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Cortico-basal ganglia circuits involved in different motivation disorders in non-human primates

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Abstract

The ventral striatum (VS) is of particular interest in the study of neuropsychiatric disorders. In this study, performed on non-human primates (NHP), we associated local perturbation with monosynaptic axonal tracer injection into medial, central and lateral VS to characterize anatomo-functional circuits underlying the respective expression of sexual manifestations, stereotyped behaviors and hypoactive state associated with loss of food motivation. For the three behavioral effects, we demonstrated the existence of three distinct cortico-basal ganglia (BG) circuits that were topographically organized and overlapping at some cortical (orbitofrontal cortex, anterior cingulate cortex) and subcortical (caudal levels of BG) levels, suggesting interactions between motivation domains. Briefly, erection was associated with a circuit involving the orbitofrontal cortex, medial prefrontal cortex (areas 10, 11) and limbic parts of BG, i.e. medial parts of the pallidal complex and the substantia nigra pars reticulata (SNr). Stereotyped behavior was linked to a circuit involving the lateral orbitofrontal cortex (area 12/47) and limbic parts of the pallidal complex and of the SNr, while the apathetic state was underlined by a circuit involving the orbital and medial prefrontal cortex but also the lateral prefrontal cortex (area 8, 45), the anterior insula and the lateral parts of the medial pallidal complex and of the ventro-medial SNr. For the three behavioral effects, the cortico-BG circuits mainly involved limbic regions of the external and internal pallidum, as well as the limbic part of the substantia nigra pars reticulata (SNr), suggesting the involvement of both direct and indirect striatal pathways and both output BG structures. As these motivation disorders could still be induced in dopamine (DA)-depleted monkeys, we suggest that DA issued from the substantia nigra pars compacta (SNc) modulates their expression rather than causes them. Finally, this study may give some insights into the structure to target to achieve therapeutic benefits from deep brain stimulation (DBS) in motivation disorders.

Keywords: monkey, sex, anxiety, apathy, food, Parkinson's disease.

Abbreviations:

AC, anterior commissure; BDA, Biotin dextran amine; cc, corpus callosum; BG, basal ganglia; Cd, caudate nucleus; CP, cerebellar peduncle; CM/Pf, centromedian and parafascicular nuclei; Cx, cortex; DBS, deep brain stimulation; fMRI, functional magnetic resonance imaging; GPe, external pallidum ; GPi, internal pallidum ; ic, internal capsule; Ins, Insula; Lv, lateral ventricle; MD, mediodorsal nucleus of the thalamus; MPTP, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine; NHP, non-human primates; OCD, obsessive compulsive disorders; OPAI,

orbital periallocortex; PD, Parkinson's disease; PARV, parvalbumin; PET, positron emission tomography; Put, putamen; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Temp, Temporal cortex; TH, tyrosine hydroxylase; VA, ventral anterior nucleus of the thalamus; VL, ventral lateral nucleus of the thalamus; VS, ventral striatum; WM, white matter.

Introduction

The ventral striatum (VS), as a part of the basal ganglia (BG), occupies over 20% of the striatum (Haber et al., 2006) and includes the nucleus accumbens, that is further subdivided into core and shell in rodents (Zaborsky et al., 1985) and monkeys (Meredith et al., 1996), the medial caudate nucleus, and the medial and ventral rostral putamen. The afferent and efferent connections of the VS are relatively complex. Thus, the VS receives glutamatergic afferents from the orbitofrontal (Selemon and Goldman-Rakic, 1985; Haber et al., 1995), medial prefrontal (Haber et al., 1995), anterior cingulate (Kunishio and Haber, 1994), insular (Chikama et al., 1997) cortices and the medial temporal lobe (Van Hoesen et al., 1981; Selemon and Goldman-Rakic, 1985). It also receives glutamatergic inputs from the thalamus (Giménez-Amaya et al., 1995) and GABAergic inputs from the ventral pallidum (Spooren et al., 1996). Like the dorsal striatum, the VS is further modulated by dopaminergic (DA) afferents from the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) (Parent et al., 1983; Lynd-Balta and Haber, 1994). The mesostriatal DA projection is one of the main anatomical substrates for reward processing, reinforcement learning and the development of addictive and compulsive behaviors (Wise, 1998; Hyman and Milenka, 2001 for reviews). The VS is also densely innervated by serotonergic (5-HT) afferents from the raphe nuclei (De Vito et al., 1980; Parent et al., 1983). This raphe-VS projection provides another basis of modulation that is involved, for example, in social reward (Dölen et al., 2013). The DA and 5-HT monoaminergic systems can be respectively targeted by neuroleptics and antidepressants, two pharmacological classes of drugs that are used in clinical practice for treating neuropsychiatric disorders such as schizophrenia (Leucht et al., 2013), anxiety (Buoli et al., 2013) and depression (Cipriani et al., 2009). Unlike the dorsal striatum, the VS also receives projections from the amygdala (Russchen et al. 1985; Fudge et al., 2002) and hippocampus (Friedman et al., 2002). In turn, the VS sends GABAergic projections to the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), the two output structures of the BG. This is performed either directly, through the direct pathway (VS-GPi/SNr) or

indirectly, via the indirect pathway through the ventral pallidum (VP) and the subthalamic nucleus (STN) (VS-VP-STN-GPi/SNr) (DeLong, 1990).

The cortico-BG loop involving the VS plays a central role in behavior through the control of motivational processes (Alexander et al., 1986; Graybiel, 2005; Haber and Knutson, 2010), whereas the cortico-BG loops involving the caudate and the putamen are involved in the processes of selection and execution of the action (Alexander et al., 1986; Middleton and Strick, 2000; Tremblay et al., 2009). The interface existing between the different striatal territories and midbrain DA neurons allows a feed-forward organization from the limbic to the cognitive and motor circuits (Haber, 2003). The VS is involved in various aspects of reward processing, motivation and goal-directed behavior (Corlett et al., 2004; Elliott et al., 2003; Knutson et al., 2001; Schultz et al., 2000; Tanaka et al., 2004). In humans, as indexed by functional magnetic resonance imaging (fMRI) studies, VS processes reward information for food or drugs but also for sexual (Ponseti et al., 2006; Politis et al., 2013), financial (Elliott et al., 2003) or social (Kohls et al., 2013) stimuli. Therefore, a dysfunction inside the VS could result in different types of behavioral disorders, such as eating disorders (Kaye et al., 2009; Tomasi and Volkow, 2013; Stefano et al., 2013 for reviews), sexual disorders (Politis et al., 2013) or anxiety disorders (Grupe and Nitschke, 2013 for review). Indeed, VS has been shown to be involved in pathological risk-taking and addictive behaviors (Kuhnen and Knutson 2005; Volkow et al., 2005). Several studies also suggest a role of the VS in aversive motivation (Schoenbaum et al., 2003; Berridge, 2004) and anxious states (Mataix-Cols et al., 2004; Fineberg et al., 2011). FMRI studies performed on humans have indeed evidenced different activation thresholds of the VS during anticipation of aversive stimuli (electrical shock to the skin) (Jensen et al., 2003), as well as during avoidance learning in response to conditioned aversive stimuli (Delgado et al., 2009). Moreover, the internal capsule and nucleus accumbens are targets for deep brain stimulation (DBS) of patients with a treatment refractory major depression (Malone et al., 2009; Aouizerate et al., 2009), obsessive compulsive disorders (OCD) (Greenberg et al., 2006) and Tourette's syndrome (Williams and Okun, 2013 for review). Altogether, these studies point to a major role for the VS in motivation and aversive processing and suggest that DBS or DA pharmacological targeting of this structure can be a common therapeutic option for neuropsychiatric disorders.

One still unresolved question is whether dysfunction inside one striatal territory or several triggers these behavioral manifestations. In non-human primates (NHP) studies, modulation of the VS activity by pharmacological GABAergic agent (bicuculline) induced sexual manifestation (erection) in the medial part of VS, hypoactivity with loss of food motivation in the lateral part, and stereotyped behavior (grooming and licking

and biting fingers and/or tail) in the central part (Worbe et al., 2009). So far, these results suggest the existence of different motivation domains in the primate VS that specifically process information on sexual behaviors, assessment of threat, aversive events, and food motivation. These different states can be assimilated into different motivation disorders, such as hypersexuality, anxiety disorders, apathy and eating disorders, which can be encountered in Parkinson's disease (PD) or under pharmacological treatment (Weintraub et al., 2010; Zahodne et al., 2011; Voon et al., 2011; Politis et al., 2013; Castrioto et al., 2014). However, it is difficult to transpose human pathologies only on the basis of behavioral expression as the same expression can be expressed as a common feature in different pathologies. The identification of the neuronal networks involved in each of these behavioral effects can help to validate anatomico-functionally these preclinical monkey models. Preclinical studies have also shown that DBS applied to another target, the subthalamic nucleus (STN), can improve the stereotyped behavior in the monkey (Baup et al., 2008). The mapping of the cerebral regions involved in the expression of such behavioral disorders is required to highlight putative new targets for DBS application. Imaging studies in Tourette patients with OCD or ADHD revealed a dysfunction of BG and associated cortical areas (Rampello et al., 2006; Marsh et al., 2009). Similarly, apathy is associated with a dysfunction of fronto-subcortical circuits, involving the ventromedian prefrontal cortex and associated BG regions (Chase, 2011).

The aim of the present work was to identify, by using a retrograde and anterograde tracer (Figure 1), the cortico-BG circuits underlying three different behavioral manifestations resulting from local perturbation of the VS: sexual manifestation, stereotyped behavior and apathetic state with loss of food motivation. The retrograde identification of thalamic and cortical regions allows face validity of this animal model of behavioral disorders by comparing the neuronal tracing data with neuroimaging studies in humans. The anterograde labeling within the BG allows the neuronal networks implicated in the behavioral effects to be compared and may highlight new targets or more specific territories of the BG for future therapeutic options such as DBS. Finally, the dopamine role in the expression of these behavioral effects is questioned. Consequently, this study includes some monkeys with DA lesions, in which these behavioral disorders could still be expressed.

Materials and methods

Ethical statement

All studies were carried out in accordance with European Communities Council Directive of 1986 (86/609/EEC). The manuscript does not contain clinical studies or patient data.

