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Involvement of white matter in cognitive flexibility in patients with right hemispherical glioma

Master thesis Neuropsychology

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Abstract

As key element of executive function, cognitive flexibility incorporates multiple component processes, enabling adaptation in response to a constantly changing environment. Preserving cognitive flexibility during surgical resection of a low-grade glioma is of great importance to maintain quality of life and recover optimally from this life event. Dysconnectivity within the fronto-parieto-temporal network of the right parietal lobe has previously been linked to cognitive flexibility deficits, suggesting white matter involvement. To further explore the involvement of white matter in cognitive flexibility, a multicentred international collaboration was established. Nineteen patients, who underwent surgical resection for a low-grade glioma in the right parietal lobe, were assessed pre- and post-surgery, using the Trail Making Test and Stroop-Color-Word-Test to administer cognitive flexibility. Volume measurements and lesion-symptom mapping analyses were performed on postoperative MRI scans. Results showed that the Superior Longitudinal Fasciculus III (SLF III), Arcuate Fasciculus (AF) and Inferior Fronto-Occipital Fasciculus (IFOF) were damaged in both cognitively declined patients (n=4) and cognitively non-declined patients (n=15). Tractographic resection simulations presented similar patterns of dysconnectivity in the right parietal lobe in both groups. In addition, a greater extent of resection was not linked to a decline in cognitive flexibility after surgery. Our findings neither confirm nor deny the proposed involvement of the SLF III, AF and IFOF in cognitive flexibility. Yet, it is clear that cognitive inflexibility is not related to the extent of resection. The integration of DTI and intraoperative monitoring in standard clinical practice is needed for localization and comprehension of cognitive outcomes after neurosurgery.

Key words: cognitive flexibility; low grade glioma (LGG); TrailMakingTest (TMT); Stroop; white matter

Introduction

Executive function encompasses a variety of higher order cognitive processes. Cognitive flexibility falls under the scope of executive function and allows for adaptation in response to changes in the environment, and is often linked to task alternation abilities and reversal learning (Logue, & Gould, 2014). Cognitive flexibility is not merely a subsidiary part of executive function, it is a key element that arises when activating several components of executive function such as attention, inhibition and working memory (Dajani, & Uddin, 2015). It enables an individual to identify what is in flux, to become aware of an old insufficient strategy, to inhibit the previous responses and to reconfigure a new strategy.

Significance of cognitive flexibility

Having greater cognitive flexibility is beneficial across the lifespan. In early and middle age childhood, cognitive flexibility contributes to academic achievements and predicts better development in math skills and reading skills (Buttelmann, & Karbach, 2017; Colé, Duncan, & Blaye, 2014). While cognitive flexibility is still developing throughout adolescence and early adulthood, drastically changing life events demand high cognitive flexibility to adjust to the new requirements that arise in adolescence (Buttelmann, & Karbach, 2017). Failure to flexibly adjust may result in social exclusion, limited professional development and psychiatric disorders (Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015).

In adulthood, cognitive flexibility is associated with the ability to recover from negative life events and being more resilient to minor stressors (Genet, & Siemer, 2011), increasing the quality of life. Taken together, the necessity of cognitive flexibility cannot be overstated in cognitive functioning; it is critical for social interactions, personal development and dealing with life events.

Measuring cognitive flexibility

A wide variety of neuropsychological instruments can be administered to assess cognitive abilities. Since cognitive flexibility incorporates multiple component processes of executive function, combining several neuropsychological tests is preferred to assess the concept. Commonly used terms to describe cognitive flexibility tests are set-shifting and task-switching (Kortte, Horner, & Windham, 2002; Müller et al., 2007; Ravizza, & Carter, 2008). The terms are used intertwined and often refer to the same experimental paradigm, in which the experimental task involves changing strategies between different cognitive tasks (Ravizza, & Carter, 2008). Widely used tasks to assess cognitive flexibility are the Trail

Making Test (TMT) and the Stroop-Color-Word Test (SCWT) (Arbuthnott, & Frank, 2000; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2008). The TMT is a measure of set-shifting and sustained attention, whereas the SCWT is considered to be a measure of inhibition and, selective and sustained attention (Brugnolo et al., 2016).

Brain networks connected to cognitive flexibility

Despite the common neuropsychological assessment of cognitive flexibility, and the well reported benefits of cognitive flexibility and down-sides of cognitive inflexibility, great heterogeneity exists when it comes to the location of the function in the brain. Cognitive flexibility is primarily associated with the prefrontal cortex (Logue & Gould, 2014). However, cognitive flexibility is also associated with the ability to update strategies (Taconnat et al., 2009), and Danckert, Stöttinger, Quehl and Anderson (2011) provide evidence for the connection between update strategies deficits and brain damage in right parietal regions. In addition, the right parietal lobe is considered to be a network hub, as it covers a region in which multimodal information can be received and send, and broad anatomical connections enable the integration of information (Seeley et al., 2007). This could indicate an involvement of white matter tracts in cognitive flexibility.

Lesion-symptom mapping

The current lesion-based brain-behaviour study builds upon previous knowledge and involves patients with a low-grade glioma to research the functional location of cognitive flexibility. Low-grade gliomas are slow growing brain tumours making up approximately 10 to 20% of all primary brain tumours (Kumpthekar, Raizer, & Singh, 2015). Even though it is almost inevitable that gliomas are fatal, treatments are implemented to optimize the quality of life and prolong overall survival. Glioma surgery is often required to accomplish this goal, resulting in resection of glioma tissue and might possibly give rise to changes in cognitive functioning. Research has shown that a greater percentage of resection and less residual glioma tissue have the advantage of delaying the reoccurrence of the glioma (Berger, Deliganis, Dobbins, & Keles, 1994; McGirt et al., 2008; Smith et al., 2008). However, resection could also lead to the worsening of already existing deficits, or the occurrence of new neurocognitive deficits (Duffau, 2009; Teixidor et al., 2007). Due to this uncertainty it is highly important to fully understand the consequences of the resection of the glioma with respect to potential damage to functional brain tissue. Linking pre- and postoperative

neuropsychological test data to the area of resection could provide more insight into key areas associated with cognitive flexibility.

