Parietal/premotor lesions effects on visuomotor cognition in neuro-oncology patients: A multimodal study

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ABSTRACT

Background: Assessing prior to surgery the functionality of brain areas exposed near the tumor requires a multimodal approach that combines the use of neuropsychological testing and fMRI tasks. Paradigms based on motor imagery, which corresponds to the ability to mentally evoke a movement, in the absence of actual action execution, can be used to test sensorimotor areas and the functionality of mental motor representations.
Methods: The most commonly used paradigm is the Limb Laterality Recognition Task (LLRT), requiring judgments about whether a limb belongs to the left or right side of the body. The group studied included 38 patients with high-grade (N = 21), low-grade (N = 11) gliomas and meningiomas (N = 6) in areas anterior (N = 21) and posterior (N = 17) to the central sulcus. Patients before surgery underwent neuropsychological assessment and fMRI. They performed the LLRT as an fMRI task. Accuracy, and neuroimaging data were collected and combined in a multimodal study. Structural MRI data analyses were performed by subtracting the overlap of volumes of interest (VOIs) plotted on lesions from the impaired patient group vs the overlap of VOIs from the spared group. The fMRI analyses were performed comparing the impaired patients and spared group.
Results: In general, patients were within normal limits on many neuropsychological screening tests. Compared with the control group, 17/38 patients had significantly different performance. The subtraction between the VOIs overlay of the impaired patients' group vs. the VOIs overlay of the spared group revealed that the areas maximally involved by lesions in the impaired patients' group were the right postcentral gyrus, right inferior parietal lobe, right supramarginal gyrus, right precentral gyrus, paracentral lobule, left postcentral gyrus, right superior parietal lobe, left inferior parietal lobe, and left superior and middle frontal gyrus. Analysis of the fMRI data showed which of these areas contributes to a correct LLRT performance. The task (vs. rest) in the group comparison (spared vs. impaired patients) activated a cluster in the left inferior parietal lobe.
Conclusion: Underlying the altered performance at LLRT in patients with lesions to the parietal and premotor areas of the right and left hemispheres is a difference in activation of the left inferior parietal lobe. This region is involved in visuomotor processes and those related to motor attention, movement selection, and motor planning.

Author contributions

B.T. P.B. and M.S. designed the research; B.T., M.M. S.D'A. performed the research; B.T., M.M. S.D'A. analyzed the data; B.T. and P.B. wrote the paper; all authors edited the paper; B.T., M.M. S.D'A. and M.S. collected the data; all authors revised the final version of the manuscript.

1. Introduction

It is becoming an increasingly standard approach that neurosurgical operations are preceded by functional magnetic resonance imaging (fMRI). Very simple (but robust) tasks are designed in order to be performed by patients in the fMRI environment. fMRI scanning time is limited to the patients' cooperation, thus task should be short and simple. A series fMRI maps related to motor, language and other

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cognitive abilities are obtained for each patient. The benefit of using fMRI maps during surgical planning is that the maps could help in predicting functionality of tissue prior to surgery. During surgery, the fMRI can be loaded along with the MRI structural images on the neronavigation system showing in real time the position of the surgical act on a T1-or T2-weighted MRI image. The information provided by fMRI can help the neurosurgeon ascertain whether functional activity persists within or near the lesion and to plan before surgery for the optimal surgical approach. Intra-operatively, it helps the neurosurgeon orient himself by providing structural and functional information. In addition, the fMRI outcome is used to select the tasks that can be used for the patient operated in awake surgery.

In evaluating the effects of lesions to the sensorimotor network, fMRI motor localizers can be used. The patient is asked to perform mouth, hands and feet movements, which are alternated with rest blocks, to obtain sensorimotor maps of the mouth, hands and feet representations. In addition to map the movement execution areas, it may be necessary to evaluate other aspects, given the role of this network in cognitive processing (e.g., Craighero, 2022). One of the domains to be evaluated is the status of motor representations, which also is a topic of long interest in several neuroscientific disciplines. One way to access motor representations is through the mental simulation of movements (Decety et al., 1994). The benefit of using mental imagery in the context of pre-surgical mapping is that also patients with arm or leg weakness, due to the lesion, can perform the task, as it does not require active real movements. Indeed motor simulation corresponds to the ability to mentally evoke a movement in the absence of its actual execution. The most widely used paradigm for accessing motor representations is the Limb Laterality Recognition Task (LLRT). The LLRT has been used as a behavioral index of motor imagery ability for decades (e.g., for a review of the literature, Moreno-Verdú and Hardwick, 2022; Kim and Yi, 2021). In the LLRT, subjects analyze an image representing a hand or foot that is rotated in space, and decide whether this corresponds to the right or left hand or foot. In performing the task subjects implicitly use a strategy of imagining moving their hand or foot towards the position and orientation of that shown in the image (Parsons, 1987). This task activates the motor system, as it relies on sensory-motor information and egocentric reference system (Parsons, 1994; Mibu et al., 2020).

Hands pictures are the most widely used stimulus type in LLRT neurophysiological studies. Single-pulse transcranial magnetic stimulation (TMS) experiments confirm the involvement of the primary motor cortex in solving the LLRT. As an example (Hyde et al., 2017), in one of the TMS studies subjects solved the LLRT while TMS was delivered to the motor and premotor areas and motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseous. It was found that MEPs were greater for more complex simulated hand movements: increased for biomechanically awkward movements (i.e., hands requiring lateral rotation) vs. hands requiring medial rotation (Hyde et al., 2017). In addition subthreshold TMS to the primary motor area impairs performance in LLRT but not in mental rotation of objects (Pelgrims et al., 2011). Evidence from electroencephalography studies has shown that motor imagination and LLRT share activation of a common sensorimotor network (Osuagwu and Vuckovic, 2014). Other methods such as near-infrared spectroscopy show that another area, the superior parietal lobe, highly contributes to task performance (Meng et al., 2016). Lastly, fMRI studies confirm the role of the parietal-premotor network in carrying out the LLRT. Early neuroimaging studies associated with this task showed activation in several dominant regions including the posterior parietal (superior parietal and intraparietal sulcus), premotor and primary motor cortex, SMA, and cerebellum (Seurinck et al., 2004; Vingerhoets et al., 2002; Kosslyn et al., 1998; Parsons et al., 1995). The fMRI study by Ferri et al. (2012) for example, revealed a network including the SMA and pre-SMA, anterior insula, and occipital cortex, bilaterally. LLRT-related activation is selective for the hand stimulus as compared to whole-body mental rotation (Perruchoud et al., 2016). Hamada et al. (2018) compared activation during LLRT and a motor imagination task and reported a common bilateral activation in premotor areas and supplementary motor area. Qu et al. (2018) showed that images of hands congruent with hand image posture evoked significant activation in the left inferior parietal lobule, right SMA, bilateral middle frontal gyrus, left inferior frontal gyrus, and bilateral superior frontal gyrus.

Patient-based fMRI studies on LLRT are rare. One of them (Kashuk et al., 2017) reported a greater activation, in healthy controls vs. adults with probable Developmental Coordination Disorder group, in the occipito-parietal and parieto-frontal network, including the middle frontal gyrus bilaterally, the left superior parietal lobe, and the cerebellum. In another fMRI study, Kohler et al. (2019) reported that although both patients with regional pain syndrome complex and a control group showed a typical activation pattern, only the controls showed activation in the right intraparietal sulcus. It is well known that fMRI studies offer correlational rather than causation data. Thus, performing fMRI studies on patients with selectively damaged areas is crucial. Patients' studies can measure the relevance of the areas involved in the performance of LLRT.

