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Converging evidence for a cortico-subcortical network mediating lexical retrieval

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Neurological insults that damage the left hemisphere are frequently associated with a variety of language disorders. Of these, lexical retrieval impairments are the most commonly observed, and often constitute the residual but lasting disturbance in patients with good functional outcomes. The current study was specifically designed to understand the anatomical factors that prevent full recovery of lexical retrieval in patients having undergone a neurosurgery for a left diffuse low-grade glioma, with a special focus on white matter disconnection. One hundred and ten patients operated on under local anaesthesia with intraoperative language mapping were included in this study. All benefited from an examination of language in the chronic phase using a picture-naming task. We derived from this task two well-controlled regressed measures of lexical retrieval based on the number of anomic responses and response times. We mapped the resection cavities and the postoperative residual lesion infiltrations (mainly located along the white matter tracts), and used a combination of voxelwise and tractwise lesion-deficit analyses to process the data. All results were corrected for multiple comparisons. For the purpose of comparison, 105 neurologically healthy control participants were further enrolled. At the cortical level, lexical retrieval impairments were mainly associated with resection of the mid-to-posterior part of the left inferior temporal gyrus, as revealed by standard voxel-based lesion–symptom analyses. Multilevel tractwise analyses, including correlations, ridge multiple regressions and group analyses, showed a strong involvement of the left inferior longitudinal fasciculus and, to a lesser extent, of the posterior superior longitudinal fasciculus. Further regression analyses indicated that lasting lexical retrieval impairments were better predicted by considering together both resection-related volume loss in the posterior inferior temporal gyrus and postoperative residual lesion volume in the left inferior longitudinal fasciculus. We conclude that the mid-to-posterior inferior temporal cortex and its underlying connections, especially the left inferior longitudinal fasciculus, are critical structures in the lexical retrieval network. Beyond this new insight, our data have important implications for both intraoperative language monitoring and rehabilitation strategies.

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Abbreviations: DLGG = diffuse low-grade glioma; IFOF = inferior fronto-occipital fasciculus; ITG = inferior temporal gyrus; ILF = inferior longitudinal fasciculus; MTG = middle temporal gyrus; Resid-anomia/TS/PS = standardized residuals from multiple regressions for the dependent variables anomia, total score and semantic paraphasia; SLF = superior longitudinal fasciculus; VLSM = voxel-based lesion-symptom mapping

Introduction

Impaired naming performance is a quintessential feature of acquired language disorders and may persist chronically despite intensive language rehabilitation programmes (Benson, 1988; Goodglass and Wingfield, 1997). This is particularly true in the context of acute brain conditions such as ischaemic strokes but also, albeit with lower rates, in the context of slow-growing lesions such as diffuse low-grade glioma (DLGG). Patients who have undergone a neurosurgery under local anaesthesia with intraoperative cortical and subcortical stimulation mapping for a left DLGG do not generally suffer from long-term severe aphasia-like impairments (Duffau *et al.*, 2002, 2005; Teixidor *et al.*, 2007) (i.e. expressive or receptive language impairments impacting verbal communication) even if severe but transient language deficits are regularly observed in the immediate postoperative phase. However, residual long-lasting naming impairments are sometimes observed in these patients, impacting quality of life (Moritz-Gasser *et al.*, 2012). Understanding the pathophysiological origins of these low to moderate but disabling impairments is an irreplaceable step toward the building of efficient and individual-based strategies of neuropsychological rehabilitation. Hence, the primary goal of the present study was to give clues about the anatomical factors that prevent full recovery of lexical retrieval in patients having undergone a neurosurgery for a DLGG.

Irrespective of the aetiology considered, it is increasingly acknowledged that disconnection may be a critical predictor of a lack of recovery after cerebral damage (Hope *et al.*, 2013; Corbetta *et al.*, 2015; Cristofori *et al.*, 2015; Herbet *et al.*, 2015*a*). Such observations have recently been reported in patients with DLGG in whom a small part of the lesion is voluntarily left during surgery because stimulation of infiltrated structures elicits a functional response. These remaining infiltrations are typically located along the spatial course of white matter associative pathways making them to some extent dysfunctional (Herbet *et al.*, 2016). Consistent with this, the volume of residual infiltration in certain white matter tracts has been recently shown to predict impairments of social cognition, including empathy (Herbet *et al.*, 2015*b*) and mentalizing (Herbet *et al.*, 2014). Therefore, we hypothesize that the presence of disconnection might impede the efficiency of functional compensation after surgery, by interfering with inter-regional, long-range cortico-cortical communication subsequently reducing the possibility of brain-wide functional reorganization.