The application of lesion-symptom mapping in patients with a low-grade glioma is a commonly used method in the field of neuropsychology and neurosurgery to gain major insights into brain-cognition relationships (Gläscher et al., 2009). Despite the differences between the two disciplines, the two approaches share the interest in exploring the regional distribution of cognitive functions in the brain (Kimberg, Coslett, & Schwartz, 2007). This study is devoted to exploring the collective interest in the relationship between cognitive flexibility and white matter tracts in the right parietal lobe, with the aim to provide groundworks for future research in neuropsychology and neurosurgery. Furthermore, it is of great importance to understand the consequences of resecting a low-grade glioma on cognitive flexibility to enable preservation of cognitive flexibility during glioma surgery. From a clinical perspective, this would offer an unprecedented opportunity to maintain quality of life and optimally recover from this life event.

Case report

A previous case report written by Mandonnet and colleagues (2017), illustrates that a white matter focal lesion can generate a decline in cognitive flexibility after surgical resection of a low-grade glioma in the right supramarginal gyrus, which altered the connectivity in the fronto-parieto-temporal network and damaged tracts, such as the Superior Longitudinal Fasciculus III and Arcuate Fasciculus. Suggesting a causal role of the white matter underlying the right non-dominant supramarginal gyrus in cognitive flexibility.

Current study

Through a multicentred international collaboration we were able to operationalize our aim to include a larger series of patients to investigate the involvement of white matter tracts in the right parietal lobe in cognitive flexibility. Based on Mandonnet and colleagues' (2017) clinical report, we hypothesize that specific dorsal and medial regions of the parietal lobe, where white matter bundles are crossing, are crucial for cognitive flexibility. This is strengthened by the findings of Danckert and colleagues (2011), who define the crucial role of the parietal lobe in the integration of information, as it is located at the hub of a large neural network. Based on neurosurgical experience in clinical practice, we are specifically interested in the Superior Longitudinal Fascicle III (SLF III), Arcuate Fascicle (AF) and Inferior Fronto-Occipital Fascicle (IFOF).

Methods

2.1 Ethics statement

The study was approved by the UMCU Institutional Review Board; informed consent was not obtained for this observational study on data that were obtained as part of routine clinical care in the participating centres.

2.2 Participants

In this retrospective multicentre study, data was obtained from 34 primary low-grade glioma patients, diagnosed according to the WHO criteria. The eligibility criteria included patients who were at least 18 years old, who had a low-grade glioma (WHO II and III) located in the right parietal lobe and who underwent their first surgical resection. All patients were surgically treated between 2010 and 2017 at 7 hospitals in Europe: Hospital Universitario Quirónsalud Madrid (Madrid, Spain) (n = 2), Centre Hospitalier Saint-Anne (Paris, France) (n = 3), Hospital Lariboisière (Paris, France) (n = 3), Centre Hospitalier Universitaire de Poitiers (Poitiers, France) (n = 4), Centre Hospitalier Régional Universitaire de Nancy (Nancy, France) (n = 3), Amsterdam University Medical Centre (Amsterdam, the Netherlands) (n = 14) and University Medical Centre Utrecht (Utrecht, the Netherlands) (n = 5). Availability of preoperative and postoperative MRI scans and neuropsychological data was necessary for inclusion in the study.

2.3 Neuropsychological testing

Neuropsychological assessments have been administered preoperatively (1 - 10 days) and postoperatively (3 – 6 months) including the Trail Making Test (TMT) and Stroop-Color-Word-Test (SCWT). The TMT consists of two parts; part A requires the patient to draw a line to connect 25 encircled numbers in numerical order as quickly as possible. In part B, the patient connects numbers and letters in numerical and alphabetical order, while alternating between the numbers and letters (e.g. 1-A-2-B-3-C, etc.) (Bowie, & Harvey, 2006; Tombaugh, 2004). The total time of completion of each part is the direct score of the task. Part A reflects motor and percentual speed, whereas part B is linked to several parts of executive function, such as set-shifting, task-shifting, inhibition and working memory (Oosterman et al., 2010; Sánchez-Cubillo et al., 2009). The purest index of cognitive flexibility is represented by the derived score of the B to A ratio since this score eliminates the attentional speed affect measured in part A (Arbuthnott, & Frank, 2000).

The second measure of cognitive flexibility is the SCWT (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006). Multiple versions have been developed but the basic paradigm remains the same. The most commonly used version in this study consists of three subtasks (Stroop, 1935). The first subtask consists of 100 colour words (yellow, green, blue and red) printed in black ink, which are arranged in random order. The second subtask displays 100 rectangular coloured patches, again arranged in random order. The task here is to correctly name either the word on subtask 1 or the colour patch on subtask 2. The third subtask consists of colour words printed in an incongruent ink colour (e.g. the word "blue" is printed in yellow ink) (Comalli, Wapner, & Werner, 1962). Unlike the first two subtasks where an individual reads/names the congruent stimuli, the third subtasks requires an individual to suppress the automatic reading of the word and instead name the incongruent colour of the ink (Stuss, Floden, Alexander, Levine, & Katz, 2001). Again, the best index of cognitive flexibility is the derived interference score where the attentional speed affect is cancelled out by subtracting the average time of card 1 and 2 off the time on card 3.

2.4 Image acquisition

Magnetic Resonance Image (MRI) data were acquired axially pre and post-surgery. Based on the availability and quality of the images, the protocol included T1-weigthed 3D images, T2-weighted 3D images and FLAIR-weighted 3D images. In each image volume, 19 – 640 axial slices were acquired.