Animals

Nine adult male macaque monkeys (eight *Macaca fascicularis* MI 59, MI 60, MI 64, MI 65, MI 66, MI 69, MI 70, MF-2 and one *Macaca mulatta*; MM 37) and two male African green monkeys (*Cercopithecus aethiops sabaues*, CA 34, CA 37) were used in this study. According to international recommendation for animal experimentation, the three Rs were taken into consideration (Reduction, Refinement, and Replacement). Some of the behavioral data obtained on three monkeys (MI 65, MI 69 and CA 34) had been previously reported (Worbe et al., 2013). All monkeys weighed between 4 and 6 kg and were aged between 3 and 5 years. They were kept under standard conditions (12-hour light cycles, 23°C and 50% humidity).

Dopamine depletion

Three of these monkeys (CA 34, CA 37 and MF-2) were recovered Parkinsonian monkeys that had been involved in previous studies (Mounayar et al., 2007; Neumane et al., 2012). Briefly, dopamine depletion was obtained following 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) injections (0.3 to 0.4 mg/kg, i.m) performed under light anesthesia (ketamine 0.5 mg/kg, atropine 0.05 mg/kg) at an interval of 4 to 5 days until the emergence of Parkinsonian symptoms. MPTP intoxication was stopped once most of the motor Parkinsonian symptoms had appeared. The appearance of symptoms was assessed by using the rating scale of Schneider and Kovelowski (1990) which includes several items that are rated with a total score of 29. The higher the score was, the more symptomatic the monkey (see Table 1).

Microinjections of bicuculline and behavioral analysis

Three different types of bicuculline effects were searched for using the injection of an anatomical tracer: erection manifestation, stereotyped behaviors characterized by an increase in grooming and licking or biting fingers, and apathetic-like behavior characterized by a hypoactive state associated with a lack of food motivation. Detailed descriptions of the behavioral effects and the schedule of the experimental sessions are provided in a previous study (Worbe et al., 2009). Briefly, the coordinates of the striatal microinjection site were determined according to either stereotaxic maps obtained from monkey brain atlases (Paxinos et al., 2008; Saleem and Logothetis, 2007) or following a T1-weighted MRI scan (1.5 T; CERMEP, Lyon, France). The striatum was identified by its neuronal activity using extracellular single-unit electrophysiological recordings to determine the exact depth of the microinjection to apply. Bicuculline methiodide (Sigma-Aldrich, France) at a concentration of 15 µg/µl (29.5

mmol/l) in saline was delivered via microinjection cannula by pressure at a rate of 1 μ l/min, in steps of 0.5 μ l with a total volume of 3 μ l.

Monkeys' spontaneous behaviors were video-recorded and evaluated during a control period of 15 min before the microinjections of bicuculline, followed by two post-injection observational periods of 20 min. In addition, separate control sessions with saline injections in the same striatal sites and control sessions without microinjections were performed to evaluate any possible contextual induction of abnormal behaviors.

Behaviors were defined as follows: (1) resting without other behaviors; (2) mouth, (3) arm and (4) leg movements (normal movements without a goal); (5) touching equipment; (6) body examination; (7) grooming (cleaning fur with fingers); (8) licking and/or biting fingers; (9) erection; (10) other (behaviors characteristic of each monkey) and (11) dyskinesia. All types of behaviors and abnormal movements were evaluated and quantified in 3-min segments.

Simple Food Retrieval Task

The monkeys were trained to perform a simple choice task that consisted of grasping and retrieving food from an 18-well board placed in front of them, the left and right sides of the board being separated by a central plaque. During the training period, the monkeys learned to pick up rewards from the left and right part of the board with their left and right hand, respectively, 15 times across 5 sessions of presentation. This training enabled us to study each monkey's own spatial strategy, and its perturbation, under bicuculline microinjection. We identified the errors in the tasks: crossover hand errors and non-initiated reward, the latter defined as the difference between the rewards available and the number of rewards retrieved. We also measured the average retrieval time, defined as the time taken to perform the task divided by the number of rewards retrieved. Non-taken rewards and retrieval times are considered to be behavioral markers of motivation (Pessiglione et al., 2004). To distinguish motor perturbation from a changed motivational state in task execution, we evaluated the temporal organization of average retrieval time, which included two supplementary measures: 1) time of movement to retrieve, which represented the time from the movement initiation to pick-up and consumption of the reward, and 2) inter-retrieval time, measured between two movement initiations. Both measures were analyzed using "Vigie Primates" software (View-point, Lyon, France), which enables images recorded by video cameras to be digitized every 40 ms and shown on a computer screen. The software detects and measures movement between two successive images by analyzing the number of pixels that have changed in brightness. Within the digitalized

image, we defined two windows over the reward board to record the hand movements for the right and left hand, separately. Further details of the Vigie Primates software are given in Pessiglione et al., (2003).

Statistical analysis of behavioral effects.

Detailed statistical analysis of behavioral effects is provided in previous publications (Worbe et al., 2009; Worbe et al., 2013). To compare behavioral effects across the experimental sessions we used two-way ANOVA tests with post-hoc two-sample paired t-test comparison. The microinjection was considered to have produced an effect if the duration of one or more behaviors or movements was statistically different ($p < 0.05$) from control measurements.

Injections of axonal tracer

Injections of axonal tracer were performed in the striatum of the monkeys after all behavioral studies had been completed (Figure 1). Under Ketamine (0.1 mg/kg) anesthesia, from 1 to 1.5 μ l of biotin dextran amine (BDA) (Sigma-Aldrich, France) diluted (10 %) in PBS (0.01 M, pH 7.4) was injected into the striatum using the same device as for the bicuculline microinjections.

Eight of ten monkeys received injections into the striatum of both hemispheres to limit the number of animals. To control the percentage of contralateral labeling, two monkeys (*CA 34* and *CA 37*) received BDA injection unilaterally into striatal sites, one producing stereotyped behavior and one producing erection. Other monkeys received BDA injections into the contralateral dorsal striatum for another anatomical study (Worbe et al., 2013). No anterograde crossover labelling was observed from the striatum to the GPi, SNr and GPe.

Ten days after the BDA injections, the animals were deeply anesthetized and perfused transcardially with 400 ml of saline (0.9% at 37°C) followed by 5 liters of 4% paraformaldehyde (in 0.1 M PBS, pH 7.4 at 4°C) and 1 liter of PBS with 5% sucrose. The brains were removed from the skull, rinsed in PBS complemented with 10% sucrose for 1 day and 20% sucrose for 1 day, then frozen and cut into 50- μ m-thick sections transversally with reference to the ventricular anterior (AC) and posterior commissures (PC) on a freezing microtome.

Immunohistological staining

Staining was performed on regularly interspaced brain sections (1/10) pre-treated with 1 % Triton X100 in PBS and then incubated using avidin-biotin complex staining (ABC, Elite, Vector Laboratories) in PBS with 1 %

triton for 48 hours at 4 °C. The sections were treated with nickel (0.2 %) and DAB (0.05 %) as peroxidase chromogen.

For the substantia nigra, staining for the tyrosine hydroxylase (TH) and parvalbumin (PARV) was performed on the adjacent sections used for BDA revelation. Sections were incubated with the primary antibody (anti-TH 1/5000 mouse monoclonal from Euromedex, Souffelweyersheim, France; or anti-parvalbumin 1/5000 mouse monoclonal from Sigma-Aldrich, Saint Quentin Fallavier, France) for 72 hours at 4 °C. After three rinses, the sections were incubated with the corresponding secondary biotinylated antibody (1/500; from vector laboratories, Abcys, Paris, France) for two hours at room temperature. The sections were washed and incubated for 90 min at room temperature in avidin–biotin–peroxidase complex (ABC) solution (final dilution 1/50) (Vector Laboratories, Abcys, Paris, France) before being placed in 0.1 % 3,3'-diaminobenzidine (DAB; 50 mg/100 ml) and developed by incubation with H₂O₂ (0.02 %).

Brain cartography

Contours of cerebral structures were traced under a microscope with an XY plotter connected to a microscope by Mercator software (Explora Nova, La Rochelle, France). The antero-posterior position of each brain section was referred to the AC-PC axis, taking AC as the origin of the system of axes. All the sections were transformed into maps drawn in relation to the AC-PC coordinates so that the contours of structures mapped in different monkeys could be directly compared. All cartographic data obtained from the left hemisphere of the monkeys were transferred to the right hemisphere for easier comparison.

The cortical segmentation in the Brodman areas was made using an atlas of monkey's brain (Paxinos et al., 2008; Saleem and Logothetis, 2007). The data for the same behavioral effects were firstly compared among three injection sites and then pooled together for final comparisons. We presented all labelled regions as a percentage of labelling relative to the most labelled region. All these regions were considered for network comparison.

Results

Overview of bicuculline microinjections effects

Microinjections of bicuculline into the ventral striatum triggered three different effects in the monkeys, as previously described (Worbe et al., 2009): sexual manifestations were produced from the more medial part of the VS, stereotyped behavior from the central part, and a hypoactive state associated with diminished food motivation from the ventrolateral part (Figure 2). For the purpose of this study, we selected the striatal sites

where the most characteristic behavioral effects were produced in order to perform injections of the axonal tracer. The localization of these microinjection sites is illustrated in Figure 2 panel C, with detailed pictures D, G, J, and examples of each behavioral effect are provided in panels E, H and K. Erection was induced in the three monkeys MM 37, MI 64 and CA 37 (Fig. 2, panels D and E) with no additional behavioral effects compared to the control conditions. There was no effect on performance in the simple food retrieval task (Fig. 2, panel F). Stereotyped behaviors were induced in the three monkeys MI 69, MI 65 and CA 34 (Fig. 2, panels G and H). They were characterized by intense repetition of grooming as well as licking or biting parts of the body (usually the fingers or tail). No further behavioral changes or effect on performance in the simple food retrieval task (Fig. 2, panel I) were observed compared to the control conditions. An apathetic-like state was induced in the three monkeys MI 70, MI 69, MI 66 (Fig. 2, panels J and K) as well as MF-2 (data not shown) and was characterized by an increase in resting (paralleled by a decrease in other behavioral manifestations when present under control conditions) associated with a perturbation of the simple food retrieval task (Fig. 2, panel L). For MI 66, 80 % of choices were initiated. For MI 70, only 69.3 % of choices were initiated as it refused to perform the task during the fourth presentation. Finally, for MI 69, only 20 % of choices were initiated as it refused to perform the task after the second presentation. For the three monkeys, we observed an increase in the retrieval time for initiated choices (data not shown). Of note, we observed MI 70 spitting out apple pieces just before stopping the task. Moreover, behavioral effects were also induced in DA-depleted monkeys, i.e. erection in CA 37, stereotypy in CA 34 and apathy in MF-2. These monkeys exhibited a total DA cell loss of 78%, 68% and 73%, respectively (Table 1, Mounayar et al., 2007; Neumane et al., 2012).