In the present work, we analyzed both neuropsychological and neuroimaging data of neurosurgical patients and combined them together in a multimodal assessment that can be used to map the function of areas involved in the sensorimotor network. The clinical objectives of the study were i) to test the feasibility of LLRT as an fMRI task performed with neurosurgical patients; ii) to investigate whether LLRT can be a good localizer of the parietal-premotor network. The third aim was to test which nodes of the network supporting LLRT can be altered in terms of activation in the presence of a lesion to sensorimotor areas, an objective that is more research oriented. For the latter objective, hypotheses were made based on the results of fMRI studies of patients reported above. Differences in activation between the group of patients performing LLRT pathologically and the group of patients in the normal range are expected in the areas of the occipito-parietal and parieto-frontal network (Kashuk et al., 2017) or the right intraparietal sulcus (Kohler et al., 2019). The laterality and location will depend greatly on the compromised voxels and the maximum overlap of the groups formed in the case series involved in this study.

2. Methods and materials

2.1. Participants

In the present retrospective study, we included neurosurgical patients who met the following inclusion criteria: Age >18 years; preoperative Magnetic Resonance Imaging (MRI) suggestive of supratentorial high-grade (HGG) or low grade (LGG), glioma or meningioma; preoperative neuropsychological assessment; no previous surgery, chemo- or radio-therapy; normal or corrected vision; right handedness. Exclusion criteria were: precedent biopsy; precedent surgery for brain glioma. The local Ethics Committee, Comitato Etico Unico Regionale del Friuli Venezia Giulia, approved this investigation (protocol N.007670/P/GEN/EGAS, ID study 4251). Considering that the study was retrospective, written consent to participate in the study was not applicable. Written informed consent was obtained for surgery. All patients underwent pre-surgical brain MRI and fMRI, and neuropsychological assessment. Data were collected as part of clinical-care-as-usual. Data collected were demographic, neuropsychological, MRI and fMRI images, years of education, tumor side and localization, histology.

2.2. Neuropsychological screening

On the same day as the fMRI was performed, patients underwent neuropsychological screening including a battery of tests: the Raven's colored matrices test (Basso et al., 1987), buccofacial apraxia (Spinnler and Tognoni, 1987), ideomotor apraxia (De Renzi et al., 1980), short-term memory (Digit span, Monaco et al., 2015), Token Test

(Spinnler and Tognoni, 1987), naming of living and nonliving entities (Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993), constructive apraxia (Spinnler and Tognoni, 1987), Balloon Test (Edgeworth, Robertson, MacMillan, 1998), and the Birmingham Object Recognition Battery's (Riddoch and Humphreys, 1993) subtest 8 (Foreshortened view).

2.3. Magnetic resonance imaging study

Data were routinely acquired pre-surgery. A Siemens 1.5 T MRI whole-body scanner (Siemens AVANTO, Erlangen, Germany) was used. Functional MR images were acquired using a standard head coil and a custom-built head restrainer to minimize head movements. Functional images were obtained using a single-shot gradient echo, echoplanar imaging (EPI) sequence. Each subject was scanned first for the LLRT experiment and then again for the anatomical acquisition. EPI volumes for the main experiment (mental rotation task, N = 85 EPI volumes) contained 27 axial slices (TR = 3000 ms, TE = 60 ms, FOV = 224 mm, matrix: 64 × 64; slice thickness of 5 mm, 90° flip angle, voxel size: 3.5 × 3.5 × 5 mm) and were preceded by 5 dummy images that allowed the MR scanner to reach a steady state.

After functional neuroimaging, high-resolution anatomical images were acquired using a T1-weighted 3-D magnetization-prepared, rapid acquisition gradient-echo (MP-RAGE) pulse sequence (TR = 2300 ms, TE = 2.86 ms, FOV = 256 mm, 176 sagittal slices of 1 mm thickness, flip angle = 20°, voxel size: 1 × 1 x 1).

2.3.1. fMRI task

The LLRT was used in a blocked design including blocks of task (N = 4 blocks of hand task and N = 4 blocks of foot task) and 9 blocks of rest (fixation point). Each block (15 s each) included 8 trials. Two sets of color photographs (resolution: 574 × 596 pixels) were used as stimuli and were repeated twice, one including 34 open hands and the other 34 feet (all fingers fully extended, 50% right and 50% left) for a total of 136 stimuli. In each of the two sets, view (palm up or palm down for hands/plant up or plant down for feet) and orientation (rotated in 45° increments; range: 0°–315°, Fig. 1A) were manipulated.

The instruction was "Decide whether is a right or left body part". For each experimental trial, the stimuli were presented for 1875 ms. Silent responses were chosen to minimize interference between response preparation and execution and the predicted task-related activity in central area. Prior to the fMRI experiment, subjects performed the experimental task outside the scanner to collect accuracy and we collected their voice onsets as response times. If no response was given, the next trial was moved on and a score of 0 was given. The pilot study was performed on a group of 15 healthy (Edinburgh Inventory test (Oldfield, 1971), right-handed subjects (mean ± SD age: 43.46 ± 12.01 years; 8 females) who performed the same LLRT. All subjects had comparable educational attainment (mean ± SD 12.66 ± 2.96), had normal or corrected-to-normal vision, and reported no history of neurological, psychiatric, or drug abuse illnesses. Their mean test accuracy was 115.266 ± 8.547 (range: 102–136). Subjects responded using a mouse. They lay supine with their head fixated by firm foam pads and were asked to keep their arms along the body with the palms toward the legs for the whole duration of the experiment. Presentation of the stimuli and their synchronization with the MR scanner was realized by the software package Presentation (Neurobehavioral Systems Inc., Albany, CA, USA). Subjects viewed the stimuli via a VisuaStimDigital (Resonance Technology Inc., Los Angeles, CA, USA) Goggle.

2.4. Statistical methods

2.4.1. Behavioral data

For each test of the neuropsychological screening, we converted the Raw Score (RS) into Correct Score (CS) for age, schooling and gender. Then each CS was converted in the correspondent Equivalent Score (ES) using a 0–4 scale, in which 0 corresponds to a score below the 5% tolerance limits, 4 corresponds to a score equal to or better than the outer nonparametric tolerance limit of adjusted scores, according to the standardization of the tests. The ES were derived from the reference articles of each task. 1, 2 and 3 are intermediate (Capitani and Laiacona, 1988).

For some cognitive test, the normative study includes only a cut-off score. In this case, a score under the cut-off means a performance below the normal range. For the cut-off score of each individual test see Table 2's legend.

For the analyses of the LLRT, total correct responses of individual patients were compared with data from controls (mean and standard deviation). We performed independent t-tests modified for small sample sizes using the Crawford and Garthwaite (2002) method with their SINGLIMS.EXE program. The Crawford and Garthwaite (2002) method tests whether an individual's score is significantly different from a control (or normative) sample and provides a point estimate of score abnormality, that is, it estimates the percentage of the population that would score lower. It then provides 95% confidence limits on this percentage.