2.5 Image processing

Image files in DICOM format were converted to NIFTI files using the dcm2nii application in MRIcron. Pre-processing steps were performed on each postoperative MRI before conforming the data to the standardized Montreal Neurological Institute (MNI) space, using the Clinical Toolbox in SPM12 (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012), implemented in MATLAB (release R2018b, The Mathworks, Inc., Natick, Massachusetts, USA). Since the size, shape and location of glioma tissue and resection vary considerably across patients, manual segmentation has been chosen over automatic segmentation techniques (Menze et al., 2014). A rater, supervised by a skilled operator, performed spatial segmentation using ITK-SNAP software (Yushkevich et al., 2006). This involved masking the area of resection and residual glioma tissue by masking segmentation, to prevent the lesion area to contribute to the normalization process (Brett, Leff, Rorden, & Ashburner, 2001). In addition, resection segmentation was performed to outline the resection area. The

manual segmentation and spatial normalization were followed by inspection and correction as necessary. Figure 1 shows the flow-chart used for image registration.

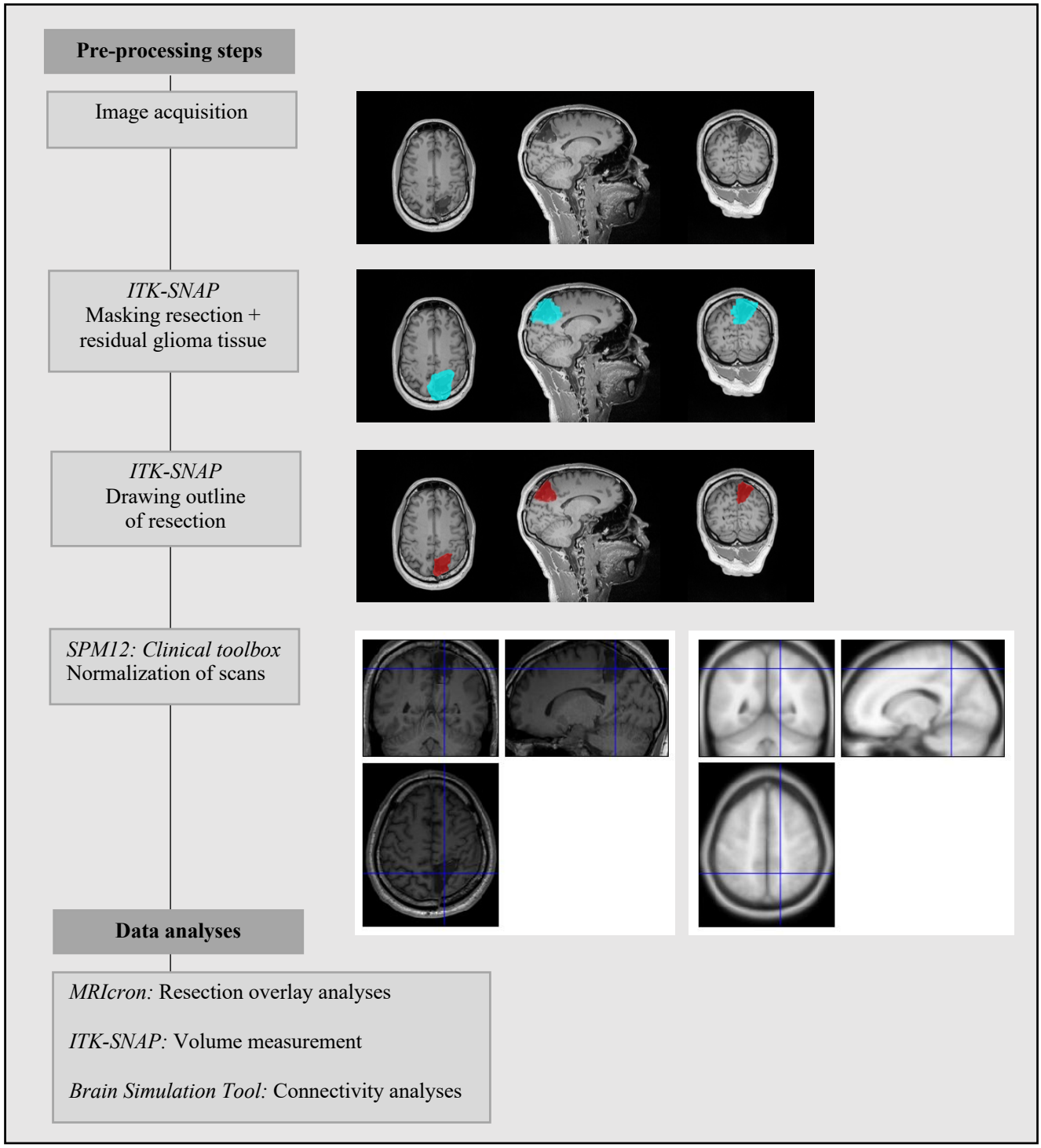

Figure 1. Flow-chart image registration

2.6 Neuropsychological data analyses

As cognitive function becomes a more commonly reported outcome measure of glioma surgery, pre- and postoperative neuropsychological test results were compared to understanding the effect of glioma surgery (Klein, Duffau, & Hamer, 2012). Moreover, in order to investigate the relationship between glioma resection and cognitive decline, patients were divided into a cognitively declined group and a control group of patients who were not cognitively declined after surgery (Lee, & Lim, 2016). Z-scores were calculated to analyse neuropsychological data. Normative scores from published norming studies were used for each cognitive test to compare results with outcomes from healthy adults. As for the TMT norm scores, Arbuthnott and Frank (2000) calculated ratio scores, with a mean of 2.6 (*SD* = 1.1), from a sample of 34 healthy adults aged from 18 to 48 years. Raw TMT ratio scores were used to calculate derived z-scores as [(preoperative TMT ratio – mean)/ *SD*]. Results on the SCWT were compared to norms scores from a total sample of 987 people aged from 49 to 81 years (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2008). The SCWT derived contrast z-scores, were calculated as [completion time in seconds on card 3 – [{completion time in seconds on card 1 + completion time in seconds on card 2}/2], with a mean of 50.4 (*SD* = 19.7) (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006). To align results, derived z-scores were recoded. Thus, a decline in performance was presented as a negative z-score. Change in performance in an individual after surgical resection of the low-grade glioma was measured by calculating the change index, that is, [postoperative TMT recoded z-score – preoperative TMT recoded z-score] and [postoperative SCWT recoded z-score – preoperative SCWT recoded z-score]. A significant decline in cognitive performance was defined as $z \leq -1$ and a significantly improved performance was defined as $z \geq +1$.

