orbitofrontal cortex in primates and humans, although the extent of similarity remains to be established.

Current data clearly show that the rat orbital cortex can be further subdivided into smaller subareas on the basis of cytoarchitectonic and chemoarchitectonic characteristics, as well as on differences in cortical and subcortical connections [23,25,33,35]. However, the afferent and efferent connectivity of these different orbital subareas has not been systematically studied. The aim of the present study is to determine the striatal target area of the projections of the orbital cortex as well as the topographical arrangements within these corticostriatal projections. To this aim, small injections of the anterograde tracers biotinylated dextranamine (BDA) and *Phaseolus vulgaris*-leucoagglutinin (PHA-L) were placed in individual orbital subareas. Our results show that the orbital cortical areas primarily reach the central parts of the caudate–putamen complex and largely maintain a medial to lateral point-to-point relationship.

Twenty-four adult female Wistar rats (Harlan, Zeist, The Netherlands) weighing 180–250 g were used. All animals were fed ad libitum and housed in cages with enriched food. All experimental procedures were performed according to the guidelines of the ethical committee of animal experimentation, Vrije Universiteit, Amsterdam, that are in accordance with the European Community Council Directive 86/609/EEC.

Prior to surgery, animals were anesthetized with a mixture of ketamine and xylazine (i.m., four parts of 1% solution of ketaset [ketamine; Aesco, The Netherlands] and three parts of a 2% solution of Rompun [xylazine; Bayer, Belgium], total dose 1 ml/kg body weight). Adequacy of anesthesia was checked throughout surgery and additional anesthetics were given when necessary. During surgery, body temperature was maintained at 36–37 °C with a homeothermic mat. In addition, 10% lidocaine (Astra Pharmaceutica, The Netherlands) was used as local anesthetic at the site of incision.

The tracers biotinylated dextranamine (10.000 MW, Molecular Probes Inc., Eugene, OR) and *P. vulgaris*-leucoagglutinin (Vector, Burlingame, CA) were iontophoretically injected in different subareas of the orbital cortex in the same hemisphere (resulting in 48 injections in 24 animals). The tracers were delivered through a glass micropipette (CG-150F-15; Clark, Reading, UK) with an external tip diameter of 13–15 μm (BDA) or 13–15 μm (PHA-L). Pipettes were filled with 5% BDA or 2.5% PHA-L in 0.1 M NaH_2PO_4/Na_2HPO_4 (phosphate buffer [PB], pH 7.4). A positive DC current of 6.0 μA (BDA) or 7.5 μA (PHA-L)(7 s on/7 s off) was delivered to the micropipette, 10 min for BDA and 13 min for PHA-L.

Seven days postoperatively, the animals were deeply reanesthetized with sodium pentobarbital (Nembutal, 1 ml/kg, i.p.; Ceva, Paris, France) and rapidly perfused transcardially with 0.9% saline (NaCl), followed by a mixture of 4% paraformaldehyde (Merck, Germany) and 0.05% glutaraldehyde (Merck) in PB (0.1 M, pH 7.4) for 15 min. Brains were post-fixed for 1.5 h and cryoprotected by storage for 18–48 h at 4 °C in a mixture of 20% glycerin (Merck) and 2% dimethyl sulfoxide (DMSO; Merck). Frozen 40 μm thick sections were cut coronally. Sections were collected sequentially in six receptacles. Series of sections were stained for either BDA or PHA-L with or without 'counterstaining' with Nissl or immunohistochemistry for calbindin-D_{28kDA}.