Retrograde labeling relative to sexual manifestations, and stereotyped and apathetic states.

The general features of retrograde labeling in relation to the behavioral effects induced by bicuculline microinjections into VS are presented in Figures 3, 4 and 5. In all cases, retrogradely-labelled cell bodies (Fig. 1 and panel C for photomicrographs) were found within the cortex and the thalamus (Fig. 3 & 4, respectively). The retrograde labelling was also considered in the SN and VTA (Figure 5).

At the cortical level (Figure 3), the sexual manifestations were related to a strong labeling in the orbitofrontal cortex (areas 10, 11, 47/12 and 13), medial prefrontal cortex (areas 14, 25 and 24), lateral prefrontal cortex (area 9/46) and temporal cortex. The apathetic state was related to strong labeling in the medial (areas 24, 32), dorsal (area 8) and lateral (areas 44, 45), prefrontal lateral (area 45), and ventral premotor (area 44) cortices as well as in the insula and the temporal cortex. Regarding the orbitofrontal cortex, only area 47/12 exhibited some

labeling. Finally, the strongest labeling for stereotyped behavior was observed in the orbitofrontal cortex (areas 47/12, 13 and 14). Additional labeling was noticed in the medial and lateral prefrontal cortex (areas 45 and 32). The overlapping cortical labelling among all three behavioral effects was observed in area 47/12. Areas 13 and 14 were associated with both erection and stereotypy, while area 24 was commonly associated with erection and apathy, and area 45 was associated with stereotypy and apathy (Figures 3 and 9).

Within the thalamus (Figure 4), the erection manifestation was associated with labeling in the ventral anterior (VA) and mediodorsal (MD) nuclei. The stereotyped behavior was linked to labeling in both the VA and MD as well as in the centromedian and parafascicular (CM/Pf) nuclei. Finally, the apathetic state was characterized by highly reproducible labelling in VA, MD and CM/Pf. All three behavioral effects were linked to the VA and MD thalamic nuclei, while CM/Pf was solely associated with stereotypy and apathy.

Within the mesencephalon (Figures 5 and 7), BDA-positive somas were observed in both the VTA and SNc, regardless of the type of behavior induced. Furthermore, in the SNc, neurons were restricted to the medial portion. The additional staining of tyrosine hydroxylase (TH) (Figures 5 and 8) and parvalbumin (PARV) (Figure 8) performed adjacently to the BDA-labeled sections, shows the presence of BDA-positive somas in both the VTA (Fig. 5, panels B, 1 and 2) and medial part of the SNc (Fig. 5, panels B, 1 and 3; Fig. 8, panels D and 1). Distribution of BDA-positive somas in the VTA and/or SNc was not specific to behavioral effects (Figure 7). Hence, far fewer BDA-positive neurons in the mesencephalic region of CA 34 and CA 37 were observed, which was consistent with the previous dopaminergic depletion of these two MPTP-recovered monkeys (Table 1).

Anterograde labeling relative to sexual manifestations, and stereotyped and apathetic states.

Figures 6, 7 and 8 present the general features of anterograde labeling in relation to the effects induced by bicuculline microinjections into the VS. In all cases, anterogradely-labelled fibers (Fig. 1 and panel D for photomicrographs) were found within the pallidal (Figure 6) and the VTA/SN (Figures 7 and 8) complexes. For sexual manifestations and stereotypy, we provide here the example with the strongest BDA labeling effect. For the apathetic state, the labeling on all three monkeys is illustrated to highlight the reproducibility of BDA staining.

Thus sexual manifestation was related to terminal fiber labeling in the medial part of both the external (GPe) and internal (GPi) globus pallidus (Fig. 6A) and the SNr (Fig. 7A). The apathetic-like state was also associated with a strong labeling in the limbic part of the GPe, GPi (Fig. 6C) and SNr (Figures 5B, 5C; 7C and 8F), but more laterally, and this was highly reproducible for all three monkeys. For all monkeys, we performed

immunostaining for tyrosine hydroxylase (TH) and parvalbumin (PARV) at the level of the SN on adjacent sections to those used for BDA labeling. While TH labels dopaminergic neurons, parvalbumin is a calcium-binding protein that is strictly confined to GABAergic neurons of the SNr (Parent et al., 1996). As shown on figures 5 and 8 in the case of apathy, we showed that the majority of BDA-positive fibers are in the SNr (Figures 5B, 5C and 8E, F) while BDA-positive soma were both in the VTA (Fig. 5C) and the SNc (Fig. 5C, 8D-E). Finally, the labeling underlying stereotyped behavior was found in the pallidal and nigral sub-territories, which were situated in between the other two behavioral effects (see Fig. 6D and 7D for merging). In addition to dense BDA-positive fibers in the SNr, a light labeling of BDA-fibers in the VTA was also observed for each behavioral effect. Finally, strong overlaps of labeling within the pallidum and SNr were observed between erection and stereotypy, compared to the apathetic state. Moreover, for the latter effect, labeling overlap with stereotypy was observed in the ventral pallidum and the SNr at caudal levels (Figure 7 at level AC - 7).

Discussion

In this study, performed in the NHP and combining local perturbation with monosynaptic axonal tracer injection into different parts of the VS, we found three distinct anatomo-functional circuits underlying the expression of three different behavioral disorders: sexual manifestations, stereotyped behaviors, and hypoactive state associated with loss of food motivation (Figure 9). These circuits involve both direct VS-GPi/SNr and indirect VS-VP-STN-GPi/SNr striatal pathways through both BG output structures, GPi and SNr, and are potentially modulated by DA neurons from VTA/SNc.

1) Impact of the experimental approach

In the present study, using a previously validated approach of anatomo-functional correlation (Worbe et al., 2013), we focused on behavioral effects obtained from VS and associated neuronal circuits. We first identified, by pharmacological microinjection, the striatal sites from which bicuculline could induce, from median to lateral VS, sexual manifestation (erection with ejaculation), repetitive grooming with licking/biting fingers or tail, and hypoactive state associated with loss of food motivation. We then injected BDA anatomical tracer in the identified striatal sites and finally analyzed the corresponding BDA-labeled cortico-BG circuits. The selected striatal sites were those for which we had a specific and reproducible response consisting of a strong behavioral effect with a short latency of appearance after bicuculline microinjection. The BDA labeling,

obtained retrogradely (somas) and anterogradely (fibers) in first order structures and observed from the three selected sites for each behavioral effect, showed good reproducibility. Furthermore, the labeling obtained from injections in the VS was in accordance with previous anatomical studies aimed at characterizing the connections of the VS (Selemon and Goldman-Rakic, 1985; Haber et al., 1995; Haber and McFarland, 1999; Haber et al., 2006). However, the strength and novelty of our study rely on establishing the link between behavioral dysfunctions specific to these different ventral striatal sites and cortico-BG networks involved in the behavioral effects.

Cortico-BG circuits of sexual manifestation

The sexual manifestation (erection) induced by reversible perturbation of the median territory of the primate VS, is associated with an anatomical circuit involving orbitofrontal, antero-medial (areas 10 and 11) and lateral prefrontal cortices, thalamic nuclei (VA and MD) and median elements of BG. Previous fMRI studies performed on healthy subjects (Redouté et al., 2000; Arnow et al., 2002; Walter et al., 2008) and PD patients with hypersexual disorder (Politis et al., 2013) showed that the activity of VS and medial prefrontal (areas 10, 11) was driven by visual sexual cues. Other regions such as the cingulate and orbitofrontal cortices are activated and might sustain other components than the sexual manifestation itself. A positive correlation has been found between the level of thalamic activation in the ventral lateral nucleus and the magnitude of erection in normal humans (Moulier et al., 2006). Of note, erection can be elicited in the NHP by electrical stimulation of the thalamic rostral pole (MacLean and Ploog, 1962), of the MD (MacLean et al., 1963) and of midline nuclei (Robinson and Mishkin, 1968). Taken together, these data suggest the direct involvement of these regions in sexual motivation, which is also broadly in accordance with the view that the neuronal network is involved in the erection, as described in our study. Nonetheless, our data highlight a more restricted network than those revealed by functional neuroimaging studies in humans. We specifically point to a neuronal network including the median part of the VS, the median prefrontal cortex (areas 10, 11) and the medial thalamus as key structures involved in the expression of erection (Georgiadis et al., 2010). In a normal condition, this medial circuit could be involved in sexual attraction (Bray and O'Doherty, 2007) and preference (Ponseti et al., 2006). In contrast, abnormal activity of this medial cortico-striatal circuit could drive hypersexuality, which has been observed in PD patients as a result of DA treatment.

Cortico-BG circuits of compulsive behavior and anxious state

The stereotyped behavior, driven by perturbation of the central territory of VS, suggests the expression of a compulsive behavior expressed by repeated action of grooming and licking/biting the fingers or tail (Fineberg et al., 2011; Robbins et al., 2012) or the induction of an aversive emotional state such as anxiety which is responsible for this subsequent behavior (Grupe and Nitschke, 2013). We hypothesize that our anatomical study could determine which of these processes is involved. In agreement with pure anatomical studies (Haber et al., 1995; Ferry et al., 2000), we found very dense labeling in the orbitofrontal cortex with a high level in the lateral part (area 12), a region known to be involved in abnormal behavioral persistence in rodent (Chudasama et al., 2003) and NHP (Clarke et al., 2008). An elegant study recently demonstrated that optogenetic stimulation of the lateral orbitofronto-striatal pathway in mice modulates pathological repetitive behavior (Burguière et al., 2013). In humans, compulsivity correlates with changes in the structure, connections and activity of the orbitofrontal cortex and the anterior striatum in OCD patients (Chamberlain et al., 2008; Ersche et al., 2011; Meunier et al., 2012; Milad et al., 2012; Beucke et al., 2013). Alternatively, the stereotyped behavior could reflect an anxious state. Indeed, anxiety disorders are associated with structural and functional orbitofrontal cortex abnormalities (Jackowski et al., 2012). In any case, the central region of the VS may be involved in the anticipation of aversive events during learning of avoidance (Jensen et al., 2003; Delgado et al., 2009). DBS of the ventral capsule and the adjacent VS has been used to treat refractory OCD in patients (Lipsman et al., 2007; Burdick et al., 2009; Greenberg et al., 2006; 2010) but can also produce behavioral expression of panic and fear (Shapira et al., 2006). DBS of the VS enhances extinction of conditioned fear in rodents (Rodriguez-Romaguera et al., 2012). Altogether, these results strongly suggest the involvement of the central VS and the lateral orbitofrontal cortex in a cortico-BG network processing aversive information related to an anticipation (with an anxious state) or to a behavioral manifestation (avoidance). Even with human neuroimaging studies, it is difficult to dissociate the brain regions involved in OCD from anxiety disorders (Radua et al., 2010). The role of the central VS in compulsivity and anxiety disorders needs further investigation.

