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Long-term functional consequences of quinolinic acid striatal lesions and their alteration following an addition of a globus pallidus lesion assessed using pharmacological magnetic resonance imaging

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Abstract

The present study tested the hypothesis that lesion to the rat globus pallidus (GP) can "normalize" the functioning of the basal ganglia–thalamocortical circuits in striatal-lesioned rats by assessing the functional connectivity of these regions using functional magnetic resonance imaging (fMRI). Changes in brain activation following systemic administration of amphetamine were assessed in (1) rats sustaining a unilateral lesion to the striatum, (2) rats sustaining a combined striatal and pallidal lesion, and (3) control rats. Striatal-lesioned rats showed attenuated cortical activation following amphetamine administration and lower correlations between the responses to amphetamine in different brain regions compared to control rats. Although the addition of an excitotoxic GP lesion failed to prevent striatal lesion-induced attenuation of cortical activation by amphetamine, it was effective in "normalizing" the correlations between the responses to amphetamine in the different areas. These results suggest that, although the GP lesion is ineffective in correcting the global changes in activity caused by the striatal lesion, it may have the capacity to partially restore alterations in functional connectivity resulting from the striatal lesion. These results are further discussed in view of our previous demonstration that lesions to the GP can reverse several behavioral deficits produced by a striatal lesion.

Keywords: fMRI; Basal ganglia circuitry; Striatal lesion; Pallidal lesion; Animal studies; Amphetamine

Introduction

It is widely accepted that the frontal cortex and basal ganglia operate in tandem to produce behavioral output and that disruption of the circuits linking these structures underlies several of the most debilitating psycho- and neuropathologies. An important assumption of current views of basal ganglia–thalamocortical circuitry is that behavioral symptoms resulting from damage to a station within the circuit reflect dysfunction of the circuit as a whole and can therefore be alleviated by manipulations of a different component of the circuit. To date, most of the support for this notion has come from the demonstration that in Parkinson's disease patients and in parkinsonian non-human primates a lesion to the internal segment of the globus pallidus (GP) or to the subthalamic nucleus (STN) alleviates symptoms resulting from degeneration of dopaminergic neurons (Alterman and Kelly, 1998; Baron et al., 2000; Bergman et al., 1990; Lai et al., 2000; Marsden and Obeso, 1994). Recently, we have advanced a similar approach with regard to another basal-ganglia-related disorder, in which the primary pathology is degeneration of striatal neurons, namely, Huntington's disease (Joel, 2001; Joel and Weiner, 1997; Joel et al., 1998). Using a rat model of this disease, namely, quinolinic acid lesions to the striatum, we (Ayalon et al., 2004; Joel et al., 1998, 2003) have shown that behavioral deficits resulting from the striatal lesion can be ameliorated by an excitotoxic lesion to the GP (the rat analogue of the primate external segment of the GP).

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These data suggest that lesion to the rat GP "normalizes" the functioning of the basal ganglia–thalamocortical circuits in striatal-lesioned (Adachi et al., 2001) rats. The aim of the present study was to test this hypothesis by assessing the functional connectivity of these regions using functional magnetic resonance imaging (fMRI). The most common use of fMRI is the assessment of regional cerebral changes in blood flow, blood volume, and/or blood oxygenation using 'blood oxygen level dependent' (BOLD) contrast. The BOLD sequence is typically used to assess changes in brain activation associated with sensory stimulation and task performance in conscious humans but has also been applied to investigate changes in brain activation in response to pharmacologic challenges in both humans and animals (Chen et al., 1997; Willson et al., 2004). The present study combines two recent uses of the latter approach, namely, the assessment of changes in brain activation in response to pharmacologic challenges in lesioned animals (Chen et al., 1997, 1999; Nguyen et al., 2000) and the assessment of changes in functional connectivity following a pharmacological challenge (Li et al., 2000). The latter use was developed on the basis of Friston et al.'s (1993) definition of functional connectivity as the temporal correlation of a neurophysiological index measured in different brain areas.

The present study therefore used a pharmacological challenge to assess the temporal correlations between the BOLD signal in different brain regions in control rats, in rats sustaining a unilateral lesion to the striatum, and in rats sustaining a combined striatal and pallidal lesion (i.e., "treated" rats; the pallidal lesion was performed at the same time as the striatal lesion). We expected different patterns of activation in rats sustaining a striatal lesion compared to rats with intact striatum and hypothesized that the pallidal lesion would lead to a normalization of the activation pattern in striatal-lesioned rats. Because the basal ganglia are rich in dopaminergic innervation, the dopamine releaser and transport blocker, amphetamine, was used. This drug has previously been shown to lead to changes in brain activity that can be detected using fMRI in rats (Chen et al., 1997; Dixon et al., 2005; Nguyen et al., 2000).

Materials and methods

Subjects

Thirty six Wistar male rats approximately 4 months old weighting 400–500 g at the time of surgery. Rats were housed four in a cage with food and water ad libitum, under reversed cycle lighting (lights on 19:00–07:00). All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of the Tel Aviv and Hebrew Universities.