To visualize BDA, sections were rinsed with PB followed by 0.05 M Tris/HCl (Merck) supplemented with 0.15 M NaCl, pH 7.6 (Tris-buffered saline; TBS) and 0.5% Triton X-100 (TBS-Tx; Merck). Then, they were incubated in avidin–biotin–peroxidase complex (1:1 mixture of reagents A [avidin] and B [biotinylated horseradish peroxidase]; Vector, Burlingame, CA) in TBS–Tx for 1.5 h at room temperature (if unspecified, incubation steps were done at room temperature). After rinsing with Tris/HCl, the sections were stained with nickel-enhanced diaminobenzidine (DAB-Ni) substrate: 6.25 mg 3,3′-diaminobenzidine-tetrahydrochloride (DAB; Sigma, St. Louis, MO), 0.5 ml 1% nickel-ammonium sulfate (Boom, The Netherlands), 3.33 μl of 30% H_2O_2 in 50 ml PB, pH 7.4, for 10–30 min. To visualize PHA-L, sections were incubated for 24 h at 4 °C in rabbit anti-PHA-L (Vector), diluted 1: 2000 in TBS-T. After rinsing with TBS-Tx, the sections were incubated for 1 h in swine anti-rabbit IgG (Dako, Denmark), diluted 1:100 in TBS-Tx, followed by an incubation in rabbit peroxidase–antiperoxidase (rPAP; Nordic), diluted 1: 800 in TBS–Tx for 1 h. After rinsing with Tris/HCl, the PHA-L was visualized by incubating the sections in DAB substrate: 5 mg DAB (Sigma), 3,3 μl of 30% H_2O_2 in 10 ml Tris/HCl, pH 7.6, for 10–30 min.

For details on the double staining procedure for the tracers BDA or PHA-L and calbindin-D_{28kDA} see [36].

Sections were mounted on glass slides from a Tris/HCl solution containing 0.2% gelatin and air-dried. Counterstaining for Nissl was done with 0.3% Cresyl Violet (in H_2O) for 0.5–1 min. Mounted sections were dehydrated and coverslipped with Entellan (Merck).

The subdivision of the orbital cortex into different subareas is based on the cytoarchitectonic descriptions by [23] and the recent revisions by [35]. According to the delineations of the latter authors, the following areas can be recognized from medial to lateral: the medial orbital (MO), ventral orbital (VO), ventrolateral orbital (VLO), lateral orbital (LO) and dorsolateral orbital areas (DLO). The lateral orbital area merges caudally with the ventral agranular insular area, the dorsolateral orbital area with the dorsal agranular insular area.

Four injections were placed in MO, two of which also included part of the laterally adjacent VO. Following the BDA injection in case 04046, which is restricted to MO (Fig. 1A), labeled fibers enter the striatum from rostral and reach the most medial part of the caudate–putamen. They form a restricted ter-