2.4.2. MRI structural data analysis

The volumes of interest (VOIs) of the patients' lesions were drawn on their T1 MRI scans using MRIcron software (https://www.nitrc.org/projects/mricron). VOIs were then normalized to MNI space (Montreal Neurological Institute) using the "Clinical Toolbox" (https://www.nitrc.org/projects/clinicaltbx/) for SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). Two mean frequency maps of the VOIs were created, one for the patient group having a LLRT normal performance and one for the patient group performing pathologically. Finally, the two mean frequency maps were subtracted to detect maximally lesioned voxels in the impaired patient group.

2.4.3. fMRI data analysis

All calculations were performed on UNIX workstations (SUN Microsystems Computers, CA/USA) using MATLAB 2018a (The Mathworks Inc., Natick, MA/USA) and SPM12 (Statistical Parametric Mapping software, SPM; Welcome Department of Imaging Neuroscience, London, UK http://www.fil.ion.ucl.ac.uk/spm). Dummy images were discharged prior to further image processing. Pre-processing included spatial realignment of the images to the reference volume of the time-series, segmentation producing the parameter file used for normalization of EPI data to a standard EPI template of the Montreal Neurological Institute template provided by SPM12, re-sampling to a voxel size of 2 × 2 × 2 mm, and spatial smoothing with a 6-mm FWHM Gaussian kernel to meet the statistical requirements of the General Linear Model and to compensate for residual macro-anatomical variations across subjects.

We performed a whole brain random effects analysis. Low-frequency signal drifts were filtered using a cut-off period of 128 s. To correct for motion artifacts, subject-specific realignment parameters were modelled as covariates of no interest. The presentation of task was modelled as the regressor of main interest. Separate regressors modelled the presentation of the resting blocks (Rest). At the single subject level, specific effects were assessed by applying appropriate linear contrasts to the parameter estimates of the experimental conditions resulting in t-statistics for each voxel.

For second-level random effects analyses, contrast images obtained from individual participants were entered into a two-sample *t*-test to create an statistical parameter map of the t-statistics, indicative of significant activations specific to this contrast at the group level (patients spared vs. impaired patients and vice versa).

We used a threshold of $p < .05$, corrected for multiple comparisons at the cluster level (using family-wise error (FWE)), with a height threshold at the voxel level of $p < .001$, uncorrected. Furthermore, the localization of these individual activations peaks was confirmed by the SPM Anatomy toolbox (Eickhoff et al., 2005).

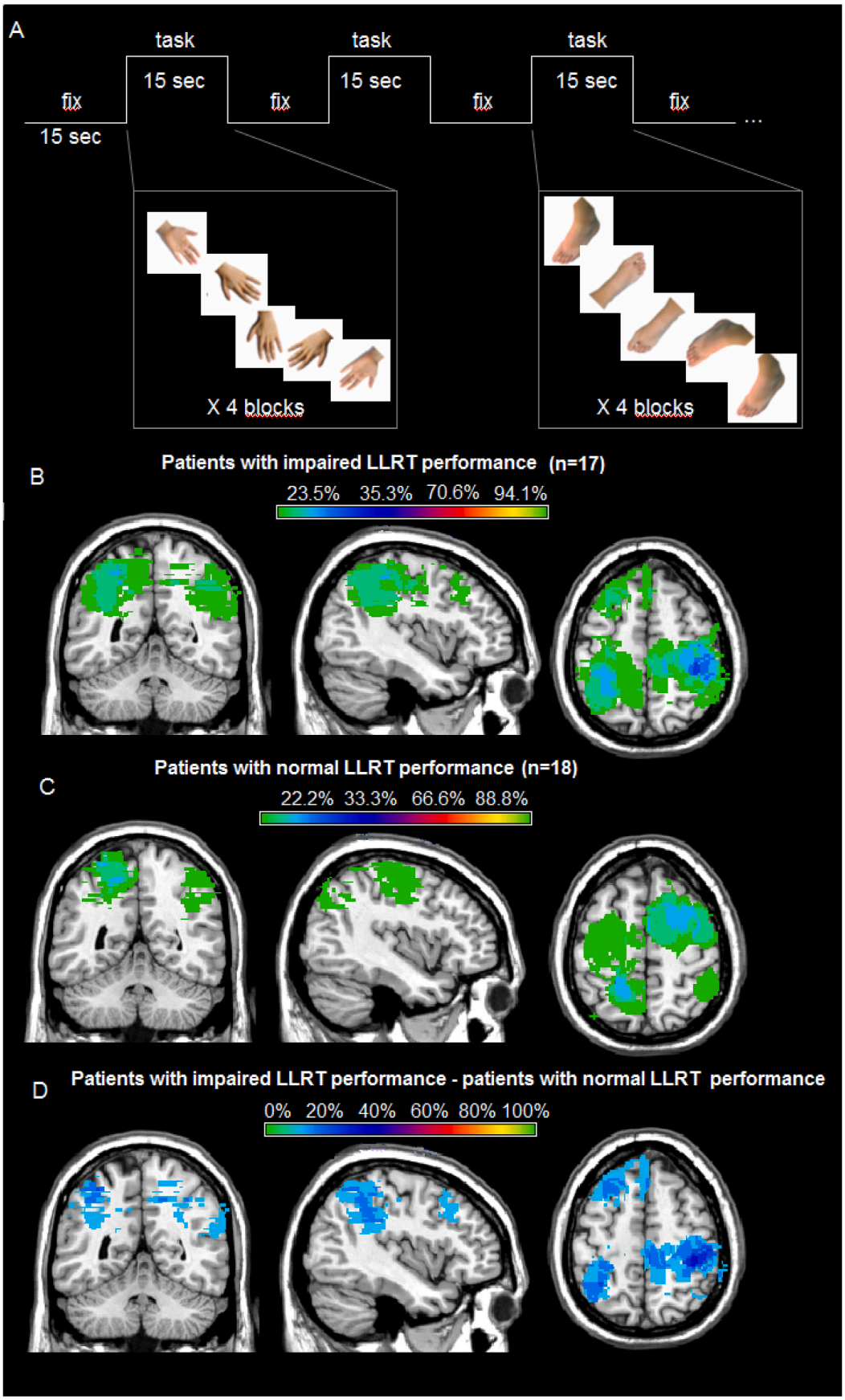

Fig. 1. Experimental Design and stimuli (A); Overlay of Volumes of Interest drawn on the patients' lesion volumes (VOIs) for the group of patients impaired at the LLRT (B) and the overlay of VOIs of the group of patient with normal performance at LLRT (C); Subtraction of VOIs group of patients impaired at the LLRT vs. superimposition of VOIs of the group of patient with normal performance at LLRT (D).

3. Results

3.1. Study population

The group studied included 38 patients (see Table 1). Histology included HGG (N = 21), LGG (N = 11) and meningiomas (N = 6). The lesions involved areas anterior (N = 21) and posterior (N = 17) to the central sulcus, as detected by the neuroradiologist (S.D'A). Supplementary Table 1 shows that the localization for each patient was parasagittal (N = 10), premotor (N = 9), postcentral (N = 7), central area (N = 3), anterior frontal or temporal (N = 10). The hemisphere involved in the lesion is either right (N = 21) or left (N = 17). Mean age of patients is 52.26±14.055 years (range 26–76), schooling is 11.18±4.09 years (range 5–19).