Surgery

Prior to surgery, rats were injected with diazepam (8 mg/kg i.p) and anaesthetized with avertin (10 ml/kg, i.p.). They were placed in a stereotaxic frame, and an incision was made into the scalp to expose the skull. The vertical coordinates of bregma and lambda were measured in order to align them in same (level head) plane. Lesion coordinates were according to the atlas of Paxinos and Watson (1986). All lesions were performed unilaterally, on the left hemisphere. *Striatal lesion.* Twenty six-gauge cannulae were vertically lowered into the brain through holes drilled in the skull. The striatal coordinates were: 1.0 mm anterior to bregma, 2 mm lateral to the midline, and 5 mm ventral to dura. One microliter of QA was infused using a manually driven pump (Kopf, microinjection unit, model 5000) over 3 min. QA (Sigma Chemicals) was dissolved in 1 N NaOH and diluted with phosphate-buffered saline (PBS) to a final pH of 7.4 and a concentration of 120 nmol/μl. The cannula was left in place for additional 5 min to reduce upward diffusion of the solution. *Pallidal QA lesion*. The pallidal lesion was performed at the same time as the striatal lesion. 0.3 μl of QA (120 nmol/μl) was infused at the coordinates: 0.6 mm posterior to bregma, 3.3 mm lateral to the midline, and 5.5 mm ventral to dura. *Sham lesion.* Same as the striatal lesion, but PBS was injected instead of QA, at coordinates 1 mm more dorsal than those used in the striatal lesion. Sterispon was used to cover the holes in the bone, the scalp incision was sutured by Michel clips, and an additional dose of 3 mg/kg diazepam was given about 30 min following surgery. Thirty six rats were assigned to four experimental groups: striatal lesion (n = 12), combined striatal and pallidal lesion (n = 12), sham-operated (n = 6), and unoperated (n = 6).

MRI

One month after the operation, rats were anesthetized by Nembutal (40 mg/kg, i.p.) and placed in a 47/40 Bruker-Biospec 4.7 T MRI device (Bruker Biospec 4.7 T system). A transmit/receive 20-mm surface coil (customer build volume coil of 5 cm diameter), placed over the skull and centered over the rat midline, was used. For structural imaging, seven 1 mm width anatomical axial images were recorded: TR = 300 ms, TE = 13 ms, matrix size = 256 × 256, FOV = 2.56 cm. For functional imaging, gradient echo images were acquired using FLASH sequence: TR = 605 ms, TE = 40 ms, matrix size = 128 × 64, FOV = 2.56 cm, acquiring seven 1 mm thick slices over 77 s. After 12.9 min of baseline recording (pre-drug period), rats were injected i.p. with amphetamine and tested for additional 64.5 min. Thus, each slice was acquired 10 times during the pre-drug period and 50 times following drug administration.

Given the well-documented anatomical connections between the striatum and the prefrontal cortex (Beckstead,

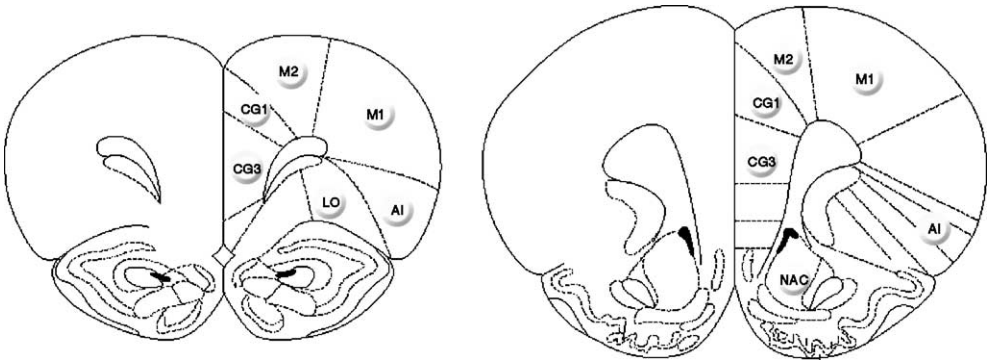

Fig. 1. ROIs defined: agranular insular cortex (AI), primary motor cortex (M1), secondary motor cortex (M2), cingulate gyrus 1 (CG1), cingulate gyrus 3 (CG3), lateral orbital cortex (LO), nucleus accumbens (NAC), and the thalamus (which does not appear in the figure since it was measured at 1.3 mm posterior to bregma).

