*Title page

Anatomical predictors of successful prism adaptation in chronic visual neglect

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Abstract

Visual neglect is a frequent and disabling consequence of right hemisphere damage. Previous work demonstrated a probable role of posterior callosal dysfunction in the chronic persistence of neglect signs. Prism adaptation is a non-invasive and convenient technique to rehabilitate chronic visual neglect, but it is not effective in all patients. Here we aimed to assess the hypothesis that prism adaptation improves left neglect by facilitating compensation through the contribution of the left, undamaged hemisphere. We assessed the relationship between prism adaptation effects, cortical thickness and white matter integrity in a group of 14 patients with unilateral right-hemisphere strokes and chronic visual neglect. Results showed that patients who benefitted from prism adaptation had thicker cortex in temporo-parietal, prefrontal and cingulate areas of the left, undamaged hemisphere. Additionally, these patients had a higher microstructural integrity in the body and genu of the corpus callosum. Results from normal controls show that these callosal regions connect temporo-parietal, sensorimotor and prefrontal areas. Finally, shorter time intervals from the stroke tended to improve patients' response to prism adaptation. We concluded that prism adaptation may improve left visual neglect by promoting the contribution of the left hemisphere to neglect compensation. These results support current hypotheses on the role of the healthy hemisphere in the compensation for stroke-induced, chronic neuropsychological deficits, and suggest that prism adaptation can foster this role by exploiting sensorimotor/prefrontal circuits, especially when applied at early stages post-stroke.

Key words: visual neglect, rehabilitation, prism adaptation, diffusion imaging, cortical thickness

1. Introduction

A major challenge of precision medicine is to relate individual patients' characteristics to their clinical outcomes. Patients with right hemisphere damage and left visual neglect are unable to pay attention to left-sided objects, with consequent loss of autonomy and poor functional outcome (Bartolomeo, 2014; Heilman & Van Den Abell, 1980; Mesulam, 1981). At least 80% of patients with a right hemispheric stroke show signs of visual neglect in the acute stage (Azouvi et al., 2002). Impaired integration of attention-related processes within the right hemisphere (Corbetta & Shulman, 2011; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008), as well as between the hemispheres (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Heilman & Adams, 2003), contributes to neglect behaviour. About half of neglect patients still show signs of neglect one year or more after their stroke (Lunven et al., 2015), perhaps because posterior callosal dysfunction prevents attention-critical regions in the healthy hemisphere to access information processed by the damaged right hemisphere (Lunven et al., 2015).

Prism adaptation (PA) is a convenient technique to improve the ratio of recovering patients because it is totally non-invasive and easy to administer (Rossetti et al., 1998; Yang, Zhou, Chung, Li-Tsang, & Fong, 2013). Prismatic goggles displace the whole visual field rightwards and induce an initial rightward bias in manual reaching movements, which disappears after a few trials. After removal of the prisms, reaching initially deviates towards the left neglected side, and neglect eventually disappears. Unfortunately, neglect does not improve in all treated patients (Luauté et al., 2006; Rode et al., 2015; Rousseaux, Bernati, Saj, & Kozlowski, 2006; Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013), for unknown reasons (Barrett, Goedert, & Basso, 2012; Chokron, Dupierrix, Tabert, & Bartolomeo, 2007).

Drawing on our previous evidence suggesting a role for posterior callosal dysfunction in the chronic persistence of neglect (Lunven et al., 2015), we hypothesized that PA might improve neglect by facilitating compensation through the contribution of the left, undamaged hemisphere. To test this hypothesis, we assessed the relationship between PA effects, cortical thickness and white matter integrity in a group of 14 patients with unilateral right-hemisphere stroke and chronic left visual neglect.

2. Methods

2.1. Standard Protocol Approvals, Registrations, and Patient Consents

The study was promoted by the Inserm (C10-48) and approved by the Ile-de-France I Ethics Committee (2011-juin-12642). All participants gave written informed consent to participate in the study.

2.2. Subjects

A group of 14 patients with a single right hemisphere haemorrhagic or ischemic stroke, which had occurred at least 3 months before testing, showing stable signs of left visual neglect, gave written informed consent to participate in the study. None of the patients had a prior history of neurological disease or psychiatric disorders. Table 1 reports patients' demographic, clinical and neuropsychological data. Visual neglect was assessed by using six paper-and-pencil tasks: letter cancellation (Mesulam, 1985), copy of a linear drawing of a landscape (Gainotti, D'Erme, & de Bonis, 1989), drawing from memory of a daisy (Rode, Rossetti, & Boisson, 2001); text reading (Azouvi et al., 2006), bisection of five 20-cm horizontal lines (Azouvi et al., 2006) and landmark task (Harvey & Milner, 1999). All patients performed these tests on three occasions: (1) the day before PA, (2) two hours before PA, and (3) soon after PA. For each assessment, a neglect severity score was computed as previously reported (Lunven et al.,

2015), by using the percentage of left omissions for letter cancellation, drawing and reading tasks, the percentage of rightwards deviation for line bisection, and the percentage of left lateralised errors for the landmark task. Ten age-matched healthy subjects (mean age, 62.8 years; SD, 4.54; Mann-Whitney-Wilcoxon test, p ns) served as controls for neuroimaging.