Cortico-BG circuits of apathetic state and/or eating disorder

The last motivation disorder exhibited by our monkeys was an apathetic state associated with a loss of food motivation, driven by perturbation of the lateral territory of the VS. Whether this behavioral disorder is more likely to be related to a motivation disorder or an eating disorder has to be determined. In agreement with previous anatomical studies (Selemon and Goldman-Rakic, 1985; Haber et al., 1990; Parent et al., 1997; Haber et al., 1995; Kunishio and Haber, 1994; Chikama et al., 1997), we found an anatomical circuit involving different

cortical regions such as the orbital and medial prefrontal cortex, the insula, and limbic parts of the BG. In Parkinsonian monkeys, it was shown that the dopamine pathway loss in VS and VTA was predictive of behavioral expression of an apathetic state (Brown et al., 2012). Apathy is often observed after lesion of the prefrontal cortex (Eslinger and Damasio, 1985) or focal lesion of the caudate or pallidum (Ali-Cherif et al., 1984; Laplane et al., 1989). It is caused by a dysfunction of the prefrontal-BG network (Levy and Dubois, 2006; Lewy, 2012). In a positron emission tomography (PET) imaging study performed on PD patients, the binding of a non-selective ligand for dopamine and noradrenalin transporters in VS was inversely correlated with apathy (Remy et al., 2005). PD patients with apathy have a reduced dopaminergic tone in both the dorsal and ventral striatum and also in the prefrontal cortex (Thobois et al., 2010). In PD, high apathy scores correlate with low gray matter density in a number of cortical brain regions including the insula (Reijnders et al., 2010), a region in which we found high BDA labeling in our monkey model of hypoactivity associated with loss of food motivation. Numerous imaging studies in humans have documented that the insula, especially its anterior part, is involved in emotional control (Lamm and Singer, 2010). The feeling of disgust (Wicker et al., 2003) and vomiting (Catenoux et al., 2008) are strongly linked to activation of the anterior insula in humans. Increased activity is also found in the antero-ventral putamen and anterior insula in normal subjects experiencing nausea (Napadow et al., 2012). In the monkey, stimulation of the ventral part of the insula evokes affiliative behavior (with lip-smacking) while stimulation of its anterior part (both dorsally and ventrally) triggers food disgust (with facial grimace) (Caruana et al., 2011; Jezzini et al., 2012). It was notable that in our monkey model, bicuculline microinjection in the ventrolateral VS could elicit food refusal, even vomiting (Worbe et al., 2009). So far, the BDA labeling observed in the anterior insula strongly supports a link with this negative emotional state and might therefore orientate the implication of the lateral VS in a circuit engaged in the restraint of food intake, as in rodents (Jean et al., 2007; 2012), through negative outputs such as disgust and vomiting. In support of this hypothesis, some BDA labeling is specifically observed in ventral premotor regions (areas 44, 6V), that are involved in preparation and execution of grasping movements (Hoshi and Tanji, 2007) and mouth action related to ingestive functions (Ferrari et al., 2003). The orbitofrontal and temporal cortices, whose activities have been linked to the severity of appetite loss in patients with Alzheimer's disease (Ismail et al., 2008) and a feeling of satiety in healthy controls (Hinton et al., 2004) were also characterized by important BDA labeling. Activity in the ventral pallidum and orbitofrontal cortex is also modulated by food pleasantness inferences in healthy subjects (Simmons et al., 2014). Overall, our results suggest that we identified an area in VS engaged in the

control of food seeking, and potentially involved in eating disorders such as binge eating, obesity, anorexia or bulimia.

2) Interactions between the cortico-BG circuits of motivation and BG intrinsic organization

In our previous NHP study (Worbe et al., 2013), which was aimed at characterizing cortico-BG circuits underlying hyperactivity and motor tics, symptoms characteristic of Tourette's syndrome, we had few overlaps from one functional territory to another. In the present study, combining behavior and anatomy, we identified the cortico-BG circuits underpinning three different motivation disorders elicited from different limbic sub-territories of the VS. Interestingly, we obtained a clear medio-lateral gradient for positive and negative motivation and found many more overlaps at both cortical and subcortical levels (Figure 9). The lateral orbitofrontal cortex (area 12/47) and the anterior cingulate cortex (areas 32/24) are known to be involved in aversive anticipation (Bolstad et al., 2013) and promote active behavioral response to avoid an aversive context (Jensen et al., 2003; Amemori and Graybiel, 2012; Klavir et al., 2013). The emphasizing of these cortical regions in behavioral disorders fits well with these data since stereotypy and food apathy are related to an anxious- and avoidance-state respectively. At the BG level, we observed overlaps between the behavioral responses (in particular, sexual manifestation and stereotyped behavior) in both the pallidal complex and the SN. Apathy shows overlaps with erection and stereotypy in the ventral pallidum and the caudal SNr. Beyond this overlap phenomenon, the data further show that both the GPe and GPi are labeled independently of the behavioral effect involved, suggesting that both direct and indirect BG pathways mediate the behavioral expression of these motivation disorders. Although the subtypes of striatal neurons on which bicucullin acts are unknown, it is clear that in each territory of VS, the intra-striatal organization involves the presence of efferent striatal neurons of the direct or indirect pathways, whose actions are supposed to be opposed: the direct pathway facilitating motivation and the indirect pathway inhibiting this motivation or another one (DeLong, 1990; Tremblay et al., 2009). In addition the two output BG structures GPi and SNr are systematically labeled whatever the motivation behavior expressed, suggesting the involvement of several processing loops. We also found retrograde labeling in the VTA/SNc region, a result in agreement with known projections of DA neurons to the VS (Parent et al., 1983; Lynd-Balta and Haber, 1994). The regions of overlap could be the substrates where motivation domains influence each other and influence attention and motor functions (Figure 9). As motivation impacts on attentional processes and action initiation, we compared the cortico-BG circuits involving motivation (VS) disorders with the cortico-BG circuits of attention (caudate) and action (putamen) disorders that we have

previously described (Worbe et al., 2013), and we show the results of this comparison in Figure 9. Crucially, our data highlight that, despite the existence of distinct neuronal circuits for each reported behavioral effect, there are several convergent cortical and BG levels. From a clinical point of view, these data might give insights into mechanisms towards certain neuropsychiatric disorders that may be caused through dysfunctions inside different functional domains (for example, Bipolar disorder, Anorexia Nervosa), or concerning psychiatric comorbidities involving dysfunction inside different motivation domains (for example, OCD/Anxiety or Anxiety/Anorexia or Impulsivity/Bulimia).

3) Potential implications for future therapeutic options

This study brings a set of new information that could be used to better understand and orientate research on future therapeutic strategies for motivation disorders. One interesting feature of our study is that positive and negative motivational/emotional states are independent of the integrity of the DA system, as the three different behavioral effects could still be induced in partially DA depleted monkeys. Moreover, the majority of BDA-positive fibers terminate in the SNr and not in the SNc for all behavioral effects. DA neurons are mutually connected to VS (Haber, 2003; Haber and Knutson, 2010) and have projections on both segments of the pallidum (Jan et al., 2000). Dopamine can therefore modulate the behavioral effects at several levels, including the VS itself, and the principal output of these cortico-BG circuits, GPi and SNr, the latter via dendritic release (Cheramy et al., 1981). Therefore, without being required for behavioral expression, the DA projections can certainly act as important modulators. In this respect, DA dysfunction is involved in behavioral disorders affecting these three types of motivation, as seen for example in disorders of impulse control in Parkinsonian patients treated with selective DA receptor agonists (Weintraub et al., 2010). As an example, the D3 receptor subtypes, which are enriched in the limbic cerebral regions (Sokoloff et al., 1990) including the VS (Morissette et al., 1998), would explain the beneficial effects of D2/D3 DA receptor agonists on motivational deficits in Parkinsonian rats (Favier et al., 2014) or on apathy in PD patients (Thobois et al., 2013).

Altogether, our data could be interesting for further consideration of deep brain stimulation (DBS) targets for these motivation disorders. Indeed, previous studies have shown the efficacy of DBS targeting the VS for treatment of OCD in humans (Greenberg et al., 2010). Our data suggest that treatment involving the VS or “limbic parts” of the thalamus could be applied for treating phobias or panic disorders resistant both to pharmacological and behavioral therapy. In Tourette’s syndrome, several targets have been tested for DBS including the VS (Williams and Okun, 2013), and the anterior part of the GPi or CM/Pf (Welter et al., 2008).

Our data point to the involvement of both output structures in behavioral disorders and tic-like movements. So far, DBS applied to the targets of the GPe or STN may be the best therapeutic approach as both send projections to both output structures (GPi/SNr). The ventral pallidum has never been used and more studies are required to validate the use of such a target to reverse motivation disorders. Our monkey model is suitable for discovering new DBS therapeutic targets. We have shown in a previous study the efficacy of DBS applied to anterior STN to suppress stereotyped behavior induced from the limbic GPe (Baup et al., 2008). STN DBS is now used to treat OCD in humans (Mallet et al., 2008). It remains to investigate whether STN DBS might reduce an anxious state (produced from the central VS) or food refusal (produced from the lateral VS) in our monkey model of behavioral disorders. The question of DBS as a treatment option for anorexia nervosa has now also been raised (Oudijn et al., 2013). Conceptually, the demonstration that STN DBS might reduce such behavioral disorders, would support the hypothesis that STN can brake action, cognitive and motivational processes as well (Mink, 1996; Nambu, 2002; Baunez and Lardeux, 2011).

Conclusion

We addressed the anatomo-functional circuits underlying the expression of sexual manifestations, compulsive behavior and an anxious state, as well as an apathetic state and/or eating disorders, respectively induced by dysfunction of the medial, central and lateral parts of the VS. We demonstrated the existence of three cortico-BG circuits with partial overlaps in the orbitofrontal cortex and limbic parts of both GPi/SNr output structures, suggesting interactions between motivation domains. The behavioral expression of these motivation disorders was independent of an intact DA system and required both direct and indirect pathways, suggesting that STN DBS could be efficient in treating medication-resistant behavioral disorders.

Table and Figures legend

Table 1: Characteristics and consequences of MPTP intoxication.

