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Focal left prefrontal lesions and cognitive impairment: a multivariate lesion-symptom mapping approach

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Abstract

Despite network studies of the human brain have brought consistent evidence of brain regions with diverse functional roles, the neuropsychological approach has mainly focused on the functional specialization of individual brain regions. Relatively few neuropsychological studies try to understand whether the severity of cognitive impairment across multiple cognitive abilities can be related to focal brain injuries. Here we approached this issue by applying a latent variable modeling of the severity of cognitive impairment in brain tumor patients, followed by multivariate lesion-symptom methods identifying brain regions critically involved in multiple cognitive abilities. We observed that lesions in confined left lateral prefrontal areas including the inferior frontal junction produced the most severe cognitive deficits, above and beyond tumor histology. Our findings support the recently suggested integrated albeit modular view of brain functional organization, according to which specific brain regions are highly involved across different sub-networks and subserve a vast range of cognitive abilities. Defining such brain regions is relevant not only theoretically but also clinically, since it may facilitate tailored tumor resections and improve cognitive surgical outcomes.

Keywords: Cognitive Dysfunction; Principal Component Analysis; Multivariate Lesion-Symptom Mapping; Brain Tumor; Frontal Lobe; Dorsolateral Prefrontal Cortex.

1. Introduction

The valuable information derived from neuropsychological studies resides in uncovering the critical role of damaged brain regions for the tested ability. One of the main assumptions is that the ability being tested relates to a defined cognitive process, which is supported by a specific brain region. However, rarely there is a clear one-to-one relationship between damage and deficit, which is even more evident from a clinical aspect. More often focal lesions give rise to multiple deficits, and sometimes even extensive lesions can result in transient or mild symptoms. Recently, with the advance of large-scale network studies in patients with focal brain injuries it has been observed that lesions in hub locations, which mediate the interactions among other regions (Warren et al., 2014; Zhu et al., 2016), or subcortical white matter regions, in which many fiber tracts converge (Corbetta et al., 2015), produce deficits across several cognitive domains, with respect to cortical/subcortical minor nodes with a more peripheral network position. In line with these recent findings, we explored whether the severity of post-surgical cognitive impairment in brain tumor patients can be related to lesions in specific or broad brain regions. To obtain a cognitive functioning measure not related to selective processing impairments (e.g., language, visuo-spatial attention), but capturing the severity of symptoms across multiple cognitive abilities, we applied a latent variable analysis to a number of measures obtained from standardized neuropsychological tests. The selection of neuropsychological tests was based mainly on their low complexity and reliance on different low-level processes. This is a fundamental requirement for the extraction of a latent variable

capturing only common variance across multiple measures and thus mostly unaffected by low-level impairments (Friedman & Miyake, 2017). The impact of brain damage on this broad cognitive functioning measure was examined by means of lesion-symptom mapping analysis. We employed a recently developed multivariate approach based on machine learning algorithms (Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014) which allows to assess the interaction between lesions across multiple brain regions, therefore being better suited to detect critical regions supporting multiple cognitive abilities with respect to univariate approaches which assess the lesion-symptom association at each voxel separately (Yourganov, Fridriksson, Rorden, Gleichgerrcht, & Bonilha, 2016; Zhang et al., 2014). Furthermore, we were interested in determining if damage to specific cortical/subcortical hub regions (van den Heuvel & Sporns, 2011, 2013) or to broad functionally general regions (Fedorenko, Duncan, & Kanwisher, 2013) lead to more severe post-surgical cognitive impairments. To this end we examined the correspondence between the location of critical areas obtained from the lesion-behavior correlation, and the location of hub brain regions highly connected to each other (i.e., "rich club" organization, van den Heuvel & Sporns, 2011), and brain regions implementing broad general functions.

The clinical population of interest were patients with brain tumors (gliomas, either high or low grade, meningiomas, or metastasis). As compared to stroke, which has a predominantly subcortical distribution at the population level (Corbetta et al., 2015), brain tumors more frequently involve also cortical regions. Furthermore, brain tumors allow for a longitudinal assessment, before and after surgery, which controls for inter-individual baseline differences in cognitive abilities or reserve (e.g., Vallesi et al., 2007). Based on previous studies (Campanella, Fabbro, Ius, Shallice, & Skrap, 2015; Desmurget, Bonnetblanc, & Duffau, 2006; Talacchi,

Santini, Savazzi, & Gerosa, 2011), we predicted that patients with low-grade tumors will present with more prominent post-surgical cognitive decline as compared to other tumor types. This cognitive outcome is mainly explained by the slow-growing infiltrative nature of low-grade tumors, that allows functional activity within the tumor mass (Schiffbauer, Ferrari, Rowley, Berger, & Roberts, 2001). Regarding other tumor types, in high-grade tumors we expected to observe decreased cognitive functioning both before and after surgery (Campanella et al., 2015; Habets et al., 2014; but see Talacchi et al., 2011), while for meningiomas and metastatic tumors there is contrasting evidence in the literature regarding the impact of tumor and surgery on cognitive functioning (Campanella et al., 2015; Gerstenecker et al., 2014; Hendrix et al., 2017; Tucha et al., 2003; van Nieuwenhuizen et al., 2007), and including them allowed us to assess this impact and compare them to other tumor types.

2. Materials and methods

2.1. Participants

Patients with age ranging from 18 to 85 years and undergoing a brain tumor operation at the local university hospital were recruited on a voluntary basis to participate in the study. Recurring brain lesions and previous neurological and psychiatric disorders were considered as a priori exclusion criteria. Seventy-nine patients were tested on a neuropsychological battery both before and after surgery. Twenty-five patients were excluded a posteriori mainly due to acute post-surgical difficulties (e.g., motor and language impairments) or to logistical issues. According to the histopathological exam of the lesion, from the remaining 54 patients (19 female; mean age = 53.3, SD = 15.2), there were 24 patients with high-grade glioma (HGG), 9

with low-grade glioma (LGG), 14 with meningioma (MEN) and 7 with metastases (META). According to the location of the tumor center of mass and the area with the highest number of damaged voxels, 15 patients had left prefrontal lesions, 14 had right prefrontal lesions and 25 had non-prefrontal lesions (15 left and 10 right laterilized). A lesion overlap map obtained from structural MRI (n = 50) or CT (n = 4) scans is shown in Figure 1.

In order to control for learning effects and to examine the pre-operative effects of the tumor, 49 well-matched healthy control participants were tested with the same procedure twice, on average after 8.1 days (SD = 3.2) from the first session. Difference in days between the two sessions was comparable across tumor type patient groups and controls (p = .1). Gender, age and education were comparable in tumor type and control groupings (all ps > .05). All but three participants were right-handed (two from the patient group and one from the control group), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Demographic and aetiological data are reported in Supplementary Table S1.

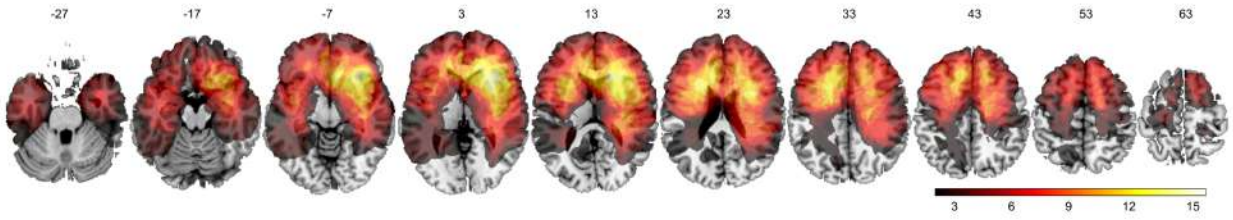

Figure 1. Lesion overlap map. The color bar indicates the number of patients whose lesions overlap on one voxel. The values above the slices indicate the z coordinates in the Montreal Neurological Institute space. In this figure, left is left.