2.3. Prism adaptation

Following a previously described procedure (Rossetti et al., 1998), patients were asked to wear prismatic goggles that shifted the visual field 10 degrees towards the right. While wearing prisms, patients were required to make, as quickly as possible, a series of approximately 100 pointing responses with the right hand towards left and right targets. The starting point of the hand was occluded to ensure optimal adaptation. The head of the patients was aligned with their body sagittal axis. Patients were eye-blinded and asked to point ten times straight-ahead with their right arm before and after the PA. Recovery scores were defined as the percentage of neglect improvement after PA using the following formula: (neglect score post-PA – neglect score pre-PA) / (neglect severity score pre-PA). We adopted an arbitrary cutoff of 20% change, which is often used in clinical studies (Brunt et al., 2002; Cockcroft, 2010), to divide patients into two groups according to their recovery score. Patients with a recovery score above 20% were attributed to the “high-responder” group (N=8), whereas patients with a recovery score below 20% were considered as “low-responders” (N=6). This classification was in good agreement with the clinical assessment of neglect (see Table 1).

2.4. Imaging data acquisition and lesion analysis

2.4.1. Data acquisition

An axial three-dimensional MPRAGE dataset covering the whole head was acquired for each participant (176 slices, voxel resolution = 1 × 1 × 1 mm, TE = 3 msec, TR = 2300 msec, flip angle = 9°) on a Siemens 3 T VERIO TIM system equipped with a 32-channel head coil.

Additionally, a total of 70 near-axial slices was acquired using an acquisition sequence fully optimized for tractography of DWI, which provided isotropic (2 × 2 × 2 mm) resolution and coverage of the whole head. The acquisition was peripherally-gated to the cardiac cycle with an echo time (TE) = 85 msec. We used a repetition time (TR) equivalent to 24 RR intervals assuming that spins would have fully relaxed before the repetition. At each slice location, six images were acquired with no diffusion gradient applied. Additionally, 60 diffusion-weighted images were acquired, in which gradient directions were uniformly distributed in space. The diffusion weighting was equal to a b-value of 1500 sec mm^{-2}. One supplementary image with no diffusion gradient applied but with reversed phase-encode blips was collected. This provides us with a pair of images with no diffusion gradient applied with distortions going in opposite directions. From these pairs the susceptibility-induced off-resonance field was estimated using a method similar to that described in (Andersson, Skare, & Ashburner, 2003) and corrected on the whole diffusion weighted dataset using the tool TOPUP as implemented in FSL (Smith et al., 2004).

2.4.2. Study of grey matter

Abnormal tissues were delineated on the T1-weighed images using MRIcroN for each patient (Rorden & Brett, 2000). T1-weighted images were normalized in the Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca/) using rigid and elastic deformation tools provided in the software package Statistical Parametric Mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Deformation was applied to the whole brain except for the voxels contained in the lesion mask, in order to avoid deformation of the lesioned tissue

(Brett, Leff, Rorden, & Ashburner, 2001; Volle et al., 2008). Finally, the lesion was carefully drawn in the MNI space by an expert neuropsychologist (ML) and checked by an expert neurologist (RM). Subsequently, lesions were overlapped for each of the high-responders and low-responders group.

2.4.3. Cortical Thickness preprocessing

Cortical thickness was derived from the T1-weighted imaging dataset using a registration-based method (Diffeomorphic Registration based Cortical Thickness, DiReCT) (Das, Avants, Grossman, & Gee, 2009) optimised for patients with a brain lesion in BCBtoolkit (http://toolkit.bcblab.com) (Foulon et al., 2018). This approach has good scan-rescan repeatability and good neurobiological validity, as it can predict with a high statistical power the age and gender of the participants (Tustison et al., 2014). These data were then normalized to MNI space with the previous deformation estimated to normalize the T1-weighted imaging dataset.

2.4.4. Study of white matter

We extracted brain using BET implemented in FSL and we corrected diffusion datasets simultaneously for motion and geometrical distortions by using ExploreDTI (http://www.exploredti.com) (Leemans & Jones, 2009). The tensor model was fitted to the data by using the Levenberg-Marquardt non-linear regression (Marquardt, 1963).

A fractional anisotropy (FA) map was extracted for each subject by using the function "extract stuff", which is part of the ExploreDTI software package. FA maps were further processed using Tract-Based-Spatial Statistics (TBSS) implemented in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) (Smith et al., 2006), taking in consideration a mask of the damage tissues as in (Lunven et al., 2015). Next, an average FA map was created

and a skeleton map representing the centre of the white matter (FA > 0.2) common to all patients computed. Finally, the registered FA maps were projected into the skeleton.

2.4.5. Statistical analysis

We statistically compared FA and cortical thickness values between low-responder and high-responder patients. Visual field defects and lesion volume were included as co-variables of non-interest. Lesioned voxels were excluded from these analyses. We used the FSL function "Randomise" (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/), with 5,000 random permutation tests and a Threshold-Free Cluster Enhancement option (Smith & Nichols, 2009). Results were adjusted for family wise error (FWE) corrections for multiple comparisons and thresholded at $p<0.05$. In addition, we applied the same analyses to explore potential between-group differences in mean diffusivity, axial diffusivity and radial diffusion.

