The Functional Connectivity of Intralaminar Thalamic Nuclei in the Human Basal Ganglia

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Abstract: Projections of the centromedian-parafascicularis neurons of the intralaminar thalamus are major inputs of the striatum. Their functional role in the activity of human basal ganglia (BG) is not well known. The aim of this work was to study the functional connectivity of intralaminar thalamic nuclei with other BG by using the correlations of the BOLD signal recorded during “resting” and a motor task. Intralaminar nuclei showed a marked functional connectivity with all the tested BG, which was observed during “resting” and did not change with the motor task. As regards the intralaminar nuclei, BG connectivity was much lower for the medial dorsal nucleus (a thalamic nucleus bordering the intralaminar nuclei) and for the default mode network (although intralaminar nuclei showed a negative correlation with the default mode network). After the “regression” of intralaminar nuclei activity (partial correlation), the functional connectivity of the caudate and putamen nuclei with other BG decreased (but not with the primary sensorimotor cortex). Present data provide evidence that intralaminar nuclei are not only critical for striatal activity but also for the global performance of human BG, an action involving subcortical BG loops more than cortico-subcortical loops. The high correlation found between BG suggest that, similarly to that reported in other brain centers, the very-slow frequency fluctuations are relevant for the functional activity of these centers. *Hum Brain Mapp* 36:1335–1347, 2015. © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Basal ganglia (BG) are arranged in three closed-loop cortico-subcortical circuits, the direct, indirect, and hyperdirect circuits [Albin et al., 1989; Alexander et al., 1986; DeLong, 1990; Penney and Young, 1986]. According to the origin of their cortical input, these circuits have been subdivided into four main components [Alexander et al., 1986; Hoover and Strick, 1993; Nambu, 2011], one of which is the somatosensory-motor circuit (SM-C). The SM-C

transmits information from the primary somatosensory (S1) and motor (M1) cortex to the caudal striatum and subthalamic nucleus (STN), and then to the internal globus pallidum (GPi), external globus pallidum (GPe), and substantia nigra pars reticulata (SNr). Information from GPe and SNr goes to the anterior-ventral thalamus (motor thalamus; MTal) and returns to S1 and M1 (Fig. 1I) [Alexander and Crutcher, 1990; DeLong, 1990; Obeso et al., 2000]. Animal studies have shown that these long cortico-subcortical closed-loop circuits are accompanied by short subcortical loops, which interconnect BG bypassing the cortical structures [McHaffie et al., 2005; Redgrave et al., 1992]. The centromedian-parafascicularis complex of the thalamus (also referred to as caudal intralaminar nuclei of the thalamus; ILTal) is the key center of one of these subcortical loops. ILTal receives input from the SNr and GPi and projects to the striatum [Benarroch, 2008; Galvan and Smith, 2011; Huerta-Ocampo et al., 2014; Smith et al., 2004, 2009b], thus forming a short closed-loop circuit (ILT short circuit; ILTsc) with components of both the direct pathway [ILTal-caudate (Cau)/putamen (Put)-SN/GPi-ILTal] and the indirect pathway (M1-Cau/Put GPe-STN-GPi/SN-ILTal). ILTal has been associated with different physiological functions [Leon-Dominguez et al., 2013; Schiff, 2008; Schiff et al., 2007] and brain disorders [Benarroch, 2008; Henderson et al., 2000b], including Parkinson's disease where ILTal presents an early degeneration [Halliday, 2009; Morales et al., 2013].

Information about the connectivity and functions of the ILTal has mainly been obtained in experimental animals [Galvan and Smith, 2011; Huerta-Ocampo et al., 2014], which limits the understanding of the ILTsc functions in the human BG and the functional consequences of the ILTal disturbances [Halliday, 2009; Halliday et al., 2005; Henderson et al., 2000a; Villalba et al., 2014]. By using magnetic resonance imaging (MRI) methods, the aim of this work was to study the interaction of ILTal with the BG of the SM-C in humans. This was performed by correlating the blood-oxygen-level-dependent (BOLD) signal obtained from the ILTal with that obtained from other BG (functional connectivity MRI; fcMRI). We used the BOLD-signal correlation (instead of other fcMRI methods such as the independent components analysis), because it provides a quantitative estimation (correlation coefficient, r) of the "strength" or "magnitude" of the interaction between centers which can be used to study the influence of particular interventions on this interaction [Fox et al., 2007; Greicius et al., 2003; Treserras et al., 2009; Van Dijk et al., 2010]. A blocked-task paradigm with interleaved "resting"/"motion" intervals was used to estimate (fine-tuning of r) the influence of motor tasks (a sequence of finger movements) on the functional connectivity of ILTsc [Fair et al., 2007; Greicius et al., 2003]. Partial correlation (intercenter correlation after eliminating external influences of other centers) was used to estimate the consequences of the withdrawal of the ILTal influence on the functional connectivity of the Cau and Put with the other BG during the

resting intervals [Zhang et al., 2008, 2010a]. fcMRI has been widely used to study cortical networks [Fox and Raichle, 1986; Fox et al., 1988; Kim and Ugurbil, 1997; Raichle, 1998; Van Dijk et al., 2010], but its application to the study of BG is less frequent [Baudrexel et al., 2011; Greene et al., 2014; Marchand et al., 2011; Wu et al., 2011; Ystad et al., 2011]. Since fcMRI has never been used to examine the ILTal connectivity with centers of the ILTsc [Metzger et al., 2013], data obtained in the ILTal were contrasted with those obtained in a thalamic nucleus located just above the ILTal (medial-dorsal nucleus of the thalamus; MD); [Metzger et al., 2010, 2013], or in a cortical area (Brodman area 31; BA31) involved in the default mode network (DMN) [Buckner et al., 2008; Smith et al., 2009a; Uddin et al., 2009].