2.7 Image data analyses

Imaging data was analysed by using three complimentary techniques. Firstly, lesion-symptom mapping was performed, involving overlay plots using the MRIcron program (Rorden, Karnath, & Bonilha, 2007) (https://people.cas.sc.edu/rorden/mricron/main.html). To map the areas of interest, white matter tract atlases were downloaded from http://toolkit.bcblab.com, which provided tractography of the SLF III, IFOF and AF based on high-resolution diffusion-weighted imaging datasets (Rojkova, Volle, Urbanski, Humbert, Dell'Acqua, & De Schotten, 2016). Secondly, resection volumes were measured in ITK-SNAP to determine the extent of resections. Thirdly, dysconnectivity between regions of

interest (ROI) was calculated with the Brain Simulation Tool (Raemaekers, & Smits, in development). Simulated resection tractograms were generated and resection connectomes were computed. Since resection connectomes represent the estimated amount of dysconnectivity between two anatomical cortical regions, seed points of the SLFIII, IFOF and AF were defined according to the Harvard-Oxford atlas. Due to the wide anatomical distribution of the white matter tracts, multiple seed points per white matter tract were included (see table 2; Appendix A) (Catani, & De Schotten, 2008; Kaplan, et al., 2010;. Kikinis, et al., 2010; Bartolomeo, De Schotten, & Chica, 2012; Ciaraffa, Castelli, Parati, Bartolomeo, & Bizzi, 2013; Güngör, Baydin, Middlebrooks, Tanriover, Isler, & Rhoton, 2017).

Results

3.1 Demographic data

Nineteen patients fulfilled the entry criteria (10 female, 8 males, 1 unknown). The mean patient age was 40 years (range 21 – 67 years).

3.2 Neuropsychological data

As presented in table 1, preoperative and postoperative test results of the TMT ratio scores and the SCWT contrast scores were calculated into z-scores. The change index showed a significant decline in performance on the TMT and/or SCWT ($z \leq -1$) in four patients who underwent glioma surgery (A, H, L, N). The performance of two patients (E, I) significantly improved ($z \geq +1$) after glioma surgery. The majority of patients (n=13) did not perform significantly different on the neuropsychological tasks.

Table 1 *Results neuropsychological tests*

	TMT			SCWT		
	preoperative*	postoperative*	Change index	preoperative*	postoperative*	Change index
A	+1,0	-0,3	- 1,3	+1,3	+1,0	- 0,3
B	+0,3	+0,4	+0,1	+1,0	+0,7	- 0,3
C	+1,1	+0,9	- 0,2	+1,8	+1,7	- 0,1
D	+0,5	+0,2	- 0,3	+0,6	+0,1	- 0,5
E	- 0,6	+0,4	+1,0	-	+0,2	-
F	+0,3	+0,3	+0,0	+0,4	+0,3	- 0,1
G	+0,1	- 0,8	- 0,8	- 0,6	+0,1	+0,7
H	- 0,1	- 1,9	- 1,8	- 0,2	- 2,4	- 2,2
I	+0,3	+0,4	+0,1	- 1,8	- 0,7	+1,2
J	+1,0	+0,7	- 0,3	- 1,0	- 0,1	+0,9
K	- 0,1	- 0,8	- 0,8	- 0,3	- 1,2	- 0,8
L	- 1,2	- 3,3	- 2,1	+0,7	+0,1	- 0,6
M	+0,2	+0,3	+0,1	+0,8	+0,6	- 0,2
N	- 0,1	- 0,5	- 0,4	+0,2	- 1,9	- 2,2
O	+0,9	+0,3	- 0,6	+0,5	+1,2	+0,7
P	+0,4	+0,5	+0,1	+0,8	+0,8	+0,0
Q	-	-	-	+1,1	+1,0	- 0,1
R	-	-	-	+2,2	+2,4	+0,2
S	-	-	-	+0,1	+0,7	+0,6

Data are z-scores (*recoded).

3.3 *Resection overlay analyses*

To identify regions in the right parietal lobe that are involved in cognitive flexibility, resection overlay plots were compared between the group of patients who showed less cognitive flexibility after surgery and the control group of patients who did not decline in performance on cognitive flexibility tasks. As shown in Figure 2, three colour-encoded regions were identified, revealing a specific region (red) solely resected in patients who showed less cognitive flexibility after surgery. In addition, a subtraction analysis was performed to measure the relative frequency of damaged brain tissue specific to a decline in

cognitive flexibility. However, results were uninterpretable since our population did not meet the criteria of equal group sizes (Rorden, Karnath, & Bonilha, 2007).