Figure 1: The biotin dextran amine (BDA) was used as an anatomical antero/retrograde tracer to identify the neuronal circuits involved in the expression of the different behavioral disorders. Injection of BDA was done on 10 monkeys on which the striatal site of injection induced specific behavioral disorders with bicuculline. BDA can label (A) anterogradely structures of projection (such as pallidal and nigral complexes) and (B) retrogradely neurons innervating the striatum (such as cortical, thalamic and nigral dopaminergic neurons). (Panels C and D):

Photomicrographs at low (x4) and high (x40, insert 1 in C and 2 in D) magnifications of coronal sections of *macaca fascicularis* MI 66, exemplifying retrograde and anterograde BDA labelling obtained at the level of cortical area 24 (C) and GPi (D), respectively. Abbreviations: BDA, Biotin Dextran Amine; Cx, Cortex; GPe, external Globus Pallidus ; GPi, internal Globus Pallidus ; SNc, Substantia Nigra pars compacta; SNr, Substantia Nigra pars reticulata; WM, White Matter.

Figure 2: Schematic representation of the functional (A) and behavioral (B) territories, as well as BDA injection sites (C) from which different behaviors, namely erection (in green), stereotypias (in blue) and apathy (hypoactivity associated to an alteration of motivation for food) (in orange) were induced following bicuculline injection. In panels D, G, J, example of photomicrographs of striatal sections showing the BDA injection site (*) for sexual manifestation (D), stereotypias (G), apathy (J), respectively obtained from three *macaca fascicularis* MI 64, MI 65 and MI 66. In panels E, H, K, the histograms show the behavioral effects for bicuculline microinjections producing erection (E), stereotypy (G) or apathy (I) (that include 3 monkeys for each behavioral effect). In panels F, I, L, the histograms show the percentage of initiated choices during execution of the simple food retrieval task for monkeys exhibiting sexual manifestation (F), stereotyped behavior (I) and apathetic state (L). Abbreviations: cc, Corpus Callosum; Cd, Caudate nucleus; ic, internal capsule; IV, lateral Ventricle; Put, Putamen; VS, Ventral Striatum.

Figure 3: Histogram (A) representing the mean percentage of maximal labelling in different cortical and subcortical regions (data from three injections for each behavioral effect). Erection, stereotypy and apathy are respectively represented in green, blue and orange. Graphical representation (B1 to B5) of coronal hemi-brain sections interspaced from anterior to posterior levels to illustrate the cortical distribution of BDA positive cells relative to erection, stereotypy and apathetic state (respectively in green, blue and orange). All labelled regions are referred in accordance with Brodmann's classification. Abbreviations: Ins, Insula; OPAI, orbital periallocortex; OPRO, orbital proisocortex; ProM, promoter cortex; Temp, Temporal cortex.

Figure 4: Schematic representation of BDA labelling distribution in the thalamus at three different anteriority levels according to the anterior commissure. (A) Distribution of BDA-positives cells when erection was induced in monkey CA 37. (B) Distribution of BDA-positives cells when stereotypy was induced in monkey CA 34. (C) Three distributions of BDA-positives cells when apathy was induced in monkeys MI 70, MI 69 and MI 66. Note

the reproducibility of the labelling among the injections. (D) Merging (erection in green, stereotypy in blue, apathy in orange). Abbreviations: AC, Anterior Commissure; CM/Pf, Centromedian and Parafascicular nuclei; MD, Mediodorsal nucleus; VA, Ventral Anterior nucleus; VL, Ventral Lateral nucleus.

Figure 5: Photomicrographs at low (x 2.5 or x 6.3) and high (x 16) magnifications of adjacent coronal sections labelled for TH (panel A) and BDA (panels B, 1, 2 and 3) at the mesencephalic level (AC - 7) for *macaca fascicularis* MI 66 that did exhibit an apathetic state. While both the SNc and VTA are visualized on panels A, B (x 2.5) and 1 (x 6.3), VTA and SNc at higher magnification (x 16) are respectively shown on panels 2 and 3. Note that BDA-positive somas can be found in both VTA and SNc. Note also the presence of BDA-positive fibers (star) in the medioventral part of the SNr (panels B, x 2.5 and 1, x 6.3). Abbreviations: III, third cranial nerve; BDA, Biotin Dextran Amine; Ru, Red nucleus; SNc, Substantia Nigra pars compacta; SNr, Substantia Nigra pars reticulata; TH, Tyrosine Hydroxylase.

Figure 6: Schematic representation of BDA terminal fibers labelling distribution in the pallidal complex at four different anteriority levels according to the anterior commissure. (A) Distribution of BDA-positives fibers when erection was induced in monkey CA 37. (B) Distribution of BDA-positives fibers when stereotypy was induced in monkey CA 34. (C) Three distributions of BDA-positives fibers when apathy was induced in monkeys MI 70, MI 69 and MI 66. (D) Merging (erection in green, stereotypy in blue, apathy in orange). Abbreviations: AC, Anterior Commissure; GPe, external Globus Pallidus; GPi, internal Globus Pallidus.

Figure 7: Schematic representation of BDA terminal fibers and somas labelling distribution in the mesencephalic region at four different anteriority levels according to the anterior commissure. (A) Distribution of BDA-positives fibers and somas when erection was induced in monkey CA 37. (B) Distribution of BDA-positives fibers and somas when stereotypy was induced in monkey CA 34. (1) Photomicrograph at low magnification (x 6.3) of a coronal section labelled for BDA at the mesencephalic level (AC - 6) for CA 34. Note the presence of BDA-positive somas (arrows) in VTA and of BDA-positive fibers (stars) in both VTA and SNr. (C) Three distributions of BDA-positives fibers and somas when apathy was induced in monkeys MI 70, MI 69 and MI 66. (D) Merging (erection in green, stereotypy in blue, apathy in orange). Dashes lines separate SNc from VTA medially and from SNr laterally. Abbreviations: SNc, Substantia Nigra pars compacta; SNr, Substantia Nigra pars reticulata; VTA, Ventral Tegmental Area.

Figure 8: Photomicrographs at low (x 2.5 or x 4) and high (x 40) magnifications of adjacent coronal sections labelled for TH (panels A, B, C and 2), BDA (panels D, E, F, 1 and 3) and PARV (panels G, H, I and 4) at the nigral level (AC - 6) for *macaca fascicularis* MI 66 that did exhibit an apathetic state. While both pars compacta and pars reticulata are visualized on the central panels (x 2.5 magnification; B, E and H), pars compacta and pars reticulata at higher magnification (x 6.3, x 40) are respectively shown on left (A, D, G, 1, 2) and right (C, F, I, 3, 4) panels. Note that BDA-positive somas are found in the SNc, while BDA-positive fibers are found in the SNr. Abbreviations: TH, Tyrosine Hydroxylase; BDA, Biotin Dextran Amine; PARV, parvalbumin; CP, Cerebellar Peduncle; SNc, Substantia Nigra pars compacta; SNr, Substantia Nigra pars reticulata.

Figure 9: Schematic summary of the comparisons of the cortico-BG circuits underlying behavioral disorders, i.e. sexual disorders, anxiety and food disorders, induced from pharmacological perturbation of the ventral (current study) and dorsal (from Worbe et al., 2013) striatum. Color code is as follows: Erection in green, Stereotypy in blue, Apathy in orange, Hyperactivity and simple tic in yellow.

Conflict of interest

The authors declare that they have no conflict of interest.