2.2. Neuropsychological assessment

All patients were tested on average 4 days before (SD = 7.1) and 5.6 days after (SD = 2.2) the operation (respectively, pre- and post-operative sessions) and, besides the neuropsychological tests, they completed other computerized tasks reported elsewhere (Arbula et al., 2017). The neuropsychological assessment included the Mini Mental State Exam (MMSE; Measso et al., 1993) and the Italian version of the National Adult Reading Test – TIB (Sartori, Colombo, Vallar, Rusconi, & Pinarello, 1997), which provided measures of general cognitive functioning and intellectual ability. We also assessed verbal and spatial short-term memory (Digit Span - Mondini, Mapelli, Vestri, Arcara, & Bisiacchi, 2011; Corsi - Spinnler & Tognoni, 1987), visuo-spatial abilities (Trail making test - A) and phonemic fluency (letters: C, P, S; Mondini et al., 2011). The latter four neuropsychological tests were selected because of their low complexity and their reliance on distinct lower-level processes. Data from each patient and the references for each test are reported in Supplementary Table S1. Additionally, a brief denomination and comprehension test (Rodolfi, Gasparini, & Ghidoni, 2011) was included in the assessment in order to exclude patients with language deficits that could invalidate results from other tests. All participants gave their written informed consent before the testing sessions. The study was approved by the local bioethical committee and was conducted according to the guidelines of the Declaration of Helsinki.

2.3. Data preparation and statistical analysis

Neuropsychological data from both patient and control groups were corrected for age, sex and/or education based on the normative sample data provided in the above referenced test manuals. Due to technical issues, some of the participants did not perform all tests and the

following imputation procedure was performed to fill the missing data (3.64%). First we performed a multiple regression analysis on all tests but separately for each session, and excluded outlier data that had absolute standardized residuals higher than 2.5. Then we filled missing data with values predicted from a secondary multiple regression analysis, which did not consider outliers[1]. All patients' and controls' test scores were z-transformed with respect to the mean and standard deviation of the entire sample, to have the same relative scale before proceeding to the statistical analysis.

A principal component analysis (PCA) was performed on the data to obtain fewer measures (i.e., factors) that explain as much common variance between the tests' scores as possible, across all participants. In order to assess the impact of surgery, a PCA was first carried out on neuropsychological scores from the first (pre-operative) session. The loadings from this factor solution were then used to compute the factor scores from the second (post-operative) session[2]. These pre- and post-operative factor scores where thus compared between different groups of patients based on tumor type and controls by means of mixed-design ANOVAs with Surgery (pre- vs. post-surgery) as a within-subject factor.

[1] Additional analyses revealed that the imputation procedure we used did not bias our subsequent PCA analysis. We indeed performed a PCA on the pre-operative data using the alternating least squares algorithm as implemented in Matlab, a procedure that is able to effectively handle missing data. The resulting factor scores were highly correlated to the ones obtained in our principal analysis (n = 103; r > .99, ρ > .99; both ps < 10^{-107}). We also performed additional PCA analyses with both pair-wise and case-wise deletion of missing data. Again, the resulting factor scores were virtually identical to those obtained in our principal analysis (in both cases, n = 89; r > .99, ρ > .99; ps < 10^{-115}).

[2] A secondary PCA was conducted only on post-operative measures and control analyses were performed on the resulting scores. All reported results remained unchanged.

2.4. Multivariate lesion-symptom mapping analysis

Structural gadolinium-enhanced T1-weighted and FLAIR MR images were all acquired as part of the preoperative protocol for 44 out of 54 patients, and were used concurrently to identify the areas affected by the tumor mass. For the remaining patients, 6 had only one of these two types of MRI scans available, and 4 had only CT images available. Tumor lesions were manually drawn on pre-operative structural MRI or CT axial slices with MRIcroN (Rorden & Brett, 2000). Both images and lesions were normalized to an age-appropriate template brain using the Clinical Toolbox (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) for SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm) with enantiomorphic normalization (Nachev, Coulthard, Jäger, Kennard, & Husain, 2008). This lesion reconstruction procedure was conducted on pre-operative scans, since in the post-operative scans the lesion boundaries are often displaced by the neighboring tissue.

In order to pinpoint more circumscribed lesion locations that might be causing more severe cognitive impairments, a multivariate lesion-symptom mapping (MLSM) analysis was performed with the post-operative factor scores as the dependent variable. Pre-operative factor scores were not included because of the histopathology-related dissimilarities in cognitive deficits observed in the pre-operative session, while in the post-operative session there were no differences in the performance between different tumor types (see Results). The relationship between lesions and post-surgical impairments was modeled using the support vector regression lesion-symptom mapping toolbox (SVR-LSM; Zhang et al., 2014) with linear kernel. The kernel C parameter was evaluated across the range from $C = 10^{-6}$ to $C = 10^{6}$ by measuring both the prediction accuracy of the behavioral scores and the reproducibility of the SVR-LSM. Following Zhang et al. (2014), the model prediction accuracy was determined by

calculating the mean Pearson's correlation coefficient between predicted and actual scores obtained from 40 iterations of a 5-fold cross-validation procedure. Specifically, for each C, the model was trained on lesion data and behavioral scores from 4/5 of all patients and was used to estimate the behavioral score from the left-out 1/5 of patients. To evaluate the reproducibility of the SVR-LSM, the analysis was performed on 10 different subsets of 43 randomly selected patients. The reproducibility index for each C was calculated as the mean Pearson's correlation coefficient between any two pairs of SVR-LSM β-maps from different subsets, across 40 iterations. The C parameter was selected to have both prediction accuracy and reproducibility as high as possible (see Supplementary materials for parameter evaluation results). Once optimally trained, the resulting β-map, representing the predictive weight of each voxel, was compared to a probabilistic β-map obtained by permuting 2000 times the behavioral scores, with a false-discovery rate (FDR) of $p < 0.005$ and cluster size > 50 thresholds. Lesion volume effects were controlled for with the direct total lesion volume control (dTLVC) option, as implemented in the SVR-LSM toolbox. A supplementary analysis with lesion size regression instead of dTLVC was also performed, as suggested by a recent comparison of these two methods showing the latter to be more lenient (DeMarco & Turkeltaub, 2018). In order to minimize possible outlier effects, only voxels damaged in three or more patients were included in the analysis (Fig. 1). To assess a possible left-lateralization bias driven by the verbal nature of the three measures that we employed in the main PCA (i.e., Digit span, Phonemic fluency and TIB) we performed an additional MLSM analysis on the factor scores obtained from a different PCA carried out on the scores from the three tasks not relying exclusively on verbal abilities (i.e., TMT-A, Corsi and MMSE). For this purpose, the MMSE scores were recalculated by removing the items assessing language skills (i.e., naming, repetition, 3-stage command,

reading and writing) and proportionally recalculating the scores without these items. We also performed additional MLSM control analyses on each single test measure from the post-operative session.

To examine the hypothesized correspondence between the location of critical areas and the location of functionally general and cortical hub regions, the resulting critical areas were overlaid onto two different atlases, one showing brain regions engaged across a wide range of cognitive tasks (obtained from http://imaging.mrc-cbu.cam.ac.uk/imaging/MDsystem) and the other showing brain regions with dense connections exhibiting the rich club organization (obtained from the Human Connectome Project (HCP) data; http://www.humanconnectome.org/). See Supplementary Material for a more detailed description.

3. Results

3.1. Factor scores

The PCA on pre-operative scores yielded two factors with an eigenvalue > 1 (2.41 and 1.09). The optimal number of factors to be extracted was determined by carrying out a permutation-based parallel analysis (Horn, 1965) and the Velicer's minimum average partial correlation test (Velicer, Eaton, & Fava, 2000). Both procedures indicated that only one factor had to be retained, which accounted for 40.1% of variance in participants' performance. The factor loadings for each test are given in Table 1. The retention of one factor was motivated also by its methodological and theoretical significance, since our main aim was not to study specific processes or functions, but instead to have a single measure that captures the severity of cognitive impairment before and after brain surgery. An additional multivariate control analysis

was performed to further substantiate our choice of using a single principal component to investigate the impact of surgery on the severity of cognitive impairment across different tumor types (see Supplementary Material for more details).