3.2. Neuropsychological screening

Overall, the patients were within normal limits at many neuropsychological screening tests (Table 2): at Raven's colored matrices test (Basso et al., 1987) they all obtained an equivalent score (PE) greater than 0 (and no borderline with PE of 1), at short-term memory (Digit span, Monaco et al., 2015) 12/38 (31.57%) scored a PE of 0 (with 5 borderline patients with Pes of 1), 1/38 were below the cut-off at the buccofacial apraxia test (Spinnler and Tognoni, 1987), at the ideomotor apraxia test (De Renzi et al., 1980) all scored in the normal range, on the Token Test (Spinnler and Tognoni, 1987), all scored in the normal range (with 5 borderline patients with PEs of 1) on the Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993), living and nonliving entity naming test all scored in the normal range, as well as on sub-test 8 (Foreshortened view) of the Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993), on the Constructive Apraxia Test (Spinnler and Tognoni, 1987) all scored in the normal range (with 1 patient borderline with PE of 1), and no patient was found to have spatial neglect or attention deficit as measured by the Balloon Test A (parallel processing, automatic) and B (serial processing, intensive visual search) (Edgeworth, Robertson, MacMillan, 1998) (Table 2; for individual patients' data see Supplementary Table 2).

3.3. LLRT results: accuracy

The test on the difference between the score of the individual patient and the performance of the group of healthy subjects (Crawford & Howell, 1998; Crawford, J.R., & Garthwaite, 2002) identified 19 patients with performance significantly different from normal (N = 7 patients with lesion at the LH and N = 12 patients with lesion at the RH, Table 3). Based on this analysis, groups of patients were formed for fMRI data analysis: impaired and spared. Analysis of the fMRI data was performed on 35 patients (the data of 3 patients had not met the prerequisites of spatial realignment, i.e., motion parameters), two patients had higher scores than controls (trend, $p < .064$), so they were included in the group of patients with scores in the normal range. Thus for the fMRI analysis we included 17 impaired patients: 10 with RH injury and 7 with LH injury. The comparison was performed on two groups: impaired patients listed above, and group of patients with scores in the normal range (total of 18): 9 with lesion to the RH and 9 with lesion to the LH.

As the present study included patients with meningioma and gliomas of different grade, we inspected the role of histology. A Kruskal Wallis Test showed that there was no significant effect of histology on LLRT performance (H (2) = 0.714, P = .7), nor on the number of impaired patients (H (2) = 0.56, P = .75).

Looking at patients' neuropsychological performance 5/17 impaired patients have a E.S. = 0 on the short term memory test (7/17 have a E.S. = 0 among patients in the normal range at LLRT); 2/17 impaired patients have a E.S. = 1 (3/17 have a E.S. = 1 among patients in the normal range at LLRT). To exclude that the difference between impaired and spared patients could be determined by differences in the short term memory test, a Mann-Whitney Test was performed on the E.S. at the short term memory with the grouping variable impaired patient/spared patient at the LLRT, which was found to be non-significant ($Z = -0.062$, $p = .951$). In addition, the correlation between C.S. on the short term memory test and score on the LLRT was non-significant ($r = 0.111$, $p = .505$, n.s.).

Furthermore, a Mann-Whitney Test on the neuropsychological performance between the two groups (impaired vs spared) confirmed that the two groups were comparable in terms of their neuropsychological profile. Only performance at the Baloon Test B was significantly different between groups ($Z = -2.35$ $p = .019$), nonetheless none had neglect as reported in Table 2. By contrast, performance at all the other test did not significantly differ between groups (Raven $Z = -0.706$, $p = .480$; STM $Z = -0.117$, $p = .906$; IMA $Z = -0.126$, $p = .899$; oral praxis $Z = -0.808$, $p = .419$; Token test $Z = -1.03$, $p = .303$; Naming living z

Table 1
Demographic and clinical data of patients (N = 38) involved in the study.

Age	Mean 53,26±14,05
Education	Mean 11,15±4,04
Hemisphere	21 right hemisphere; 17 left hemisphere
Histology	21 high grade glioma; 11 low grade glioma; 6 meningioma
Lesion localization: posterior/anterior to the central sulcus	21 anterior; 17 posterior
Symptoms	11 body part seizures; 3 seizure with loss of consciousness; 15 tingles; 4 oral rhyme deviation; 4 objects falling from the hand; 10 body part weakness; 8 sensory perception decrease 3 paresis 3 stiffness; 2 pain 2 other: vertigo, nausea arm ataxia

Table 2
Results at pre-FMRI neuropsychological screening tests.

	Min	Max	Mean	s.d	N of impaired patients
R handedness	50	100	89.66	15.7	–
Raven RS	27	36	33.34	2.66	–
Raven CS	29	41	34.34	3.01	–
Raven ES	3	4	3.92	0.27	–
STM RS	3	7	4.78	0.99	–
STM CS	2.27	6.68	4.70	0.83	–
STM ES	0	4	1.55	1.32	12
Oral apr RS	16	20	19.66	0.91	–
Oral apr CS	16	20	19.52	0.9	1
IMA	40	72	68.75	7.08	–
Token_CS	28	36	33.11	3.01	–
Token_CS	26.75	36.25	31.6	3.23	–
Token_ES	1	4	2.7	1.35	–
Nam_L	11	15	14.11	1.21	–
Nam_NL	18	20	19.7	0.68	–
Cost A_RS	10	14	13.61	1.02	–
Cost A_CS	9	14.75	12.91	1.34	–
Cost A_ES	1	4	3.71	0.78	–
Bal_A	18	22	21.71	0.9	–
Bal_B	17	22	20.71	1.45	–
Later	40	47.62	45.27	2.002	–
Borb8	24	25	24.8	0.4	–

RS = raw score; CS = corrected score; ES = equivalent score; STM = short term memory; Oral apr = oral apraxia (cut-off <17,4); IMA = ideomotor apraxia (cut-off <53); token = token test; nam liv = naming living (cut-off 8/15); nam non liv = naming non-living (cut-off 17/20); cost A = constructional apraxia; Bal = balloon test; later = laterality B (cut-off neglect <45% and Balloon B < 17).

Table 3
Test results (Crawford & Howell, 1998) on the difference between the individual patient's score and the performance of the group of healthy subjects.

