Supplementary Materials

Altered sense of agency in Gilles de la Tourette Syndrome: behavioral, clinical and fMRI findings

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Running title. Sense of agency in Tourette Syndrome.

Materials and Methods

Sample size calculation

In order to determine the sample size of the study, we carried out an a-priori power analysis on the basis of the scientific literature. Since there were not published studies that investigated the intentional binding phenomenon in Gilles de la Tourette (GTS) patients, we used as a reference a published study addressing a similar topic in patients affected by another movement disorder (Parkinson's disease, Moore *et al.*, 2010). In particular, we observed that the effect size of the difference between the intentional binding phenomenon in Parkinson's disease patients and healthy controls was 1.14. On the basis of these data, we calculated that the selection of a sample of 40 participants (20 for each group) would allow to detect a significant difference between the two groups in terms of intentional biding, with a power of 0.8 and an alpha of 0.01. On the basis of this analysis, we recruited 25 participants for each group (to take into account the possible drop-outs).

Neuropsychological and clinical evaluation

In order to exclude subjects with cognitive deficits, we administered to each participant a brief neuropsychological screening which included the Mini-Mental State Examination (MMSE, Folstein et al., 1975), the Raven's Colored Progressive Matrices (Raven's Matrices, Raven et al., 1998) and the Frontal Assessment Battery (FAB, Dubois et al., 2000). None of the subjects had pathological scores at any of the aforementioned tests.

GTS participants were submitted to a psychopathological test battery, which included, as suggested by the European clinical guidelines for Tourette Syndrome and other tic disorders (Cath et al., 2011): the Baratt Impulsivity Scale (BIS) for impulsivity (Fossati et al., 2001); the Yale-Brown Obsessive Compulsive Scale for obsessive-compulsive disorder (YBOCS, Goodman et al., 1989), the Beck Depression Inventory for depression assessment (BDI, Beck, 1961) and the Adult ADHD Self-Report Scale for the attention deficit hyperactivity disorder (ASRS, Adler et al., 2006).

Moreover, GTS patients underwent a detailed interview about the severity of their motor symptoms, including to the Yale Global Tic Severity Scale (YGTSS, Leckman et al., 1989) and the Premonitory Urge Tics Scale (PUTS, Woods et al., 2005). Clinical and neuropsychological data are presented in Table 1.

fMRI data acquisition and analysis

MRI scans were performed using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=40 msec, TR=2000 msec, FOV=250 mm and matrix=64x64). The overall number of the fMRI volumes collected varied from 269 to 292 volumes depending on the individual speed in generating the responses. The first 15 volumes of each sequence (corresponding to presentation of the instructions) were discarded from the analyses.

Pre-processing

After the image reconstruction, raw data visualization and conversion from DICOM to the NIFTI format were performed with MRIcron (www.mricro.com) software. All subsequent data analyses were performed in MATLAB R2014a (Mathworks. Natick. MA. USA) using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). First, fMRI scans were realigned to the first image of the run to account for any movement during the experiment. Then the structural T1 image was coregistered to the functional mean image to allow a

more precise normalization; the unified segmentation and nonlinear warping approach of SPM12 was applied to normalize structural and functional images to the MNI (Montreal Neurological Institute) template to permit group analyses of the data (Friston et al., 1995; Ashburner and Friston, 1999); at this stage, the data matrix was interpolated to produce 2 x 2 x 2 mm voxels. The stereotactically normalized scans were smoothed using a Gaussian filter of 10 x 10 x 10 mm to improve the signal-to-noise ratio, making the data suited for cluster level correction for multiple comparisons (Flandin and Friston, 2017).

Analysis of head motion parameters measured on the fMRI data

We compared the degree of absolute motion between the healthy controls and the GTS patients during the fMRI scan, to test for any difference between groups. The six realignment parameters identified by SPM during the fMRI data realignment were compared by means of multiple Mann–Whitney U tests, since the distribution of these data was not normal (Shapiro Wilk's $p < 0.05$, for each parameter, in at least one of the groups).

First level fixed-effect analyses

The BOLD signal associated with each experimental condition was analyzed by a convolution with a canonical hemodynamic response function (Worsley and Friston, 1995). Global differences in the fMRI signal were removed from all voxels with proportional scaling. High-pass filtering (128 s) was used to remove artefactual contributions to the fMRI signal, such as physiological noise from cardiac or respiratory cycles. A fixed-effect analysis was performed for each subject to characterize the BOLD response associated with the task before entering the relevant individual contrast images into a random-effect analysis.

In order to exclude fMRI scans contaminated by tics, we use the Artifact detection Tools (ART, Withfield-Gabrieli https://www.nitrc.org/projects/artifact_detect/). This toolbox allows identifying and discarding from the analyses the scans that could lead to artefactual statistical effects due to excessive movement. Thresholds were set at 2 mm scan-to-scan head movement and 9 standard deviation of scan-to-scan global signal intensity change. Experimental subjects that exhibited more than 20% outlier scans in the whole experimental run were excluded from the subsequent statistical analyses. None of the participants included in the final sample exceeded these thresholds.

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Supplementary Table 1. Head Movement Parameters: comparison between groups.