The analysis of pre- and post-operative factor scores between different tumor types revealed a main effect of tumor type [$F(4, 98) = 20.78$, $p < .001$, $\eta^2_p = .46$] and critically, an interaction between tumor type and surgery [$F(4, 98) = 3.61$, $p = .009$, $\eta^2_p = .13$] (Fig. 2). Post-hoc test showed that in the pre-operative session all patients, apart the LGG group, performed significantly worse than controls (all ps $< .01$) and that there was a significant difference in performance between LGG and HGG patients ($p < .01$). However, in the post-operative session, the four groups of patients did not differ between each other (all ps $> .05$) and they were all significantly different from the controls (all ps $< .01$). Moreover, only LGG patients had a significant decrease in cognitive performance after surgery ($p < .001$), while in all the other groups the post-operative performance did not change with respect to pre-operative one (all ps $> .27$). Finally, the impact of surgery (i.e., the pre – post-operative change in performance) in the LGG patients was significantly different when compared to all the other patient and control groups (all ps $< .012$; Fig. 2).

Table 1. Factor loadings for each test

Test	Factor loadings
Digit span	0.6821
TMT-A	0.5748
Phonemic fluency	0.7301
Corsi	0.5503
MMSE	0.5807

TIB	0.6627
Variance explained	40.13%

TMT-A = Trail Making Test A; MMSE = Mini Mental State Exame; TIB = Test d'Intelligenza Breve – Italian version of the National Adult Reading Test.

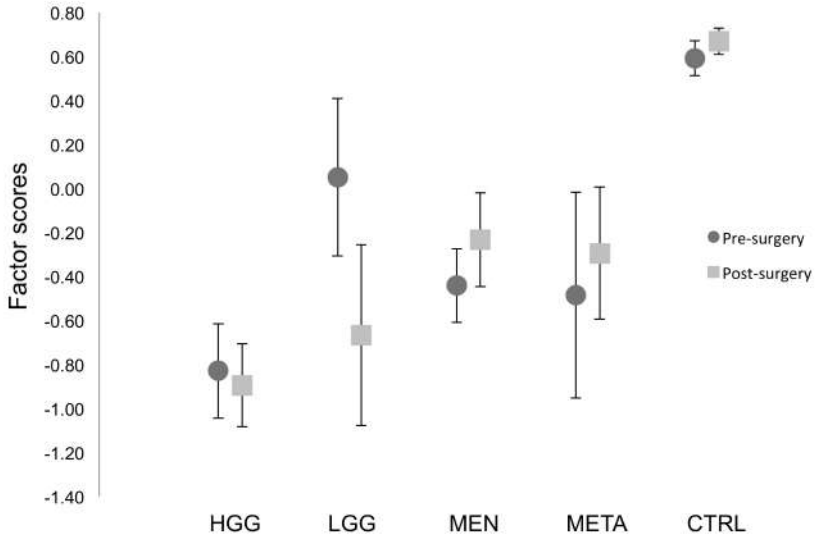

Figure 2. Factor scores on pre- and post-surgical sessions across different tumor types.

3.2. Multivariate Lesion-Symptom Mapping (MLSM)

The 5-fold cross-validation procedure yielded a significant correlation between the post-operative factor scores and those predicted by the linear SVR model ($r^2 = .24$, $p < .001$). The MLSM analysis showed a significant association between the post-surgical cognitive impairment and lesions localized to the left inferior frontal junction (peak permutation-based $p < .001$; MNI coordinates: -45, 9, 27) and the left posterior middle frontal gyrus (peak permutation-based $p = .0025$; MNI coordinates: -43, 18, 38) (Fig. 3). The former region also

partially overlapped with one of the brain regions belonging to the rich club (Supplementary Material Fig. S3; van den Heuvel & Sporns, 2011) and to the Multiple Demand System (Supplementary Material Fig. S4; Fedorenko et al., 2013), namely the opercular part of the inferior frontal gyrus. The supplemental analysis with lesion size regressed out of post-operative factor confirmed the above reported results (see Supplementary Material Fig. S5). The control analysis on factor scores obtained from "non-verbal" task measures confirmed the above reported findings: lesions localized to the left inferior frontal junction (peak permutation-based $p < .001$; MNI coordinates: -45, 4, 19) were also predictive of the "non-verbal" factor scores ($r^2 = .1$, $p = .02$; Fig. S6). In the control analyses on single test measures, only the post-operative MMSE scores were significantly predicted by the SVR model ($r^2 = .14$, $p = .005$; Fig. S7). The significant cluster was localized in the left inferior frontal junction and underlying white matter (peak permutation-based $p = .0025$; MNI coordinates: -37, 8, 30). Finally, out of 9 LGG patients included in the study, only one had a lesion that included the two regions associated with more severe cognitive impairment.

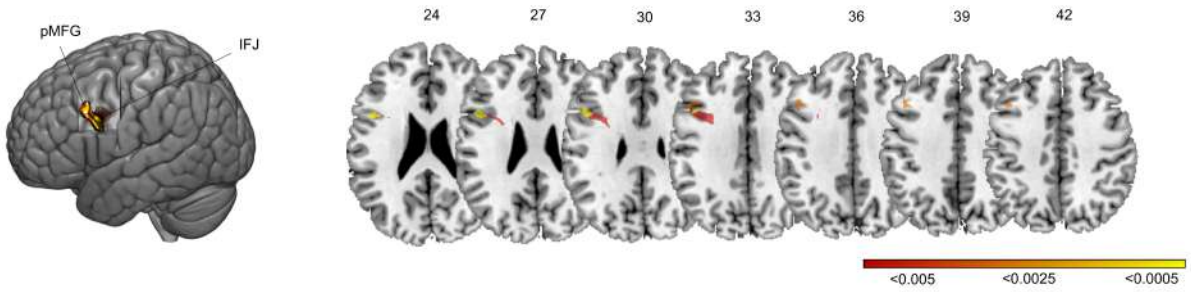

Figure 3. Areas significantly associated with more severe post-surgical cognitive impairment. Color bar indicates permutation-based *p*-values. The values above the slices indicate the z coordinates in the Montreal Neurological Institute space. In this figure, left is left.

4. Discussion

In the present study, we investigated whether the severity of post-surgical cognitive impairment in brain tumor patients can be related to damage in specific brain regions, in order to determine which confined or broad brain regions might be critically involved in multiple cognitive abilities. Results from the multivariate lesion-symptom mapping analysis showed that the severity of cognitive impairment, as measured by the latent variable obtained from distinct cognitive test scores, was associated with lesions involving the left inferior frontal junction (IFJ) and the underlying white matter, and the left posterior middle frontal gyrus (pMFG). In line with this finding, lower scores on the MMSE, assessing general cognitive functioning, were also associated with damage to the left IFJ.