1979; Berendse and Groenewegen, 1990, 1991; Berendse et al., 1992; Cesaro et al., 1985; Groenewegen et al., 1990; McGeorge and Faull, 1989; Parent, 1990; Reep et al., 1984; Sesack et al., 1989), 13 different anatomical regions of interest (ROI) were manually defined bilaterally on BOLD images (see Fig. 1). For each ROI, the proportion of change in each time point relative to the mean behavior of the area during the 12.9 min pre-drug recordings was calculated. Changes in BOLD signal reflect modulation in the ratio of oxy- and deoxy-hemoglobin in blood vessels (Fox and Raichle, 1986; Seiyama et al., 2004). Because a change in this ratio can reflect blood flow and/or blood volume modulations[1] and because the present study aimed to identify neuronal response to drug injection without differentiating between responses generated due to blood flow or blood volume modulation, we used the absolute values of change in BOLD signal relative to baseline. The absolute proportion of change over 10 consecutive time points (i.e., over 12.9 min) was averaged and multiplied by 100, thus creating five values after drug administration representing the percent of change relative to baseline throughout time.

Statistical analysis

In order to assess the effects of striatal lesion and combined striatal and pallidal lesion on the reaction to amphetamine administration, the average percent of change after drug administration was compared between the three experimental groups (control, striatal, and combined) by means of 3 × 5 × 2 × 13 mixed model ANOVAs with a between subjects factor of condition (operation) and repeated measures of time after drug injection (five periods of 12.9 min), hemisphere (left (lesioned) vs. right (non-lesioned)), and anatomical region (the 13 ROIs defined above).

To assess changes in functional connectivity between the ROIs, the inter-structural correlations within each rat were calculated for the absolute values of the 50 time points of change in BOLD signal relative to baseline. Next, for each of the three experimental groups, the individual inter-structural correlations of all the rats in the group were averaged to create a mean inter-correlation matrix.

Drugs

Amphetamine (Sigma) was dissolved in saline to a concentration of 2 mg/ml and injected in a volume of 1 ml/kg.

Results

Anatomical

Fig. 2a presents the injection site in the striatum of striatal-lesioned rats, assessed in structural MRI images. Fig. 2b presents the injection site in the striatum and in the pallidum of rats sustaining a combined striatal and pallidal lesion. As can be seen, in all rats, the injection site is located in the center of the striatum and, in rats sustaining a combined lesion, within the borders of the globus pallidus. Figs. 2c and d present micrographs of a representative lesion in the striatum and in the GP of rats that have undergone striatal and pallidal lesions using the same parameters as those reported in the present study, 6 months after surgery.

Pharmacological MRI

Fifteen rats were excluded from the study because of motion artifacts (Berendse and Groenewegen, 1990) or death on MRI sessions (Alexander and Crutcher, 1990). Thus, the final analysis included 7 striatal rats, 6 combined striatal and pallidal rats, 4 sham-operated and 4 unoperated rats. Since no statistical differences were obtained between sham-operated

[1] Increase in blood flow will raise the hemoglobin ratio (more oxy-hemoglobin) resulting in BOLD signal increase. However, increase in blood volume will increase the total amount of deoxy-hemoglobin resulting in BOLD signal decrease. To complicate matters further, the balance between the two processes depends on the depth and type of anesthesia (Baudelet and Gallez, 2004).