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Figure 1

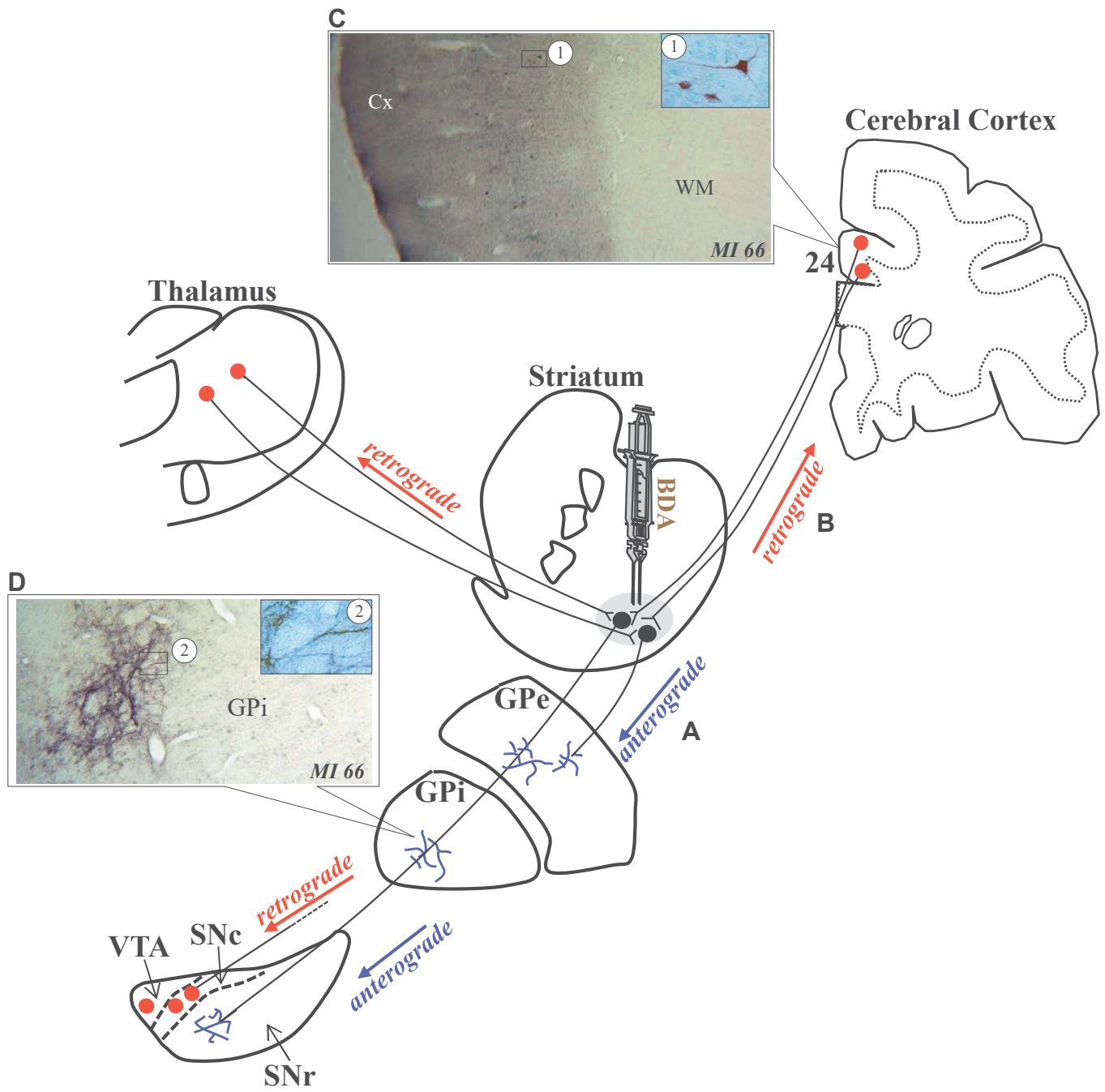


Figure 2 New

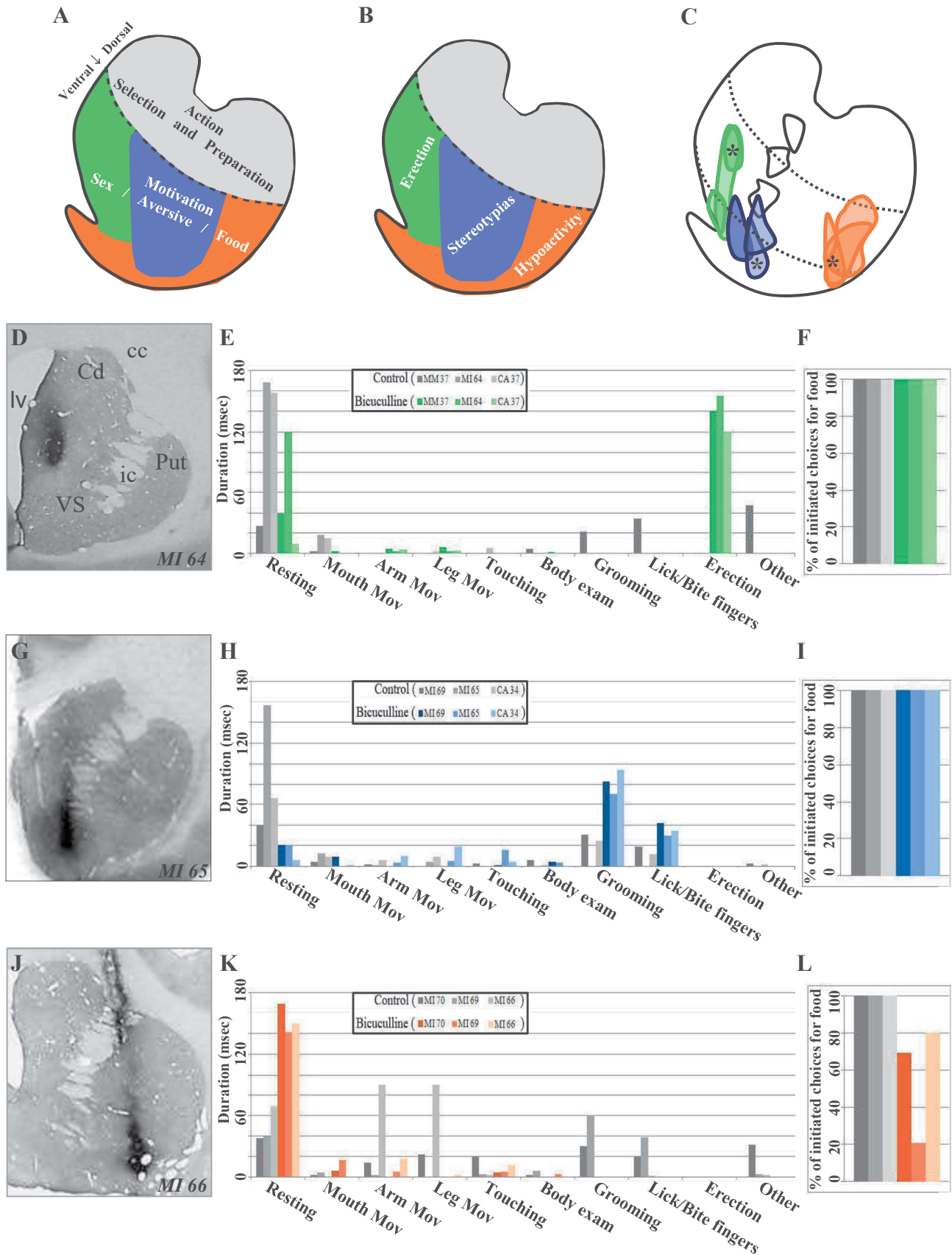
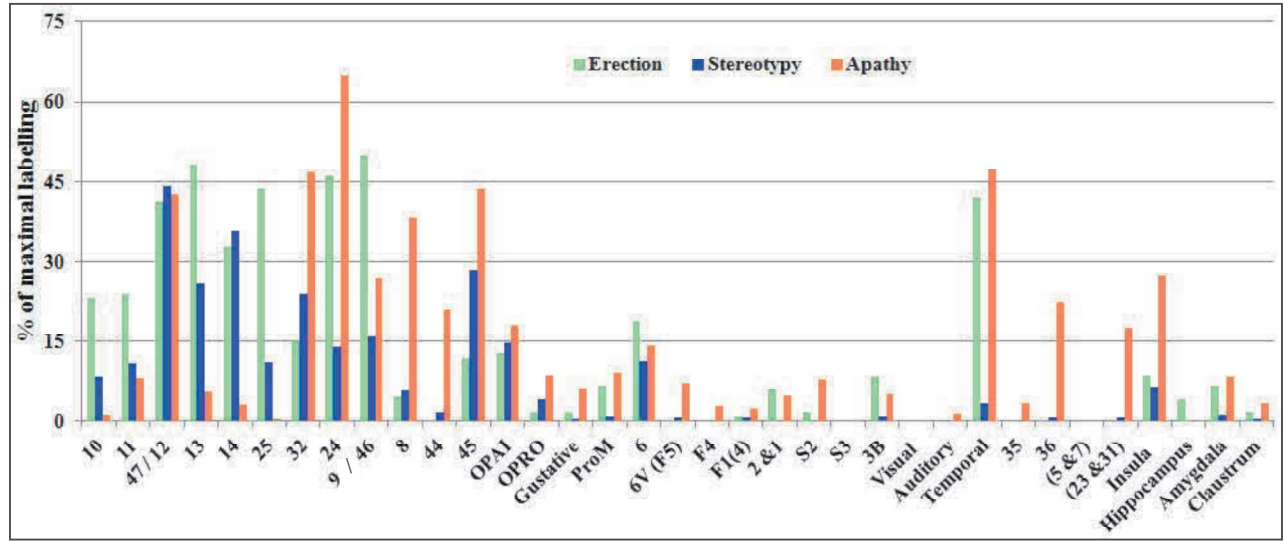
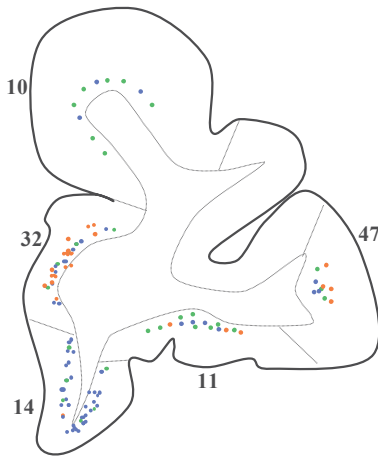


Figure 3

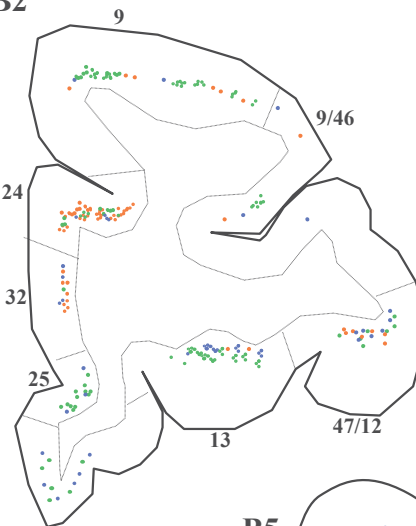
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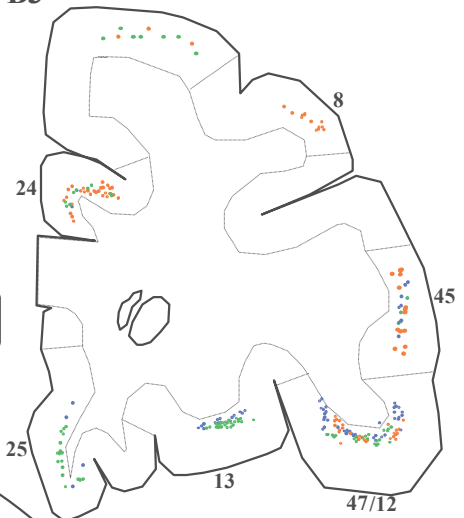
B1