The finding that damage in defined cortical areas can lead to more severe cognitive impairment across multiple behavioral domains supports the existence of functionally general brain regions associated with a variety of cognitive abilities. However, a region to be characterized as such should also be associated in the literature with many different cognitive functions, which is the case for both the left IFJ and MFG. Specifically, the left IFJ has been observed in previous fMRI studies and meta-analyses as consistently involved across different cognitive control tasks (Derrfuss, Brass, Neumann, & von Cramon, 2005; Derrfuss, Brass, & von Cramon, 2004; Fedorenko et al., 2013; Kim, Cilles, Johnson, & Gold, 2012; Kim, Johnson, Cilles, & Gold, 2011), but also in other abilities like short-term memory encoding (Sneve, Magnussen, Alnæs, Endestad, & D'Esposito, 2013) and selective visual attention (Baldauf & Desimone, 2014), and its functional role has been proposed to include the integration of information across motor control, language and working memory domains (Brass, Derrfuss, Forstmann, & von Cramon, 2005). Despite the fact that we did not aim to assess cognitive

control, which requires more targeted tasks, it is possible that our findings might be in part related to cognitive control impairment, given its involvement in a wide range of processes responsible for task execution. Consistent with this hypothesis and also with our findings, a decline across various neuropsychological executive function measures in early dementia was reported as related to glucose hypometabolism in left IFJ (Schroeter et al., 2012), confirming the importance of this brain region for cognitive control processes in general. Similarly, at least one region within the posterior part of the left MFG was identified by two different methods (i.e., lesion mapping and fMRI) as sensitive to different domains of tasks involving high levels of processing (Volle et al., 2008), suggesting its global role in cognitive control. A larger tumor overlap in the left MFG has also recently been associated with worse performance in complex attention and cognitive flexibility domains (De Baene et al., 2019). Although this finding was observed in meningioma patients in the pre-operative phase, in a concurrent study the authors found that their performance remained stable up to 12 months after surgery (Rijnen et al., 2019).

From a network-level perspective, we observed that lesions associated with broad cognitive impairment might be centered on highly connected hub regions (i.e., rich club, see Supplementary Material Fig. S3) implicated in integration across multiple, specialized sub-networks (van den Heuvel & Sporns, 2013), and also within the multiple demand (MD) network (Supplementary Material Fig. S4, Duncan & Owen, 2000), engaged in a wide range of cognitive abilities (Fedorenko et al., 2013). This assumption is supported by brain lesion literature evaluating the consequences of focal damage across functional brain networks (Gratton et al., 2012; Yuan et al., 2017; see Aerts et al., 2016 for a review). Damage to regions important for communication between networks has been shown to cause the largest disruptions in network organization. In a recent study that evaluated the neuropsychological consequences of altered

functional connectivity (Warren et al., 2014), the authors found that focal lesions in regions mediating interactions among sub-networks cause more widespread cognitive impairments with respect to comparable lesions in less participating regions. Critically, one of the six identified target regions was located in the posterior part of the left MFG. With a somewhat different approach in identifying the network organization following stroke, Zhu and colleagues (2016) found dysfunctional connections mainly in the left prefrontal areas. Interestingly, the altered nodal centrality (i.e., number of nodes showing correlation with a given node) of the left MFG was associated with a decline in general cognitive functioning, as indexed by a low MMSE score, a measure that was also included in our factorial analysis, which however in our case was found to be related to the integrity of the neighboring but not identical left IFJ.

Clinically, defining brain regions highly involved across different sub-networks, and thus supporting a broad range of cognitive abilities, may facilitate tailored tumor resections and improve cognitive surgical outcomes in regions that are usually treated as "silent" following a classical neurosurgical point of view. Recently, findings from intraoperative electrical stimulation mapping in patients undergoing awake tumor surgery contributed to an increase of anatomo-functional associations, especially at subcortical levels (see Duffau, 2017 for a recent review). In the neurosurgical approach, this led to a hodotopical model of the brain anatomo-functional organization, according to which cognitive functions are supported by extensive networks comprising both cortical functional epicenters ('topo' or sites) and white matter connections between these sites ('hodo' or pathways) (De Benedictis & Duffau, 2011). Thus, the hodotopical model could also account for our results in which surgical lesions in defined frontal regions were found to be associated with cognitive impairments across different neuropsychological measures. Nevertheless, according to these authors, even extensive frontal

lobe resections are not supposed to cause permanent cognitive deficits (Duffau, 2012), probably because of compensatory mechanisms, which especially occur in slowly growing tumors. Indeed, our results show that the strongest cognitive impairment is caused by surgery in defined left prefrontal areas that were however least involved in LGG patients. This highlights the importance of considering tumor histology, that is, distinguishing between slowly growing and fast growing tumors, when studying cognitive processes in tumor patients, but also the importance of individual pre-surgical planning in preserving cognitive functioning, which should take into account both tumor type and tumor location.

Finally, the left-lateralized prefrontal involvement in general cognitive functioning that we observed might partially be due to the fact that three out of six measures we adopted relied on verbal abilities, even though patients with notable language impairments were excluded a priori. In particular, impairments on the phonemic fluency task, which had the highest factor loading in our study, were previously related to damage within pre-central regions (Baldo, Schwartz, Wilkins, & Dronkers, 2006) but also other left frontal regions not found in our study (e.g., inferior frontal gyrus in Robinson et al., 2012). We performed additional lesion-symptom mapping control analyses on factor scores from "non-verbal" measures and on single test measures in order to check for these possible biases. The former analysis evidenced the same regions as being involved in more severe cognitive impairment, confirming the main MLSM results. On the other hand, no specific area emerged as being related to phonemic fluency, nor any other measured impairment except the general cognitive impairment as measured by the MMSE. Furthermore, the areas that were found to be associated with a broad cognitive deficit are not always found as strictly related to language impairments. As mentioned before, the MFG has been characterized as a multimodal region underlying both verbal and spatial

cognitive control processes (Volle et al., 2008), while the IFJ was associated with both verbal and non-verbal executive function deficits (Schroeter et al., 2012). Moreover, the asymmetrical involvement of left prefrontal areas within different cognitive functions is rather consistent across studies that investigated the neural correlates of general intelligence and executive functioning in stroke patients, while controlling for lower-level processes (Barbey et al., 2012; Gläscher et al., 2010).

Yet, the underpinnings of prefrontal asymmetries and why they emerge is still not fully understood. However, differences between inter- and intra-hemispheric interactions observed between the two hemispheres might shed some light on their processing specializations. In particular it has been observed that, while left-lateralized regions have stronger interactions within the same hemisphere, right-lateralized regions interact equally strongly with regions from both hemispheres (Gotts et al., 2013), and therefore might suffer from left-lateralized lesions as well. However, asymmetries in inter- and intra-hemispheric interactions have only recently started to be explored in brain-damaged patients and to be related to behavioral impairments (Siegel et al., 2016) and more research is required in this field.

Although we controlled for various possible biases, there are some limitations that need to be acknowledged. First, the assessment battery was limited by time-constraints and did not cover all cognitive functions thoroughly. Some of these functions (e.g., long-term memory, working memory, language) were only marginally tested within the MMSE screening test. Although this issue limits the generalizability of our findings to all cognitive domains, our main aim was not to measure the severity of impairment in all cognitive domains, but instead to capture cognitive impairment across multiple domains, which we believe was achieved by extracting only one latent variable from tasks tapping very different processes. However, broadening the

neuropsychological assessment should certainly be considered in future developments of this research line. Secondly, a number of patients that were not able to complete the post-surgical session due to post-surgical acute impairments were excluded. Due to this reason, the overall impact of neurosurgery on cognition in the acute phase was certainly underestimated. Besides, the sample size might not have been sufficient for adequate MLSM modeling (see Sperber, Wiesen, & Karnath, 2018). However, the reproducibility scores of our beta maps (Fig. S1), which assess the generalizability of the model, were comparable to the scores obtained by Sperber and colleagues for most of the simulated region models at a sample size of 100. Future studies should consider assessing brain tumor patients also in a less acute stage, both to avoid high dropout rates and to examine whether damage to similar regions causes more severe cognitive impairment even when allowing enough time for functional reorganization to occur. Even though functional localization studies have been regularly conducted on brain tumor patients, the results should be interpreted cautiously because of the possible effect that spreading tumor cells outside the lesion maps could have on cognitive functioning. To that end, replications across different brain-damaged populations are needed to make valid inferences on structure-function relationship.

In summary, our finding of rather confined left prefrontal areas critically involved in cognitive deficits across different neuropsychological measures is in line with the suggested modular and integrated view of brain functional organization, according to which restricted brain regions are highly involved across different sub-networks and subserve a vast range of cognitive abilities (Bertolero, Yeo, & D'Esposito, 2015). Future studies should investigate whether functional network alterations after tumor resection in cohesively connected brain regions can be related to more widespread cognitive impairments, with the final aim of

improving cognitive surgical outcomes by sparing these regions as much as possible during operation.