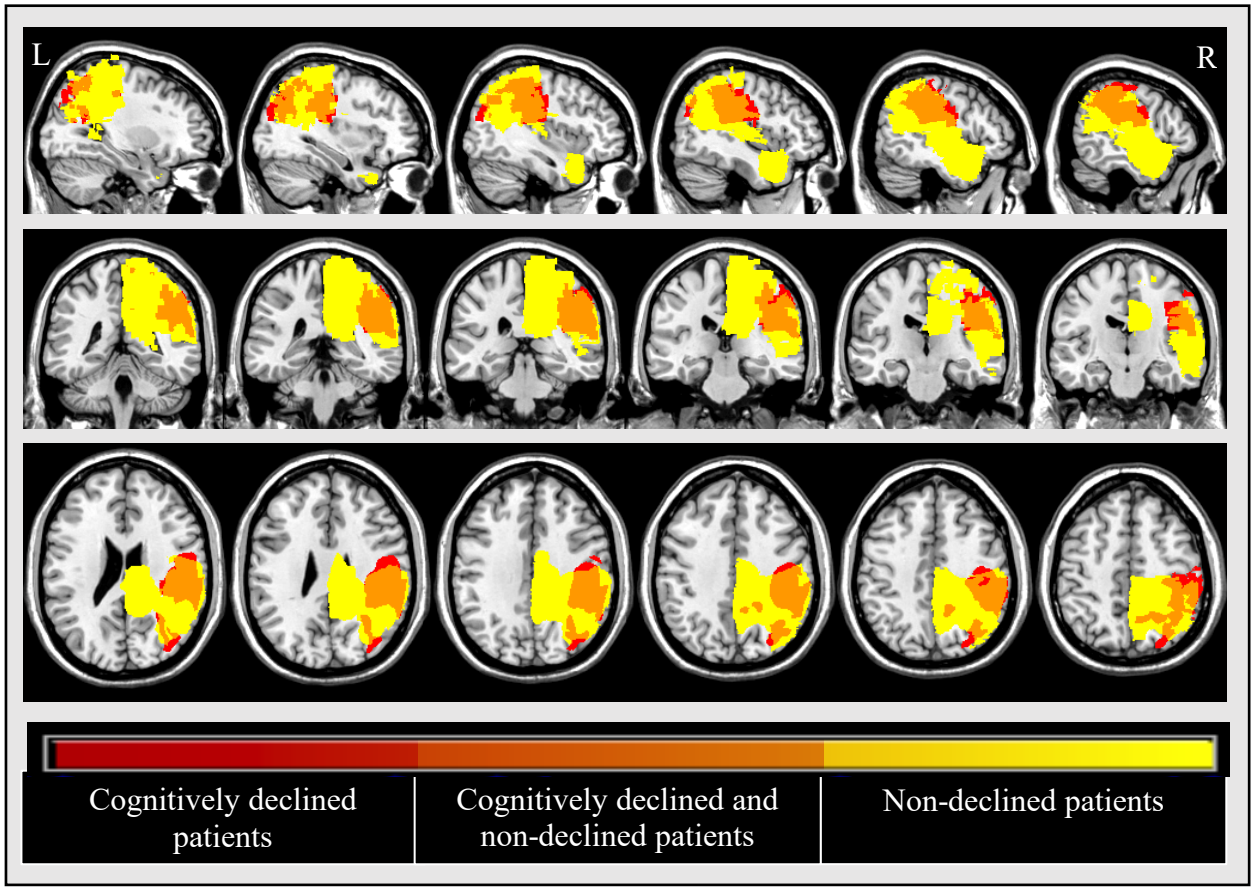

Figure 2. Sagittal, coronal and axial representations of the anatomical results of resection overlay plots using the MRIcron program (Chris Rorden, University of South Carolina, Colombia, SC, USA). Red represents the resection overlay of cognitively declined patients, yellow represents the resection overlay of cognitively non-declined patients and orange represents the area that is resected in both groups.

To visualize white matter involvement, tractography of the SLF III, IFOF and AF was incorporated in the combined resection overlay plots. Voxel values presented in MRIcron showed that all three colour-encoded regions interfered with white matter tracts that are involved in the right fronto-parieto-temporal network. Note that these values could not be used in a voxelwise statistical analysis due to the limitations of examining relatively small groups of patients (Rorden, Karnath, & Bonilha, 2007). Therefore, additional individual analyses of the cognitively declined patients were performed to provide a more detailed visualisation of white matter involvement. As illustrated in Figure 3, individual results showed interference with the SLF III and AF in three patients (A, H, N) and interference with the IFOF in one patient (L). Great heterogeneity was observed in the individual analyses of

resection location, which complicated an unequivocal interpretation of the group- based analysis.