Although a large neuropsychological and neuroscientific literature has focused on naming cortical underpinnings, highlighting the participation of distributed areas including the left inferior and middle posterior temporal gyri, the fusiform gyrus, the superior temporal gyrus, the temporal pole, the inferior temporo-occipital junction, the posterior part of the inferior frontal gyrus and the inferior parietal lobule (Damasio *et al.*, 1996; Indefrey and Levelt, 2004; Baldo *et al.*, 2013; Tate *et al.*, 2014; Gleichgerrcht *et al.*, 2015*a*), the white matter network subserving this ability is to date less understood. However, current data suggest that disconnection of a number of pathways, including the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the superior longitudinal fasciculus/arcuate fasciculus, can lead to naming deficits (Duffau *et al.*, 2013, 2014; Han *et al.*, 2013; Mehta *et al.*, 2015; Sarubbo *et al.*, 2015; Hope *et al.*, 2016). This overall pattern of results, underlining a complex and distributed network involved in naming, is consistent with current psycholinguistic models of word production. Naming is indeed a complex behaviour that involves a number of cerebral processes including perception and recognition of the picture, concept identification and semantic processing, retrieval of the corresponding lexical unit and phonological word form (the so-called lexical retrieval stage), planning and execution of articulatory programmes (Caramazza *et al.*, 1997; Foundas *et al.*, 1998; Levelt *et al.*, 1999; Baldo *et al.*, 2013). In this study, we were particularly interested by the lexical retrieval stage of naming, a processing step that is rarely examined in isolation.

Beyond the clinical relevance of better understanding the anatomical underpinnings of lexical retrieval impairments in patients with DLGG, such a study has the potential to provide new insights into the cortico-subcortical anatomy of lexical retrieval. Most of the neuropsychological studies examining naming abilities are based on the behavioural performances of stroke patients. However, the cerebral location of strokes is constrained by the distribution of the middle cerebral artery, which is the most affected by cerebrovascular insults. This vessel mainly supplies, at the superficial level, the perisylvian regions. As a consequence, certain cerebral territories, such as the temporal pole and the inferior temporal regions, are rarely covered in large-scale neuropsychological studies, not allowing one to disentangle their causal implications in the language network in general. By contrast, DLGG affects more frequently the inferior and basal temporal structures (Herbet *et al.*, 2016). Therefore, DLGG constitutes a valuable and complementary pathophysiological model for examining the role of these structures and their underlying connexions in cerebral processes thought to be partly subserved by the ventral networks such as lexical retrieval and semantic processing.

In brief, the current study was specifically designed to disentangle the role of disconnection in residual long-lasting lexical retrieval impairments after neurosurgery for a left DLGG and, from a fundamental standpoint, to highlight the core white matter network sustaining lexical retrieval. For these purposes, we retrospectively analysed naming picture performance in a large sample of patients using a fully exploratory approach.

Materials and methods

Participants

A total of 110 French native speakers (45 females and 65 males; mean age 38.78 ± 9.65 years, range 22–66) having undergone a surgical resection for a left DLGG were recruited in our centre over a period of 4 years (2011–15). In accordance with our standard surgical procedure, all patients were operated on by the same well-experienced neurosurgeon (H.D.) under local anaesthesia with cortical and subcortical brain mapping achieved by direct electrical stimulation (Duffau *et al.*, 2002, 2005). Importantly, language was systematically mapped during the procedure. Exclusion criteria were set as follows: anaplastic or high-grade glioma; previous radiotherapy or chemotherapy; other neurological diseases than low-grade glioma; history of previous psychiatric disease; presence of neurological impairment that would potentially compromise the objectivity of the language assessment (i.e. right spatial neglect; visual agnosia).

Language testing was performed by the same senior speech therapist (S.M.G.) during the chronic epoch (i.e. at least 3 months after surgery; mean months after surgery 12.24 ± 18.72 range 3–84), as part of the standard medical care. It is important to note that none of the patients enrolled in this study suffered from debilitating language impairments at the time of the behavioural assessment, albeit with residual difficulties for some of them. All patients benefited from systematic postoperative language rehabilitation (three to five sessions per week for at least 12 weeks) and resume a normal socio-professional life 3 months after surgery.

For the purpose of comparison, a sample of 105 neurologically healthy participants (60 females and 45 males; mean age 38.2 ± 12.2 years, range 20–60) was enrolled. The sociodemographic characteristics of patients and healthy participants were comparable in terms of age [$t(213) = 0.39$, $P = 0.69$], level of education [$t(213) = -1.48$, $P = 0.14$] and sex ratio ($P = 0.33$). Patients agreed for the retrospective extraction of their medical records after informed consent.

Language measures and data preprocessing

To assess picture naming abilities, we used the 'DO 80' task (Metz-Lutz *et al.*, 1991). This test includes 80 black and white pictures belonging to various living and manufactured semantic categories. Importantly the same task was used during neurosurgery to map language processes, as precisely detailed in previous studies (Tate *et al.*, 2014). The behavioural task was presented on a laptop, and implemented in Matlab environment (2008b, version 7.7, The Mathworks Inc.). The script was generated using Cogent2000 toolbox (http://www.vislab.ucl.ac.uk).