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References

Aerts, H., Fias, W., Caeyenberghs, K., & Marinazzo, D. (2016). Brain networks under attack: robustness properties and the impact of lesions. *Brain*, *139*(12), 3063–3083. https://doi.org/10.1093/brain/aww194

Arbula, S., Pacella, V., De Pellegrin, S., Rossetto, M., Denaro, L., D'Avella, D., Della Puppa, A., Vallesi, A. (2017). Addressing the selective role of distinct prefrontal areas in response suppression: A study with brain tumor patients. *Neuropsychologia*, *100*. https://doi.org/10.1016/j.neuropsychologia.2017.04.018

Baldauf, D., & Desimone, R. (2014). Neural Mechanisms of Object-Based Attention. *Science*, *344*(6182), 424–427. https://doi.org/10.1126/science.1247003

Baldo, J. V, Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus

temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society : JINS*, *12*(6), 896–900. https://doi.org/10.1017/S1355617706061078

Barbey, A. K., Colom, R., Solomon, J., Krueger, F., Forbes, C., & Grafman, J. (2012). An integrative architecture for general intelligence and executive function revealed by lesion mapping. *Brain*, *135*(4), 1154–1164. https://doi.org/10.1093/brain/aws021

Bertolero, M. A., Yeo, B. T. T., & D'Esposito, M. (2015). The modular and integrative functional architecture of the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(49), E6798-807. https://doi.org/10.1073/pnas.1510619112

Brass, M., Derrfuss, J., Forstmann, B., & von Cramon, D. Y. (2005). The role of the inferior frontal junction area in cognitive control. *Trends in Cognitive Sciences*, *9*(7), 314–316. https://doi.org/10.1016/j.tics.2005.05.001

Campanella, F., Fabbro, F., Ius, T., Shallice, T., & Skrap, M. (2015). Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. *Neuro-Oncology*, *17*(8), 1121–1131. https://doi.org/10.1093/neuonc/nov065

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C. D., Siegel, J. S., … Shulman, G. L. (2015). Common behavioral clusters and subcortical anatomy in stroke. *Neuron*, *85*(5), 927–941. https://doi.org/10.1016/j.neuron.2015.02.027

De Baene, W., Rijnen, S. J. M., Gehring, K., Meskal, I., Rutten, G.-J. M., & Sitskoorn, M. M.

(2019). Lesion symptom mapping at the regional level in patients with a meningioma. *Neuropsychology*, *33*(1), 103–110. https://doi.org/10.1037/neu0000490

De Benedictis, A., & Duffau, H. (2011). Brain hodotopy: from esoteric concept to practical surgical applications. *Neurosurgery*, *68*(6), 1709–1723. https://doi.org/10.1227/NEU.0b013e3182124690

DeMarco, A. T., & Turkeltaub, P. E. (2018). A multivariate lesion symptom mapping toolbox and examination of lesion-volume biases and correction methods in lesion-symptom mapping. *Human Brain Mapping*, *39*(11), 4169–4182. https://doi.org/10.1002/hbm.24289

Derrfuss, J., Brass, M., Neumann, J., & von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and stroop studies. *Human Brain Mapping*, *25*(1), 22–34. https://doi.org/10.1002/hbm.20127

Derrfuss, J., Brass, M., & von Cramon, D. Y. (2004). Cognitive control in the posterior frontolateral cortex: Evidence from common activations in task coordination, interference control, and working memory. *NeuroImage*, *23*(2), 604–612. https://doi.org/10.1016/j.neuroimage.2004.06.007

Desmurget, M., Bonnetblanc, F., & Duffau, H. (2006). Contrasting acute and slow-growing lesions: a new door to brain plasticity. *Brain*, *130*(4), 898–914. https://doi.org/10.1093/brain/awl300

Duffau, H. (2012). The “frontal syndrome” revisited: Lessons from electrostimulation mapping studies. *Cortex*, *48*(1), 120–131. https://doi.org/10.1016/j.cortex.2011.04.029

Duffau, H. (2017). A two-level model of interindividual anatomo-functional variability of the brain and its implications for neurosurgery. *Cortex*, *86*, 303–313. https://doi.org/10.1016/j.cortex.2015.12.009

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences*. https://doi.org/10.1016/S0166-2236(00)01633-7

Fedorenko, E., Duncan, J., & Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, *110*(41), 16616–16621. https://doi.org/10.1073/pnas.1315235110

Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*, *86*, 186–204. https://doi.org/10.1016/j.cortex.2016.04.023

Gerstenecker, A., Nabors, L. B., Meneses, K., Fiveash, J. B., Marson, D. C., Cutter, G., … Triebel, K. L. (2014). Cognition in patients with newly diagnosed brain metastasis: profiles and implications. *Journal of Neuro-Oncology*, *120*(1), 179–185. https://doi.org/10.1007/s11060-014-1543-x

Gläscher, J., Rudrauf, D., Colom, R., Paul, L. K., Tranel, D., Damasio, H., & Adolphs, R. (2010). Distributed neural system for general intelligence revealed by lesion mapping. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(10), 4705–4709. https://doi.org/10.1073/pnas.0910397107

Gotts, S. J., Jo, H. J., Wallace, G. L., Saad, Z. S., Cox, R. W., & Martin, A. (2013). Two

distinct forms of functional lateralization in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(36), E3435-44. https://doi.org/10.1073/pnas.1302581110

Gratton, C., Nomura, E. M., Pérez, F., & D'Esposito, M. (2012). Focal Brain Lesions to Critical Locations Cause Widespread Disruption of the Modular Organization of the Brain. *Journal of Cognitive Neuroscience*, *24*(6), 1275–1285. https://doi.org/10.1162/jocn_a_00222

Habets, E. J. J., Kloet, A., Walchenbach, R., Vecht, C. J., Klein, M., & Taphoorn, M. J. B. (2014). Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochirurgica*, *156*(8), 1451–1459. https://doi.org/10.1007/s00701-014-2115-8

Hendrix, P., Hans, E., Griessenauer, C. J., Simgen, A., Oertel, J., & Karbach, J. (2017). Neurocognitive status in patients with newly-diagnosed brain tumors in good neurological condition: The impact of tumor type, volume, and location. *Clinical Neurology and Neurosurgery*, *156*, 55–62. https://doi.org/10.1016/j.clineuro.2017.03.009

Horn, J. L. (1965). A rationale and test for the number of factors in factor analysis. *Psychometrika*, *30*(2), 179–185. https://doi.org/10.1007/BF02289447

Kim, C., Cilles, S. E., Johnson, N. F., & Gold, B. T. (2012). Domain general and domain preferential brain regions associated with different types of task switching: A Meta-Analysis. *Human Brain Mapping*, *33*(1), 130–142. https://doi.org/10.1002/hbm.21199

Kim, C., Johnson, N. F., Cilles, S. E., & Gold, B. T. (2011). Common and distinct mechanisms of cognitive flexibility in prefrontal cortex. *Journal of Neuroscience*, *31*(13), 4771–4779. https://doi.org/10.1523/JNEUROSCI.5923-10.2011

Mah, Y.-H., Husain, M., Rees, G., & Nachev, P. (2014). Human brain lesion-deficit inference remapped. *Brain*, *137*(Pt 9), 2522–2531. https://doi.org/10.1093/brain/awu164

Measso, G., Cavarzeran, F., Zappalà, G., Lebowitz, B. D., Crook, T. H., Pirozzolo, F. J., … Grigoletto, F. (1993). The mini‐mental state examination: Normative study of an Italian random sample. *Developmental Neuropsychology*, *9*(2), 77–85. https://doi.org/10.1080/87565649109540545

Mondini, S., Mapelli, D., Vestri, A., Arcara, G., & Bisiacchi, P. S. (2011). L'Esame Neuropsicologico Breve 2. *Raffaello Cortina, Milano*.