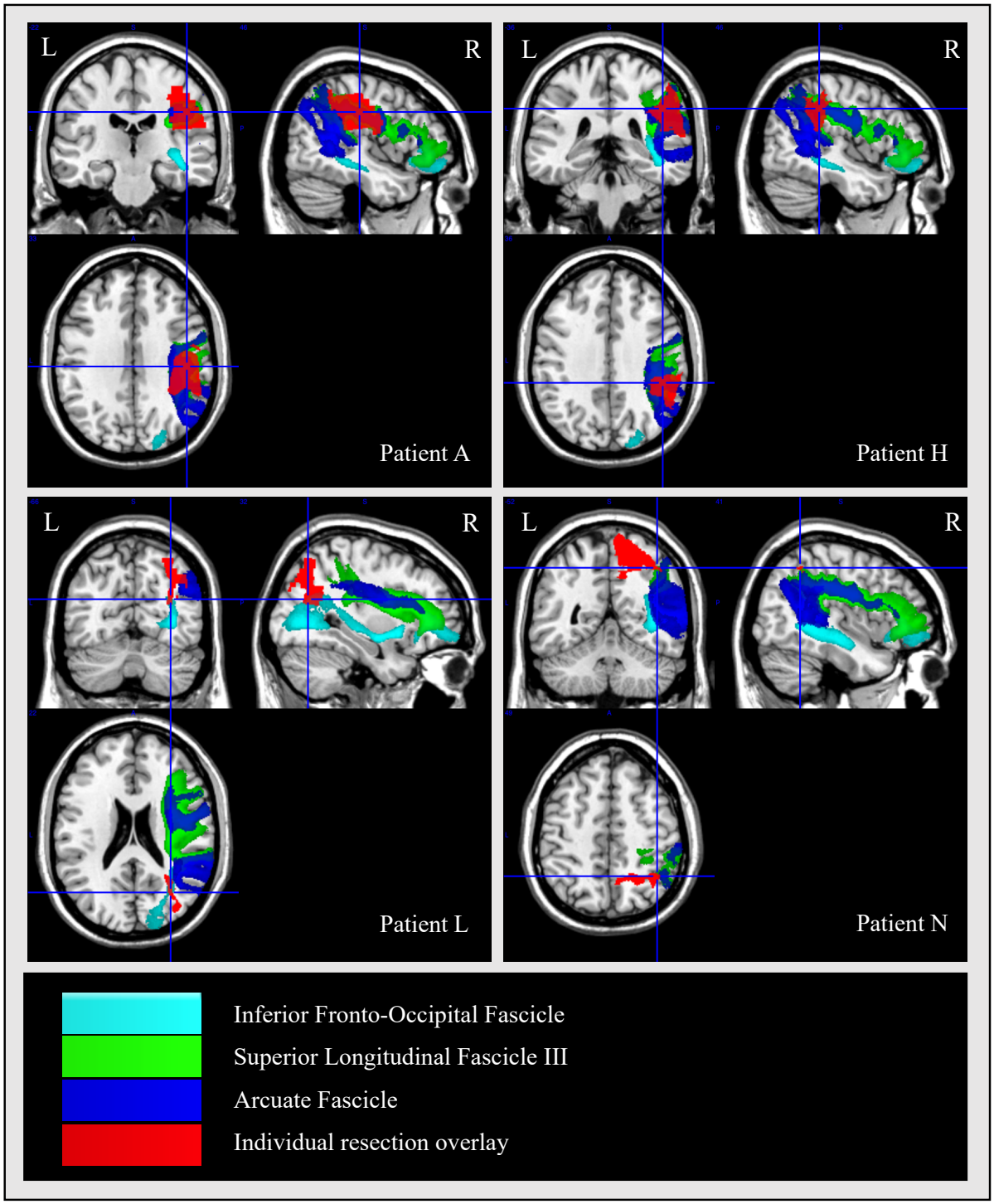

Figure 3. Colour-encoded white matter tracts (SLFIII = green, AF = dark blue, IFOF = light blue) incorporated in individual resection overlays (resection = red).

3.4 Resection volume measurements

Resection volumes were between 2744 mm^3 and 59490 mm^3 (*Mdn* = 17480). As shown in Figure 4, patients who cognitively declined had resection volumes between 6355 mm^3 and 26870 mm^3. Interestingly, patients who had the largest resection volumes (40810 – 59490 mm^3) did not cognitively decline (Patient C, M, Q, R). These results suggested that resection volume is not directly linked to a decline in performance on the TMT and/or SCWT after surgery.

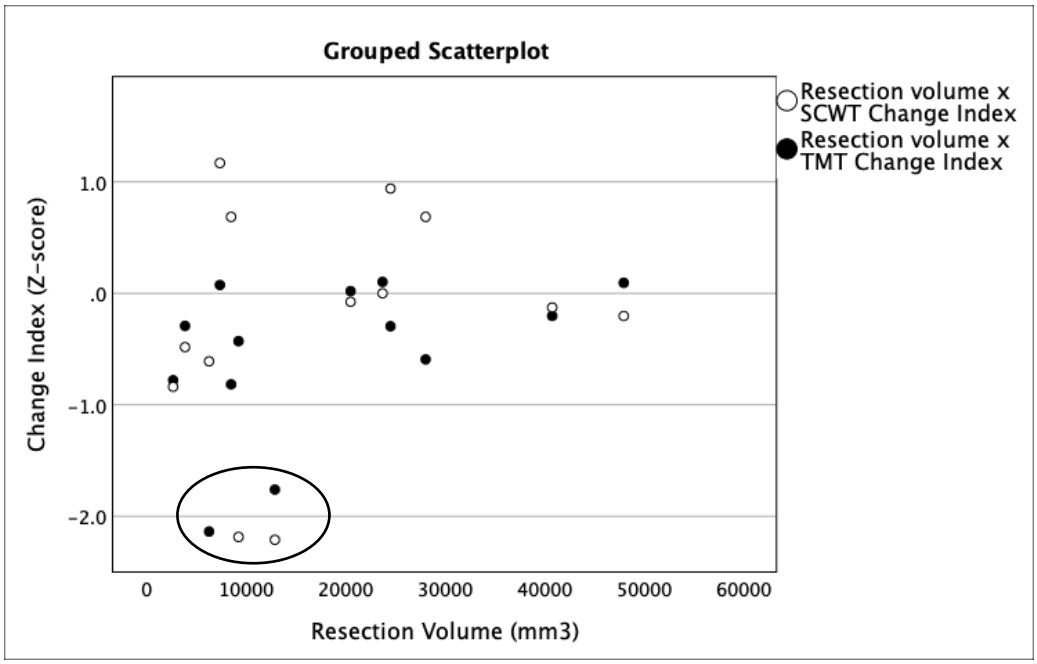

Figure 4. Resection volumes compared to change index scores of TMT and SCWT.

3.5 Brain Simulation analysis

Resection tractograms were visualized and showed structural connectome damage in the area of resection (Fig. 5). Unfortunately, the corresponding resection connectome computations could not be statistically analysed since a group-based analysis could not be performed due to the relatively small population. In addition, norm scores for individual analyses are currently unavailable since the Brain Simulation Tool is still in development. Due to this inconvenience, the amount of dysconnectivity between ROI-pairs could not be accurately interpreted.