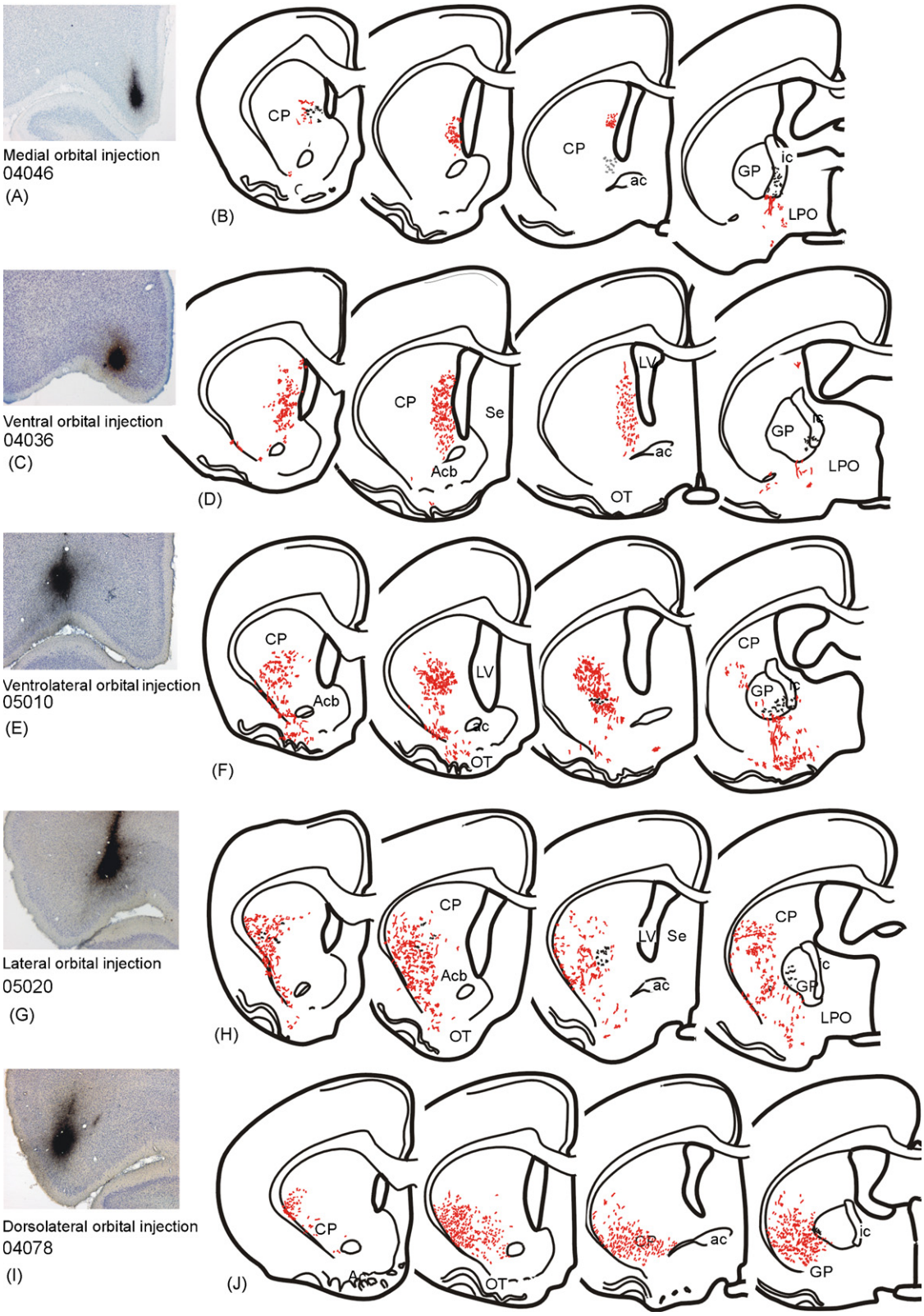

Fig. 1. Photomicrographs of the anterograde tracer injection sites in the orbital cortex (A, C, E, G and I) and schematic drawings of the projection areas in four rostrocaudal levels of the striatum (B, D, F, H and J). Note, the mediolateral shift of the terminal fields in the striatum in relation to the mediolateral position of the injection sites shown in the left hand column. Also note, the scarcity of labeling in the ventral striatum, the most lateral extension of the shell of the nucleus accumbens excepted (F and G).

minal area close to the ventral half of the lateral wall of the lateral ventricle (Fig. 1B). The dorsomedial part of the caudate–putamen remains free of labeling. The striatal terminal area does not reach further caudally than the crossing of the anterior commissure.

Three injections were placed in VO, one with spill of tracer in the injection track through MO and the prelimbic area. In case 04036 (Fig. 1C), the BDA injection is restricted to layers 2–5 of MO. Labeled fibers enter the caudate–putamen from rostral, traversing the dorsomedial parts of the core of the nucleus accumbens and terminating in a medial zone of the caudate–putamen (Fig. 1D). The most medial strip of the nucleus bordering the lateral ventricle is only sparsely labeled. Also, the dorsomedial one-third of the caudate–putamen and the core of the nucleus accumbens contain only sparse terminal labeling. Caudal to the level of the crossing of the anterior commissure, sparse terminal labeling is present in the medial part of the caudate–putamen (Fig. 1D).

Twenty-two injections were placed in VLO, six in the medial, nine in the central and seven in the lateral part of this orbital area. Case 05010 with a BDA injection in the central part of VLO is chosen as a representative example to illustrate the widespread projections from VLO to the striatum. In this case, the center of the injection site was located in layers 3 and 5 (Fig. 1E). Labeled fibers enter rostral parts of the striatum from the external capsule and travel in a dorsal and medial direction though the caudate–putamen. The main terminal field is located centrally in the caudate–putamen, leaving its medial one-quarter and lateral one-third free of labeling (Fig. 1F). Also the most rostral part remains free of labeling while in the caudal half of the nucleus a sparse plexus of terminal labeling is still located centrally. There is a distinct terminal area in the lateral shell of the nucleus accumbens (Fig. 1F). Injections in VLO located in its medial part tended to result in terminations located slightly more medially in the caudate–putamen, while laterally located injections resulted in labeling that concentrated more laterally in the general terminal field described for case 05010.