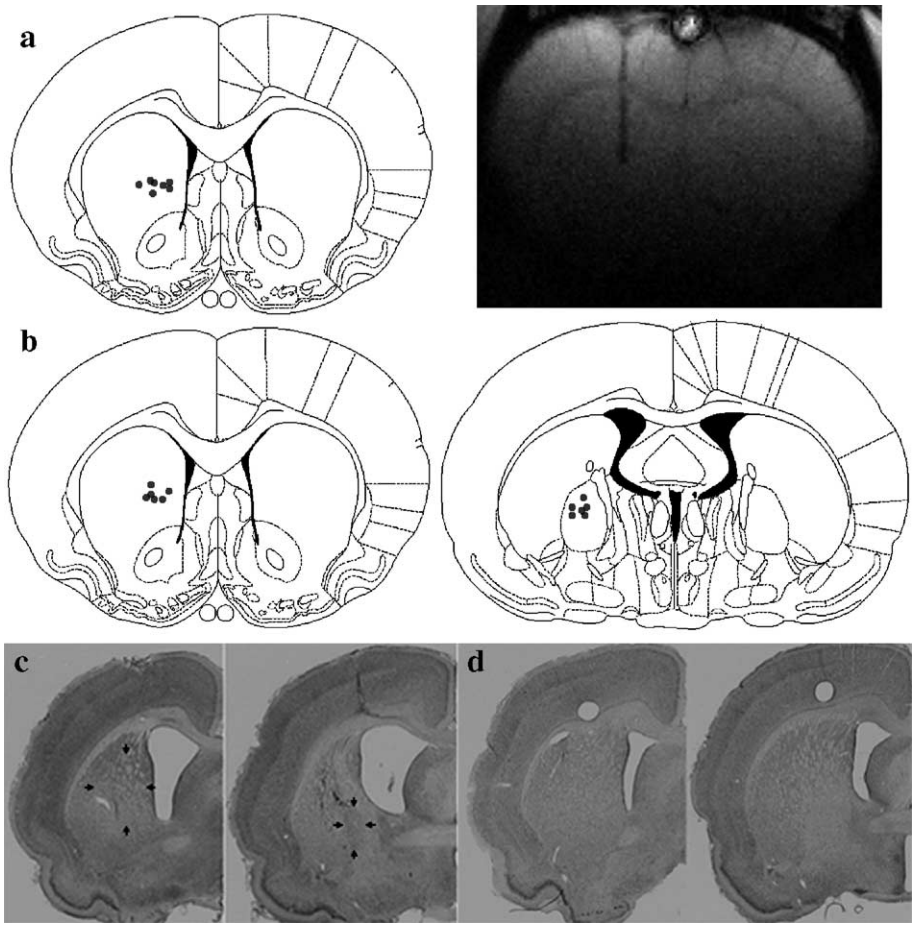

Fig. 2. The injection site in the striatum of striatal-lesioned rats (a), the striatum and the pallidum of rats sustaining a combined striatal and pallidal lesion (b), micrographs of a representative lesion in the striatum and in the GP of rats that have undergone striatal and pallidal lesions using the same parameters as those reported in the present study, 6 months after surgery (c), and of striatum and GP in sham-operated rats (d).

and unoperated rats, these two groups were merged for statistical analyses.

Bold

Administration of amphetamine resulted in either a monotonic change in the BOLD signal or in no change. The latter, however, was more prevalent in rats sustaining lesion to the striatum or a combined striatal and pallidal lesions. Fig. 3a presents maps of regional BOLD response in a (i) control, (ii) striatal, and (iii) combined striatal and pallidal rat after infusion of 2 mg/kg amphetamine. These maps were created by calculating the correlations between the absolute BOLD signal and a model function (a step function that anticipates signal increase at time of injection) for each voxel. The color overlay indicates the correlations for each voxel having $r > 0.6$. The magnitude and duration of change in the BOLD signal after amphetamine administration were further analyzed in 13 ROIs bilaterally (defined under Materials and methods). A mixed ANOVA of the absolute percent of change after drug administration in the 13 ROIs bilaterally in the three experimental groups over the 5 time periods after drug administration yielded a significant CONDITION × REGION × TIME interaction ($F(96,864) = 1.28$, $P < 0.05$). As the linear trend of TIME was significant[2] and did not interact significantly with any of the other variables, the data are presented, for sake of simplicity, as the mean difference of change in the BOLD signal between the last and first time periods after drug administration (Fig. 3b). As can be seen, the reaction to amphetamine was more pronounced in control rats as compared to the two lesioned groups, which reacted similarly. In addition, the reaction to amphetamine was more pronounced in the left compared to the right hemisphere in control rats, but not in rats sustaining lesion to the striatum or a combined striatal and pallidal lesions.

Fig. 4 presents the mean inter-correlations matrices obtained in each of the three experimental groups. As can

[2] In order to rule out the possibility that the linear trend of the BOLD signal following amphetamine administration reflects the action of some non-specific variables, such as anesthesia, pH, and pO_2 modifications, the BOLD signal of the head muscles has been analyzed. A 3 × (2) × (5) ANOVA of the absolute percent of change of the BOLD signal in head muscles measured bilaterally in the three experimental groups over the 5 time periods after drug administration yielded no significant effects.