METHODS

Subjects

Twenty-five healthy volunteers 23–68 years of age (14 males and 11 females; 47.8 ± 14.7 mean $\pm$ standard deviation) with no history of neurological or psychiatric diseases participated in this study after providing informed consent. All subjects were right-handed according to the Edinburgh inventory [Oldfield, 1971]. The study was performed with the approval of our local Institutional Human Studies Committees.

Global Planning of the Study and Motor Tasks

The BOLD-signal provides information about neuronal activity [Fox and Raichle, 1986; Fox et al., 1988; Kim and Ugurbil, 1997; Raichle, 1998] even when its spontaneous fluctuation is recorded in subjects who are not performing particular tasks ("resting" condition). The correlation of low-frequency BOLD-fluctuations was used to establish the functional connectivity between BG during resting and finger-motion conditions. Data were recorded with a two-block paradigm ("motor-task" vs. "resting"). The "motor task" was a continuous sequence of right-hand movements (successive extensions and flexions of the little-finger $\rightarrow$ ring-finger $\rightarrow$ middle-finger $\rightarrow$ forefinger $\rightarrow$ thumb $\rightarrow$ little-finger). The instruction for the resting blocks was "Stop moving and do not do anything. A voice will tell you when to start a new motor task." Resting-activity transitions were orally announced with a single word, "MOVE" to start motion and "STOP" to finish motion. The motor-resting blocks were intermixed as follows: motor (100 frames) $\rightarrow$ resting (100) $\rightarrow$ motor (100) $\rightarrow$ resting (100). The 400 recorded frames were split into three portions to prevent the effect of block transitions: 1: frames 6 to 94 of each "resting" block (0 in Fig. 1H), 2: frames 6 to 94 of each "motor" block (1 in Fig. 1H), and 3: frames 1 to 5 and 95 to 100 of all blocks which were not included in the study (2 in Fig. 1H) [Fair et al., 2007].

Figure 1.

Identification of centers, VOI position, and main structural connections of BG. **A–G:** Slices used to identify BG centers were 4–26 mm posterior to the AC. The different MRI images show the position of VOIs in the external pallidum (GPe; A), postcommissural Put (B), internal pallidum (GPi), and Cau (C), ventral anterior/ventral lateral nuclear complex of the thalamus (motor thalamus, MTal; D), STN (E), centromedian-parafascicularis intralaminar thalamic nuclei (ILTal), and medial-dorsal nucleus of the thalamus (MD) (F), and substantia nigra (SN; G). These centers were identified according to external cues including the opt, MFB, ic, om, cp, and p. Areas marked with small green squares show the position of VOIs in each center. Pulvinar (Pul), ventral posterior lateral thalamic nucleus (VPL), ventral posterior lateral thalamic nucleus internal part (VPLI), red nucleus (R), and cerebral aqueduct (Ac). **H:** blocked task paradigm showing “resting” intervals (0), “motor

task” intervals (1), and transitions between the motor and resting blocks (2). Correlation in the “resting” condition was computed by using 6–94 frames of each of the two blocks 0, the “motor” condition was computed by using 6–94 of frames of each of the two blocks 1. The transition block (2) was not included in the study. **I:** The main structural connections between BG are shown in the periphery of the diagram (excitatory pathways are in red and inhibitory pathways are in blue). I: indirect pathway; D: direct pathway; H: hyperdirect pathway; M1: primary motor cortex; S1: primary somatosensory cortex. The relationship of the input (Cau and Put) and output BG centers, and of the thalamic (IL-Tal and M-Tal) and cortical (M1 and S1) centers are shown in the center of the diagram (r in green shows the correlation coefficient). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I. List of VOIs