Seven injections included LO, three of which were restricted to this area, the other four involving small parts of adjacent areas, i.e., the ventral agranular insular area or VLO. The PHA-L injection in case 05020 primarily involves the deeper layers 3–6 of LO with some spill of tracer in the white matter (Fig. 1G). Labeled fibers enter the striatum from the lateral side and terminate in the lateral half of the caudate–putamen, leaving the dorsolateral part free (Fig. 1H). Terminal labeling is densest rostrally in an area abutting the lateral border of the caudate–putamen and extends into the most lateral part of the shell of the nucleus accumbens. More caudally labeling is sparser and located more centrally (Fig. 1H).

Five injections were situated in DLO, three of which included parts of adjacent cortical areas (dorsal agranular insular and granular insular cortices). The BDA injection in case 04078 is virtually restricted to DLO with slight involvement of the dorsally adjacent granular insular cortex (Fig. 1I). Labeled fibers enter from lateral to terminate in the lateral half of the caudate–putamen complex. Compared to case 05020 (LO injection) the terminal labeling is denser caudally and extends slightly more medially into the caudate–putamen (Fig. 1J).

In sections double-stained for BDA and Calbindin-D_{28kDA} striatal patch and matrix compartments and shell and core in the nucleus accumbens could be easily distinguished. Most injections of either BDA or PHA-L primarily involved the superficial layers II and III, and the outer parts of layer V. In those cases, varicose fibers in the caudate–putamen showed a strong preference for the matrix. In cases with an injection primarily in the deeper layers V and VI, there was a preference for terminal labeling in the patch compartment. The latter pattern could only be established for VLO, LO and DLO since there were no injections in VO and MO that selectively included the deep layers. Injections involving most of the cortical layers resulted in terminal labeling in both patch and matrix.

The results of the present study show that the different orbital areas, i.e. MO, VO, VLO, LO and DLO, mainly project to central parts of the caudate–putamen, leaving the dorsal one-third and the most rostral and caudal parts of the caudate–putamen, as well as the ventral striatum largely free of orbital projections. Thus, the core of the nucleus accumbens receives only sparse projections from VO, and the most lateral part of the shell from VLO and LO. There appears to be a clear medial-to-lateral topography such that MO projects most medially and LO and DLO most laterally in the caudate–putamen. In addition, medially located orbital areas (MO, VO) tend to project more rostrally in the striatum than the more lateral areas (LO, DLO). However, terminal fields from the different orbital areas show a considerable overlap. Finally, projections from VLO are strongest and occupy a ‘central’ position in the caudate–putamen.

The present study is the first systematic analysis of the corticostriatal projections from the various orbital areas in rats. Although [2] included the orbital areas in their analysis of the prefrontal corticostriatal projections, only few injections were located in the orbital areas and those primarily involved caudal parts. Our present results are largely in agreement with previous studies that likewise showed that orbital areas project to central parts of the caudate–putamen [24,25]. Thus, the most ventral parts of the striatum, i.e., shell and core of the nucleus accumbens, do not receive orbital projections. An exception forms the most lateral part of the shell (lateral to the anterior limb of the anterior commissure) that receives moderate projections from VLO and LO. Our present results further suggest that the association of superficial layers (II, III and outer V) with the striatal matrix compartment and of the deep layer V with the patch compartment is very similar to that of the medial prefrontal areas in rats [2,12].