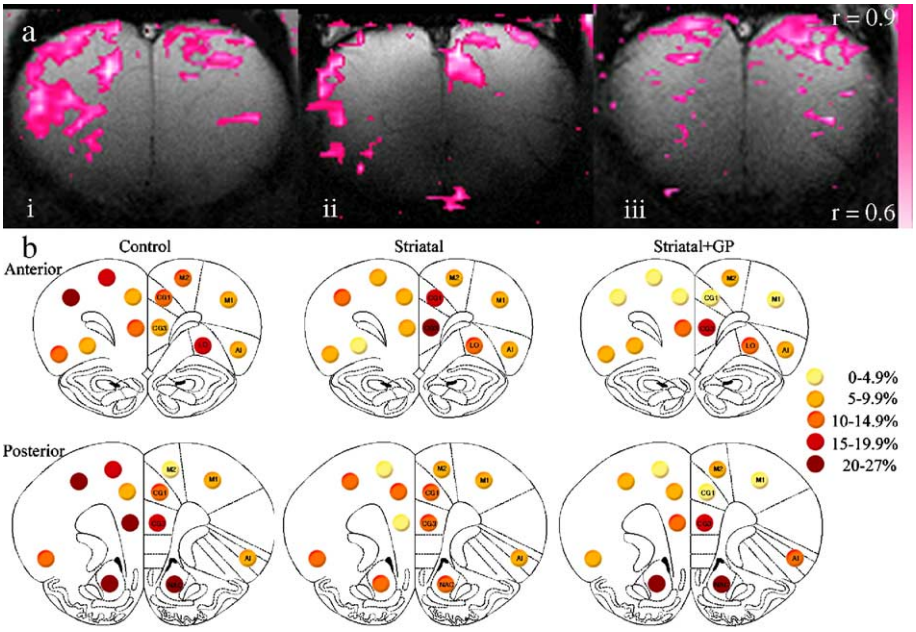

Fig. 3. (a) Maps of regional BOLD response in a (i) control, (ii) striatal, and (iii) combined striatal and pallidal rat after infusion of 2 mg/kg amphetamine. Correlations between the absolute BOLD signal and a model function (anticipating signal increase at time of injection) greater than 0.6 are depicted pseudo-color overlying the T2 image. (b) The mean difference of change in the BOLD signal between the last and first time periods after drug administration (please note that only 12 ROIs appear in the figure; the thalamus is more posterior than the brain section shown). 3 × (2) × (5) × (13) ANOVA of the absolute percent of change after drug administration in the 13 ROIs bilaterally in the three experimental groups over the 5 time periods after drug administration yielded significant effects of region ($F(12,216) = 7.58$, $P < 0.001$), time ($F(4,72) = 27.28$, $P < 0.001$), hemisphere by region ($F(12,216) = 3.72$, $P < 0.01$), hemisphere by time by condition ($F(8,72) = 2.82$, $P < 0.001$), region by time ($F(48,864) = 3.50$, $P < 0.001$), condition by region by time ($F(96,864) = 1.28$, $P < 0.05$), and hemisphere by region by time ($F(48,864) = 2.08$, $P < 0.001$).

be seen, a large number of the correlations were higher than 0.6 (colored) in the control group, indicating a synchronized response to amphetamine in most of the areas studied. The number of high correlations was markedly reduced in the striatal group, and some of these correlations were restored in the combined striatal + GP group. For each of the combinations of two regions out of the 26 (13 ROIs bilaterally), the inter-structural correlations of the three experimental groups were compared using one-way ANOVAs. ANOVAs that yielded a significant effect of CONDITION were further analyzed using least significant difference post hoc comparisons. Fig. 5 presents the correlations that yielded significant difference between the striatal and control groups, and these are further divided into those correlations that were “normalized” by the pallidal lesions and those that were not “normalized”. As can be seen, almost all of the correlations that were lower in the striatal group were “normalized” in rats sustaining in addition a lesion to the pallidum. In addition, most of the correlations that were affected by the striatal lesion, involved the posterior AI and the NAC on the right hemisphere.

Discussion

In control rats, systemic administration of amphetamine led to a change in BOLD signal in all the areas measured (i.e., several frontal cortex subdivisions, the nucleus accumbens, and the thalamus), and this change was typically higher in the left hemisphere (20–40%) than in the right hemisphere (10–25%). This finding is in line with previous demonstrations of changes in the activation of different cortical and subcortical brain regions following amphetamine (Chen et al., 1997; Dixon et al., 2005; Nguyen et al., 2000) or cocaine (Marota et al., 2000) administration in intact rats.

In rats sustaining a unilateral lesion to the striatum, the response to amphetamine was much weaker than in control rats. This finding is similar to previous findings of decreased activation of the frontal cortex following systemic amphetamine administration in rats sustaining a unilateral 6-hydroxydopamine lesion of the substantia nigra (Chen et al., 1997; Nguyen et al., 2000). It should be noted, however, that, in contrast to these studies, the present study employed quinolinic acid lesions to the striatum, which have been reported not to affect DA neurons (Figueredo-Cardenas et al., 1994; Stefanis and Burke, 1996).

Before we attempt to interpret the present results, several cautionary notes are in order. First, although simultaneous fMRI and electrophysiological recordings suggest that the BOLD contrast reflects neural responses, this signal appears to be better correlated with the local field potentials rather than the spiking activity of neurons (for a review, see, Logothetis, 2003). Therefore, activation (in terms of the