	X	Y	Z	Size
Primary motor cortex	38.1 ± 5.3	-19.5 ± 4.8	48.5 ± 5.4	35.5 ± 10.9
Primary sensitive cortex	36.2 ± 8.2	-23.6 ± 2.8	51.3 ± 7.4	38.1 ± 9.3
Cau	8.9 ± 0.9	12.6 ± 1.2	4.2 ± 1.7	55.9 ± 12.2
Put	27.9 ± 1.7	-4.4 ± 1.2	0.2 ± 0.6	31.8 ± 3.7
External pallidum	15.3 ± 3.1	-2.1 ± 1.1	2.9 ± 1.1	30.2 ± 3.6
Internal pallidum	14.7 ± 2.0	-5.9 ± 1.4	-2.2 ± 1.9	26.5 ± 2.5
STN	11.1 ± 1.6	-13.4 ± 2.1	-4.6 ± 2.2	21.0 ± 2.3
Substantia nigra	7.2 ± 0.8	-18.5 ± 1.3	-8.6 ± 1.9	320.7 ± 50.5
Intralaminar thalamic nuclei	4.4 ± 1.3	-16.9 ± 1.4	3.9 ± 1.7	54.6 ± 19.3
Ventral-anterior thalamus	9.3 ± 1.3	-6.7 ± 1.1	7.2 ± 2.4	52.5 ± 12.5
Medial dorsal thalamus	6.5 ± 1.4	-17.7 ± 1.9	14.3 ± 1.7	63.4 ± 13.1
Brodmann area 31	11.1 ± 1.4	-38.1 ± 26.2	35.1 ± 3.1	144.1 ± 61.3

Coordinates (Talairach) are shown in mm (X shows the right/left distance in mm from the middle line). The size of the VOIs is shown by the number of their voxels.

Scanning Procedure

During fMRI studies, subjects lay in the supine position with the head attached to the circular head-coil to prevent movements. BOLD contrast image volumes were acquired at 3.0 T (General Electric Medical System) with gradient-echo, echo-planar imaging (repetition time 1600 ms; echo time 21.6 ms; flip angle 90°). Images were acquired in the coronal plane with a 250×250 mm field of view, and a 64×64 sampling matrix (brain slices 4-mm thick and 4×4 mm voxels in-plane resolution); 400 volumes were recorded in each session (100 volumes $\times$ 2 motor-blocks $\times$ 2 resting-blocks). fMRI data were coregistered with 3D anatomical images (repetition time 7.6 ms; echo time 1.6 ms; flip angle 12° ; 250×250 mm field of view; 256×256 sampling matrix; 1 mm slices thickness and 1×1 mm voxel resolution), and all data sets were normalized to the Talairach space.

fMRI Preprocessing

Data were preprocessed and analyzed using the Brain-Voyager software (version 2.1.2 of BVQX). The preprocessing of data included a slice scan time correction (cubic spline), a 3D motion correction (trilinear interpolation), and a temporal filtering (high-pass GLM-Fourier filter which removed frequencies below 0.009 Hz). fMRI time-series contain coherent fluctuations originating from residual motion artifacts and physiological signals (respiration, cardiac activity ...), which are unrelated to neural processes. Since these artifacts introduce unwanted BOLD-correlations and cause an overestimation of functional connectivity strengths, they should be removed before the functional connectivity study. Different procedures have been proposed to prevent the influence of artifacts on BOLD-correlation (e.g., censoring head motion during the fMRI recording, interpolating artifactual signals, "regressing" motions, "regressing" the global BOLD-signal, ...), but

none of them provide a perfect way to prevent the effects of noise [Jo et al., 2013; Power et al., 2014]. Two procedures were used to diminish noise in the fMRI images, one procedure that efficiently restricts the head movements during the BOLD-signal recording, and another mathematical procedure ("regression" of BOLD-signal) that reduces the recording noise during the processing of images. The BOLD-signal regression is unquestionably useful to decrease the influence of noise in fMRI studies. The question is which of the BOLD-signals recorded all over the brain is the most useful. One possibility is to regress, the average of the BOLD-signals recorded in all the voxels. This global BOLD-signal contains a combination of artifactual and neural sources, which normally produce undesirable side-effects (e.g., removal of neuronal signals, artifactual anticorrelations ...) [Anderson et al., 2011; Murphy et al., 2009; Saad et al., 2012]. We used the average of the BOLD-signals recorded in the white matter and brain ventricles (which are largely independent of the neural activity but which are sensitive to confounding variables including scanner instabilities, subject motion, respiration, cardiac effects ...) as "regressors". Thus, the BOLD signal time-series of all the voxels were "regressed" with these predictors, and the regression "residuals" were used to study functional connectivity in BG.

Correlation Methods

Functional connectivity was computed by using the average of BOLD-signals of the voxels of each VOI. Small VOIs centered in each BG were always planned to prevent the inclusion of wrong voxels in VOIs, (see location and size of VOIs in Table I). The position of VOIs in big centers was selected by functional criteria. VOIs located in the postcommissural Put represented striatal motor circuits and VOIs located in the head of Cau represented striatal cognitive circuits. VOIs in the right and left brain were grouped together [Gopinath et al., 2011].

