A network-level approach of cognitive flexibility impairment after surgery of a right temporo-parietal glioma

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ABSTRACT

Objective. – The right “non-dominant” temporo-parietal junction is usually not considered as a highly eloquent area. This contrasts with its mirrored left “dominant” counterpart, which is known as highly eloquent regarding language function. The question arises about which functions should be monitored when operating lesions of the right temporo-parietal junction under awake conditions.

Methods. – We report the case of a patient who underwent a surgical resection of a glioma located in the right temporo-parietal junction. Cognitive evaluations were performed preoperatively and 4 months after surgery, as well as resting state fMRI and diffusion-based tractography.

Results. – Long-term postoperative cognitive examination revealed an important deterioration of cognitive control abilities, especially regarding set-shifting abilities as measured by Trail making test part B. Based on pre- and postoperative resting state fMRI and diffusion-based tractography, we demonstrate that surgical resection massively impacted structural and functional connectivity of the right fronto-parieto-temporal network, a network that is classically involved in cognitive control, reasoning and working memory.

Conclusion. – This case clearly illustrates how a white matter focal lesion can generate a neuropsychological deficit by remotely disconnecting distant cortical areas belonging to a functional network. Furthermore, our observation strongly supports the use of intraoperative cognitive control tests during surgery of the right temporo-parietal junction and promote the interest of pre and postoperative resting state functional connectivity to explore the potential mechanisms causing cognitive deficits.

1. Introduction

Set-shifting abilities belong to executive functions, which are classically associated with the frontal lobes. Among several others tasks, the Trail making test (TMT) is commonly used to assess executive functions clinically [1]. In particular, the part B of the test (TMT–B) emphasizes set-shifting abilities.

Task-related fMRI studies of the TMT–B have indicated increased activation in a large set of frontal, parietal and temporal areas in both hemispheres [2,3]. Lesion based analyses have revealed significant correlations between TMT–B error rate and damage to the dorsolateral prefrontal cortex [4]. However, this notion was recently challenged by other studies that showed inconsistent results [4–10] or that failed to supply supportive evidence of any difference in TMT–B performance between frontal and non-frontal lesions groups regarding error rate [11] and completion time [8]. Very few studies have investigated the link between lesions of white matter tracts and deficit in set-shifting abilities. One study in a population of healthy aging reported a correlation between decrease in TMT–B performance and decrease in fractional anisotropy of the corpus callosum, inferior fronto-occipital

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fasciculus (IFOF), superior longitudinal fasciculus (SLF) and uncinate fasciculus [12]. More recently, a lesional study in stroke patients supported a strong involvement of the left superior longitudinal fasciculus and the lateral cholinergic pathways in TMT-B performance [13]. On the whole, lesion studies have failed to produce concordant findings on the mechanisms supporting set-shifting abilities and to reconcile with fMRI reports in healthy controls.

From a hodotopic point of view [14], set-shifting abilities may depend on the interaction between frontal, parietal and temporal regions. Such a delocalized pattern would explain the discrepancy of the results of classical focal lesion studies [15]. In line with this hypothesis, we report the case of a patient who experienced a marked deterioration of performance on TMT-B after the removal of a glioma located in the right temporo-parietal junction. Based on pre and postoperative MRIs, we analyzed changes in structural and functional connectivity, with the aim to understand the mechanisms leading to cognitive flexibility loss in this patient.

2. Methods

2.1. Ethics statement

Patient gave full informed consent to participate to this study, which was approved by the ethics committee of Saint-Louis hospital (reference 2013/51).

2.2. Clinical case

A 40-year-old woman with no previous medical history was diagnosed on MRI with a right parietal diffuse low-grade glioma (see Fig. 1A), revealed by a generalized seizure. Seizures were controlled under anti-epileptic medication (Levetiracetam, 500 mg twice a day). After a short period of follow-up (3 months) confirming the slow evolution of the tumor (5 mm/year), the patient underwent a surgical resection in an awake condition, as described below. Resection was complete (see Fig. 1B) and there was no neurological complication (postoperative Karnofsky score unchanged, at 90/100). In particular, visual field test performed 3 months later was normal. She could resume her job as a cleaning lady 4 months after surgery.

2.3. Diffusion-weighted imaging (DWI)

Diffusion imaging was acquired 4 months after the surgery. A 3T Siemens Skyra system (Siemens, Erlangen, Germany) with a 64-channel phased-array head coil, was employed to acquire DWI of the entire head with an anterior-posterior phase of acquisition. DWI parameters consisted of a matrix of acquisition of 108 × 108 × 120 voxels of 2.3 mm³ with a total field of view of 250 × 250 × 120 mm. DWI was acquired along 64 directions with a weighting b = 2000 s/mm². Additionally non-weighted (b = 0) volumes were also acquired. Echo Time (TE) was set at 95 ms and Repetition Time (TR) at 7700 ms. The whole sequence lasted 9 min 45 s.