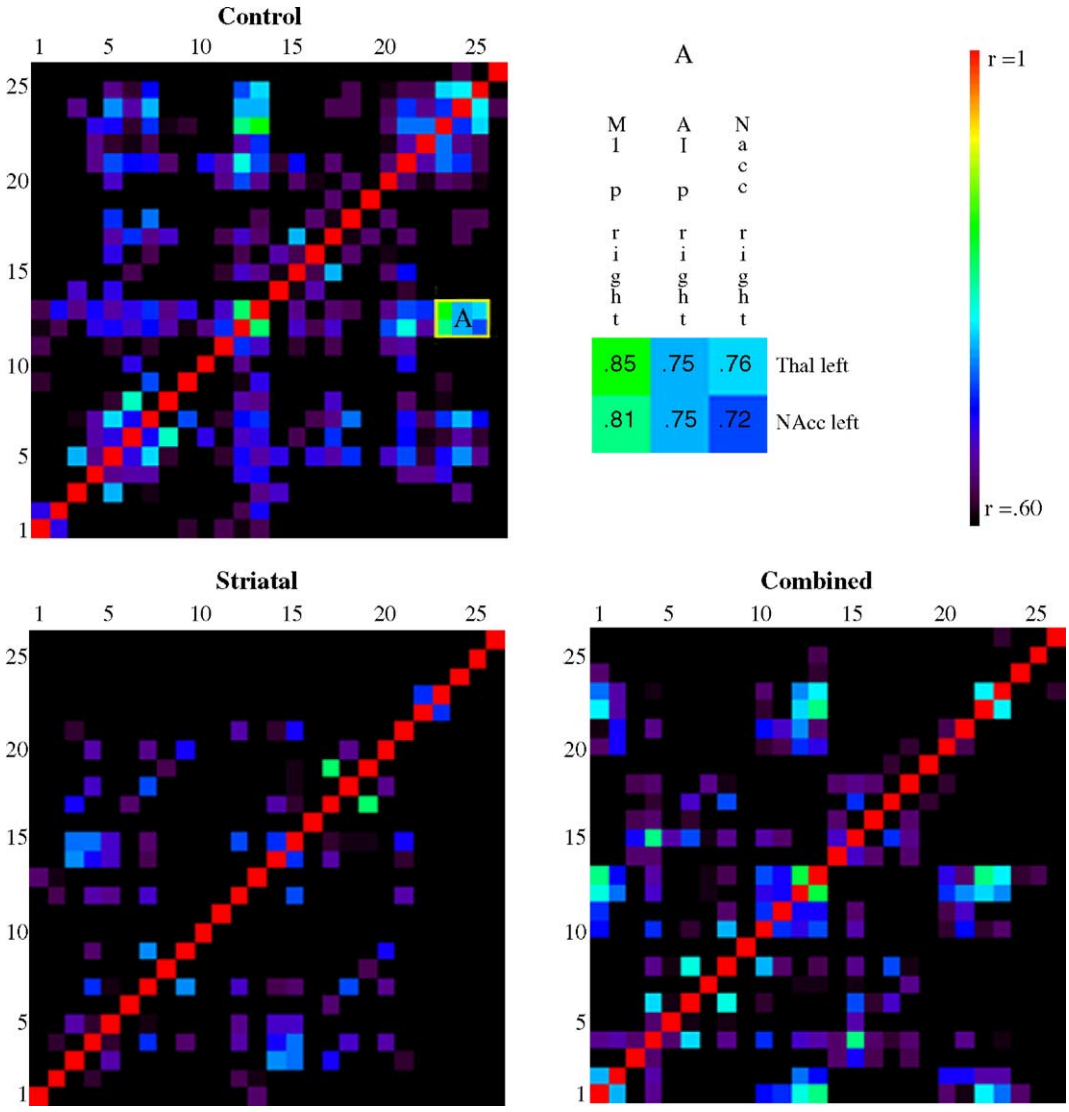

Fig. 4. Mean inter-correlations between the 26 regions assessed in the control, striatal, and striatal + GP groups (note that by definition the matrices are symmetrical on both sides of the diagonal singularity). Only correlations higher than 0.6 are presented. The correlation coefficients are color-coded according to the scale on the right side of the plate. The anatomical regions measured are represented by numbers ranging between 1 and 26 as follows: left hemisphere (1) CG3 ant; (2) CG1 ant; (3) M2 ant; (4) M1 ant; (5) AI ant; (6) LO ant; (7) CG3 post; (8) CG1 post; (9) M2 post; (10) M1 post; (11) AI post; (12) NAC; (13) Thal; right hemisphere (14) CG3 ant; (15) CG1 ant; (16) M2 ant; (17) M1 ant; (18) AI ant; (19) LO ant; (20) CG3 post; (21) CG1 post; (22) M2 post; (23) M1 post; (24) AI post; (25) NAcc; (26) Thal. For a clearer understanding of the matrices, A depicts an enlarged portion of the control group matrix. As an example, the correlation coefficient between right M1 posterior (area 23) and left thalamus (area 13) in the control group was $r = 0.85$ and is colored green.

BOLD contrast) in a given brain region is likely to reflect the incoming inputs and the local processing in this region, and not necessarily its output activity (Logothetis, 2003). Second, it should be born in mind that we have studied the effects of amphetamine on the BOLD contrast in Nembutal-anesthetized rats. Because Nembutal may alter GABAergic transmission in the basal ganglia and associated thalamic and cortical circuitry, the present results may reflect the interaction between Nembutal and amphetamine rather than the effects of amphetamine only. Although most previous studies have used halothane (Chen et al., 1997; Dixon et al., 2005; Marota et al., 2000), we have chosen not to use this substance because it acts on the glutamatergic system and because there is evidence that halothane potentiates the effect of nomifensine, a dopamine reuptake inhibitor, on extracellular dopamine levels in rat striatum (Adachi et al., 2001).