The mean time-course of BOLD-signals of each VOI was processed by a statistical program (Statistica; Statsoft, Tulsa), which used the Pearson correlation coefficient (r) with a statistical significance $P < 0.001$ (two-tailed). Partial correlations [Zhang et al., 2008, 2010a] were used to eliminate the IL-Tal (“regressor”) influence on the functional connectivity between the Cau and Put and the other BG. The IL-Tal action on the interaction between two centers was considered relevant when the r between these centers changed significantly after “regressing” the IL-Tal activity. Statistical differences between two correlation coefficients were computed using the r -to-Fisher- z transformation [$r' = 0.5 * (\ln(1 + r) - \ln(-r))$]; r' is the Fisher- z transformed r and a two-sided t comparison (mean and standard error of each sample evaluated against the t distribution with $df = n_1 + n_2 - 4$ degrees of freedom; n_1 and n_2 being the sample sizes). The same procedure was used to identify functional connectivity changes induced by the motor task, testing, in this case, the statistical differences between the r of the “resting” and “motor” blocks [Greicius et al., 2003].

Identification of BG and VOI Location

The study of the functional interactivity of BG is hampered by the fact that some of them are small nuclei surrounded by fiber tracts or are near to other nuclei of the BG. Thus, ROIs were defined manually, paying particular attention to identifying each BG and to defining representative VOIs on a subject-by-subject basis. VOIs were individually positioned by using the T1 weighted templates (normalized 3D-anatomical spaces) of each subject and three main indications: 1. coordinates in the Talairach space; 2. the shape of the nucleus; and 3. the anatomical relationship of the nucleus with other structures (external cues). The resolution of the fMRI ($4 \times 4 \times 4$ mm) and T1 ($1 \times 1 \times 1$ mm) images was planned in such a way that one fMRI voxel corresponded with a whole number of T1 voxels (one fMRI voxel containing 64 T1 voxels). The T1 and fMRI studies were then performed in a single recording session, using the same field of view in both cases, and keeping the head position stable throughout the T1 and fMRI studies (the subject's head was attached to the head-coil to prevent movement). Thus, there was a marked spatial correspondence between the structural and functional images which, in each subject, remained stable throughout the study. The T1-fMRI correspondence did not need spatial motions during their coregistration, and two subjects that showed no exact T1-fMRI adaptation during the image processing were not included in the study (there was a mistake in the field of view location in both cases, which was produced when the fMRI study was planned). The first step to obtain representative VOIs of centers was to identify their anatomical boundaries in T1 images. After this, the low-resolution fMRI images were co-registered with the high-resolution T1 images, and the voxels of the fMRI images located in the central points of each BG were used to obtain the VOI of the center. The

VOI size was always big enough to represent the center and small enough to prevent the inclusion of the center boundaries. VOIs were later reviewed by another researcher, which confirmed their position inside the corresponding center (not touching the center boundary, surrounding centers, or fiber tracts). To prevent any overlapping of VOIs of neighboring centers, VOIs were initially selected in separated slices (see Fig. 1) and their positions were simultaneously displayed to confirm they did not overlap.

Centers were identified in coronal slices located 4–27 mm posterior to the anterior commissure (AC). The optic tract (opt; Fig. 1), internal capsule (ic; Fig. 1), and medial forebrain bundle (MFB; Fig. 1) were used as external cues to identify the GPe (Fig. 1A), Put (Fig. 1B), GPi (Fig. 1C), and MTal (Fig. 1D). GPi was initially identified ≈ 6 mm posterior to AC just above the opt (see opt, GPi and GPi boundaries—continuous black line—in Fig. 1C). The VOI for the Put was located at postcomissural level because the somato-sensorimotor regions project primarily to the posterior Put [Haber, 2003; Nambu, 2011; Parent, 1990; Selemon and Goldman-Rakic, 1985], and the post-commissural Put was identified ≈ 5 mm posterior to AC (Fig. 1B). GPe was located ≈ 3 mm posterior to AC (Fig. 1A). MTal was located ≈ 11 mm posterior to AC (5 mm posterior to the GPi) (Fig. 1D). Special care was taken to identify the STN (Fig. 1E). Four external cues were used in this case, the oculomotor nerve (om), cerebral peduncle (cp), opt, and pons (p). Initially, coronal images were moved backwards and forwards (between 10 and 18 mm posterior to AC) to identify the slice where the om was trapped in the most medial region of the contact between the p and cp (Fig. 1E). The backward-forward movements of the slices were also used to follow the lateralization of the opt and to identify the slice where the om was trapped between the p and cp (Fig. 1E). The STN was identified, in this slice, as the center located 10 mm medial to the opt, just above a horizontal line crossing this tract (red discontinuous line in Fig. 1E) and near the medial boundary of the cp (Fig. 1E). The STN, in this position, was mainly surrounded by tracts and located anterior to the SN (the boundary between STN and SN is not clear in more caudal positions). So as not to mix data on specific centers with those of the surrounding centers, the VOIs were generally small and clearly located within each nucleus. This was not the case of the SN (Fig. 1G). In humans, the SN pars compacta (SNc) is intermixed with the SN pars reticulata (SNr) and both portions of the SN cannot be clearly separated in MRI images. Thus, the VOI in this case included the whole SN (Fig. 1G), and was located between the red nucleus (R) and cp in slices 19 to 25 mm posterior to AC. The MD and ILTal were identified according to previous studies of Metzger et al. [2013] (Fig. 1F). The identification of the hand representation in M1 and S1 was performed in the precentral and postcentral gyrus according to a previously reported procedure [Rodriguez et al., 2004]. Since the comparison of the BOLD signal between the resting and the motor task activated the hand

representation in M1 and S1, the fMRI response was also used to verify the location of these cortical areas.