	HC	**GTS**	**Mann-Whitney U test (p-value Bonferroni-corrected)**
Traslation - x			
Mean	0.004	0.071	U=223, df=43, p>0.99
SD	0.365	0.300	
Traslation - y			
Mean	0.041	0.073	U=226, df=43, p>0.99
SD	0.140	0.245	
Traslation - z			
Mean	-0.061	0.096	U=235, df=43, p>0.99
SD	0.430	0.349	
Rotation - x			
Mean	0.000	0.004	U=139, df=43, p=0.06
SD	0.004	0.009	
Rotation - y			
Mean	-0.002	0.000	U=201, df=43, p>0.99
SD	0.003	0.006	
Rotation - z			
Mean	-0.002	-0.001	U=223, df=43, p>0.99
SD	0.004	0.006	

Supplementary Table 2. Results of the comparison between Active > Passive trials and between Passive >Active trials (independently from the different action-outcome delay). *p<0.05 FWER corrected (voxel level).

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	z	Z-score	x	y	z	Z-score
a) Active > Passive trials (independently from the group and the different action-outcome delay)								
Rolandic opercular gyrus	--	--	--	--	44	8	14	3.6
Inf. frontal op. gyrus	-50	14	0	4.1	44	12	16	3.5
	-52	18	22	3.6	44	10	22	3.2
Inf. frontal op. gyrus (44)	-46	8	26	3.6	52	10	32	4.1
	-46	4	28	3.5	40	12	12	3.3
Inf. frontal tri. gyrus (45)	-42	36	20	4.3	--	--	--	--
	-46	28	20	3.8	--	--	--	--
	-52	22	20	3.6	--	--	--	--
	-36	44	14	3.3	--	--	--	--
	-42	34	8	3.5	--	--	--	--
Mid. frontal gyrus (46)	-36	52	16	3.5	38	44	24	4.7*
	--	--	--	--	38	38	30	4.4
	--	--	--	--	30	52	20	4.1
Mid. frontal gyrus (6)	--	--	--	--	36	4	60	3.8
	--	--	--	--	36	-4	62	3.2
Mid. cingulum (24/32)	--	--	--	--	0	12	44	5.7*
	--	--	--	--	8	12	40	5.4*
Sup. frontal gyrus (6)	--	--	--	--	36	-4	62	3.2
Precentral gyrus (6)	--	--	--	--	38	-16	64	3.6
	--	--	--	--	42	-10	58	3.3
	--	--	--	--	48	-8	50	3.2
SMA (6)	-2	-14	54	5.2*	0	-10	52	5.3*
	-2	2	50	4.6	4	0	58	4.3
Precentral gyrus (4)	-34	-22	60	7.3*	32	-20	48	4.0
	--	--	--	--	32	-16	44	4.0
	--	--	--	--	36	-14	42	3.8
	--	--	--	--	40	-16	54	3.8
Postcentral gyrus (2)	--	--	--	--	46	-28	42	3.8
Postcentral gyrus (3)	--	--	--	--	38	-20	46	3.9
					36	-20	50	4.0
	--	--	--	--	42	-24	44	3.6
Insula	--	--	--	--	38	24	0	4.1
	--	--	--	--	40	20	0	4.0
	--	--	--	--	38	14	4	4.0
	--	--	--	--	46	12	0	4.0
Sup. parietal gyrus (7)	-14	-68	48	3.8	24	-66	48	4.8*
	-24	-64	38	3.9	--	--	--	--
	-20	-62	48	3.7	--	--	--	--
	-22	-68	46	3.5	--	--	--	--

Sup. temporal pole	-48	10	-2	4.0	--	--	--	--
Supramarginal gyrus (40)	--	--	--	--	46	-32	44	3.8
	--	--	--	--	48	-38	44	3.8
	--	--	--	--	52	-40	42	3.3
Fusiform gyrus (19)	-34	-66	-12	4.4	--	--	--	--
Sup. occipital gyrus (19)	-24	-64	30	3.3	24	-82	32	3.6
Mid. occipital gyrus (19/18)	-32	-82	16	4.9*	30	-88	6	4.8*
	-40	-78	0	4.7*	28	-70	34	3.6
	-40	-80	4	4.6	--	--	--	--
	-32	-90	16	4.4	--	--	--	--
Inf. occipital gyrus (19)	-36	-68	-8	4.4	32	-80	-6	4.6
Lingual gyrus (17)	-2	-72	6	4.5	--	--	--	--
Calcarine fissure (17)	-10	-84	12	4.4	--	--	--	--
Cerebellum_6	-18	-56	-16	5.7*	28	-52	-20	5.4*
	-22	-68	-18	4.5	36	-64	-24	4.5
	--	--	--	--	32	-42	-28	4.5
Vermis	--	--	--	--	4	-70	-14	4.9*
b) Passive > Active trials (independently from the group and the different action-outcome delay)								
Rolandic opercular gyrus (SII)	-46	-28	20	5.2*	52	-28	24	4.6*
Supramarginal gyrus	-58	-26	22	3.7	--	--	--	--
	-58	-30	24	3.7	--	--	--	--
Mid. temporal gyrus (37)	-46	-64	14	5.0*	48	-60	14	4.4
	-48	-60	14	4.9*	52	-60	12	4.4
	-58	-46	10	3.8	54	-60	24	3.7
Mid. temporal gyrus (39)	--	--	--	--	52	-66	24	3.7

Supplementary Figure 1. Results of the main effects. (a) Main effect of active>passive conditions; (b) Main effect of passive>active conditions.