Nachev, P., Coulthard, E., Jäger, H. R., Kennard, C., & Husain, M. (2008). Enantiomorphic normalization of focally lesioned brains. *NeuroImage*, *39*(3), 1215–1226. https://doi.org/10.1016/j.neuroimage.2007.10.002

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

Rijnen, S. J. M., Meskal, I., Bakker, M., De Baene, W., Rutten, G.-J. M., Gehring, K., & Sitskoorn, M. M. (2019). Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. *Neuro-Oncology*. https://doi.org/10.1093/neuonc/noz039

Robinson, G. A., Shallice, T., Bozzali, M., & Cipolotti, L. (2012). The differing roles of the

frontal cortex in fluency tests. *Brain*, *135*(Pt 7), 2202–2214. https://doi.org/10.1093/brain/aws142

Rodolfi, C. B., Gasparini, F., & Ghidoni., E. (2011). *KIT del Neuropsicologo Italiano*. Società Italiana di Neuropsicologia.

Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., & Karnath, H.-O. (2012). Age-specific CT and MRI templates for spatial normalization. *NeuroImage*, *61*(4), 957–965. https://doi.org/10.1016/j.neuroimage.2012.03.020

Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, *12*(4), 191–200. https://doi.org/http://dx.doi.org/10.1155/2000/421719

Sartori, G., Colombo, L., Vallar, G., Rusconi, M. L., & Pinarello, A. (1997). TIB: Test di Intelligenza Breve per la valutazione del quoziente intellettivo attuale e pre-morboso. *La Professione Di Psicologo*, *1*, 2–24.

Schiffbauer, H., Ferrari, P., Rowley, H. A., Berger, M. S., & Roberts, T. P. (2001). Functional activity within brain tumors: a magnetic source imaging study. *Neurosurgery*, *49*(6), 1313-20; discussion 1320-1.

Schroeter, M. L., Vogt, B., Frisch, S., Becker, G., Barthel, H., Mueller, K., … Sabri, O. (2012). Executive deficits are related to the inferior frontal junction in early dementia. *Brain*, *135*(Pt 1), 201–215. https://doi.org/10.1093/brain/awr311

Siegel, J. S., Ramsey, L. E., Snyder, A. Z., Metcalf, N. V, Chacko, R. V, Weinberger, K., … Corbetta, M. (2016). Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proceedings of the National Academy of Sciences of the*

United States of America, *113*(30), E4367-76. https://doi.org/10.1073/pnas.1521083113

Sneve, M. H., Magnussen, S., Alnæs, D., Endestad, T., & D'Esposito, M. (2013). Top–Down Modulation from Inferior Frontal Junction to FEFs and Intraparietal Sulcus during Short-term Memory for Visual Features. *Journal of Cognitive Neuroscience*, *25*(11), 1944–1956. https://doi.org/10.1162/jocn_a_00426

Sperber, C., Wiesen, D., & Karnath, H. (2018). An empirical evaluation of multivariate lesion behaviour mapping using support vector regression. *Human Brain Mapping*, *40*(5), hbm.24476. https://doi.org/10.1002/hbm.24476

Spinnler, H., & Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Italian Journal of Neurological Sciences*, *8*, 1–120.

Talacchi, A., Santini, B., Savazzi, S., & Gerosa, M. (2011). Cognitive effects of tumour and surgical treatment in glioma patients. *Journal of Neuro-Oncology*, *103*(3), 541–549. https://doi.org/10.1007/s11060-010-0417-0

Tucha, O., Smely, C., Preier, M., Becker, G., Paul, G. M., & Lange, K. W. (2003). Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *Journal of Neurosurgery*, *98*(1), 21–31. https://doi.org/10.3171/jns.2003.98.1.0021

Vallesi, A., Mussoni, A., Mondani, M., Budai, R., Skrap, M., & Shallice, T. (2007). The neural basis of temporal preparation: Insights from brain tumor patients. *Neuropsychologia*, *45*(12), 2755–2763. https://doi.org/10.1016/j.neuropsychologia.2007.04.017

van den Heuvel, M. P., & Sporns, O. (2011). Rich-club organization of the human connectome. *Journal of Neuroscience* , *31*(44), 15775–15786. https://doi.org/10.1523/JNEUROSCI.3539-11.2011

van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*, *17*(12), 683–696. https://doi.org/10.1016/j.tics.2013.09.012

van Nieuwenhuizen, D., Klein, M., Stalpers, L. J. A., Leenstra, S., Heimans, J. J., & Reijneveld, J. C. (2007). Differential effect of surgery and radiotherapy on neurocognitive functioning and health-related quality of life in WHO grade I meningioma patients. *Journal of Neuro-Oncology*, *84*(3), 271–278. https://doi.org/10.1007/s11060-007-9366-7

Velicer, W. F., Eaton, C. A., & Fava, J. L. (2000). Construct Explication through Factor or Component Analysis: A Review and Evaluation of Alternative Procedures for Determining the Number of Factors or Components. In *Problems and Solutions in Human Assessment* (pp. 41–71). Boston, MA: Springer US. https://doi.org/10.1007/978-1-4615-4397-8_3

Volle, E., Kinkingnéhun, S., Pochon, J. B., Mondon, K., Thiebaut De Schotten, M., Seassau, M., … Levy, R. (2008). The functional architecture of the left posterior and lateral prefrontal cortex in humans. *Cerebral Cortex*, *18*(10), 2460–2469. https://doi.org/10.1093/cercor/bhn010

Warren, D. E., Power, J. D., Bruss, J., Denburg, N. L., Waldron, E. J., Sun, H., … Tranel, D. (2014). Network measures predict neuropsychological outcome after brain injury. *Proceedings of the National Academy of Sciences of the United States of America*,

111(39), 14247–14252. https://doi.org/10.1073/pnas.1322173111

Yourganov, G., Fridriksson, J., Rorden, C., Gleichgerrcht, E., & Bonilha, L. (2016). Multivariate Connectome-Based Symptom Mapping in Post-Stroke Patients: Networks Supporting Language and Speech. *Journal of Neuroscience*, *36*(25), 6668–6679. https://doi.org/10.1523/JNEUROSCI.4396-15.2016

Yuan, B., Fang, Y., Han, Z., Song, L., He, Y., & Bi, Y. (2017). Brain hubs in lesion models: Predicting functional network topology with lesion patterns in patients. *Scientific Reports*, *7*(1), 17908. https://doi.org/10.1038/s41598-017-17886-x

Zhang, Y., Kimberg, D. Y., Coslett, H. B., Schwartz, M. F., & Wang, Z. (2014). Multivariate lesion-symptom mapping using support vector regression. *Human Brain Mapping*, *35*(12), 5861–5876. https://doi.org/10.1002/hbm.22590

Zhu, Y., Bai, L., Liang, P., Kang, S., Gao, H., & Yang, H. (2016). Disrupted brain connectivity networks in acute ischemic stroke patients. *Brain Imaging and Behavior*, (215), 1–10. https://doi.org/10.1007/s11682-016-9525-6