To assess the dimensional relationships between FA, cortical thickness and prism-induced changes in performance, we conducted a regression analysis including all the 14 patients. Lesion volume and visual field defect were included as continuous co-variables of non-interest. We again used the FSL function "Randomise", with 5,000 random permutation tests and a Threshold-Free Cluster Enhancement option. Results were adjusted for FWE corrections for multiple comparisons and thresholded at $p<0.05$. We used BCBtoolkit to further characterise the white matter tracts passing through the voxels showing a significant difference. For each statistical analysis, effect sizes were calculated using G*power (http://www.gpower.hhu.de/en.html).

3. Results

3.1. Behavioural results

Patients demonstrated a relatively stable level of performance before PA; there was no difference between neglect scores assessed one day and two hours before PA (first session: mean score 29.08, SD 20.33; second session: mean score 30.81, SD 21.57; Wilcoxon Signed-Ranks Test, Z=-0.345, p=0.73). PA induced a sensorimotor adaptation in all patients, who deviated rightward before PA (6.47 degrees; SD, 3.51), but leftward after PA (-1.95 degrees; SD, 2.83; Z=-3.234, p=0.001). There was no correlation between neglect recovery scores and PA effect on the straight-ahead task, consistent with previous results (Pisella, Rode, Farnè, Boisson, & Rossetti, 2002).

High-responder and low-responder patients had similar age (Mann-Whitney U=34; p=0.23), with high-responders being numerically older (mean, 69.62 years, SD 6.82) than low-responders (59.50 years, SD 13.47). Low-responders had numerically larger lesion volumes, but the difference was not significant (U=14; p=0.23). Low- and high-responders had similar neglect severity scores before PA (U=28; p=0.66). However, high-responders had a shorter delay from stroke (mean number of days from stroke, 341.38; SD, 340.58; range 107-1119) than low-responders (mean, 816.33 days; SD, 484; range 319-1497; U=42, p=0.02). Homonymous hemianopia was present in three low-responders and in three high-responders.

By definition, high-responder patients demonstrated a statistically reliable neglect improvement after PA (Wilcoxon Signed-Ranks Test, Z=-2.52; p=0.012), while this was not the case for the low-responder subgroup (Z=-0.67; p=0.50). In particular, high-responders detected more left items in letter cancellation (Z=-2.39, p=0.017), drew more left-sided items in landscape copy (Z=-2.06, p=0.039) and in daisy drawing (Z=-2.24; p=0.025), and had a more symmetrical performance when bisecting lines (Z=-2.240; p=0.025). However, PA did

not significantly impact performance on tasks with minimal motor component, such as the reading task (Z=-1.604; p=0.11) and the Landmark task (Z=-0.365; p=0.715).

3.2. Lesion analysis

The maximum lesion overlap was centred in the right fronto-parietal white matter in both patient subgroups (Figure 1.1). In low-responders, damage also involved the supramarginal and angular gyri of the inferior parietal lobule. Lesion subtraction (Figure 1.2) between low and high responders mostly revealed parietal regions, including the inferior parietal lobule, the postcentral gyrus, but also frontal regions such as the precentral gyrus, the superior frontal lobe, the orbito-frontal cortex, and the fronto-parietal white matter.

3.3. Cortical thickness

A regression analysis between cortical thickness and recovery scores revealed three significant clusters in the left, undamaged hemisphere (Figure 2 and Table 2). The first cluster (p=0.037) involved the perisylvian region, including the surface of the inferior parietal lobule, the three temporal gyri, somatosensory areas and the prefrontal cortex, with a medium effect size (0.26). The second cluster (p=0.048) was located in the posterior part of the superior temporal sulcus. The third cluster (p=0.049) was situated in the anterior portion of the left inferior temporal sulcus. All the clusters had large effect sizes (>0.60).

Controls and high responders had similar values of cortical thickness; low responders had instead lower values in cluster 3 (mean, 0.73) compared with high-responders (2.17) (t=3.9751, df=12, Benjamini-Hochberg-corrected p<0.01), and with controls (mean=2.52) (t=9.48; df=14; Benjamini-Hochberg-corrected p<0.01) (Supplementary Figure 1). There were statistical trends for differences in the same direction in cluster 2 between low-responders and high-responders (means, 0.91 and 1.55, respectively; t=2.51; df=12;

Benjamini-Hochberg-corrected p = 0.082), and between low-responders and controls (controls' mean, 1.47; t=2.88; df=14; Benjamini-Hochberg-corrected p=0.055).

3.4. White matter analyses

TBSS showed that low-responders had decreased FA as compared with high-responders in three clusters, all with large effect sizes (>0.80; Figure 3, Table 3). The first cluster (p = 0.019) was located in the body of the corpus callosum. The second cluster (p = 0.049) encompassed the genu of the corpus callosum. The third cluster (p = 0.049) was localized in a portion of the genu of the corpus callosum within the left, undamaged hemisphere.

We used BCBtoolkit to visualize the white matter tracts passing through the voxels showing a significant difference between the patient subgroups. The analysis revealed that the fibres intersecting the first cluster mostly connected sensorimotor areas (Figure 4). Additional regions in the temporal lobe (middle and superior gyri), and in the parietal lobe (supramarginal gyrus, precuneus and superior parietal lobule) were also involved. The second and the third clusters mostly connected prefrontal areas. The groups did not differ in mean, axial and radial diffusivity. Regression analyses between FA values and percentage of improvement after PA did not disclose any significant correlations.