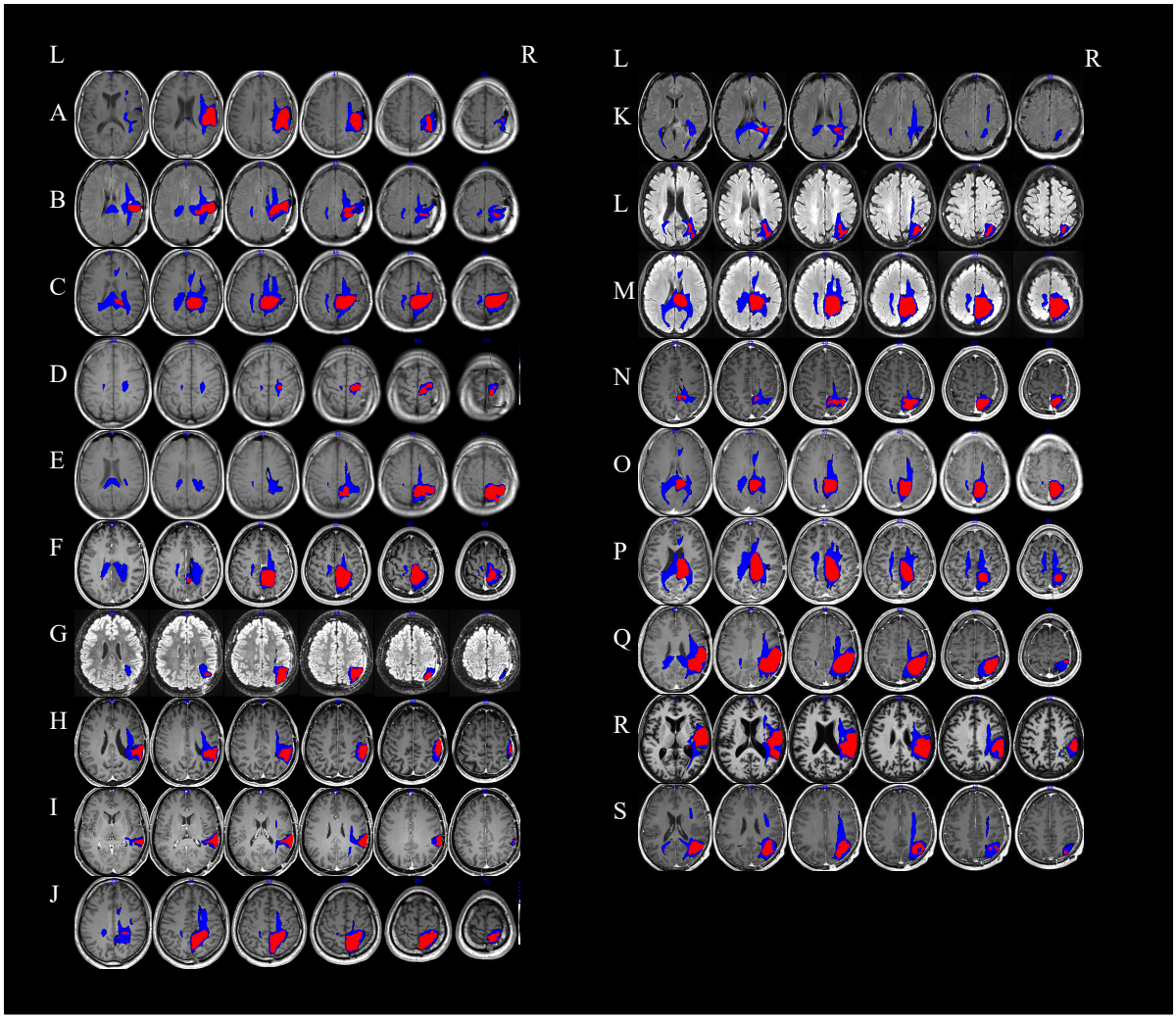

Figure 5. Original postoperative MRI scans (n = 19) with resection overlay (red) and simulated structural connectome damage (blue).

Discussion

The current lesion-based brain-behaviour study explored the relationship between cognitive flexibility and white matter tracts in the right parietal lobe, providing a foundation on which to construct clinical practice and future research in neuropsychology and neurosurgery. For the purpose of this retrospective study, a multicentred collaboration was established and data was collected from patients with a low-grade glioma in the right parietal lobe, who underwent surgical resection. Comparative analyses of pre- and postoperative neuropsychological data and postoperative MRI scans showed a heterogeneity in the relationship between cognitive flexibility and white matter tracts in the right parietal lobe. Primarily resection overlay analyses showed that a specific region in the right parietal lobe could be allocated to patients who declined in cognitive flexibility after surgery. Yet, when incorporating white matter tractography, the SLF III, AF and IFOF were found to be damaged in both patients who showed a decline in cognitive flexibility and patients who showed no change or improvement in cognitive flexibility. In addition, visualised resection tractograms generated by the Brain Simulation Tool presented similar patterns of dysconnectivity in the right parietal lobe in both groups. Furthermore, resection volumes were not directly linked to a decline in cognitive flexibility.

Psychometric properties

Since cognitive flexibility incorporates multiple component processes of executive function, the TMT and SCWT were combined to assess the concept. The long-held assumption that tests of executive function, such as the TMT and SCWT, are only sensitive to frontal lobe function has been argued over the past years and contradicted by our findings (Burgess, & Stuss, 2017). However, it is important to mention that the wide utility of the TMT and SCWT as a measure of executive function complicates our aim to exclusively measure the concept of cognitive flexibility and distinguish associated brain regions.

Furthermore, psychometric properties should be considered when interpreting neuropsychological outcomes. When calculating the SCWT interference score, the average time of card 1 and 2 was subtracted from the completion time of card 3. By combining word reading speed and colour naming speed, we did not only correct for an attentional speed affect but also for the possible influence of language deficits, increasing the specificity of the measurement (Stuss, Floden, Alexander, Levine, & Katz, 2001). As a consequence of combining two measures, the standard deviation of our norm group was

relatively large, which could have led to an underestimation of the results. To increase the sensitivity and compensate for this limitation, moderate z-score norms were used to determine a significant decline ($z \leq -1$) and a significant improvement ($z \geq +1$) in cognitive performance.

In addition, performance errors were only taken into account when calculating TMT z-scores since the completion time includes a correction time when the patient makes a mistake (Bowie, & Harvey, 2006). However, error analysis in the SCWT should also be considered since factors such as perseveration and distractibility commonly occur in brain injured populations, which influences the performance (Stuss, Floden, Alexander, Levine, & Katz, 2001). Even though self-corrections on the SCWT were included in the total completion time, errors were not part of the calculation. Interestingly, errors are commonly made by patients with damaged brain tissue in the right superior posteromedial area, increasing the importance to include error analysis in assessing cognitive flexibility (Stuss, Floden, Alexander, Levine, & Katz, 2001).

Implications of lesion-symptom mapping

The results of our lesion-symptom mapping analysis neither confirm nor deny Mandonnet and colleagues' (2017) previously suggested role of the right fronto-parieto-temporal network in cognitive flexibility. Our findings suggest that cognitive flexibility does not solely depend on the SLF III, AF and IFOF in the right parietal lobe since both cognitively declined patients and cognitively non-declined patients had damaged tracts. However, it is worth noting that the SLF III and AF were damaged in three cognitively declined patients, which is in accordance with the anatomical findings illustrated in the clinical case report of Mandonnet and colleagues (2017).