There appears to be some controversy in the literature about the precise striatal target area of the orbitofrontal cortical areas in primates. According to [30], orbitofrontal areas in primates project to the most ventral and medial parts of the caudate nucleus and putamen, while [14] include, in addition, the core of the nucleus accumbens as an orbitofrontal striatal target. The results of [11] may resolve this controversy, as they have demonstrated that the most ventromedial parts of the caudate–putamen and the core of the nucleus accumbens receive projections from areas of the so-called ‘medial prefrontal network’ that include

the medial prefrontal cortex and some of the more caudal orbital areas, whereas the central parts of the caudate nucleus and putamen receive projections from areas of the 'orbital prefrontal network that include the remaining, mostly more rostrally located, orbitofrontal areas.

Our present results show that the orbital/orbitofrontal projections in rats and primates occupy a similar region in the striatum, with some differences resulting mainly from a ventral-wards 'shift' of these projections in primates compared to rats. Thus, whereas in primates the nucleus accumbens core is innervated by caudal regions of the orbitofrontal cortex, in rats the core is almost devoid of orbital projections. This region of the nucleus accumbens is innervated, however, by the dorsal agranular insular area, which is positioned just caudal to the rat's orbital cortex ([2]; present observations). The rat's dorsal agranular insular area and the primate's caudal orbitofrontal cortex share additional anatomical similarities. Thus, both areas have connections with the medial segment of the mediodorsal thalamic nucleus and with gustatory and other visceral related cortices, and they receive projections from the magnocellular basal amygdaloid nucleus [1,6,7,39].

The "dorsal" side of this ventral-wards shift relates to the finding that the orbital projections in rats appear to extend more dorsally into the caudate–putamen complex than in primates. In primates, this striatal region is innervated by dorsolateral prefrontal areas [30] that are much less extensive in rats e.g. [33]. Interestingly, in rats this striatal region is innervated also by regions of the dorsal medial prefrontal cortex (the anterior cingulate and medial precentral, or medial agranular area; Fr2) [2,24], that have been suggested to correspond to regions of the dorsolateral prefrontal cortex of primates [21,29,33]. It is also noteworthy that in both rats and primates the striatal projections from medial prefrontal areas tend to terminate in more medial and ventral areas of the caudate–putamen compared to the orbital/orbitofrontal projections, and include the shell and core of the nucleus accumbens [2,21]. Nevertheless, in both species there appears to be a considerable overlap between medial prefrontal and orbital/orbitofrontal striatal projection areas. For example, MO and VO overlap extensively with the infralimbic and prelimbic projections to the medial caudate–putamen [2,25].

The central striatal area in rats that receives an input from the orbital areas (present results) is also projected upon by amygdaloid and thalamic nuclei and receives midbrain dopaminergic and serotonergic fibers. Specifically, it receives thalamic projections from the paracentral and central lateral nuclei of the intralaminar complex [3]; amygdaloid projections from the rostral part of the magnocellular accessory basal nucleus [38]; dopaminergic innervation from the ventral tegmental area and the medial part of the substantia nigra pars compacta [13]; and serotonergic projections from the dorsal raphe nucleus [31,32].

The convergence of projections from the orbital cortex, the serotonergic and the dopaminergic systems in the central striatum suggests that this striatal region may play a critical role in psychopathologies associated with these neural systems, such as drug addiction and OCD. Indeed, imaging data from human subjects implicate the caudate nucleus in these pathologies [4,5,37]. In rats, there are only a few studies that have manipulated specifically this striatal region. Of specific interest in the present context are two recent studies. The first reported that temporary inactivation of the central striatum has an anti-compulsive effect in a rat model of OCD (Schilman et al., in preparation). The second showed that injection of the SSRI paroxetine into the central striatum alleviated compulsive behavior induced by a lesion to the orbital cortex (Schilman et al., in preparation). This latter finding adds to a previous demonstration by the same group that lesions to the orbital cortex lead to increased compulsivity that can be blocked by systemic administration of paroxetine, and to an increase in the density of the striatal serotonin transporter [16]. Taken together these results suggest one type of interaction between structures of the basal ganglia–thalamocortical circuits that may underlie compulsions, namely that orbital dysfunction leads to alterations of the striatal serotonergic system which subsequently results in the production of compulsions.