A region of interest approach based on the clusters identified by TBSS analysis in patients was employed to extract FA values from the ten age- and education-matched healthy participants. Benjamini-Hochberg-corrected comparisons showed similar FA values in high-responders and controls in cluster 1 ($p=0.30$). Low-responders had lower FA values than both controls and high-responders in cluster 1 (all $p<0.01$) and 2 (all $p<0.01$). High- and low-responders had lower FA values than controls in cluster 3 ($p<0.01$), with a tendency for lower FA values for low-responders than for high-responders ($p= 0.081$) (Figure 3).

Cortical thickness in clusters 2 and 3 correlated with the 3 clusters of FA values (Table 4), thus suggesting a link between decreased cortical thickness and white matter degeneration. All FA and Cortical thickness clusters correlated with the delay post-stroke (in days, table 5).

4. Discussion

In this study, we followed up a group of patients with chronic visual neglect, before and after prism adaptation. The time elapsed from stroke resulted to be shorter in high-responders than in low-responders, which suggests the opportunity to administer PA therapy as soon as possible after the stroke. We used advanced neuroimaging techniques to identify the anatomical predictors of neglect patients' response to PA. First, cortical thickness analyses indicated a significant contribution of the left, undamaged hemisphere. Second, diffusion weighted imaging demonstrated an important role for inter-hemispheric connections in PA efficiency.

In the left, healthy hemisphere, cortical thickness analyses revealed a significant involvement of the temporo-parietal areas in the PA cognitive effect. These regions match areas contributing to right visual neglect after a stroke in the left hemisphere (Beume et al., 2016), and mirror classical areas reported as involved in left visual neglect after a stroke in the right hemisphere (Corbetta & Shulman, 2011). This may suggest that the left temporo-parietal junction is able to compensate for left visual neglect (Paolo Bartolomeo & Thiebaut de Schotten, 2016). Consistent with this hypothesis, previous studies reported an involvement of the left hemisphere in the recovery of neglect after PA therapy (Levin, Kleim, & Wolf, 2009; Luauté et al., 2006; Saj et al., 2013). In healthy individuals, rightward PA increased BOLD response in the left inferior parietal cortex (Tissieres, Fornari, Clarke, & Crottaz-Herbette, 2017). Our cortical thickness and diffusion results suggest an implication of left prefrontal cortex in prism-induced neglect compensation, consistent with the observation that effective PA in neglect is facilitated by TMS-based disinhibition of the left motor cortex (O'Shea et al., 2017). Altogether, these findings fit well with the fronto-parietal organization of attention networks in the primate brain (Lunven & Bartolomeo, 2017) .

Two possibilities can explain the difference in cortical thickness in the contralesional hemisphere. Some individual brains might have a better predisposition to recover than others (e.g., thanks to a thicker left temporo-parietal junction). This possibility would be consistent with the analogous results obtained in the domain of recovery from aphasia, which appears to be promoted by stronger language structures in the right hemisphere (Forkel et al., 2014; Xing et al., 2016). An alternative hypothesis might be that diaschisis and disconnection may have induced secondary atrophy in remote cortices (Cheng et al., 2015; Foulon et al., 2017). This would be consistent with previous reports suggesting that bilateral diffuse tissue loss may occur in individuals with chronic stroke (Gauthier, Taub, Mark, Barghi, & Uswatte, 2012; Kraemer et al., 2004). Thus, premorbid atrophy in left temporo-parietal areas might hamper cognitive effects related to PA after a stroke in the right hemisphere (see (Levine, Warach, Benowitz, & Calvanio, 1986). Future longitudinal studies comparing acute to chronic stages of vascular strokes may adjudicate between these possibilities.

Our results also showed that low-responder patients had a selective decrease of callosal FA in the body and genu of the corpus callosum, which mainly connect sensorimotor and prefrontal areas (Catani & Thiebaut de Schotten 2012). Analysis of other metrics of white matter integrity (RD, MD, AD) in clusters identified by TBSS was consistent with the FA results. Martín-Arévalo *et al*. (2016) showed that leftward PA alters transcallosal motor inhibition between the two motor cortices in the healthy brain, thus confirming the possibility that PA modulates inter-hemispheric interactions. This result suggests that PA improves left neglect by allowing left-hemisphere attentional networks to access information processed by the lesioned right hemisphere, through the callosal body and genu. An implication of prefrontal circuits in neglect compensation has been hypothesized on the basis of behavioural evidence (Bartolomeo, 1997; Bartolomeo, 2000), and recently confirmed by electrophysiological measures (Takamura et al., 2016). Also consistent with our results,

cathodal transcranial direct current stimulation applied over the left posterior parietal cortex interfered with the beneficial effect of PA on neglect (Làdavas et al., 2015).