2.4. Tractography

At each slice, diffusion-weighted data were simultaneously registered and corrected for subject motion and geometrical distortion adjusting the gradient accordingly (http://www.exploredti.com; see [16]). A damped Richardson Lucy Spherical Deconvolution [17] was computed to estimate multiple orientations in voxels containing different populations of crossing fibers [18–20]. Algorithm parameters were chosen as previously described [21]. A fixed-fiber response corresponding to a shape factor of α = 2 × 10⁻³ mm²/s was chosen [21]. Whole brain tractography was performed selecting every brain voxel with at least one fiber orientation as a seed voxel. From these voxels, and for each fiber orientation, streamlines were propagated using Euler integration with a step size of 1 mm (as described in Dell’Acqua et al., 2013). When entering a region with crossing white matter bundles, the algorithm followed the orientation vector of least curvature [22]. Streamlines were halted when a voxel without fiber orientation was reached or when the curvature between two steps exceeded a threshold of 45°. Spherical deconvolution, fiber orientation vector estimations and tractography were performed using in Startrack (http://www.natbrainlab.co.uk).

2.5. Resting state functional magnetic resonance imaging (rs-fMRI)

rs-fMRI was acquired pre, post and 4 months after the surgery. During this sequence the participant was instructed to rest but not sleep with her eyes closed. Images sensitive to bold contrast were acquired using a gradient echo planar imaging (EPI) sequence along 130 time points with a total matrix of 94 × 94 × 36 voxels of 2.1 × 2.1 × 3 mm and a field of view of 200 × 200 × 108 mm. Additionally TR was set at 3200 ms and TE at 30 ms. The total resting state acquisition lasted seven minutes.

2.6. Resting state analysis

To determine the location of resting state networks (RSN), we used a data-driven method based on Independent Component Analysis (ICA). It has been shown that this method is able to extract networks which resemble those recruited during the actual

Fig. 1. A. Coronal slice of T2-weighted preoperative MRI. B. Coronal slice of T2-weighted postoperative MRI.
execution of cognitive motor, sensory and cognitive abilities [23], and can therefore be used to indirectly assess the functional integrity of the latter. We employed Melodic ICA [24] to extract the RSNs, the number of which was automatically determined by the algorithm in each of the three sessions. The spatial map of each independent component is associated with a characteristic time course. Both information can be used to determine which components are likely to reflect underlying neuronal processes – i.e. RSNs – and which ones reflect uninteresting sources of structured noise associated e.g. to motion, cardiac pulsations or scanner-related artifacts. In particular, we focused on those components which met the following criteria:

- located mostly in the gray matter;
- expressing most power in the low range of frequencies (0.009–0.08 Hz) [25].

Since RSNs extracted in this way feature a robust spatial consistency both within and between subjects [26], it is possible to match the most commonly found networks [27] by visual inspection.

2.7. Intraoperative monitoring

Surgery was performed in an awake condition, following the same methodology as previously reported [28]. Based on the location of the tumor, spatial awareness was continuously tested by a tablet version of the line bisection test. This also permitted to monitor continuously sensori-motor abilities of the left upper limb, as the patient had to point on the tablet the center of the line with her left finger. The pyramid and palm tree test (PPTT) was also regularly checked, with the aim to detect parietal terminations of the IFOF [29]. The patient was video-recorded during the entire awake period. The patient camera was synchronized with the camera recording of the operative field and the video copy of the screen tablet.

2.8. Cognitive testing

Preoperative and postoperative long-term (4 months) testing assessed [28]:

- language functions, including naming 80 black and white pictures (DO 80 [30]), and literal and categorical word fluencies [31];
- non-verbal semantic association, using the PPTT [32];
- praxies: copy of Rey figure [33];
- calculus: one subtraction and two multiplications were performed;
- memory: forward and backward digital span, verbal span, free and cued selective 16-items reminding test [34]; delayed copy of Rey figure, visual implicit memory task [35];
- attention: d2 attention test [36];
- spatial awareness: Bell’s test, line bisection [37];
- executive functions: Stroop test [38], Trail making test part A and B [31], Paced Auditory Serial Addition Test (PASAT) [39].