Implications resection volume measurements

Although an unequivocal answer could not be formed based on the lesion-symptom mapping, resection volume measurements confirmed the importance of defining white matter involvement in cognitive decline. In addition to the growing evidence suggesting that a greater extent of resection of low-grade gliomas improves long-term survival and delays the reoccurrence of the glioma (Smith et al., 2008), our findings showed no decline in cognitive flexibility when a more extensive resection was performed. This implicates that cognitive inflexibility is not related to the extent of resection, strengthening the necessity of localizing

cognitive functioning in the brain to comprehend neuropsychological outcomes after surgery. In fact, three patients with the largest resection volumes showed above average performance on neuropsychological tests pre- and post-surgery. From a neurosurgical perspective, several factors are known to influence neuropsychological outcomes. Firstly, cognitive flexibility could be preserved due to the mechanism of cerebral plasticity. Given the slow growth rate of low-grade gliomas, enough time is given to the brain to compensate through functional remapping (Duffau, 2012). Secondly, cognitive flexibility could be influenced by the suppression and shifting of white matter tracts caused by the glioma. When a glioma is resected, the function of suppressed white matter tracts could improve and shifted white matter tracts could maintain their function (Abdullah, Lubelski, Nucifora, & Brem, 2013).

Limitations

The lack of convergence in our lesion-symptom mapping findings could be due to methodological limitations. The relatively small sample size limits the generalizability of our findings. Although the change index of neuropsychological results provides the purest indication of cognitive change within a patient, additional group-based analysis would enlarge the ecological value (Haneuse, & Bartell, 2011). In addition, by performing resection plots, volume measurements and brain simulation analyses, our approach was built upon derived and simulated white matter tractography. Due to the robustness of each method, our knowledge about distinct white matter tracts involved in cognitive flexibility is unfortunately still limited. While we know a considerable amount about the construct of cognitive flexibility and about white matter connectivity in the brain, a coherent methodology is needed to integrate anatomical and behavioural knowledge (Barbey, Colom, & Grafman, 2013).

Methodological suggestion

The introduction of Diffusion Tensor Imaging (DTI) as a revolutionary MRI-based methodology should be considered in future research as it provides a non-invasive tool to complement conventional MRI in functional white matter mapping. It is a framework for acquisition and analysis of directional water diffusion. Since water is primarily diffused along white matter tracts, information on the integrity of white matter in damaged brains can be captured through DTI (Schwarz et al., 2014; Assaf, & Pasternak, 2008; Alexander, Lee, Lazar, & Field, 2007). As DTI is a rapidly evolving technique, considerable effort has been devoted to decreasing its artefacts and improving registration, making this a powerful tool to collect converging evidence for white matter mapping. Combining conventional MRI with

DTI adds great potential to the design of a coherent methodology in brain-behaviour mapping.

Clinical practice

Aside from methodological inventions, new implementations in clinical practice create additional procedural chances to enhance our knowledge on the relationship between white matter and cognitive flexibility. More broadly, over the past years great progression has been made in neurosurgical and neuropsychological procedures, with the aim to improve quality of life of patients with a low-grade glioma. Awake glioma surgery with intraoperative cognitive monitoring has become a more frequently used method to reduce the risk of cognitive complications after surgery (Beez et al., 2013). Traditionally, awake glioma surgery was more common in left-hemispherical glioma patients. However, nowadays it has been extended to right-hemispherical glioma patients (Mandonnet et al., 2017). From a clinical perspective, this development offers great opportunities to assess cognitive flexibility and localize neural substrates. Furthermore, greater understanding of cognitive flexibility may advance devising appropriate neuropsychological tools for intraoperative monitoring and, defining neural substrates contributes to assure the preservation of functional brain tissue during surgical resection.

Conclusion

Taken together, we found that cognitive flexibility can decline after surgical resection of a low-grade glioma in the right parietal lobe. However, complete integrity of the SLF III, AF and IFOF in the right parietal lobe does not seem to be crucial for cognitive flexibility since not every patient with white matter damage showed a decline in cognitive flexibility after surgery. In addition, the extent of resection was not linked to a decline in cognitive flexibility.

Direct identification of damaged white matter tracts was hindered by the robustness of methodological properties. Nonetheless, this exploratory study provides the foundation for future integrational research by including a large cohort, build upon international collaboration, to analyse white matter involvement in cognitive flexibility and discuss the strengths and weaknesses of various approaches. With intraoperative cognitive monitoring and promising methodologies, further exploration in cognitive outcomes after neurosurgery is to be expected, using complementary techniques and an integrational approach to localize cognitive flexibility in the brain.

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Appendix A

Table 2. *White matter seed points defined according to Harvard-Oxford atlas*

White matter tract	Reference	Seed points	Corresponding region Harvard-Oxford atlas
SLF III	Güngör et al. (2017)	Supramarginal gyrus – anterior part of the inferior frontal gyrus	82, 83 - 69
SLF III	Bartolomeo et al. (2012)	Starts in IPL	
IFOF	Güngör et al. (2017)	Anterior and midparts of the inferior and middle frontal gyri – temporal and occipital lobe	67, 68, 69 – 76 (86)
IFOF	Ciaraffa et al. (2013)	Orbitofrontal cortex – temporal and occipital lobes	96 – 76 (86)
IFOF	Catani et al. (2008)	Orbitofrontal cortex – ventral occipital lobe	96 – 86
AF	Güngör et al. (2017)	Middle, superior temporal gyri – mid parts inferior and middle frontal gyri, passing temporal lobe, anterior part occipital lobe, angular adn supramarginal gyri, pre- and postcentral gyri and middle and inferior frontal gyri.	
AF posterior	Ciaraffa et al. (2013)	Inferior parietal lobe – superior temporal gyrus, medial temporal gyrus	82, 83, 84 – 72,73,74,75,76
AF long / anterior	Ciaraffa et al. (2017)	Inferior and middle frontal gyri – ventral precentral gyrus	67, 68, 69 – 70
		Dorsolateral prefrontal cortex – inferior parietal lobe	67 – 82, 83
AF long / anterior	Kaplan et al. (2010)	Ventral premotor cortex – inferior frontal gyrus, pars opercularis	70 – 69