Appendix

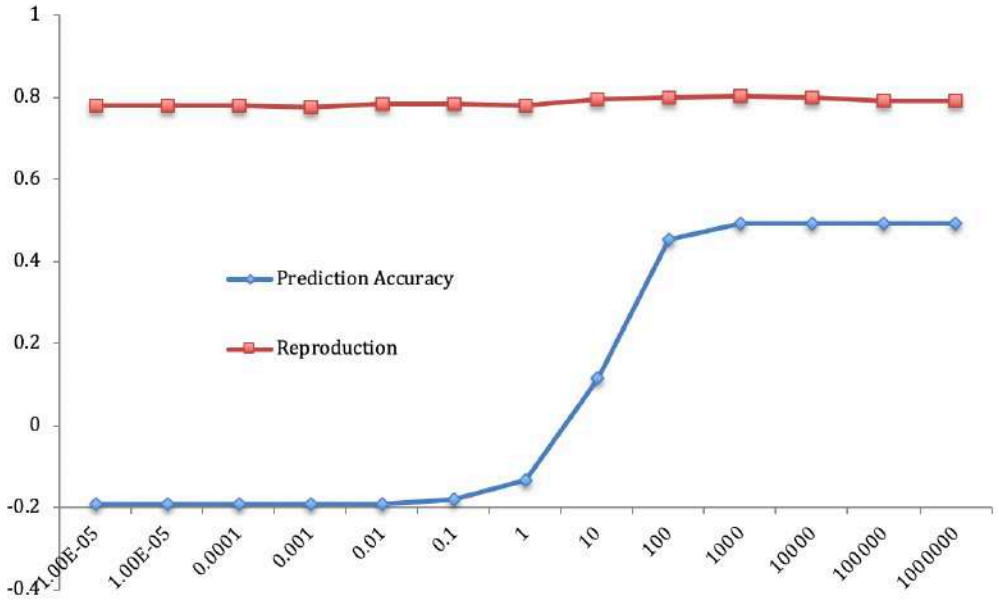

Fig. S1. Parameter C evaluation results for prediction accuracy and reproducibility.

Multivariate control analyses. We performed an additional multivariate control analysis to further substantiate our choice of using a single principal component to investigate the impact of surgery on the severity of cognitive impairment across different tumor types. Specifically, we computed the difference between the standardized post- and pre-operative scores for each of the six neuropsychological tests as detailed in the "Data preparation and statistical analysis" section and submitted these surgery-dependent differential scores to a multivariate ANOVA (MANOVA) with tumor type as between-subject factors. Note that this analysis tested for multivariate differences in the effect of surgery across groups, akin to the interaction between tumor type and surgery in the ANOVA reported in the manuscript[3]. The results of this MANOVA were further examined by performing follow-up canonical analyses, linear discriminant analyses, and ANOVAs.

The MANOVA yielded a significant results [Roy's largest root = .311, $F(6, 96) = 4.97$, $p < .001$, $\eta^2_p = .24$; Wilks' $\Lambda = .651$, $F(24, 326) = 1.78$, $p = .015$, $\eta^2_p = .12$] and revealed that no more than a single canonical root had to be extracted to explain inter-group multivariate differences [$\chi^2(15) = 15.37$, $p = .425$]. We thus extracted the first canonical root, derived the

[3] In fact, the main effects of tumor type or location yielded by these MANOVAs are equivalent to the respective interactions with the surgery factor yielded by MANOVAs performed on both pre- and post-operative scores with surgery as a within-subject factor.

relative canonical scores, and submitted the latter to a linear discriminant analysis. The result indicated that using a single latent variable allowed to discriminate across control and patients groups based on tumor type [Wilks' partial $\Lambda = .763$; $F(4, 98) = 7.61$, $p < .0001$].

Crucially, further discriminant analyses excluding control participants were also significant [Wilks' partial $\Lambda = .779$, $F(3, 50) = 4.73$, $p = .006$], indicating that the inclusion of control participants did not bias the reported results. Specifically, follow-up ANOVAs performed on the same canonical scores revealed that LGG patients exhibited a stronger surgery-dependent difference in the multivariate pattern of cognitive performance as compared to other tumor type groups, both when including or not the control participants (respectively, $F(4, 98) = 7.61$, $p < .0001$, $\eta^2_p = .24$; and $F(3, 50) = 4.73$, $p = .006$, $\eta^2_p = .22$; post-hoc comparisons: all ps < .003 and .030, respectively).

Rich Club detection

Structural connectivity data obtained from the Human Connectome Project (http://www.humanconnectome.org/) were kindly provided by Martijn P. van den Heuvel. The data were originally parcellated into 219 cortical areas using the Lausanne 2008 atlas (Hagmann et al., 2008). The group connectivity matrix was created following the steps described in van den Heuvel and Sporns (2011) by taking into account connections that were present in at least 50% of the group of subjects. The rich club coefficients were calculated and normalized with graph theory methods using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010), as described in van den Heuvel and Sporns (2011). The normalized rich club coefficients are shown in Fig. S1. The rich club coefficient with node degree $k \geq 11$ was selected as statistically significant ($p<0.05$ Bonferroni corrected; ≈57% of regions) with permutation testing compared to the coefficients of 10,000 random networks. The node degree with highest normalized rich club coefficient ($k \geq 18$) was selected for visualization purposes (≈8% of regions) in Fig. S2.

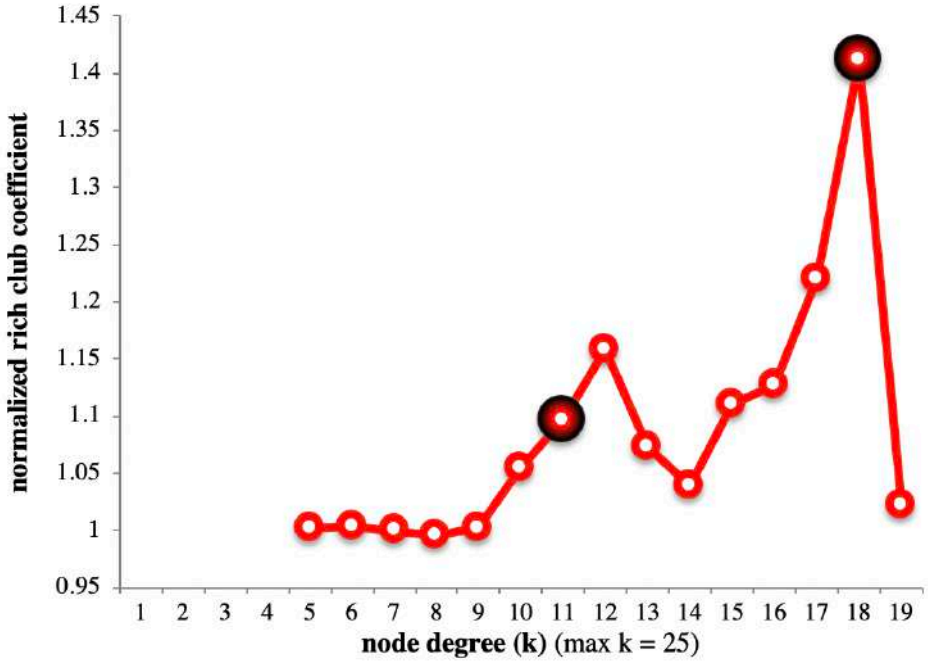

Fig. S2. Rich club curve relative to random model. The significant rich club level ($k \geq 11$; $p < 0.05$ Bonferroni corrected) and the one with the highest normalized rich club coefficient ($k \geq 18$) are indicated by a black circle.