5. Limitations of the study

We were able to include 14 chronic neglect patients for follow-up before and after PA; the design of the study required this sample to be further subdivided in two subgroups (high- and low-responders). The limited number of inclusions is representative of the difficulties of organizing a longitudinal study of patients with stable neuropsychological deficits, with the associated need of administering lengthy MRI sequences and repeated cognitive assessments. In the present study, five additional neglect patients had to be excluded because they did not tolerate the 1-hour-long neuroimaging procedure used in this study. Despite this limitation, however, the sample size was sufficient to obtain significant results with TBSS, which is a notoriously conservative technique. Also, a power analysis indicated medium to large effect sizes for the left temporo-parietal junction, temporal lobe and white matter findings. Finally, the present anatomical evidence is consistent with previous studies, showing that lesions to the right hemisphere posterior parietal cortex and the superior frontal gyrus (Rousseaux et al., 2006), the infero-posterior parietal cortex (Luauté et al., 2006), the intra-parietal sulcus, the white matter around the inferior parietal lobule, the middle frontal gyrus (Sarri et al., 2008), the occipital lobe (Serino, Angeli, Frassinetti, & Làdavas, 2006) and the right cerebellum [patient 5 in (Saj et al., 2013)] hampered PA efficiency. Thus, our patient population appears to be representative of the general lesional patterns in chronic neglect patients.

6. Conclusions and perspectives

Our results confirm the importance for recovery from neglect of the left, healthy hemisphere (Bartolomeo & Thiebaut de Schotten, 2016), as well as of efficient inter-hemispheric

connections (Lunven et al., 2015). Specifically, left hemisphere regions homologues to the fronto-parietal attention networks in the right hemisphere (Corbetta & Shulman, 2002), as well as callosal pathways passing through the body and the genu, appear to be critical for compensation of neglect signs after a single PA session. It remains to be seen whether or not similar anatomical constraints apply to more prolonged rehabilitation programmes using PA (Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002). The identification of anatomical predictors of response to different, labour-intensive rehabilitation strategies may ultimately enable clinicians to select and tailor the appropriate treatment to the specific needs of the individual patient. Even in chronic patients at more than 3 months from the stroke, early administration of PA could be important to improve patients' response. Finally, the relationship between recovery and contralesional cortical thickness suggests potential targets for future therapeutic interventions.

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Table 1: Demographical and clinical characteristics of patients, with their performance on visuospatial tests before and after prism adaptation.

	High-Responder group N=8 mean (SD)		**Low-Responder group** N=6 mean (SD)		
Descriptive data					
Age (years)	69.62 (6.82)		59.5 (13.47)		p=0.230
Education	12.25 (3.65)		12 (2.82)		p=0.895
Lesion volume (cm^3)	106.53 (110,60)		228.98 (183,21)		p=0.230
Lesion-testing delay (days)	341.40 (340.59)		816.33 (484.29)		**p=0.02**
Motor deficit (number of patients)	4		3		
Visual field defect (number of patients)	3		3		
Neuropsychological results					
MMSE	27.00 (1.69)		26.83 (2.40)		p=0.881
Recovery rate (%)	36.29 (15.36)		-1.60 (22.18)		**p<0.01**
	Pre	**Post**	**Pre**	**Post**	
Neglect severity global score (%)	32.38 (20,10)	21.64 (16.69)	32.18 (24.96)	30.72 (19.53)	
Letter cancellation (left omissions)	10.25 (7.63)	4.62 (6.09)	7.83 (11.29)	7.00 (9.63)	
Gainotti drawing (max 6)	4.50 (1.07)	5.20 (1.00)	4.33 (1.21)	4.83 (1.33)	
Reading task (max 116)	8.50 (12.75)	3.00 (3.82)	16.00 (35.78)	16.00 (37.24)	
Line bisection (rightward deviation, mm)	20.08 (22.43)	8.35 (15.87)	16.04 (28.89)	10.23 (25.27)	
Daisy drawing (max 3)	2.00 (0.92)	2.62 (1.06)	1.33 (0.82)	1.50 (0.84)	
Landmark task ("left shorter" answers, max 12)	8.00 (3.78)	7.5 (3.74)	8.00 (3.29)	9.00 (3.29)	

Table 2: Grey matter clusters showing decreased cortical thickness associated with poor recovery after PA therapy

GM clusters	MNI coordinates			CS	Corrected *P*	Effect size *d*
	x	*y*	*z*			
1. L perisylvian regions	-43	-3	-21	31947	0.037	0.26
2. L Temporo-parietal junction	-48	-55	15	1539	0.048	0.67
Angular g						
Middle temporal lobe						
3. L Temporal lobe	-33	-16	-32	670	0.049	1.24
ITg						
L fusiform g						
Parahippocampal g						

CS, cluster size (i.e., number of voxels); L, left; g, gyrus; ITL, inferior temporal gyrus; IPL, inferior parietal lobule.

Grey matter clusters significantly associated with poor recovery of neglect after prism adaptation (P_{TFCE}<0.05). Coordinates indicate the location of the cluster peak in Montreal Neurological Institute (MNI) convention.

Table 3: White matter clusters showing decreased fractional anisotropy FA (P_{TFCE}<0.05) in the low-responder group as compared with the high-responder group

WM clusters	MNI coordinates			CS	Corrected *P*	Effect size *d*
	x	*y*	*z*			
1. CC body	2	-20	24	1533	0.019	1.57
2. CC genu	0	24	0	47	0.049	1
3. L CC genu	-12	31	-2	9	0.049	0.85

CS, cluster size (i.e., number of voxels); CC, corpus callosum; L, left.

Coordinates indicate the location of the cluster peak in Montreal Neurological Institute (MNI) convention.