ID	Score	omission	t	Two-tailed probability		fMRI analyses
RH#1	100	3	−1.728	0.106		excluded
RH#2	133	0	2.009	0.064[a]	Pat > ctr trend	
RH#3	104	8	−1.275	0.223		
RH#4	75	13	−4.559	0.000	Pat < ctr	
RH#5	64	24	−5.805	0.000	Pat < ctr	
RH#6	125	0	1.103	0.289		
RH#7	109	2	−0.709	0.490		
RH#8	109	9	−0.709	0.490		excluded
RH#9	86	10	−3.314	0.005	Pat < ctr	
RH#10	87	7	−3.2	0.006	Pat < ctr	
RH#11	78	17	−4.22	0.001	Pat < ctr	
RH#12	63	20	−5.918	0.000	Pat < ctr	
RH#13	52	20	−7.164	0.000	Pat < ctr	
RH#14	69	23	−5.239	0.000	Pat < ctr	
RH#15	133	0	2.009	0.064[a]	Pat > ctr trend	
RH#16	107	9	−0.935	0.365		
RH#17	102	4	−1.502	0.155		
RH#18	114	8	−0.143	0.889		
RH#19	107	11	−0.935	0.365		
RH#20	67	27	−5.465	0.000	Pat < ctr	
RH#21	98	12	−1.955	0.071[b]	Pat < ctr trend	
LH#1	102	12	−1.502	0.155		
LH#2	123	4	0.877	0.396		
LH#3	108	11	−0.822	0.425		
LH#4	87	8	−3.2	0.006	Pat < ctr	
LH#5	87	12	−3.2	0.006	Pat < ctr	
LH#6	122	2	0.763	0.458		
LH#7	80	9	−3.993	0.001	Pat < ctr	
LH#8	111	12	−0.482	0.637		
LH#9	102	11	−1.502	0.155		
LH#10	20	33	−10.788	0.000	Pat < ctr	
LH#11	116	9	0.084	0.934		
LH#12	75	17	−4.559	0.000	Pat < ctr	
LH#13	105	9	−1.275	0.265		excluded
LH#14	74	16	−4.672	0.000	Pat < ctr	
LH#15	107	8	−0.935	0.365		
LH#16	117	9	0.197	0.847		
LH#17	82	9	−3.767	0.002	Pat < ctr	

[a] Estimated percentage of normal population falling below individual's score = 96,79%; 95% lower confidence limit on the percentage = 87,50%; 95% upper confidence limit on the percentage = 99,85%.

[b] Estimated percentage of normal population falling below individual's score = 3,54%; 95% lower confidence limit on the percentage = 0,18%; 95% upper confidence limit on the percentage = 13,33%.

= −0.586, p = .55; Naming Non living Z = −0.220, p = .826; constructional apraxia Z = −1.001, p = .317; baloon test A Z = −0.752, p = .452; Borb 8 Z = −0.982, p = .512),

Lastly, a chi-square test performed on the type of sensorimotor deficit (we arbitrarily coded as 0 = no motor deficits, 1 = body part seizures or tingles; 2 = motor impairment; weakness; sensation decrease) confirmed that the sensorimotor deficits were equally frequent in both groups (impaired vs spared, $X2$ (2, N = 38) = 0.225, p = .89).

3.4. MRI structural results

The lesion overlay showed that the maximum overlap of both the patient groups occurred in the bilateral parietal-premotor areas (Fig. 1B and C). VOIs subtraction between the lesion overlay of the normal patient group from the lesion overlay of the impaired patient group reveals that the areas maximally involved by lesions in the impaired patient group (Fig. 1D) are the right post central gyrus, right inferior parietal lobe, right supramarginal gyrus, right precentral gyrus, paracentral lobule, left post central gyrus, right superior parietal lobe, left inferior parietal lobe, and left superior and middle F gyrus (see Supplementary Table 3).

3.5. fMRI results

In general, all patients activate a parietal-premotor network that was altered by the presence of the lesion. For example, patients with RH lesion have less activation on the right side, either in the parietal lobe or premotor areas, and similarly, patients with LH lesion have less activation on the left side, either in the parietal lobe or premotor areas.

3.6. Impaired patients group

The task (vs. rest) activates the (i) left inferior occipital gyrus, extending to left and right fusiform gyrus, right middle occipital gyrus, inferior and superior parietal lobe bilaterally; (ii) left precentral gyrus, extending to left middle F gyrus and left inferior F gyrus (pars opercularis); (iii) supplementary motor area, bilaterally extending to right middle F gyrus; (iv) right inferior F gyrus (pars opercularis); (v) right superior F gyrus extending to right middle F gyrus; (vi) right inferior F gyrus (pars opercularis) extending to right precentral gyrus; (vii) left inferior F gyrus (pars orbitalis); and (viii) right inferior F gyrus (pars triangularis) extending to right middle F gyrus (Fig. 2A, Supplementary Table 4).

3.7. Spared patients group

The task (vs. rest) activates the (i) right inferior occipital gyrus, extending to the right fusiform gyrus, inferior and superior parietal lobe bilaterally; (ii) left precentral gyrus extending to left middle F gyrus and left inferior F gyrus (pars opercularis); (iii) bilateral supplementary motor area; (iv) right inferior F gyrus (pars opercularis) extending to right middle F gyrus and right precentral gyrus; (v) right inferior F gyrus (pars opercularis) (Fig. 2B, Supplementary Table 4).

3.8. Spared patients group – impaired patients group

The task (vs. rest) in the group comparison (spared vs. impaired patients) activates a cluster in the left inferior parietal lobe (Fig. 2C, Table 5). No cluster survives the predefined threshold for the opposite contrast (impaired vs. spared).

There was a significant correlation between the functional activation in the left inferior parietal lobule with the performance in the LLRT (r (1,35) = 0.607, p < .001, Fig. 2E).

As the present study included patients with meningioma and gliomas of different grade, we inspected the role of histology on fMRI activation in a subgroup analysis. No cluster survived either in a flexible factorial design including three groups of histology nor in a -test for each histology by including two groups (spared and impaired).