Pictures were randomly assigned for each participant. The type of impairment was directly entered by the experimenter using specific keys during the completion of the task. Several impairments were coded: anomia, semantic paraphasia, phonological paraphasia, perseveration and dysarthria. However only anomia and semantic paraphasia were further considered given the extremely low frequency of other categories of impairments (<2% for each type of errors). Anomia was regarded as such when the target item was not named in 8 s. To ensure that the concerned picture was recognized and the concept identified, patients were then systematically primed by a phonological cueing (e.g. if the word /rabbit/ was not produced, the experimenter said: 'this is a r…'), which was in all cases effective. This procedure allowed us to reasonably assume that the omission wasn't related to a semantic loss. Errors were considered as semantic paraphasia when the response did not reach the target item while being linguistically correct and semantically related (e.g. 'rabbit' for 'squirrel'). In the case of semantic paraphasia the incorrect response was systematically recorded for retrospective assessment and checking. Response times were also recorded for all healthy participants and 80 of 110 patients. The experimenter pressed a specific key (escape) as quickly as possible when subjects produced the correct item. Note that response times of failed trials were not further analysed.

In this study, we aimed to focus on the 'lexical retrieval' stage of naming (i.e. selecting the target word from the mental lexicon) that is the result of the interactive semantic and phonological processes leading to the 'retrieval of the word form'. For this reason, we did not process the data in raw form. To have more specific measures of lexical retrieval and to control in the same time for socio-demographic variables, we partialled out the effect of semantic paraphasia, age, level of education and chronicity from anomia and response times using two multiples regressions. Note that we did not control for phonological paraphasia and articulatory disorders given their extremely low frequency (see above). We used the standardized residuals from these regressions—termed 'Resid-Anomia' and 'Resid-RTs'—as inputs for further analyses except for group analyses where the data were controlled in a different way (see below). For the sake of completeness, we also analysed the total score obtained on the naming task and semantic paraphasia. We termed these variables 'Resid-TS' and 'Resid-PS' after regressed out the variance associated with age, level of education and chronicity.

Imaging acquisition

In all patients, structural MRI datasets were acquired at the time of the behavioural assessment in the same medical centre as part of their standard care. The images had been acquired using axial fluid-attenuated inversion recovery (FLAIR) (resolution of 0.898 × 0.898 × 6 mm, repetition time of 8 s, echo time of 108 ms, inversion time of 23.7 s, field of view of 202 × 240 mm, flip angle of 150°) and high-resolution 3D T_1-weighted sequences (resolution of 1 × 1 × 1 mm, repetition time of 1.7 s, echo time of 2.54 ms, inversion time of 0.92 s, field of view of 256 × 256 mm, flip angle of 9°) on a 3 T Siemens Skyrya scanner (Siemens Medical Systems). 3D T_1 images were only used for voxelwise lesion-symptom mapping analyses whereas FLAIR images were used for both voxelwise and tractwise lesion-symptom analyses (see below).

Image processing: lesion tracing and normalization procedure

Individual MRI datasets were normalized into a common stereotactic space (the Montreal Neurological Institute, MNI space) using cost function masking (Brett *et al.*, 2001). The method used is described elsewhere (Herbet *et al.*, 2015*a*, 2016). Briefly, the registration procedure was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London) implemented in Matlab (release 2014b, The MathWorks, Inc., MA, USA) using a combination of linear and non-linear transformations (Frackowiak *et al.*, 2004). After normalization, using MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron), resections cavities were mapped on 3D T_1 images (resolution of $1 \times 1 \times 1$ mm) whereas FLAIR images ($0.898 \times 898 \times 6$ mm) were preferred to map residual lesions infiltrations. Although the latter sequence has a lower resolution, it enables yield of the best contrast between normal brain tissue and infiltrated tissue. Lesion drawing was manually performed by author G.H. (see Fig 1 for a description of the procedure).

Voxelwise lesion–symptom mapping

To relate lexical retrieval impairments and the spatial location of surgical resections or residual lesion infiltrations, we used whole-brain voxel-based lesion-symptom mapping (VLSM) (Bates *et al.*, 2003). To generate the statistical maps, we used *NiiStat* (http://www.mccauslandcenter.sc.edu/CRNL/tools/niistat) implemented in the Matlab environment. To maintain comprehensive analyses, we excluded voxels that were resected of infiltrated in fewer than five patients. As a result, a major part of the posterior cortex (including the parietal and the occipital cortex), but not the underlying white matter fibres that were better covered (DLGG migrates preferentially along white matter tracts), was not taken into consideration in this study.

The parametric *t*-test statistic was selected to compute the Z-scores statistical maps. The VLSM technique consists of the statistical comparisons between scores for patients with and without damage in a given voxel, and that for each voxel taken into account in the analyses. To control for false positive (type I error) due to multiple comparisons, we corrected systematically the resulting statistical maps using the false discovery rate procedure with q set at 0.05 (with an extent threshold of 50 contiguous voxels). It is worth noting that the analyses were performed with and without lesion volume as an additional regressor.