Table 4: Spearman correlations between the three FA clusters identified in the TBSS analysis and the three cluster identified in the cortical thickness study

	FA Cluster 1	FA Cluster 2	FA Cluster 3	CT Cluster 1	CT Cluster 2	CT Cluster 3
FA Cluster 1						
FA Cluster 2	**0.855****					
FA Cluster 3	**0.780****	**0.864****				
CT Cluster 1	0.253	0.358	0.437			
CT Cluster 2	**0.582***	**0.692****	**0.705****	**0.873****		
CT Cluster 3	**0.701****	**0.767****	**0.771****	**0.648****	**0.798****	

** $p<0.01$; * $p<0.05$, FA Fractional Anisotropy, CT Cortical Thickness,

Table 5: Spearman correlations between imaging clusters and delay post stroke

	Cluster 1 FA	Cluster 2 FA	Cluster 3 FA	Cluster 1 CT	Cluster 2 CT	Cluster 3 CT
Correlation coefficient with delay post stroke	-0.71**	-0.58*	-0.59*	-0.49*	-0.65**	-0.62**

** $p<0.01$; * $p<0.05$, FA Fractional Anisotropy, CT Cortical Thickness,

Figure legends

Figure 1: Patients' grey matter lesion anatomy. (1) Overlap of the lesions for all the included right brain-damaged patients for each group. (2) Results of the subtraction of the probability map of the high-recovery group from the probability map of the low-recovery group. Maps show the Z-statistics rank order statistics. All peaks are significant at $p<0.05$ level

Figure 2: Cortical thickness analysis. Relationship between cortical thickness and recovery rate score represented by the four clusters. Results are represented at $p<0.05$ and corrected for multiple comparisons. LH, left hemisphere; RH, right hemisphere.

Figure 3: White matter analysis. Results of TBSS between-groups comparisons represented by the three clusters. FA differences ($p<0.05$) are represented in red.

Figure 4: Percentage maps in healthy subjects (BCB toolkit: http://www.brainconnectivitybehaviour.eu) showing the cortical projections of the voxels identified by TBSS analysis in low recovery patients compared to high-recovery patients.

LH, left hemisphere; RH, right hemisphere.

Figure 1

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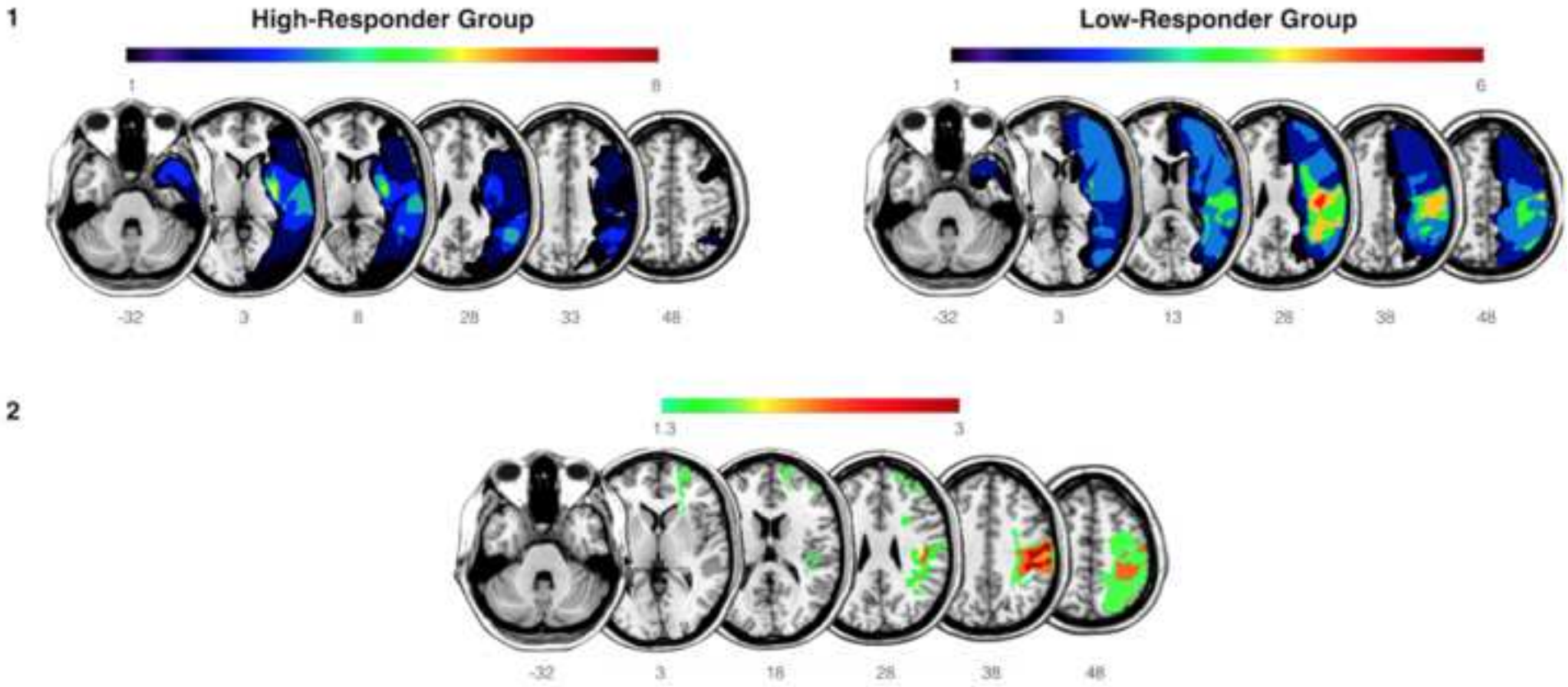