There are several possible explanations to the finding of decreased cortical response to amphetamine in striatal-lesioned rats. One possibility is that, in control rats, amphetamine-induced activation of the striatum has contributed to the metabolic change observed in the frontal cortex and that, in striatal-lesioned rats, amphetamine effects on striatal output were attenuated, therefore leading to a smaller activation of the frontal cortex. This possibility is in line with Chen et al's (1997) finding that, in intact rats, amphetamine-induced changes in cortical BOLD signal paralleled the changes in the release of dopamine in the

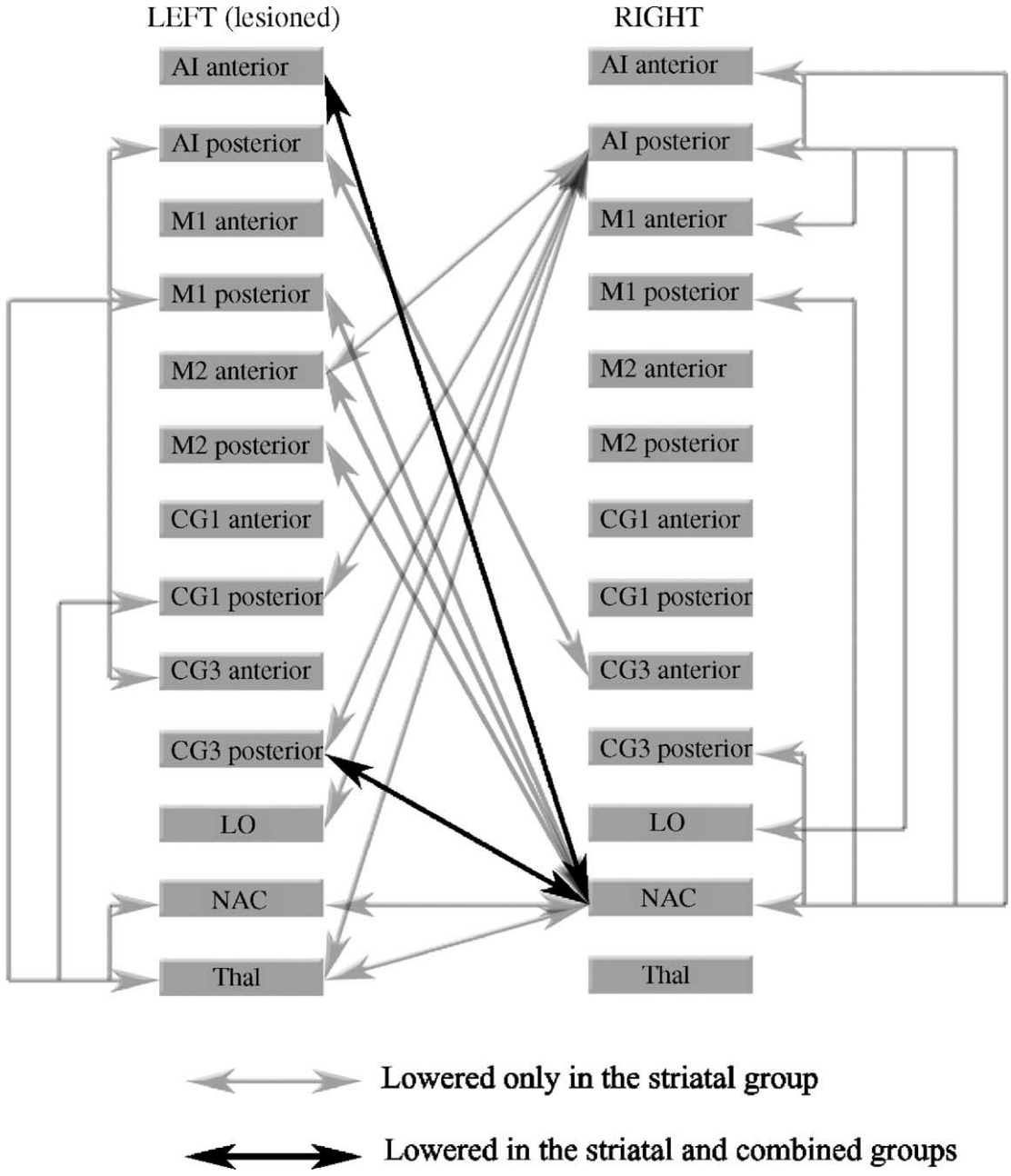

Fig. 5. Correlations that were lowered in the striatal group as compared to the control group, after amphetamine administration, divided into those that were "normalized" by the pallidal lesions, and those that were not "normalized".

striatum (the latter were assessed using microdialysis). Changes in striatal activity following amphetamine-induced changes in striatal dopamine levels may influence cortical activation via the direct and indirect striatal projections to the entopeduncular nucleus and substantia nigra pars reticulata, and the latter projections, via the thalamus, to the frontal cortex. It has been suggested that the effects of dopamine on both the direct and indirect pathways result in increased activity of thalamocortical projections (Albin et al., 1989; Gerfen and Wilson, 1996) which would be expected to be reflected in increased activation of the frontal cortex.