Tractwise lesion–symptom analyses

Correlation approach

To relate lexical retrieval impairments and disconnection of specific white matter tracts, we first estimated the degree to which white matter tracts were infiltrated. To this end, each individual residual lesion infiltration map was overlaid with the recent diffusion tensor image-based white matter atlas from Rojkova *et al.* (2016). We then selected the white matter tracts of interest (i.e. language-related tracts) including the arcuate fasciculus (termed also long arcuate fasciculus), the anterior superior longitudinal fasciculus (SLF) (termed also anterior arcuate fasciculus), the posterior SLF (termed also posterior arcuate fasciculus), the uncinate fasciculus, the inferior occipito-frontal fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF). We also selected the cingulum as a control tract (i.e. no involvement in language processing). These tracts were then thresholded at $P \geqslant 0.75$ (i.e. the probability of a given voxel to belong to a tract) for estimation of volumes. MRIcron software was used to automatically compute the amount of overlapping voxels leading to an individual volume for each tract and for each patient. The volumes obtained were then correlated with the measures of interest using the Pearson correlation. As sometimes recommended (Curtin and Schulz, 1998), we corrected the results with the Bonferroni procedure to decrease the risk of a type I error (critical value: $P = 0.007$). Note that only significant correlations after correction are discussed except when it is directly specified in the text.

Group analysis approach

In addition of the analyses described earlier, we adopted a group analysis approach. More precisely, we sought to directly contrast the volume of infiltration of each white tract between patients showing lexical retrieval impairments versus others. To do this, we segregated patients into two subgroups according the absence or the presence of deficits, as determined by the normative data from healthy participants. We considered a patient as impaired when the corresponding Z-score was $\leqslant -1.65$. Next, for each measure of interest, we ran an analysis of covariance by tract by specifying infiltration volume as the dependent variable, patient group as the predictor, and age, educational level and chronicity as covariables of non-interest. For anomia and reaction time, we added also semantic paraphasia as a covariable of non-interest. As for correlation analyses, results were corrected for multiple comparisons using the Bonferroni procedure (critical value of $P = 0.007$).

Ridge multiple regression approach

For a given patient, disconnection of several white matter tracts can be observed. For example, a glioma located in the temporo-insular structures typically affects the uncinate fasciculus, the ILF and the IFOF and sometimes other tracts. As a result, it is a possibility that complex patterns of disconnection may influence the behavioural measures (i.e. the combination of the disconnection of two tracts may induce lexical retrieval impairments, not the disconnection of one in particular). A way to assess these combined effects is to use linear multiple regressions. However, because some white matter tracts could show near-linear relationships (i.e. non-orthogonality of predictors) in our study, due to the fact that several tracts can be disconnected in one patient and that a number of fasciculi naturally cross in certain brain regions, we instead used ridge multiple regressions to overcome this problem of multicollinearity. We chose a rather low ridge regression penalty (biasing constant) of $\lambda = 0.1$ allowing however to maintain tolerance over the value of 0.25 (range: 0.27–0.99). Four ridge regressions were performed separately (one for each behavioural measure) with all white matter tracts as potential predictors. Here again, we adopted a conservative approach by applying the Bonferroni correction. A regressor was considered as making a significant contribution to the model when $P = 0.007$ was reached.