RESULTS

Figure 1I shows the structural connectivity of BG in the periphery of the diagram (excitatory pathways in red and inhibitory pathways in blue), and the functional connectivity of BG grouped by classical models in the central portion of the diagram. Thus, significant correlations ($P < 0.001$) were observed between Cau-Put (BG input centers; $r = 0.20$), GPi-SN (BG output centers; $r = 0.40$), ILTal-MTal (BG thalamic centers; $r = 0.55$), and M1-S1 (somatosensory-motor cortex linked to the motor BG; $r = 0.55$).

Functional Connectivity of ILTal with BG: Differences with the MD and DMN Connectivity

The yellow line in the images on the left side of Figure 2 shows the proximity of the ILTal (Fig. 2A) and MD (Fig. 2C) and the location of these centers in relation to the BA31 (Fig. 2E). The ILTal showed a high correlation with other thalamic centers including the M-Tal (Fig. 2B). The functional connectivity of the ILTal with the other BG was very high, showing correlation coefficients higher than 0.30 with most BG (Fig. 2B), and particularly high with the motor thalamus ($r = 0.53$). The IL-Tal correlation with M1 and S1 was not statistically significant (Fig. 2B).

The MD had high-correlations with the other thalamic nuclei (IL-Tal and M-Tal) but also with the M1 and S1 (Fig. 2D). BG connectivity of DM was significant but lower than that found for the IL-Tal (under $r < 0.10$ in most cases). The functional connectivity of the MD with the Cau showed a negative r value.

The functional connectivity between the BA31 and BG was low, showing negative correlations with the Cau, STN, GPi, and SN, and a positive correlation with the ILTal (Fig. 2F). Thus, the functional connectivity of the three centers studied was very different. The ILTal was well connected to BG but not to the somatosensory-motor cortex. The MD was well connected to the other thalamic centers and to the somatosensory-motor cortex but not as well connected to BG (except for the Put). The BA31 showed low correlations to BG and these were generally negative, thereby suggesting that the BA31 activation coincides with the BG inactivation. Therefore, fMRI showed enough space and time resolution to discriminate between three networks, which are close to each other and which have BG among their components.

Influence of Motor Tasks on the Functional Connectivity of the ILTal with BG

Figure 3 shows the correlation coefficient between the ILTal and the different BG studied during “resting” (green) and “motor-task” (red) blocks. The functional con-

nectivity between the ILTal and BG did not change during the motor tasks. The correlation of the ILTal with the M1 and S1 was very low during the “resting” block and did not change during the “motor-task” blocks.

Influence of the ILTal on the Functional Connectivity of the Cau Nucleus with Other BG

A positive correlation was found between the primary somatosensory cortex and the primary motor cortex (M1-S1; $r = 0.55$), the input centers of BG (Cau-Put; $r = 0.20$) and the output centers of BG (GPi-SN; $r = 0.40$). In the cases of Cau-Put and GPi-SN relationships, the correlation coefficient decreased after “regressing” the ILTal influence. This fact did not occur in the case of the M1-S1 connectivity.

The Cau nucleus showed a high positive correlation with all BG, which was particularly high with the GPe ($r = 0.27$), STN ($r = 0.22$), GPi ($r = 0.28$), and ILTal ($r = 0.35$) (Fig. 4A). The Cau showed a negative correlation with S1 ($r = -0.11$) and M1 ($r = -0.12$; anticorrelation). The functional connectivity of the Cau with the other BG decreased after “regressing” the ILTal influence on the other BG (partial correlation). Figure 4A shows the r value before (green) and after (red) “regressing” the ILTal activity. The decrease of the functional connectivity of the Cau reached statistical values for the GPe, STN, GPi, SN, and M-Tal.

The partial correlations observed after “regressing” the IL-Tal activity were still statistically significant in most but not in all cases. Thus, the functional relationship between the Cau and the M-Tal vanished after “regressing” the ILTal activity, suggesting that the relationship of the Cau with this center is highly dependent on ILTal action. Finally, IL-Tal “regression” did not alter the negative correlation between the Cau and M1 or S1 (red numbers in Fig. 4A).

Influence of the ILTal on the Functional Connectivity of the Put with Other BG

The Put displayed a marked and positive functional connectivity with all BG, including the GPe ($r = 0.34$), STN ($r = 0.15$), GPi ($r = 0.27$), SN ($r = 0.17$), IL-Tal ($r = 0.35$), and M-Tal ($r = 0.34$) (green values in Fig. 4B). Contrary to that found for the Cau (which showed anticorrelations), the correlation between the Put and M1 ($r = 0.18$) or S1 ($r = 0.17$) was positive. Thus, the Put showed a positive functional connectivity with all BG, and with the primary somatosensory and motor cortex.