An alternative account for the decreased cortical response to amphetamine in striatal-lesioned rats may be that in control rats amphetamine directly activates the cortex, and this activation is then amplified via cortico-basal ganglia-thalamocortical circuits. This amplification is expected to be attenuated in striatal-lesioned rats, leading to decreased cortical response to amphetamine. Indeed, previous studies have found that systemic injections of amphetamine at doses comparable to those used in the present study led to a long-lasting increase in the release of dopamine (Pehek, 1999; Pehek and Bi, 1997, but see Hedou et al., 2002) and acetylcholine (Arnold et al., 2001) in the medial frontal

cortex and that intracerebral injections of amphetamine resulted in an increase in glutamate release in this cortical region (Del Arco et al., 1998). A direct action of amphetamine in the cortex may also account for the residual activation of the cortex in striatal-lesioned rats in the present study.

Contrary to our hypothesis that lesion to the GP would "normalize" the striatal lesion-induced dysfunction of basal ganglia–thalamocortical circuitry, the pattern of brain activation following amphetamine administration in rats sustaining a GP lesion in addition to the striatal lesion was similar to that seen in striatal-lesioned rats.

In the results discussed thus far, the effects of the striatal and of the combined striatal and pallidal lesion on the response to amphetamine were assessed for each of the areas measured. Another approach we have used to assess the effects of the lesions was by means of calculating the correlations between the responses to amphetamine in the different areas within each rat. The aim of this approach was to assess the functional connectivity between the different ROIs. The novel finding of the present study is that, whereas, in control rats, a large number (35%; 114 out of 325) of the pair-wise correlations were above 0.6, indicating a synchronized response to amphetamine in these areas, a large portion (66%) of these correlations were decreased by the striatal lesion, but most (42 out of 75) of the correlations that were decreased in striatal-lesioned rats were "normalized" in the combined striatal + pallidal group, that is, the correlations in the combined group were as high as those obtained in the control group.

It should be noted that the underlying assumption in the present analysis of correlations is that correlated BOLD response is related, in some degree, to neuronal connectivity. A large body of electrophysiological evidence supports the claim of long range connectivity; however, they normally observe temporal correlation at higher frequencies. Recently, long range connectivity of very low frequencies (<0.1 Hz) was observed in the monkey brain (Leopold et al., 2003), supporting the MRI approach to assess functional connectivity by low frequency BOLD signal fluctuations (Biswal and Ulmer, 1999; Cordes et al., 2002; Friston et al., 1994; Goelman, 2004). The present results, in which the BOLD temporal response to a drug is used, are in line with these studies, in which spontaneous BOLD signal fluctuations were assessed.

Since the striatal area lesioned here provides input (via the entopeduncular nucleus, substantia nigra pars reticulata, and the thalamus) to most of the frontal regions assessed (i.e., M2, CG1, CG3, AI, and LO) (Beckstead, 1979; Berendse and Groenewegen, 1990, 1991; Berendse et al., 1992; Cesaro et al., 1985; Groenewegen et al., 1990; McGeorge and Faull, 1989; Parent, 1990; Reep et al., 1984; Sesack et al., 1989), decreased correlations between the activity of these regions in striatal-lesioned rats may be a result of changes in the functional connectivity of these regions because of altered input from the basal ganglia and the thalamus following the striatal lesion. Interestingly, most of the correlations affected by the striatal lesion involved the AI and NAC contralateral to the lesion. This finding may reflect the relatively massive input from the mPFC and AI to the contralateral NAC (McGeorge and Faull, 1989; Montaron et al., 1996) and the ipsilateral projections from the NAC (via the ventral pallidum and the thalamus) to the AI and CG3 cortices (Groenewegen and Berendse, 1994; Groenewegen et al., 1990, 1991). Thus, changes in the activity pattern of the cortical regions ipsilateral to the lesion could have led to changes in the activity pattern and/or functional connectivity of the contralateral NAC-AI/CG3 circuit, as reflected in the lower correlations between these three regions in striatal-lesioned rats.

In summary, the present study have found that an addition of an excitotoxic GP lesion failed to prevent striatal lesion-induced changes in cortical activation by amphetamine but was effective in "normalizing" the correlations between the patterns of response in the different areas in striatal-lesioned rats. It is therefore possible that, although the GP lesion is ineffective in correcting the global changes in activity caused by the striatal lesion, it may have the capacity to partially restore alterations in functional connectivity resulting from the striatal lesion. We have previously demonstrated that lesions to the GP can reverse several behavioral deficits produced by a striatal QA lesion (Ayalon et al., 2004; Joel et al., 1998, 2003). The present findings show that the beneficial behavioral effect of the GP lesion is better correlated with its effects on the correlations between the patterns of BOLD response in different brain areas than with its effects on the BOLD response in single brain regions. This finding is also consistent with the central assumption of the anatomo-functional models of basal ganglia circuitry that complex behavioral pathologies resulting from damage to one of the circuit's components reflect dysfunction of the circuit as a whole (e.g., Albin et al., 1989; Alexander and Crutcher, 1990; Alexander et al., 1986; DeLong and Georgopoulos, 1981; Groenewegen and Berendse, 1994; Joel and Weiner, 1994, 1997; Parent, 1990).

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