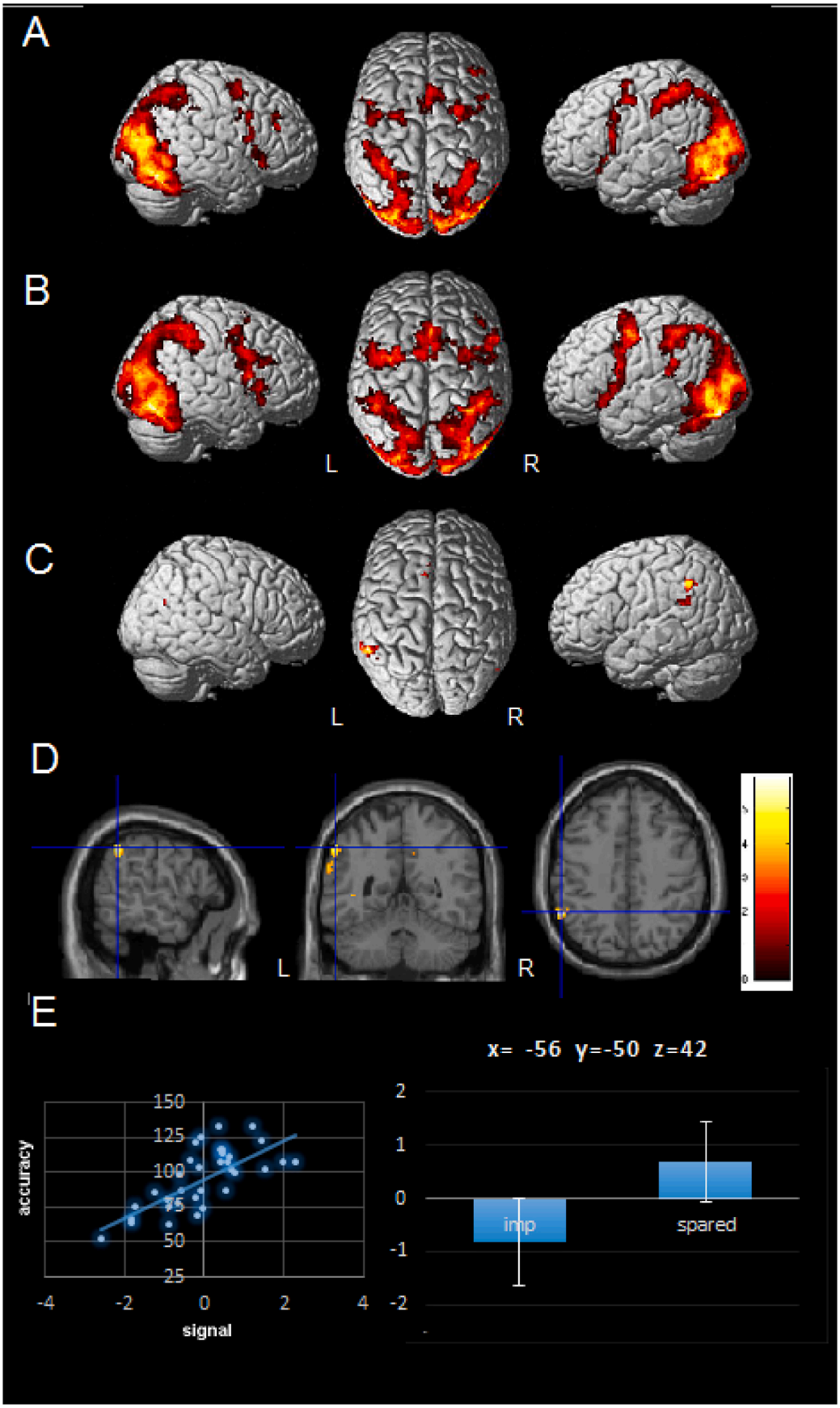

Fig. 2. Relative increases in neural activity associated with the LLRT in impaired (A) and spared (B) patients, and in the spared vs. impaired patients contrast (C). The activation cluster in the left inferior parietal cortex differentially recruited by the spared (relative to impaired patients) contrast (D), at x = −56, y = −50, z = 42 (see Table 5). The correlation between the functional activation in the left inferior parietal lobule with the performance in the LLRT and the mean fMRI signal for spared vs. impaired patients (E).

Table 5
Brain regions showing significant relative increases of BOLD response associated with each comparison of interest.

Side	Region	MNI coordinates			T	Size (k_E)
		x	y	z		
Spared patients – Impaired patients						
LH	Inferior parietal lobule (PFm)	−56	−50	42	5.93	70
Impaired patients – Spared patients						
–	–	–	–	–	–	–

For each region of activation, the coordinates in MNI space are given referring to the maximally activated focus within an area of activation as indicated by the highest T-value. LH = left hemisphere; Size = number of voxels in a cluster. All the activations are significant at $P < .05$ (corrected for multiple comparisons at the cluster level, height threshold $P < .001$, uncorrected).

4. Discussion

The present study used a paradigm derived from experimental psychology (e.g., Parsons, 1987; Parsons, 1994) to study the functionality of motor representations, adapting it to the clinical fMRI setting. The multimodal approach, combining neuropsychology and neuroimaging, allowed us to characterize in a group of 38 patients with lesions affecting sensorimotor areas, the cognitive and neural mechanisms underlying the ability to imagine movements. The first objective was to test the feasibility of LLRT as an fMRI task performed with neurosurgical patients; the study shows that the test proved feasible, the patients understood the instructions and performed the task. The activation pattern (task vs rest) found in the current patient group is in line with earlier findings showing that the LLRT triggers activation in the parietal lobe, premotor and primary motor cortex, SMA, and cerebellum (Seurinck et al., 2004; Vingerhoets et al., 2002; Kosslyn et al., 1998; Parsons et al., 1995).

The results emphasize the determined role of the neuropsychological data: the neuroimaging data without the neuropsychological data is insufficient to interpret the results that are obtained. In general, the patients were within normal limits on many neuropsychological screening tests indicating that the lesion, at the time of the study, had not deteriorated their neuropsychological profile. Administration of the LLRT identified 17/38 patients who had significantly different performance from healthy controls. The second objective was to investigate whether LLRT can be a good localizer of the parietal-premotor network in neurosurgical patients. Analysis of the fMRI data showed which of the sensorimotor areas involved by the lesion contributes to correct LLRT performance. For all patients, it was possible to identify the nodes of the parietal-premotor network that is altered by the presence of the lesion. The third objective was to test which nodes in the network supporting the LLRT may be altered in terms of activation in the presence of a lesion to sensorimotor areas. The task (vs. rest) in the group comparison (spared vs. impaired patients) activated a cluster in the left inferior parietal lobe. This cluster corresponds to one of the areas maximally involved by lesions in the impaired patient group, as demonstrated by the structural MR data study. The left inferior parietal lobe is an area known in the literature to be involved in movement planning, action selection, and motor attention (Binkofski and Buxbaum, 2013; Buxbaum et al., 2006, 2007; Lebon et al., 2012; Rizzolatti and Matelli, 2003; Rushworth et al., 2001). The result on the left lateralization of this activation is consistent with the literature. It is possible that the fMRI lateralization could be related to the distribution of left vs right lesions. The hemispheric lesion distribution was quite equal in the whole group of studied patients, with lesions involving the right (N = 21) or left (N = 17) hemisphere. In addition, the presence of lesions to the LH and RH was evenly distributed: in impaired patients the RH:LH ratio was 10:7, and in patients with LLRT normal scores the RH:LH ratio was 9:9. Still, the point that there were more patients with right than left sided lesions impaired at the task, could have influenced the fMRI findings and specifically the finding of a left dominance. Further studies could address this possibility by comparing patients with lesions to the left vs. right hemisphere LLRT performance and fMRI maps. In the present study, with our patient sample, we found a left lateralized activation, and this result points to the dominant role of the left hemisphere in action planning. This area has been shown to contain postural representations of the upper limb (Binkofski and Buxbaum, 2013; Buxbaum et al., 2006, 2007; Evans et al., 2016). Indeed, the inferior parietal lobe is an anatomical correlate, along with other areas, of motor imagination (Burianová et al., 2013; Evans et al., 2016, Kraeutner et al., 2016, Lebon et al., 2012). Using the virtual lesion technique, TMS, Kraeutner et al. (2019) showed that inhibition of the left inferior parietal lobe selectively disrupted performance in the LLRT, suggesting that this area is critical for visuomotor transformations (Binkofski and Buxbaum, 2013). The authors argue that subjects due to TMS were probably unable to access postural representations of the upper limb, which are necessary to first determine the current position of the effector and then mentally orient the effector to the hand position presented on the screen. The present results are complementary to the TMS data of Kraeutner et al. (2019), in that we show that patients who perform in the normal range at LLRT have selective activation of the left inferior parietal lobe, compared with patients with impaired performance at LLRT. The present results also complement data from a neuropsychological study by Sirigu et al. (1996). In the study by Sirigu et al. (1996) patients with lesions confined to the left inferior parietal cortex were found to be selectively unable to predict, through mental imagination, the time required to perform hand movements, compared with normal individuals and compared with a patient with a lesion to the primary motor area. The results of that study indicated that the inferior parietal cortex is important for the ability to generate mental representations of movement. Activation of the left inferior parietal lobe is not only susceptible to the presence of a lesion in the areas that support the LLRT, as the present study shows, but is also susceptible to the performance of motor imagination training (Lebon et al., 2012). More specifically, it is relevant to the present results that left inferior parietal lobe activation is reported in the literature in neuroimaging studies that have used LLRT (Hamada et al., 2018; Kosslyn et al., 1998; Parsons, 1994; Parsons et al., 1995). In a PET study (Bonda et al., 1996), comparison of the distribution of brain activity between a task that required mental hand rotation and a control task that did not require this process revealed a significant increase in blood flow in the superior parietal cortex, intraparietal sulcus, and the adjacent rostral part of the inferior parietal lobule. The authors suggested the existence of a specific system of parietal areas that are involved in mental transformations of the body in space. It is clear that the LLRT does not rely only on the activity of the inferior parietal lobe, but the areas it supports are multiple and are organized in a network. The inferior parietal lobe is only one of the nodes in the network that enables the task to be performed. The LLRT is in fact a complex cognitive task, involving several subprocesses, such as discrimination of stimulus orientation, dynamic spatial transformation of this image, mental comparison, attentional and working memory processes, decision making and implementation of this decision into a motor output (Kosslyn et al., 1998). In this flow of processing, according to the above literature, the parietal lobe plays a role in the processing of three-dimensional information, participates in the transformation of images in egocentric space, guides motor attention, and anticipates the consequences of action by simulating the movement of the upper limb. From this perspective, the present results do not indicate that a lesion at the left inferior parietal lobe causes a difference in activation between patients who perform the task correctly and those who have impaired performance. Instead, the present structural data show that lesions that cause impaired performance at the LLRT can be located at different nodes in the network that supports the LLRT, but that the node that is altered in terms of functional activation in impaired patients is the left inferior parietal lobe. The differential activation in the left parietal lobe is not free of the difficulties in the interpretability of increases vs decreases in activation patterns. On the other hand the activation correlated positively with behavioral task performance.