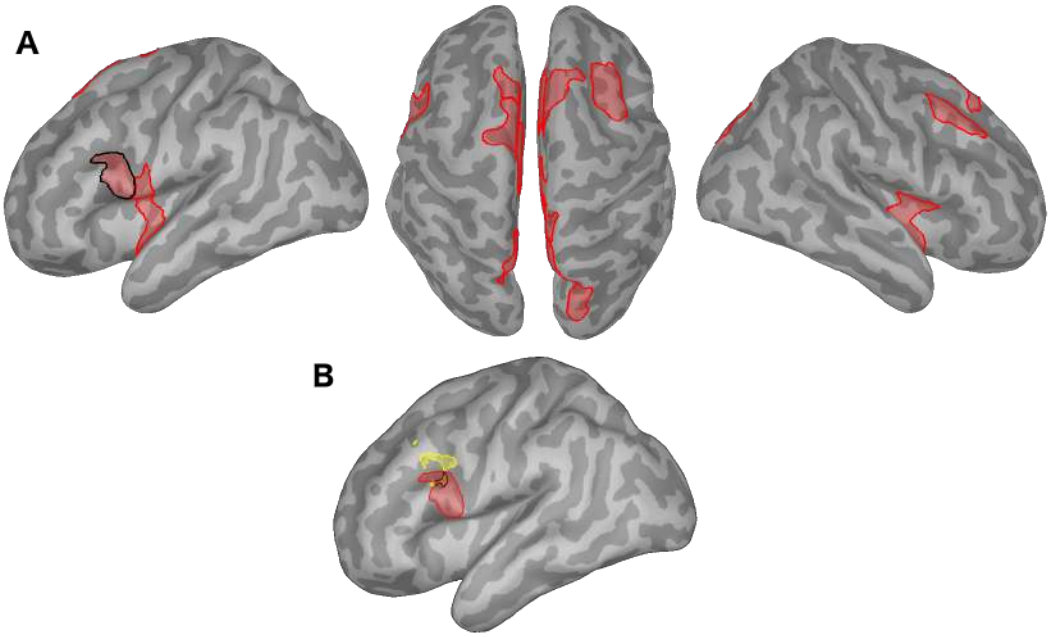

Fig. S3. Overlap of regions associated with general cognitive impairment and highly connected hub regions. A) Rich club regions with node degree $k \geq 18$. B) Comparison of the resulting MLSM critical areas (in yellow) and one of the cortical hub regions (in red, the opercular part of the inferior frontal gyrus). The overlap corresponds to 23% of the critical area. In figure left is left.

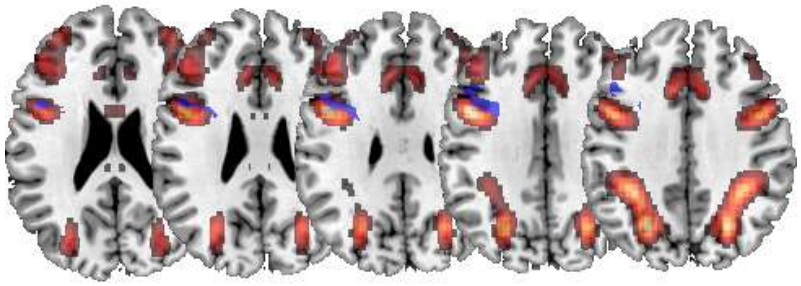

Fig. S4. Comparison of the MLSM critical areas (in blue) and the multiple demand regions (in red; Fedorenko et al., 2013). The overlap in the opercular part of the inferior frontal gyrus corresponds to 32% of the critical area. In figure left is left.

Table S1. Correlations between lesion size and each test scores, including the factor scores

Test	Lesion vol. correlation
Digit span	0.029
TMT-A	-0.311
Phonemic fluency	-0.126
Corsi	-0.098
MMSE	0.114
TIB	-0.098
Factor scores	-0.135

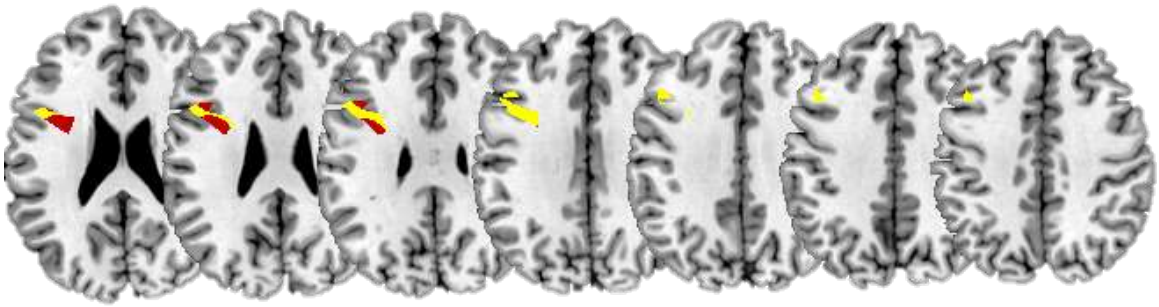

Fig. S5. Overlap of the mapping with dTLVC and the mapping with lesion size regressed out of factor scores. The yellow areas correspond to the overlapping regions, while in red are the significant regions from the SVR-LSM analysis with lesion size regression, not overlapping with the results from the main SVR-LSM. In figure left is left.

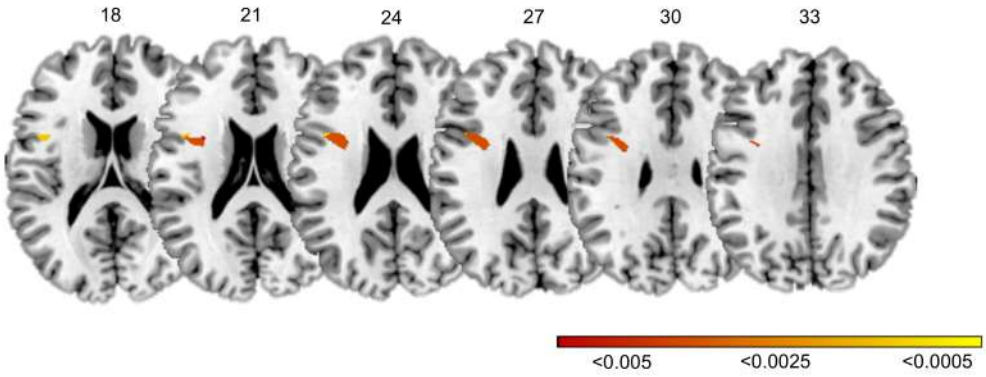

Fig. S6. Areas significantly associated with lower "non-verbal" factor scores. Color bar indicates permutation-based *p*-values. The values above the slices indicate the z coordinates in the Montreal Neurological Institute space. In figure left is left.

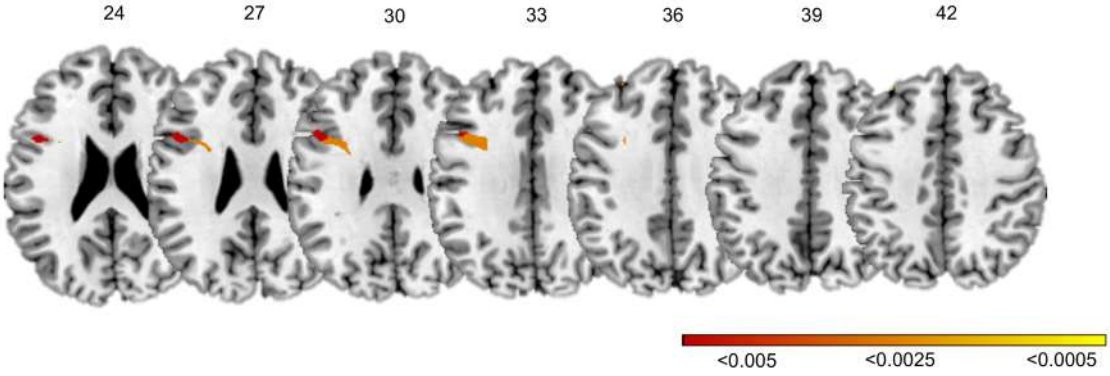

Fig. S7. Areas significantly associated with lower MMSE scores. Color bar indicates permutation-based *p*-values. The values above the slices indicate the z coordinates in the Montreal Neurological Institute space. In figure left is left.

References

Fedorenko E, Duncan J, Kanwisher N. Broad domain generality in focal regions of frontal and parietal cortex. Proc. Natl. Acad. Sci. 2013; 110: 16616–16621. https://doi.org/10.1073/pnas.1315235110

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the Structural Core of Human Cerebral Cortex. PLoS Biol. 2008; 6: e159. https://doi.org/10.1371/journal.pbio.0060159

van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. J. Neurosci. 2011; 31: 15775–86. https://doi.org/10.1523/JNEUROSCI.3539-11.2011

Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. Neuroimage 2010; 52: 1059–1069. https://doi.org/10.1016/J.NEUROIMAGE.2009.10.003