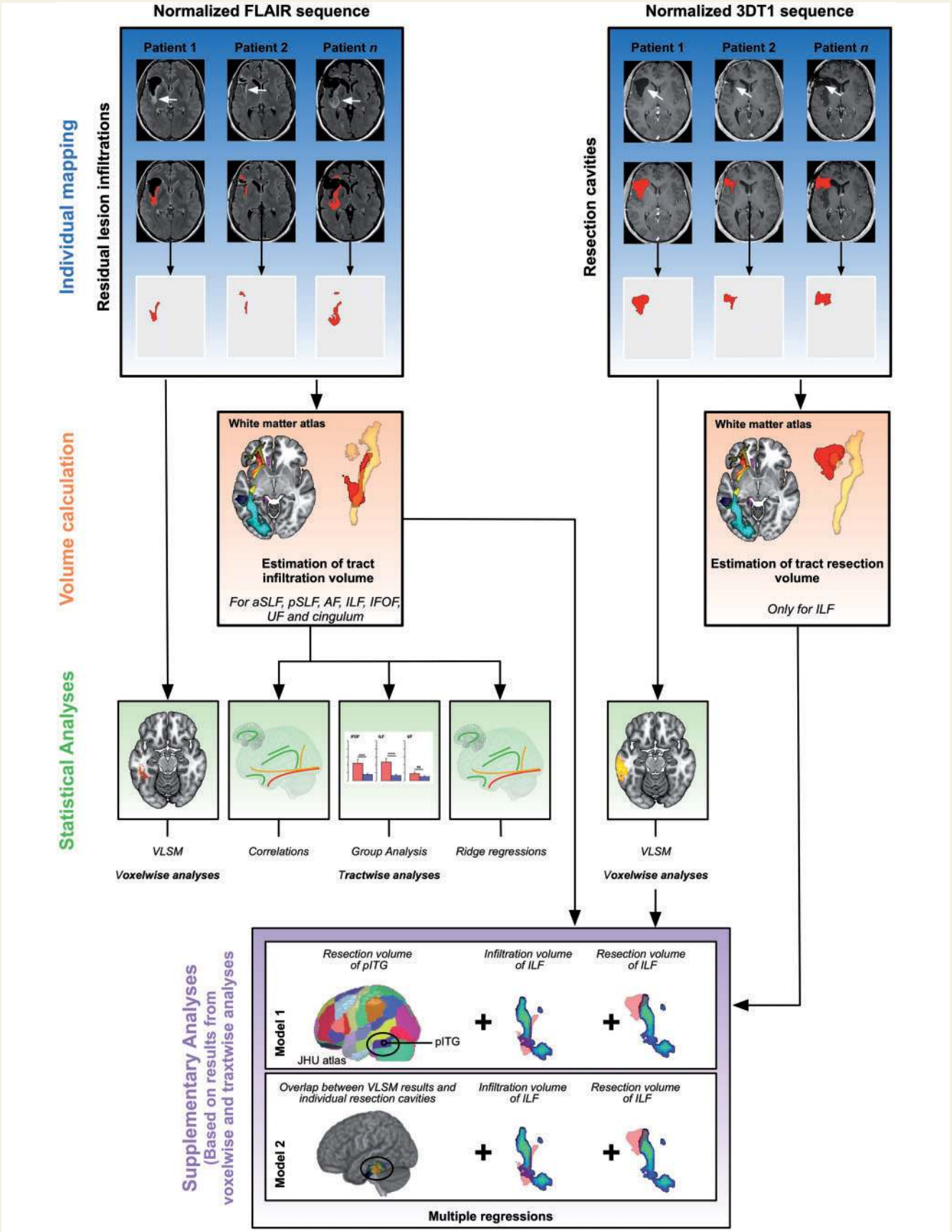

Figure 1 Schematic illustration of the experimental procedure. aSLF = anterior SLF; pSLF = posterior SLF; AF = arcuate fasciculus; UF = uncinate fasciculus.