After “regressing” the ILTal influence, the “strength” of the Put connectivity with other BG decreased. Figure 4B shows the r value before (green) and after (red) “regressing” the ILTal activity. As this figure shows, the decrease of the correlation coefficient reached statistical significance in the interaction of the ILTal with all BG (red asterisks). This was not the case for the functional connectivity of the Put and M1 or S1, which showed a correlation coefficient, which did not change after the ILTal “regression.”

Intralaminar thalamus

Medial-dorsal thalamus

Brodmann area 31

Figure 2.

Functional connectivity of the intralaminar thalamic nuclei (ILTal), medial-dorsal nucleus of the thalamus (MD) and the Brodmann area 31 (BA31) in the BG. The left hand column shows the mid-line sagittal distribution of the correlation (red-yellow) and anticorrelation (blue-green) computed with the ILTal (A), MD (C), and the BA31 (E) as VOIs (circles show the bilateral position of VOIs). The right hand column shows diagrams of the BG connectivity of the ILTal (B), MD (D), and BA31 (F). Numbers show the correlation coefficient and arrows represent the magnitude of the correlation coefficient. Green numbers and arrows indicate positive correlations with statistical value ($P < 0.001$). Blue numbers

and arrows indicate negative correlations (“anticorrelations”) with statistical value ($P < 0.001$). Numbers and arrows in black show correlation without statistical value. I: indirect pathway; D: direct pathway; H: hyperdirect pathway; M1: primary motor cortex; S1: primary somatosensory cortex; Cau: caudate; Put: putamen; GPe: external pallidum; STN: subthalamic nucleus; GPi: internal pallidum; SN: substantia nigra; IL-Tal: centromedian-parafascicular intralaminar thalamic nuclei; M-Tal: ventral anterior/ventral lateral nuclear complex of the thalamus; DMN: default mode network. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3.

Functional connectivity of the intralaminar thalamic nuclei (ILTal) with other centers of the BG. The peripheral regions of the diagram show the structural connectivity of BG with excitatory pathways in red and inhibitory pathways in blue. The numbers in the central region of the diagram are the correlation coefficients. The width of the arrows represents the amplitude of the correlation coefficient which shows the “strength” or “magnitude” of the functional relationship between the ILTal and other BG. Green numbers and arrows indicate correlations with statistical value ($P < 0.001$) computed during the “resting” block. Red numbers indicate correlations with statistical value ($P < 0.001$) computed during the “motor task” block. Numbers and arrows in black show correlations without statistical value. I: indirect pathway; D: direct pathway; H: hyperdirect pathway; M1: primary motor cortex; S1: primary sensitive cortex; Cau: caudate; Put: putamen; GPe: external pallidum; STN: subthalamic nucleus; GPi: internal pallidum; SN: substantia nigra; ILTal: centromedian-parafascicularis intralaminar thalamic nuclei; M-Tal: ventral anterior/ventral lateral nuclear complex of the thalamus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

The ILTal presented a marked functional connectivity with all BG (positive correlations) but not with the primary somatosensory and motor cortex. This connectivity was very similar during the resting and motor-task blocks. The functional relationship between the ILTal and BG was different to that found for a nearby center of the thalamus (the MD nucleus showed low connectivity with BG and high connectivity with the somatosensory/motor cortex) and for the BA31 (negative correlation with most BG and positive correlation with M1). The “regressing” of ILTal activity (partial correlation) induced a marked and generalized decrease of the functional connectivity of the Cau

and Put with the other BG. These findings were observed in a heterogeneous sample of subjects (males and females with ages ranging between 23 and 68), which facilitates the generalization of data and prevents the possible influence of sex and age [Li et al., 2014]. Morphological differences in the brain of this heterogeneous sample was an additional reason to manually identify VOIs on a subject-by-subject basis.

The Functional Connectivity of BG: Methodological Considerations

fcMRI performed by means of correlation methods applied to very-slow-frequency-fluctuations of BOLD signals has proved to be useful for studying the functional connectivity between cortical areas (e.g., feed-forward networks) and between a cortical area and a subcortical nucleus (e.g., short closed-loop networks, which reciprocally connect the brain cortex and the thalamus) [Zhang et al., 2008, 2010a]. This method proved to be useful here for studying the functional interaction between centers involved in complex closed-loop networks with feedback connections. fcMRI uses vascular behavior (indicated by the BOLD-fluctuations) to identify persistent interactions (lasting for seconds) of neuronal populations (spatial resolution of millimeters) [Logothetis, 2002, 2003; Logothetis et al., 2001; Raichle and Mintun, 2006; Sheth et al., 2004]. Under these limitations, fcMRI was good enough to identify the functional interaction between BG, regardless of whether they are adjacent (a few millimeters in the case of the Put and GPe) or distant (centimeters in the case of the Put and SN).