Figure 2

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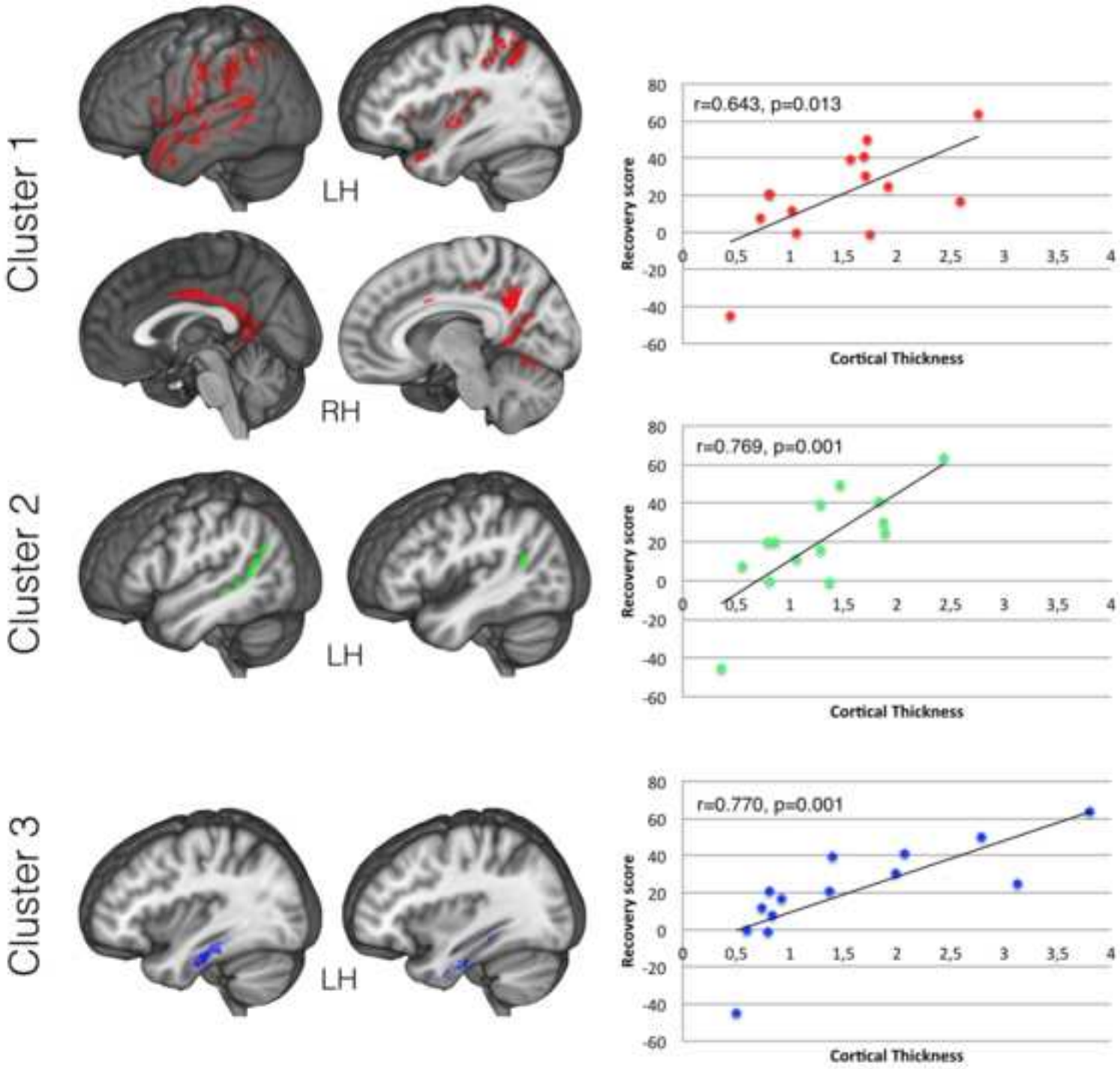