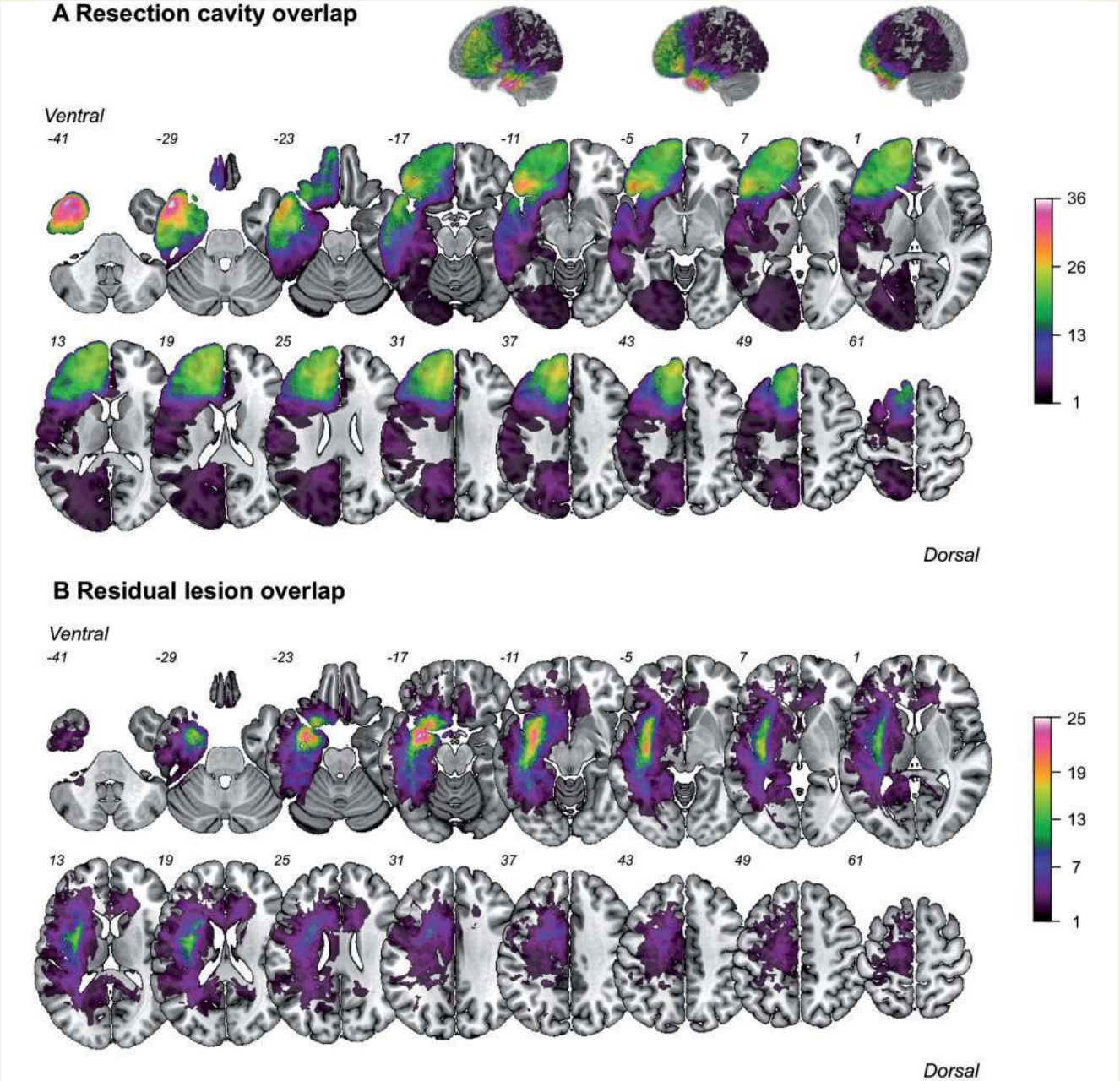

Figure 2 Spatial topography of resections and residual lesion infiltrations. (**A**) Resection cavity overlap: in accordance with the typical spatial distribution of DLGG, the maximum overlap occurred in the temporal pole (n = 36). The posterior resections were the least frequent. (**B**) Residual lesion overlap. As shown in previous works, the residual infiltrations were concentrated along the main white matter tracts, which correspond to structures not reachable by the surgical procedure for functional reasons (Herbet *et al.*, 2016). The maximum frequency was reached in the temporal stem (n = 25).

Results

Neuroanatomical and sociodemographic data

The spatial topography of resection cavities and residual lesion infiltrations is shown in Fig. 2A and B, respectively. A complete overview of patients' sociodemographic and clinical data is given in Table 1.

Raw behavioural data

The global naming performance of patients in terms of accuracy was impaired compared to healthy participants [$t(213) = -4.31$, $P < 0.00005$]. Patients made significantly more anomia [$t(213) = 3.22$, $P = 0.0015$] and semantic paraphasia [$t(213) = 3.96$, $P = 0.0001$] than controls. Patients' response times were also significantly longer [$t(183) = 5.17$, $P = 0.000001$]. Note that non-parametric statistics led to the same results.

Table 1 Sociodemographic and clinical data

Variables	Controls	Patients (total)
n	105	110
Age	38.2 ± 12.2 [20–60]	38.78 ± 9.65 [22–66]
Education level	2.89 ± 1.08 [1–4]	3.08 ± 0.82 [1–4]
Sex ratio	60F:45M	65F:45M
Handedness	102R:5L:3A	92R:10L:3 A
Chronicity		12.24 ± 18.72 [3–84]
DO80 total score	79.40 ± 0.97 [76–80]	77.2 ± 5.16 [50–80]
Number of anomia	0.42 ± 0.83 [0–4]	1.79 ± 4.28 [0–28]
Number of semantic paraphasia	0.17 ± 0.51 [0–3]	0.96 ± 1.98 [0–17]

A = ambidextrous; F = female; L = left; M = male; R = right.

Voxel-based lesion–symptom mapping

VLSM analyses showed that Resid-TS was mainly associated with the mid-to-posterior part of the inferior temporal gyrus (ITG), substantially extending to the middle temporal gyrus (MTG) and, basally, to the fusiform gyri. A small bulk of significant voxels was also identified in the superior temporal gyrus (cavity maps, Fig. 3A). VLSM performed on the infiltration maps revealed an association with the white matter fibres underlying the posterior ITG and MTG (infiltration maps, Fig. 3B).

As for Resid-TS, Resid-anomia was significantly associated with the mid-to-posterior part of the inferior temporal gyrus, substantially extending to the middle temporal and fusiform gyri (cavity maps, Fig. 3C), with extension to the underlying white matter connectivity (infiltration maps, Fig. 3D).

In convergence with these results, analyses revealed that Resid-RTs were associated with almost the same cortical areas (cavity maps, Fig. 3E). However, we did not find any significant associations when the VLSM analysis was performed on the infiltration maps.

No anatomo-functional associations were revealed when Resid-PS was considered.

It is worth noting that adding volume as a nuisance variable in all these analyses did not alter the results. The detail of VLSM results (i.e. cluster size, MNI coordinates of clusters, anatomical labels, etc.) is further expanded in Table 2.

Correlation results

A general overview of the result is displayed in Fig. 4. To summarize, Resid-TS was significantly correlated with infiltration volume in the ILF ($r_{110} = -0.44$, $P = 0.000001$), the IFOF ($r_{110} = -0.27$, $P < 0.005$) and the posterior SLF ($r_{110} = -0.27$, $P < 0.005$). Other correlations were not significant ($P > 0.15$) (Fig. 4A).