Acknowledgement

This work was partly supported by the National Institute for Psychobiology in Israel – founded by the Charles E. Smith Family, grant number 2004-5-13.

References

[1] V. Bagaev, V. Aleksandrov, Visceral-related area in the rat insular cortex, Auton. Neurosci. 125 (2006) 16–21.
[2] H.W. Berendse, Y. Galis-de Graaf, H.J. Groenewegen, Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat, J. Comp. Neurol. 316 (1992) 314–347.
[3] H.W. Berendse, H.J. Groenewegen, The organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum, J. Comp. Neurol. 299 (1990) 187–228.
[4] M.L. Berthier, J. Kulisevsky, A. Gironell, J.A. Heras, Obsessive–compulsive disorder associated with brain lesions: clinical phenomenology, cognitive function, and anatomic correlates, Neurology 47 (1996) 353–361.
[5] H.C. Breiter, S.L. Rauch, K.K. Kwong, J.R. Baker, R.M. Weisskoff, D.N. Kennedy, A.D. Kendrick, T.L. Davis, A. Jiang, M.S. Cohen, C.E. Stern, J.W. Belliveau, L. Baer, R.L. O'Sullivan, C.R. Savage, M.A. Jenike, B.R. Rosen, Functional magnetic resonance imaging of symptom provocation in obsessive–compulsive disorder, Arch. Gen. Psychiatry 53 (1996) 595–606.
[6] C. Cavada, T. Company, J. Tejedor, R.J. Cruz-Rizzolo, F. Reinoso-Suarez, The anatomical connections of the macaque monkey orbitofrontal cortex. A review, Cereb. Cortex 10 (2000) 220–242.
[7] D.F. Cechetto, C.B. Saper, Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat, J. Comp. Neurol. 262 (1987) 27–45.
[8] J.W. Dalley, R.N. Cardinal, T.W. Robbins, Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates, Neurosci. Biobehav. Rev. 28 (2004) 771–784.
[9] R. Dias, T.W. Robbins, A.C. Roberts, Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from on-line processing, J. Neurosci. 17 (1997) 9285–9297.
[10] M. El Mansari, P. Blier, Mechanisms of action of current and potential pharmacotherapies of obsessive–compulsive disorder, Prog. Neuropsychopharmacol. Biol. Psychiatry 30 (2006) 362–373.
[11] A.T. Ferry, D. Öngür, X. An, J.L. Price, Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks, J. Comp. Neurol. 425 (2000) 447–470.
[12] C.R. Gerfen, The neostriatal mosaic: striatal patch–matrix organization is related to cortical lamination, Science 246 (1989) 385–388.