Limitations of the study are not having had a larger sample size, so that the role of the two hemispheres could be investigated, dividing impaired patients and patients with normal performance by right and left hemisphere, and also factoring the hemisphere into the analysis matrix so as to determine possible differences in activation pattern. Another possible effect is the type of histology. Our group included HGG, LGG and meningioma. At behavioral level we did not find significant effect of the type of histology. This is in line with previous work showing that both meningioma (Guarracino et al., 2020) and low-grade and high grade glioma (Tomasino et al., 2011, 2022) could present LLRT impairments. Despite the fMRI analyses on sub-groups of patients stratified by the type of histology were not significant, we cannot rule out a potential role of the type of histology as the sample size of the three groups is limited. Therefore still functional MRI differences could be found among the three type of histology. Future studies will seek to address these limitations. Finally, a methodological limitation in data collection concerns the difference in response modes: while the group of healthy volunteers responded using a mouse, vocal responses were collected for patients (both impaired and spared patients).

5. Conclusions

Underlying the altered performance at LLRT in patients with lesions to the parietal and premotor areas of the right and left hemispheres is a difference in activation of the left inferior parietal lobe. This region is involved in visuospatial processes and those related to motor attention, movement selection, and motor planning.

Founding

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Declaration of competing interest

None of the authors has any conflict of interest to disclose.

Data availability

Data will be made available on request.

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References

Basso, A., Capitani, E., Laiacona, M., 1987. Raven's coloured progressive matrices: normative values on 305 adult normal controls. Funct. Neurol. 2 (2), 189–194.

Binkofski, F., Buxbaum, L.J., 2013. Two action systems in the human brain. Brain Lang. 127 (2), 222–229. https://doi.org/10.1016/j.bandl.2012.07.007.

Burianová, H., Marstaller, L., Sowman, P., et al., 2013. Multimodal functional imaging of motor imagery using a novel paradigm. Neuroimage 71, 50–58. https://doi.org/10.1016/j.neuroimage.2013.01.001.

Buxbaum, L.J., Kyle, K.M., Tang, K., Detre, J.A., 2006. Neural substrates of knowledge of hand postures for object grasping and functional object use: evidence from fMRI. Brain Res. 1117 (1), 175–185. https://doi.org/10.1016/j.brainres.2006.08.010.

Buxbaum, L.J., Kyle, K., Grossman, M., Coslett, H.B., 2007. Left inferior parietal representations for skilled hand-object interactions: evidence from stroke and corticobasal degeneration. Cortex 43 (3), 411–423. https://doi.org/10.1016/s0010-9452(08)70466-0.

Capitani, E., Laiacona, M., 1988. Aging and psychometric diagnosis of intellective impairment: some considerations on test scores and their use. Dev. Neuropsychol. 4, 325–330.

Craighero, L., 2022. The role of the sensorimotor system in cognitive functions. Brain Sci. 12 (5), 604. https://doi.org/10.3390/brainsci12050604. Published 2022 May 5.

Crawford, J.R., Garthwaite, P.H., 2002. Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. Neuropsychologia 40 (8), 1196–1208. https://doi.org/10.1016/s0028-3932(01)00224-x.

De Renzi, E., Motti, F., Nichelli, P., 1980. Imitating gestures. A quantitative approach to ideomotor apraxia. Arch. Neurol. 37 (1), 6–10. https://doi.org/10.1001/archneur.1980.00500500036003.

Decety, J., Perani, D., Jeannerod, M., et al., 1994. Mapping motor representations with positron emission tomography. Nature 371 (6498), 600–602. https://doi.org/10.1038/371600a0.

Edgeworth J, Robertson IH, MacMillan T. The Balloons Test. Bury.

Eickhoff, S.B., Stephan, K.E., Mohlberg, H., et al., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25 (4), 1325–1335. https://doi.org/10.1016/j.neuroimage.2004.12.034.

Evans, C., Edwards, M.G., Taylor, L.J., Ietswaart, M., 2016. Perceptual decisions regarding object manipulation are selectively impaired in apraxia or when tDCS is applied over the left IPL. Neuropsychologia 86, 153–166. https://doi.org/10.1016/j.neuropsychologia.2016.04.020.

Ferri, F., Frassinetti, F., Ardizzi, M., Costantini, M., Gallese, V., 2012. A sensorimotor network for the bodily self. J. Cognit. Neurosci. 24 (7), 1584–1595. https://doi.org/10.1162/jocn_a_00230.

Guarracino, I., Ius, T., Skrap, M., Tomasino, B., 2020. Meningioma can lead to pre-operative cognitive alterations even if localized in sensorimotor areas: a multimodal MRI-neuropsychological study in a series of 46 patients. Neuropsychologia 137, 107288. https://doi.org/10.1016/j.neuropsychologia.2019.107288.

Hamada, H., Matsuzawa, D., Sutoh, C., et al., 2018. Comparison of brain activity between motor imagery and mental rotation of the hand tasks: a functional magnetic resonance imaging study. Brain Imaging Behav 12 (6), 1596–1606. https://doi.org/10.1007/s11682-017-9821-9.

Hyde, C., Fuelscher, I., Lum, J.A., Williams, J., He, J., Enticott, P.G., 2017. Primary motor cortex excitability is modulated during the mental simulation of hand movement. J. Int. Neuropsychol. Soc. 23 (2), 185–193. https://doi.org/10.1017/S1355617717000029.