Resid-anomia was associated with infiltration volume in the ILF ($r_{110} = 0.37$, $P < 0.00005$) and, to a lesser extent, with infiltration volume in the posterior SLF ($r_{110} = 0.26$, $P = 0.006$). Other correlations were not significant ($P > 0.09$) (Fig. 4B). It is important to note that this behavioural measure was not correlated with the total volume of resections ($r_{110} = -0.06$, $P = 0.53$) nor with the total volume of residual infiltrations ($r_{110} = 0.006$, $P = 0.95$), increasing the specificity of the results.

Regarding Resid-RTs, a significant association was only observed with the ILF ($r_{80} = 0.36$, $P = 0.001$) (Fig. 4C). As Resid-anomia, Resid-RTs were not correlated with the total volume of resection ($r_{80} = -0.09$, $P = 0.38$) nor with the total volume of residual infiltration ($r_{80} = 0.02$, $P = 0.85$).

Although we found correlations between Resid-PS and infiltration volume in the three ventral tracts, including the IFOF ($r_{110} = 0.24$, $P = 0.012$), the ILF ($r_{110} = 0.24$, $P < 0.012$) and the uncinate fasciculus ($r_{110} = 0.19$, $P = 0.046$), they did not survive the Bonferroni correction (Fig. 4D).

Group analysis

Regarding the total score obtained on the naming task, infiltration volume in the ILF [$F(1,104) = 17.50$, $P < 0.0001$], the IFOF [$F(1,104) = 17.50$, $P < 0.0005$], and the posterior SLF [$F(1,104) = 8.83$, $P < 0.005$], was significantly larger in impaired patients ($n = 31$) than in unimpaired patients ($n = 79$) [$F(1,104) = 8.48$, $P < 0.005$] after controlling for age, educational level and chronicity (Fig. 5A).

Regarding anomia, infiltration volume in the ILF was significantly larger in impaired patients ($n = 27$) than in unimpaired patients ($n = 83$) [$F(1,104) = 8.48$, $P < 0.005$] after controlling for age, educational level, chronicity and semantic paraphasia (Fig. 5B). A group effect was also found considering the left posterior SLF but it did not survive the Bonferroni correction [$F(1,104) = 6.49$, $P < 0.012$].

The results were the same for reaction times. Only infiltration volume in the left ILF was significantly larger in impaired patients ($n = 31$) than in unimpaired patients ($n = 49$) [$F(1,104) = 11.89$, $P < 0.001$] after controlling for age, educational level, chronicity and semantic paraphasia (Fig. 4C). Other analyses were not significant.

For semantic paraphasia, infiltration volume in the ILF [$F(1,104) = 7.25$, $P = 0.008$] and the IFOF [$F(1,104) = 4.16$, $P < 0.05$] was larger in impaired patients ($n = 24$) than in unimpaired patients ($n = 86$) after controlling for age, educational level and chronicity (Fig. 5D). These results did not, however, survive the Bonferroni correction.

Ridge multiple regressions

The models for Resid-TS [$F(7,102) = 3.16$, $P = 0.007$], Resid-Anomia [$F(7,102) = 3.16$, $P = 0.007$] and Resid-RTs ($F = 3.57$, $P = 0.0025$) were all significant and accounted for ~23%, 16% and 26% of the variance, respectively. The infiltration volume in the left ILF made a unique contribution to these models [Resid-TS: $\beta = -0.48$, $t(103) = 3.86$, $P = 0.0002$; Resid-anomia: $\beta = 0.36$,