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B4



B5

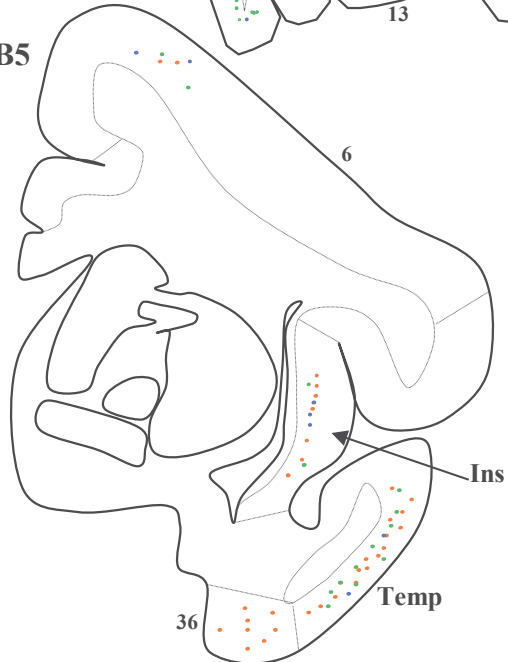


Figure 4

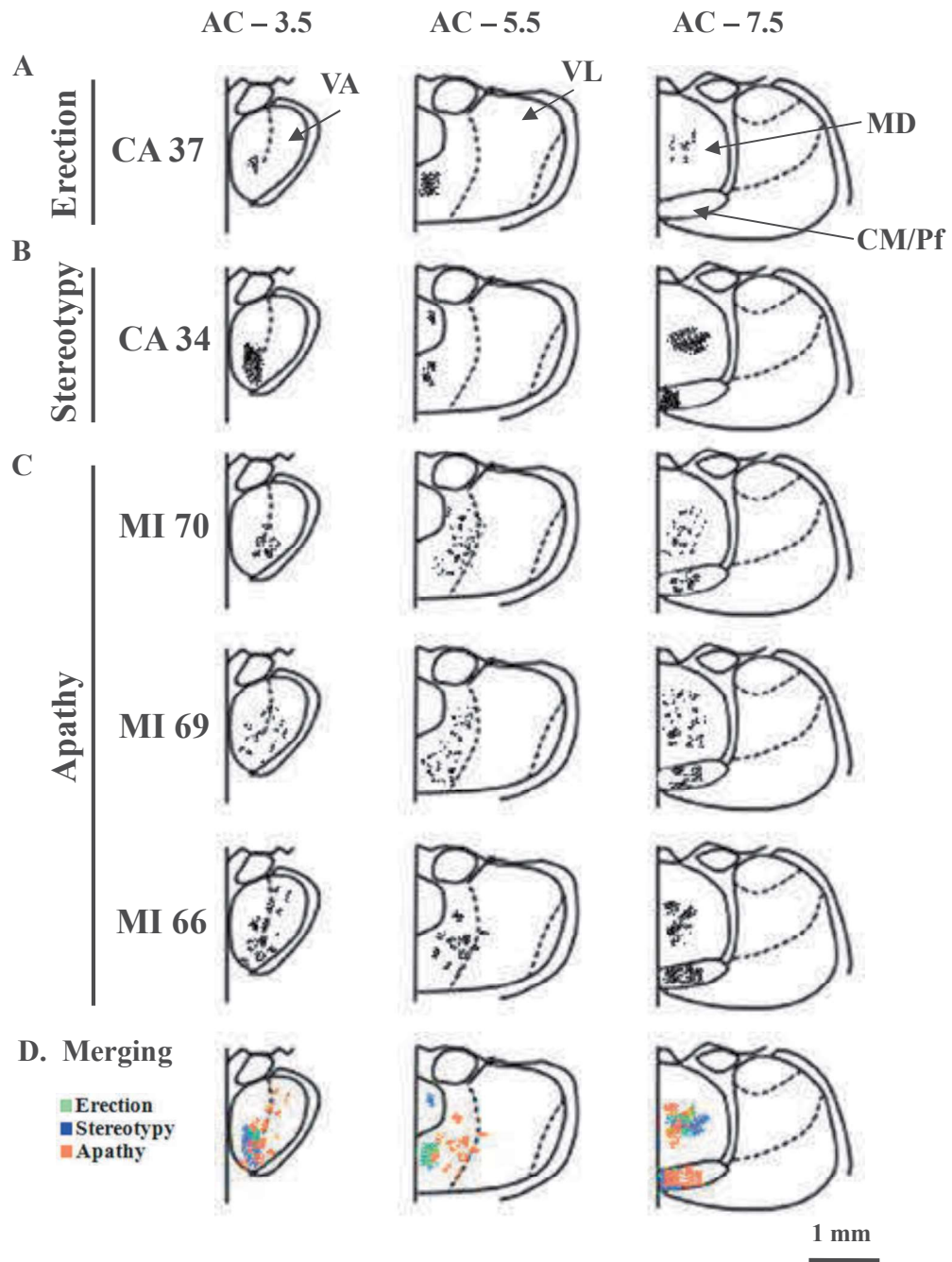


Figure 5

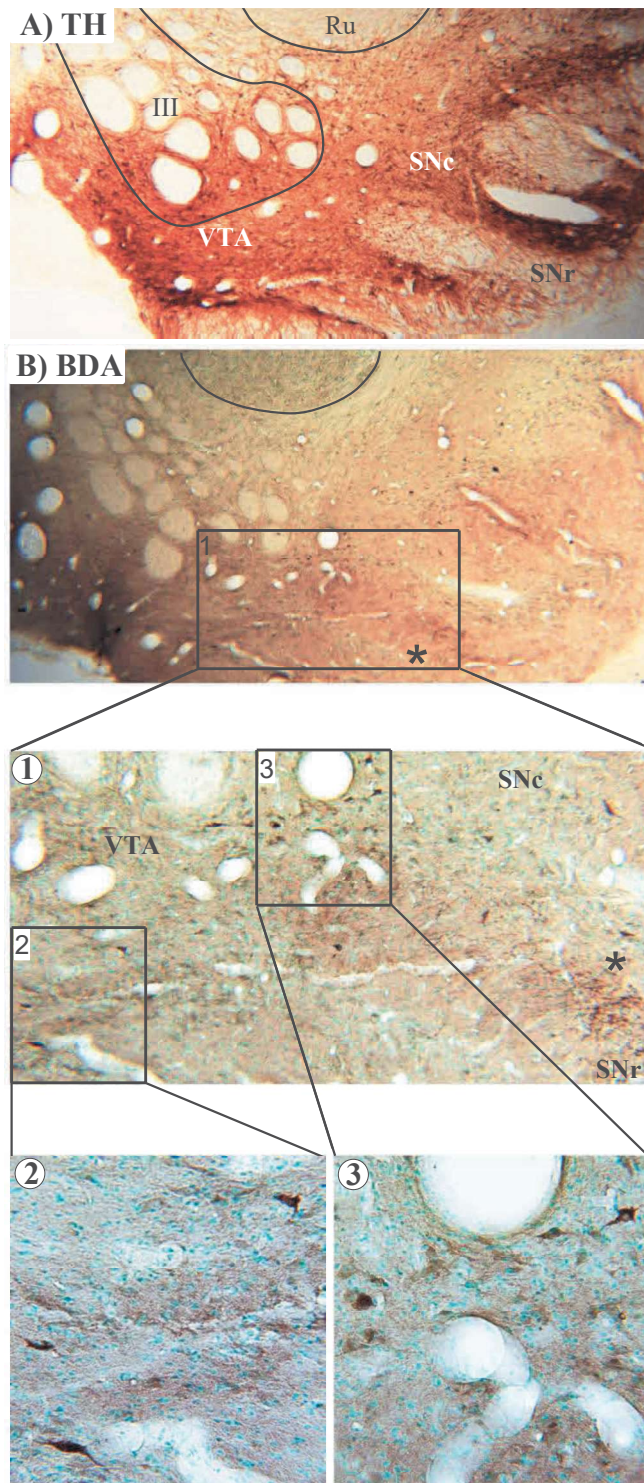


Figure 6

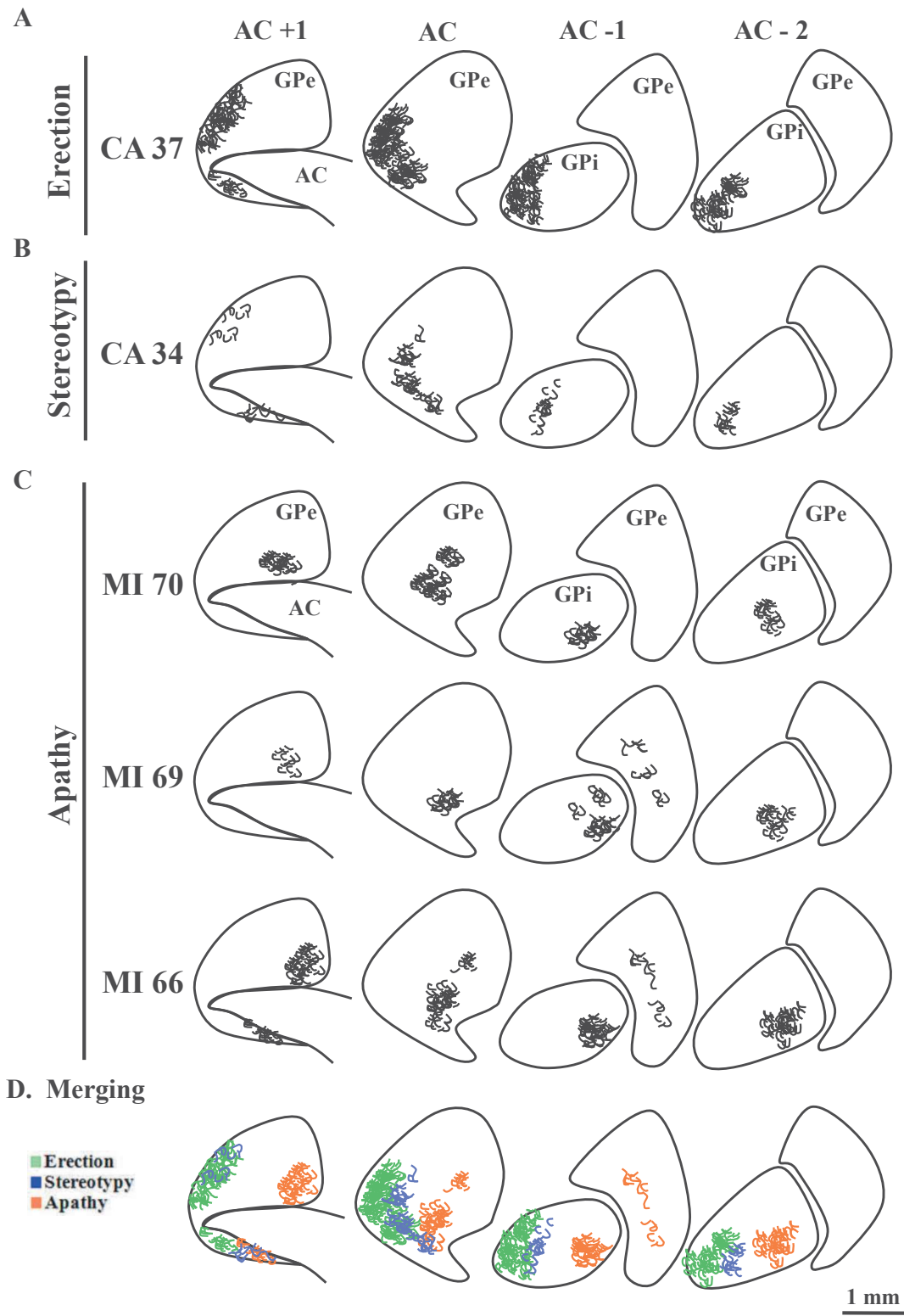


Figure 7

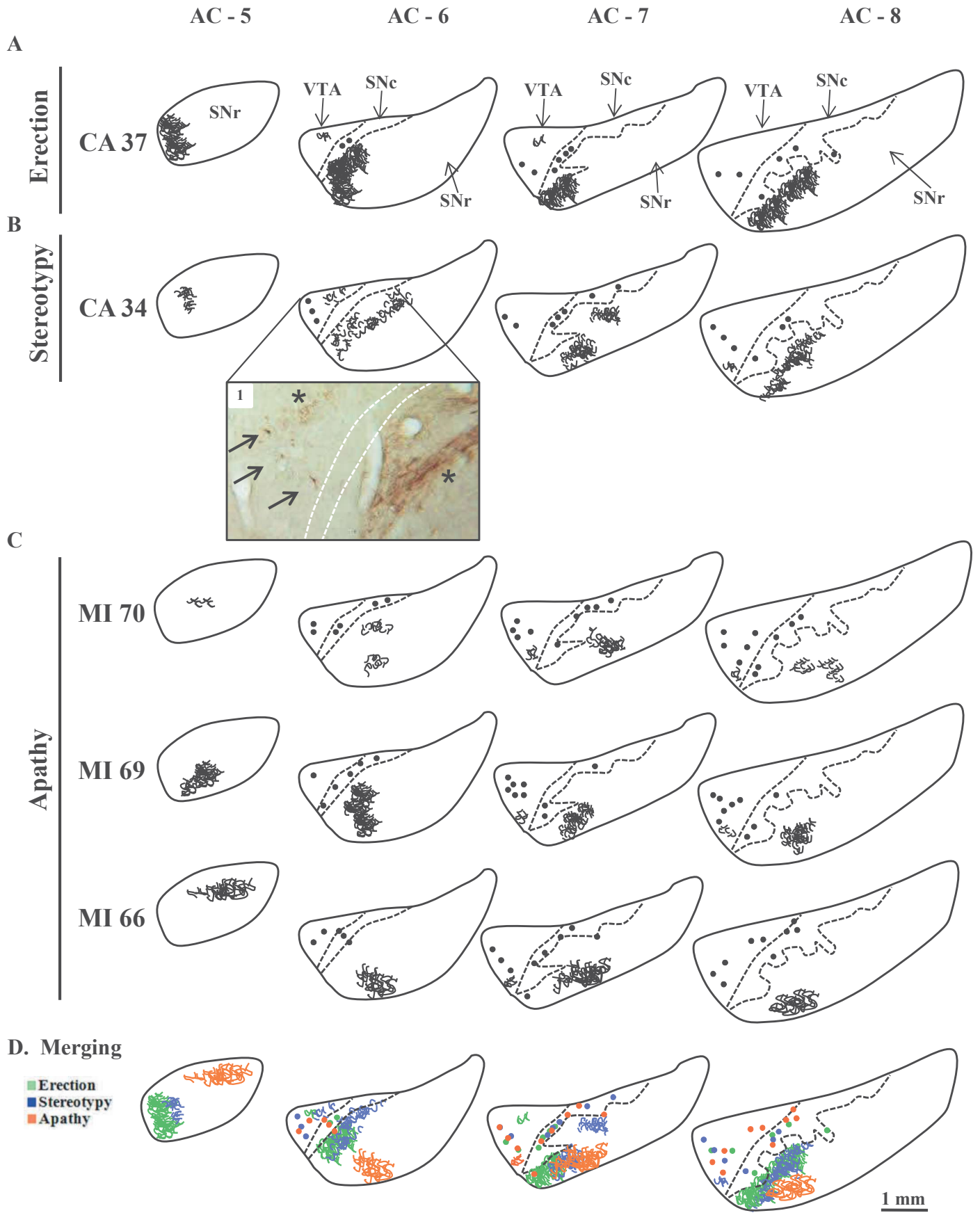


Figure 8

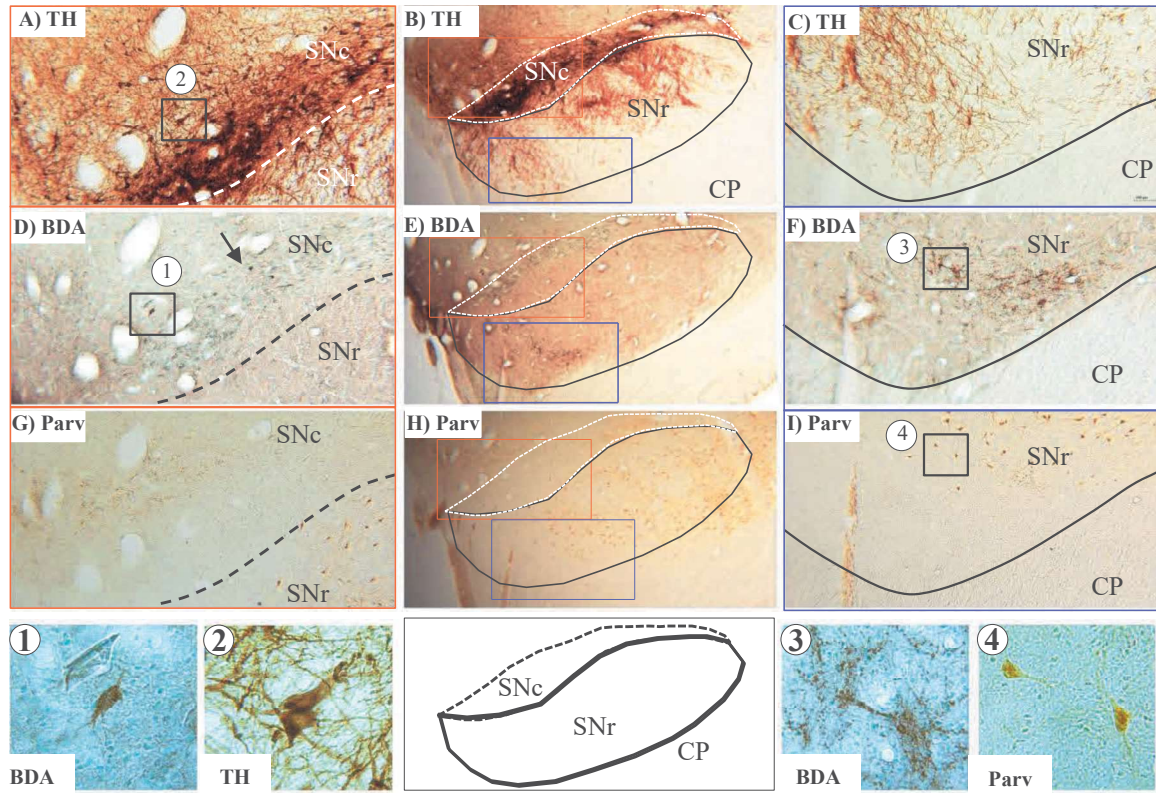