Kashuk, S.R., Williams, J., Thorpe, G., Wilson, P.H., Egan, G.F., 2017. Diminished motor imagery capability in adults with motor impairment: an fMRI mental rotation study. Behav. Brain Res. 334, 86–96. https://doi.org/10.1016/j.bbr.2017.06.042.

Kim, A., Yi, C., 2021. Understanding the Left Right Judgement Test: A Literature Review. Physical Therapy Korea. Korean Research Society of Physical Therapy. https://doi.org/10.12674/ptk.2021.28.4.235.

Kohler, M., Strauss, S., Horn, U., et al., 2019. Differences in neuronal representation of mental rotation in patients with complex regional pain syndrome and healthy controls. J. Pain 20 (8), 898–907. https://doi.org/10.1016/j.jpain.2019.01.330.

Kosslyn, S.M., DiGirolamo, G.J., Thompson, W.L., Alpert, N.M., 1998. Mental rotation of objects versus hands: neural mechanisms revealed by positron emission tomography. Psychophysiology 35 (2), 151–161.

Kraeutner, S.N., Keeler, L.T., Boe, S.G., 2016. Motor imagery-based skill acquisition disrupted following rTMS of the inferior parietal lobule. Exp. Brain Res. 234 (2), 397–407. https://doi.org/10.1007/s00221-015-4472-9.

Kraeutner, S.N., El-Serafi, M., Lee, J., Boe, S.G., 2019. Disruption of motor imagery performance following inhibition of the left inferior parietal lobe. Neuropsychologia 127, 106–112. https://doi.org/10.1016/j.neuropsychologia.2019.02.016.

Lebon, F., Lotze, M., Stinear, C.M., Byblow, W.D., 2012. Task-dependent interaction between parietal and contralateral primary motor cortex during explicit versus implicit motor imagery. PLoS One 7 (5), e37850. https://doi.org/10.1371/journal.pone.0037850.

Meng, S., Oi, M., Sekiyama, K., Saito, H., 2016. The neural mechanism of biomechanical constraints in the hand laterality judgment task: a near-infrared spectroscopy study. Neurosci. Lett. 627, 211–215. https://doi.org/10.1016/j.neulet.2016.05.069.

Mibu, A., Kan, S., Nishigami, T., Fujino, Y., Shibata, M., 2020. Performing the hand laterality judgement task does not necessarily require motor imagery. Sci. Rep. 10 (1), 5155. https://doi.org/10.1038/s41598-020-61937-9. Published 2020 Mar 20.

Monaco, M., Costa, A., Caltagirone, C., Carlesimo, G.A., 2015. Erratum to: forward and backward span for verbal and visuo-spatial data: standardization and normative data from an Italian adult population. Neurol. Sci. 36 (2), 345–347. https://doi.org/10.1007/s10072-014-2019-7.

Moreno-Verdú, M., Hardwick, R., 2022. Measuring the mind's eye: does the hand laterality judgement task really assess motor imagery ability? PsyArXiv. https://doi.org/10.31234/osf.io/g2cj3.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.

Osuagwu, B.A., Vuckovic, A., 2014. Similarities between explicit and implicit motor imagery in mental rotation of hands: an EEG study. Neuropsychologia 65, 197–210. https://doi.org/10.1016/j.neuropsychologia.2014.10.029.

Parsons, L.M., 1987. Imagined spatial transformations of one's hands and feet. Cognit. Psychol. 19 (2), 178–241. https://doi.org/10.1016/0010-0285(87)90011-9.

Parsons, L.M., 1994. Temporal and kinematic properties of motor behavior reflected in mentally simulated action. J. Exp. Psychol. Hum. Percept. Perform. 20 (4), 709–730. https://doi.org/10.1037//0096-1523.20.4.709.

Parsons, L.M., Fox, P.T., Downs, J.H., et al., 1995. Use of implicit motor imagery for visual shape discrimination as revealed by PET. Nature 375 (6526), 54–58. https://doi.org/10.1038/375054a0.

Pelgrims, B., Michaux, N., Olivier, E., Andres, M., 2011. Contribution of the primary motor cortex to motor imagery: a subthreshold TMS study. Hum. Brain Mapp. 32 (9), 1471–1482. https://doi.org/10.1002/hbm.21121.

Perruchoud, D., Michels, L., Piccirelli, M., Gassert, R., Ionta, S., 2016. Differential neural encoding of sensorimotor and visual body representations. Sci. Rep. 6, 37259 https://doi.org/10.1038/srep37259. Published 2016 Nov 24.

Qu, F., Wang, J., Zhong, Y., Ye, H., 2018. Postural effects on the mental rotation of body-related pictures: an fMRI study. Front. Psychol. 9, 720. https://doi.org/10.3389/fpsyg.2018.00720. Published 2018 May 23.

Riddoch, J.M., Humphreys, G.W., 1993. BORB: Birmingham Object Recognition Battery, first ed. Psychology Press. https://doi.org/10.4324/9781003069645.

Rizzolatti, G., Matelli, M., 2003. Two different streams form the dorsal visual system: anatomy and functions. Exp. Brain Res. 153 (2), 146–157. https://doi.org/10.1007/s00221-003-1588-0.

Rushworth, M.F., Krams, M., Passingham, R.E., 2001. The attentional role of the left parietal cortex: the distinct lateralization and localization of motor attention in the human brain. J. Cognit. Neurosci. 13 (5), 698–710. https://doi.org/10.1162/089892901750363244.

Seurinck, R., Vingerhoets, G., de Lange, F.P., Achten, E., 2004. Does egocentric mental rotation elicit sex differences? Neuroimage 23 (4), 1440–1449. https://doi.org/10.1016/j.neuroimage.2004.08.010.

Sirigu, A., Duhamel, J.R., Cohen, L., Pillon, B., Dubois, B., Agid, Y., 1996. The mental representation of hand movements after parietal cortex damage. Science 273 (5281), 1564–1568. https://doi.org/10.1126/science.273.5281.1564.

Spinnler, M., Tognoni, G., 1987. Standardizzazione e taratura italiana di test neuropsicologici. Gruppo Italiano per lo Studio Neuropsicologico dell'Invecchiamento [Italian standardization and classification of Neuropsychological tests. The Italian Group on the Neuropsychological Study of Aging]. Ital. J. Neurol. Sci. Suppl 8, 1–120.

Tomasino, B., Skrap, M., Rumiati, R.I., 2011. Causal role of the sensorimotor cortex in action simulation: neuropsychological evidence. J. Cognit. Neurosci. 23 (8), 2068–2078. https://doi.org/10.1162/jocn.2010.21577.

Tomasino, B., Guarracino, I., Ius, T., Budai, R., Skrap, M., 2022. Real-time neuropsychological testing of sensorimotor cognition during awake surgery in precentral and postsomatosensory areas. World Neurosurg 164, e599–e610. https://doi.org/10.1016/j.wneu.2022.05.018.

Vingerhoets, G., de Lange, F.P., Vandemaele, P., Deblaere, K., Achten, E., 2002. Motor imagery in mental rotation: an fMRI study. Neuroimage 17 (3), 1623–1633. https://doi.org/10.1006/nimg.2002.1290.