3. Results

3.1. Intraoperative monitoring

During the surgery, direct electrical stimulation of the cortex did not reveal any site disturbing line bisection, nor PPTT. Axionally, the fibers of the parietal motor control network [40] were found anteriorly. When stimulating at this site, the patient stopped her movement and shouted “Oh my god! I don’t feel my left arm anymore!” This effect was repeated on three separate trials. Therefore, this area defined the anterior boundary of the resection. Resection was pursued posteriorly and deeply, in the stratum sagittal, where we observed frequent significant leftward deviations during the line bisection. This effect was not reproducible. No significant rightward deviations were observed during the surgery. PPTT was also performed, without any electrostimulation-induced errors. Finally, the ependyma of the right atrium was reached, and the resection was stopped to avoid visual field deficit.

3.2. Cognitive testing

Immediate postoperative evaluations were performed between postoperative day (POD) 1 and POD 5. Due to patient’s fatigability, testing was not exhaustive in this immediate postoperative period. Line bisection and Bell’s test omissions were unaffected. The score at Montreal cognitive assessment [41] was 18/30, with the following subscores:

- visuospatial – executive functions: 1/5. In particular, the TMT-B was failed;
- naming: 3/3;
- attention: 4/6. Forward and backward digital spans were failed;
- abstraction: 1/2;
- memory: 2/5;

Full pre and long-term postoperative cognitive evaluations are reported in Table 1. The most striking change was an important loss of cognitive control abilities, marked by an inability to achieve the part B of the TMT after surgery, while it was preserved in the preoperative testing.

Language and semantic functions were unaffected before and after the surgery, although a small performance decrease was

<table>
<thead>
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<th>Pre- and postoperative results of cognitive evaluations.</th>
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<th>Postoperative scores</th>
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<tbody>
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<td>Language</td>
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<td>DO80</td>
<td>78</td>
<td>77</td>
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<tr>
<td>LWF</td>
<td>12 (−1.16)</td>
<td>7 (−2)</td>
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<td>CWF</td>
<td>14 (−2)</td>
<td>9 (−2.71)</td>
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<td>Planning</td>
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<td>IV</td>
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<tr>
<td>Score</td>
<td>30 (−2.73)</td>
<td>36 (+0.84)</td>
</tr>
<tr>
<td>Calculus (3 operations)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward span</td>
<td>5 (−0.38)</td>
<td>5 (−0.38)</td>
</tr>
<tr>
<td>Backward span</td>
<td>4 (−0.31)</td>
<td>3 (−0.91)</td>
</tr>
<tr>
<td>VEM</td>
<td>25 (−1.97)</td>
<td>31 (−0.75); 15 (+0.61); 14 (−0.63)</td>
</tr>
<tr>
<td>VIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial awareness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bell’s test omissions</td>
<td></td>
<td></td>
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<tr>
<td>Attention and executive functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASAT</td>
<td>Failed</td>
<td>Failed</td>
</tr>
<tr>
<td>TMT-B</td>
<td>152 (−1.26)</td>
<td>Failed</td>
</tr>
<tr>
<td>TMT B-A</td>
<td>96 (−1.26)</td>
<td>Failed</td>
</tr>
<tr>
<td>Stroop-c</td>
<td>111 (−0.26)</td>
<td>158′ (−1.78)</td>
</tr>
<tr>
<td>d2-KL</td>
<td>72th p.</td>
<td>&lt;70th p.</td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>56 (−0.68)</td>
<td>129′ (−2.18)</td>
</tr>
<tr>
<td>Rey</td>
<td>730 (−2.85)</td>
<td>1030 (−5.23)</td>
</tr>
<tr>
<td>Stroop-n</td>
<td>66 (−0.33)</td>
<td>72′ (−0.83)</td>
</tr>
<tr>
<td>d2-GZ</td>
<td>&lt;70th p.</td>
<td>&lt;70th p.</td>
</tr>
</tbody>
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Numbers between brackets correspond to the standard deviations to average. We reported “failed” when the patient was unable to perform the test. Full abbreviations and references are available in the supplementary material.
observed for the PPTT. Praxies, calculus and spatial awareness were preserved after the surgery. Explicit verbal memory was improved after surgery, while short-term memory remained within a normal range. Working memory was severely altered preoperatively and did not recover after surgery. Processing speed was slightly reduced after surgery, as well as the score at the conflict condition of the Stroop test. These results indicate that cognitive flexibility has been specifically impacted by the surgical resection.

3.3. Postoperative imaging

Resting state analysis showed that the right fronto-parieto-temporal (FPT) network – which was normally identified on preoperative ICA – was clearly impaired on the early and late postoperative ICA (see Fig. 2). Postoperative tractography confirmed that SLF III and arcuate fasciculus (long and short posterior segments) – and to a lesser extent middle longitudinal fasciculus and callosal fibers – were disconnected during the surgery. In contrast, the SLF I and II appeared to be relatively preserved.