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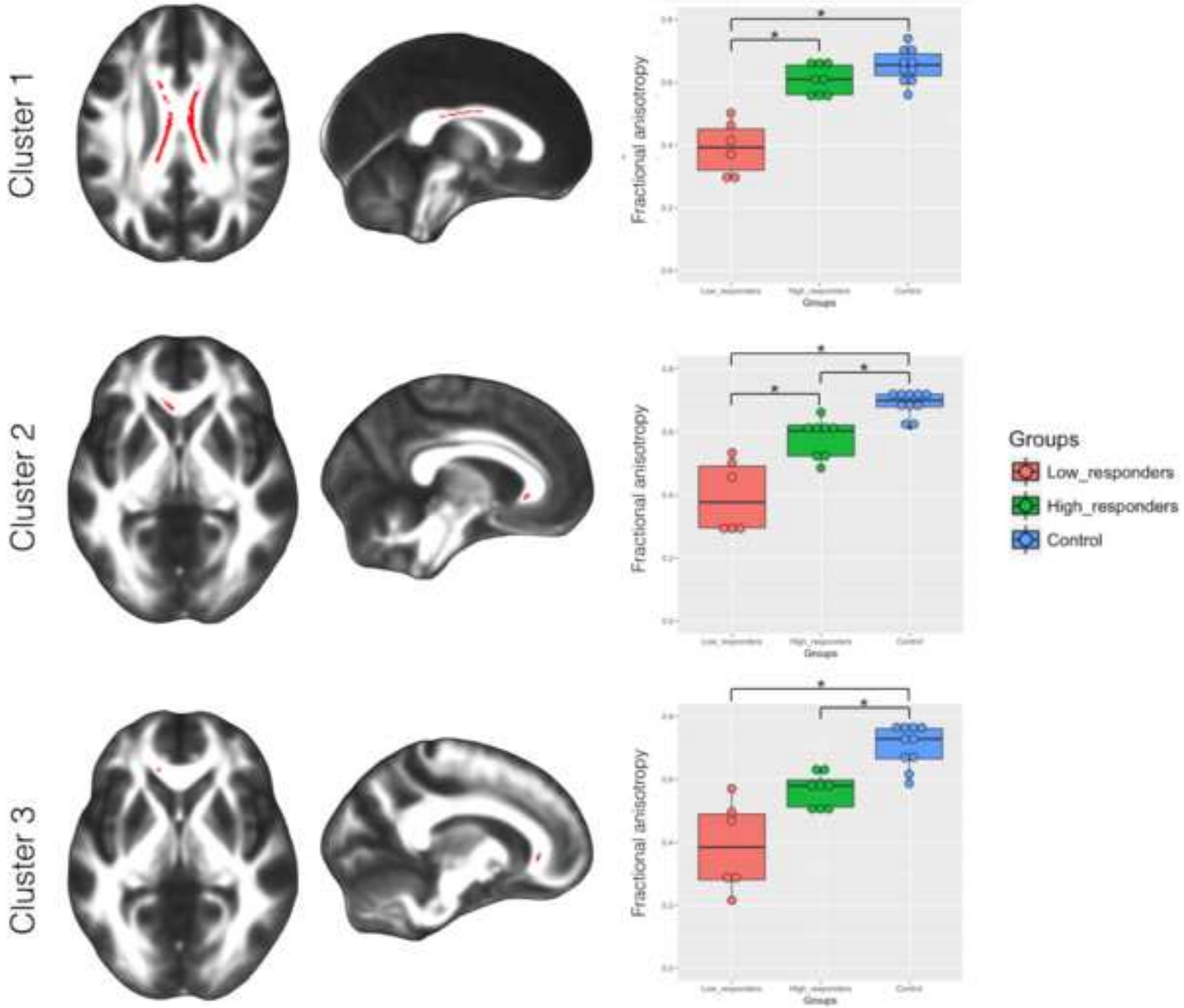

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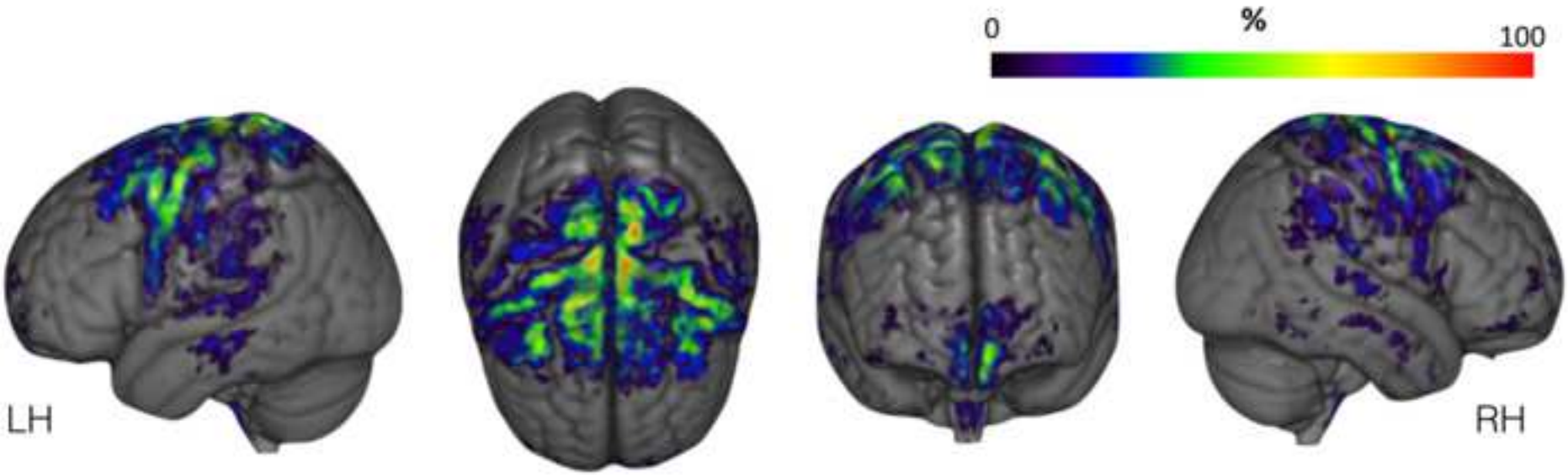

Supplementary Figure 1

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