[13] C.R. Gerfen, M. Herkenham, J. Thibault, The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems, J. Neurosci. 7 (1987) 3915–3934.
[14] S.N. Haber, K. Kunishio, M. Mizobuchi, E. Lynd-Balta, The orbital and medial prefrontal circuit through the primate basal ganglia, J. Neurosci. 15 (1995) 4851–4867.
[15] C.A. Heidbreder, H.J. Groenewegen, The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon anatomical and functional characteristics, Neurosci. Biobehav. Rev. 27 (2003) 555–579.
[16] D. Joel, J. Doljansky, N. Roz, M. Rehavi, Role of the orbital cortex and of the serotonergic system in a rat model of obsessive compulsive disorder, Neuroscience 130 (2005) 25–36.
[17] D. Joel, O. Klavir, The effects of temporary inactivation of the orbital cortex in the signal attenuation rat model of obsessive compulsive disorder, Behav. Neurosci. 120 (2006) 976–983.
[18] P.W. Kalivas, N.D. Volkow, The neural basis of addiction: a pathology of motivation and choice, Am. J. Psychiatry 162 (2005) 1403–1413.
[19] M.L. Kringelbach, The human orbitofrontal cortex: linking reward to hedonic experience, Nat. Rev. Neurosci. 6 (2005) 691–702.
[20] L. Lacroix, I. White, J. Feldon, Effect of excitotoxic lesions of rat medial prefrontal cortex on spatial memory, Behav. Brain Res. 133 (2002) 69–81.
[21] D. Öngür, J.L. Price, The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans, Cereb. Cortex 10 (2000) 206–219.
[22] J. Pujol, C. Soriano-Mas, P. Alonso, N. Cardoner, J.M. Menchon, J. Deus, J. Vallejo, Mapping structural brain alterations in obsessive–compulsive disorder, Arch. Gen. Psychiatry 61 (2004) 720–730.
[23] J.P. Ray, J.L. Price, The organization of the thalamocortical connections of the mediodorsal thalamic nucleus in the rat, related to the ventral forebrain-prefrontal cortex topography, J. Comp. Neurol. 323 (1992) 167–197.
[24] R.L. Reep, J.L. Cheatwood, J.V. Corwin, The associative striatum: organization of cortical projections to the dorsocentral striatum in rats, J. Comp. Neurol. 467 (2003) 271–292.
[25] R.L. Reep, J.V. Corwin, V. King, Neuronal connections of orbital cortex in rats: topography of cortical and thalamic afferents, Exp. Brain Res. 111 (1996) 215–232.
[26] P.L. Remijnse, M.M. Nielen, A.J. van Balkom, D.C. Cath, P. van Oppen, H.B.M. Uylings, D.J. Veltman, Reduced orbitofrontal–striatal activity on a reversal learning task in obsessive–compulsive disorder, Arch. Gen. Psychiatry 63 (2006) 1225–1236.
[27] A.C. Roberts, Primate orbitofrontal cortex and adaptive behaviour, Trends Cogn. Sci. 10 (2006) 83–90.
[28] S. Saxena, S.L. Rauch, Functional neuroimaging and the neuroanatomy of obsessive–compulsive disorder, Psychiatr. Clin. North Am. 23 (2000) 563–586.
[29] G. Schoenbaum, B. Setlow, Integrating orbitofrontal cortex into prefrontal theory: common processing themes across species and subdivisions, Learn Mem. 8 (2001) 134–147.
[30] L.D. Selemon, P.S. Goldman-Rakic, Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey, J. Neurosci. 5 (1985) 776–794.
[31] H.W. Steinbusch, Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals, Neuroscience 6 (1981) 557–618.
[32] I. Törk, Anatomy of the serotonergic system, Ann. N. Y. Acad. Sci. 600 (1990) 9–34.
[33] H.B.M. Uylings, H.J. Groenewegen, B. Kolb, Do rats have a prefrontal cortex? Behav. Brain Res. 146 (2003) 3–17.
[34] O.A. Van den Heuvel, D.J. Veltman, H.J. Groenewegen, D.C. Cath, A.J.L.M. van Balkom, J. van Hartskamp, F. Barkhof, R. van Dyck, Frontal-striatal dysfunction during planning in obsessive–compulsive disorder, Arch. Gen. Psychiatry 62 (2005) 301–309.
[35] H.J.J.M. Van de Werd, H.B.M. Uylings, The rat orbital and agranular insular prefrontal cortical areas: a cytoarchitectonic and chemoarchitectonic study, Brain Struct. Funct., in press.
[36] Y.C. Van Dongen, J.M. Deniau, C.M. Pennartz, Y. Galis-de Graaf, P. Voorn, A.M. Thierry, H.J. Groenewegen, Anatomical evidence for direct connections between the shell and core subregions of the rat nucleus accumbens, Neuroscience 136 (2005) 1049–1071.
[37] N.D. Volkow, G.J. Wang, F. Telang, J.S. Fowler, J. Logan, A.R. Childress, M. Jayne, Y. Ma, C. Wong, Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction, J. Neurosci. 26 (2006) 6583–6588.
[38] C.I. Wright, A.V.J. Beijer, H.J. Groenewegen, Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized, J. Neurosci. 16 (1996) 1877–1893.
[39] C.I. Wright, H.J. Groenewegen, Patterns of overlap and segregation between insular cortical, intermediodorsal thalamic and basal amygdaloid afferents in the nucleus accumbens of the rat, Neuroscience 73 (1996) 359–373.