The interpretation of fcMRI data should be performed with caution and knowing that they will never provide information about the structural connectivity between centers or about the mechanisms involved in their interactions. Significant correlations between two centers can be induced by the action of a third center behaving as an external modulator of their activity or simply as a route that transmits information from one center to the other (without participating in the information processing). Thus, fcMRI does not provide information about the direct structural connections between brain centers. Positive and negative BOLD-correlations do not indicate the existence of excitatory or inhibitory connections. Centers showing positive correlations (in-phase fluctuations) should be considered as belonging to the same neuronal network (correlation networks), centers showing negative correlations (antiphase fluctuations) as belonging to different networks which on average do not work simultaneously (anticorrelation networks with incompatible activities), and centers showing no significant correlations should be considered as not belonging to the same network [Fox and Raichle, 2007; Fox et al., 2005; Long et al., 2008]. Therefore, fcMRI is more suitable for analyzing the behavior of a neuronal network than for studying its “wiring” or the mechanisms involved in the interaction of its components.

Partial correlation can be used to estimate the action of a member of a network on the functional interaction between other members, a possibility used here to study the influence of the ILTal on the interaction of the Cau and Put with the other BG. The partial correlation of ILTal activity decreased the functional connectivity of the Cau/ Put with most BG, suggesting that the ILTal loss produces marked changes in the activity of the BG input centers, which could also be present in parkinsonian patients with ILTal degeneration. However, the apparent change of the Cau/Put connectivity observed after the partial correlation of the ILTal timecourse might also be a consequence of the high general correlation of BG linked to their closed-loop organization. If the ILTal BOLD-activity is markedly influ-

enced by the general activity of BG [Zhang et al., 2010b], then the “regression” of the IL-Tal activity may have general effects on the functional connectivity of BG and does not indicate a selective influence of ILTal on the functional connectivity of the striatum. The study of patients with ILTal degeneration is probably necessary to investigate this possibility.

Regarding other fMRI methods (e.g., independent components analysis...), the BOLD-correlation has the advantage of providing a quantitative estimation of the “strength” of the interaction between two centers, thereby facilitating the study of the action of external variables (e.g., tasks, brain lesions...) on this interaction. We used a blocked-task paradigm with interleaved experimental conditions to prevent BOLD-signal differences induced by small changes in the head position (frequently produced when subjects are studied over long time-intervals or in separate sessions) from being misinterpreted as an effect of the task. This was particularly relevant in this study because it was performed in small brain centers whose VOIs were composed of a few voxels. However, when using blocked-task paradigms the activity performed during one block may also influence the BOLD-signal of the following block, which increases the probability of finding false negative results in the interblock comparisons. Previous studies reporting similar BOLD-correlations in data recorded during multiple separated and continuous interleaved runs [Buckner et al., 2013; Van Dijk et al., 2010] argue against this “interblock contamination”. However, there are also data suggesting that changes of complex variables (e.g., the Hurst exponent used to analyze the fractal dynamic of networks) may persist after stopping the task [Barnes et al., 2009]. Thus, “interblock

Figure 4.

Functional connectivity of the Cau nucleus (A) and postcommisural Put (B) with other BG centers. The peripheral regions of each diagram show the structural connectivity of BG with excitatory pathways in red and inhibitory pathways in blue. The numbers in the central region of the diagram are the correlation coefficients. The width of the arrows which shows the “magnitude” of the functional relationship between the Cau or Put and the other BG. Green numbers and arrows indicate correlations with statistical value ($P < 0.001$) and red numbers indicate partial correlations with statistical value ($P < 0.001$). Asterisks ($P < 0.001$) and small circles ($P < 0.05$) indicate statistical differences between the correlation coefficient computed before and after the IL-Tal “regression.” Numbers in black show correlations without statistical value. I: indirect pathway; D: direct pathway; H: hyperdirect pathway; M1: primary motor cortex; S1: primary sensitive cortex; Cau: caudate; Put: putamen; GPe: external pallidum; STN: subthalamic nucleus; GPi: internal pallidum; SN: substantia nigra; IL-Tal: centromedian-parafascicularis intralaminar thalamic nuclei; M-Tal: ventral anterior/ventral lateral nuclear complex of the thalamus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

contamination" (and false negative results) cannot be completely ruled out.

Identifying the Short Subcortical Loops Connecting the ILTal to BG with fMRI

The ILTal showed positive correlations with all BG and nonsignificant correlations with the M1 and S1. These data suggest that the human ILTal is involved in short subcortical loops (ILTsc), which facilitates the functional interaction between BG bypassing the brain cortex [McHaffie et al., 2005; Redgrave et al., 1992], a possibility which is also supported by previous morphological and electrophysiological studies in animals [Benarroch, 2008; Galvan and Smith, 2011; Groenewegen and Berendse, 1994; Huerta-Ocampo et al., 2014; Parent and Hazrati, 1995; Sidibe and Smith, 1996; Sidibe et al., 2002; Smith et al., 2004, 2009b]. The functional connectivity of the BA31 with BG was less prominent than that observed for the ILTal. The BA31 is a key center of the DMN, which is a network mainly composed of cortical centers [Buckner et al., 2008]. This, and the fact that the functional connectivity of BG was in phase with the ILTal and in anti-phase with the BA31 suggests that the BG network linked to the BA31 and the BG network linked to ILTal behave as anticorrelation networks with incompatible activities. Previous fMRI studies have shown that goal-directed tasks which activate BG generally inhibit the DMN (usually active during the resting of voluntary task) [Buckner et al., 2008; Uddin et al., 2009], data which also suggest that the ILTsc and DMN behave as anticorrelation networks.