4. Discussion

This clinical report showed an unexpected cognitive consequence of the resection of a right supramarginal gyrus low-grade glioma, with a markedly deterioration in set-shifting abilities, as measured by the TMT-B. A comparative analysis of structural and functional connectivity before and after surgery provided possible explanations of this neuropsychological outcome. Resting state connectivity analysis revealed that the FPT network was altered in the right hemisphere postoperatively, whereas its preoperative cortical epicenters were spared by the resection (see Fig. 2). In contrast, diffusion-based tractography results revealed that several tracts were damaged during the surgery, including the whole SLF III, and the long and posterior segments of arcuate fasciculus. On the whole, these results suggest that SLF III, and the long and posterior segments of arcuate fasciculus may represent the structural connectivity underlying the functionally defined FPT network. Moreover, the postoperative decline in TMT-B argues for a causal link between damage in this network and set-shifting abilities. To our knowledge, this is the first report evidencing a causal role of the white matter underlying the right non-dominant supramarginal gyrus in cognitive flexibility.

More broadly, cognitive control – that is our ability to flexibly adapt our behavior in complex contexts – is thought to be supported by a wide bilateral network, that includes prefrontal cortex, but also cingulate, parietal, and temporal areas, as recently identified in fMRI studies [42]. This multiple-demand (MD) system is commonly activated by a variety of tasks tapping into executive functions (including goal representation and maintenance, working memory, focused attention, inhibition/initiation of action and cognitive flexibility) and its activity correlates with task-difficulty [43]. We hypothesize that the surgical resection in the present case partly injured the cognitive control network, suggesting that the right FPT network might act as a subunit within the MD system, with a special role in set-shifting functions. This hypothesis is consistent with recent studies [44–48] that have proposed a subdivision of the MD system in two subnetworks: a cingulo-opercular one – involved in goal maintenance – and a fronto-parieto-temporal one – involved in trial-by-trial adaptive control. In particular, it has been shown that the degree of resting connectivity within the right fronto-parietal network correlated with performance in TMT-B outside the scanner [48].

From a neurosurgical point of view, the white matter of the temporo-parietal junction is recognized as a highly functional zone in the left dominant hemisphere. In fact, several tracts, most of them known to be involved in some aspects of language, cross in this region [49,50]: inferior and middle longitudinal tracts, IFOF, arcuate fasciculus (long and posterior short segments), SLF III, optic radiations, and tapetum. In contrast, this area was classically not considered as “eloquent” in the so called “right non-dominant” hemisphere. However, in the past few years, as more and more attention has been focused on the functional outcomes in brain surgery, awake surgery with cognitive monitoring has been extended to the right non-dominant hemisphere [51], mainly to prevent postoperative spatial neglect [37,52,53]. In the present case, the resection extended to the white matter of the right temporo-parietal junction. Our tractography analysis revealed that 3 out of the 7 aforementioned tracts have been fully disconnected by the resection (arcuate long and short posterior segments, SLF III) and 2 others partly damaged (middle longitudinal fasciculus, tapetum). In order to maximize tumor resection, those tracts were deliberately not preserved, since intraoperative testing by axonal stimulation was negative for PPTT and line bisection. Hence, this case illustrates and strengthens the idea that TMT-B should be tested intraoperatively in the right non-dominant temporo-parietal junction. In this perspective, new multi-tasks paradigms for intraoperative monitoring [54,55] could be developed, with the aim of tapping cognitive flexibility.

Nevertheless, it is worth noting that the ecological value of this loss of cognitive control abilities will have to be evaluated in future research in order to optimize the overall onco-functional balance [56]. Moreover, in the present case, this type of impairment did not prevent the patient resuming a normal socio-professional life. Therefore, it might have been unjustified to monitor cognitive control and to stop the resection prematurely in this patient. However,

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for some professional activities, requiring a high-level of cognitive control, this type of monitoring might be essential. Moreover, as the neurosurgical practice is evolving toward a more preventive surgery [57,58], the level in terms of cognitive abilities preservation has to be raised as high as possible.

5. Conclusion

We found that surgical resection of the white matter in the depth of the right supramarginal gyrus impacted locally the structural connectivity and remotely the functional connectivity of the right FPT network. The observed long-term cognitive deficit strongly suggests a role of this right FPT network in cognitive flexibility. Our study awaits confirmation in a larger series and warrants specific cognitive flexibility testing when operating in the right non-dominant temporo-parietal junction. Moreover, it illustrates how to reconcile a lesional localizationism with physiological hodotopism [14], and argues for a quantitative network-level approach of lesion-symptom mapping [15].

Disclosure of interest

The authors declare that they have no competing interest.

References