Figure 9

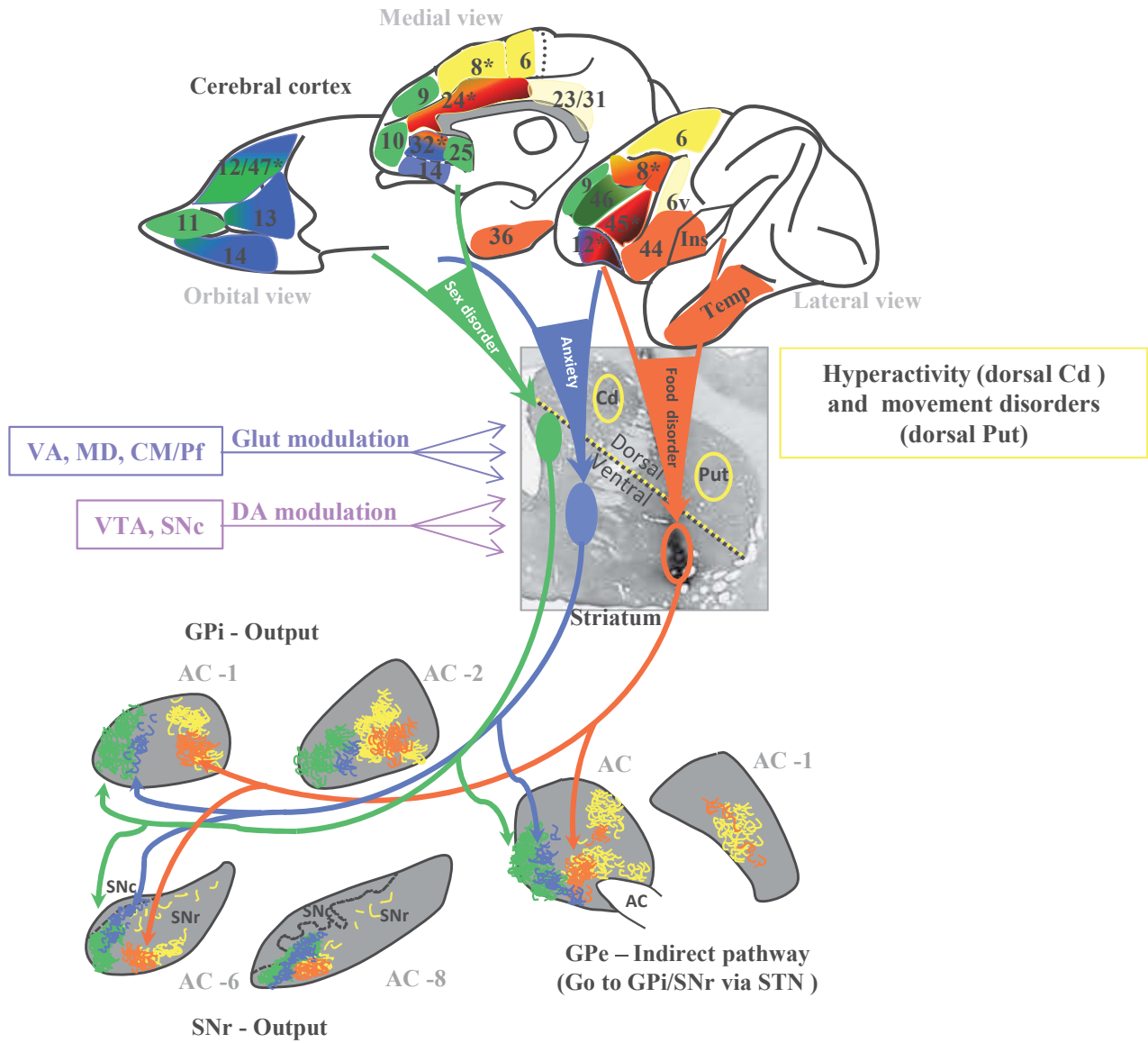


Table 1

Monkeys	MPTP injections	MPTP cumulative dose (mg/kg)	Maximal motor score	DA cell loss (%)	Recovery time (weeks)	Score at recovery	Homecage activity (% of control state)	
							At the symptomatic peak	After recovery
CA 34	4	1,4	12	68	4	0	18	106
CA 37	4	1,3	22	78	7	2	1	111
MF-2	3	1,2	25	73	12	0	15,6	100