The MD showed functional connectivity with both M1/S1 (not observed for the ILTal) and BG (less marked than that of the ILTal but more marked than that of the BA31). Present data agree with previous DTI tractography studies in humans showing that the MD is preferentially connected with cortical structures and that the ILTal is preferentially connected with BG [Eckert et al., 2011]. In addition, these data support the previous hypothesis that the MD and ILTal are important neighboring hubs of structurally and functionally segregated networks [Metzger et al., 2010, 2013], with the MD being involved in emotional processing [Walter et al., 2008a,b] and the ILTal in attention processing [Haber and Calzavara, 2009; Van der Werf et al., 2002; Walter et al., 2008b]. The reentry of information from the output to the input BG performed by the ILTal could be useful for the attention tasks attributed to this center.

What fMRI Methods Suggest about ILTsc Connectivity

The high BOLD-correlation between two centers does not necessarily imply their "direct" interaction, because other nuclei, which are structurally connected to both centers, could be facilitating their "indirect" interaction. Bearing this

possibility in mind, and considering previous animal studies, present data suggest different possibilities to explain the ILTal interaction with BG of the direct and indirect pathways. A high positive correlation was observed between the ILTal and the two centers of the indirect pathway (GPe and STN). Although ILTal projects to both centers [Berendse and Groenewegen, 1990; Feger et al., 1994], these ILTal projections are not as massive as those sent to the striatum [Doig et al., 2010; Huerta-Ocampo et al., 2014; Kitai et al., 1976; Lapper and Bolam, 1992; Sidibe and Smith, 1999; Thomas et al., 2000; Vandermaelen and Kitai, 1980; Wilson et al., 1983] where terminals of ILTal neurons innervate both GABA neurons of the indirect pathway [Doig et al., 2010; Huerta-Ocampo et al., 2014] and interneurons connected to these GABA neurons [Kitai et al., 1976; Lapper and Bolam, 1992; Sidibe and Smith, 1999; Thomas et al., 2000; Vandermaelen and Kitai, 1980; Wilson et al., 1983]. Thus, the functional connectivity between ILTal and GPe/STN could be the result of direct ILTal projections to these centers combined with the action of ILTal projections to striatal cells linked to the indirect pathway. ILTal neurons also innervate both striatal neurons of the direct pathway, [Doig et al., 2010; Huerta-Ocampo et al., 2014] and striatal interneurons projecting to these striatal neurons [Kitai et al., 1976; Lapper and Bolam, 1992; Sidibe and Smith, 1999; Thomas et al., 2000; Vandermaelen and Kitai, 1980; Wilson et al., 1983]. Thus, the functional connectivity of the ILTal with the output centers of BG (GPi and SN) could be the consequence of a combined influence of ILTal on the direct and indirect pathways.

The functional connectivity found between the three thalamic centers studied was more marked than that found between these centers and BG. SNr and GPi projections to the M-Tal send collaterals to the ILTal [Parent and Hazrati, 1995; Sidibe et al., 2002; Smith et al., 2004], which probably contributes to the ILTal vs. M-Tal correlation. However, collateral projections do not justify, in our opinion, the very high correlation observed here. The ILTal vs. M-Tal correlation was double that found between the ILTal vs. SN and between the ILTal vs. GPi. In addition, the axonal collateralization does not explain the high correlation found between the ILTal vs. MD and between the MD vs. M-Tal ($r = 0.44$). Direct projections between the MD, M-Tal, and ILTal have not been reported and cannot be used to explain the marked functional connectivity observed between these centers. However, the three thalamic nuclei are interconnected with the reticular nucleus of the thalamus [Cornwall and Phillipson, 1988; Kolmac and Mitrofanis, 1997; Steriade et al., 1984; Velayos et al., 1989], which is a center which synchronizes most thalamic centers [Huguenard and McCormick, 2007; Klimesch, 1999; Klimesch et al., 2007; Quiroga-Varela et al., 2013; Sabate et al., 2011; Steriade, 2001; Steriade and Deschenes, 1984; Wang, 2010]. Thus, the reticular nucleus could be a good candidate to induce the high functional connectivity of the ILTal, M-Tal, and MD. In this case, the synchronizing action of this center on the ILTal, M-Tal, and MD activity

could promote the somatosensory-motor integration performed by the reticular nucleus of the thalamus [Leon-Dominguez et al., 2013; Min, 2010].

Finally, the correlations observed during resting were very similar to those observed when the subjects performed motor tasks. As these correlations were computed for different time-intervals, this similarity suggests a high internal reliability of the methods used. These data also suggest that the ILTsc works similarly in different task conditions, with the functional connectivity of the ILTal and BG remaining unchanged even when motor tasks, which modify the functional connectivity of other motor networks, are executed [Biswal et al., 1995]. This last conclusion should be taken with caution because, as mentioned above, an “interblock contamination” capable of reducing differences between the resting and movement blocks cannot be completely ruled out.

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