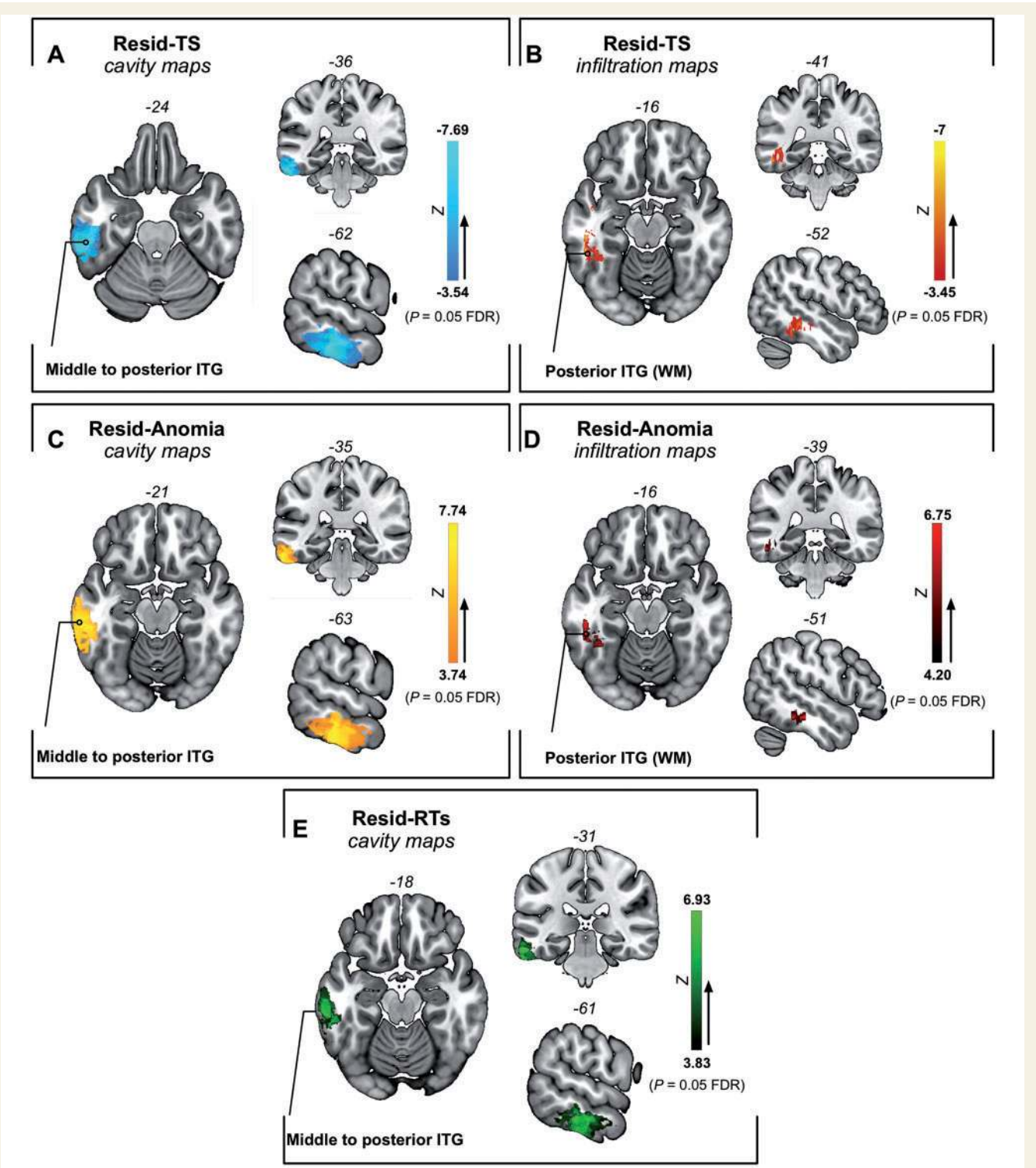

Figure 3 VLSM results. (**A**) VLSM of Resid-TS performed on resection cavity maps. (**B**) VLSM of Resid-TS performed on residual infiltration maps. (**C**) VLSM of Resid-Anomia performed on resection cavity maps. (**D**) VLSM of Resid-Anomia performed on residual infiltration maps. (**E**) VLSM of Resid-RTs performed on resection cavity maps. Only voxels surviving to the correction for multiple comparisons (false discovery rate at q = 0.05 with a cluster extent of 30 contiguous voxel) are shown. The detail of VLSM analyses, including cluster size and MNI coordinates of clusters, is displayed in Table 2.

Table 2 Brain structures associated with lexical behavioural measures

Behavioural measures	Number of voxels analysed	Volume regressed	Z-range	Threshold ($P < 0.05$ FDR)	Significant regions (JHU)		Cluster size (min = 30 voxels)	MNI coordinates		
					Labels	Z-max		x	y	z
Resid-TS	Cavity maps (resolution: 1 × 1 × 1 mm)									
	288 644	No	[−7.69, 2.25]	−3.54	Posterior ITG	−7.69	14757	−62	−36	−24
					STG	−4.16	77	−60	−4	−16
		Yes	[−7.67, 2.21]	−3.54	Posterior ITG	−7.67	14594	−62	−35	−23
					STG	−4.21	135	−60	−3	−16
	Infiltration maps (resolution: 0.898 × 0.898 × 6 mm)									
	19601	No	[7, −1.88]	−3.45	Posterior ITG	−7	692	−52	−41	−16
					Fusiform	−5.47	208	−34	−10	−33
		Yes	[−6.90, 2.06]	−3.69	Posterior ITG	−6.90	367	−52	−41	−16
					Fusiform	−5.11	53	−34	−10	−34
Resid-Anomia	Cavity maps (resolution: 1 × 1 × 1 mm)									
	288644	No	[−2, 7.74]	3.74	Posterior ITG	7.74	12706	−63	−35	−21
		Yes	[−1,91, 7.73]	3.74	Posterior ITG	7.73	12696	−63	−35	−21
	Infiltration maps (resolution: 0.898 × 0.898 × 6 mm)									
	19601	No	[−1,73, 6.75]	4.20	Posterior ITG	6.75	124	−51	−39	−16
					Fusiform	5.48	50	−37	−42	−22
		Yes	[−2.29, 6.53]	4.29	Posterior ITG	6.53	91	−52	−41	−16
Resid-RTs	Cavity maps (resolution: 1 × 1 × 1 mm)									
	251507	No	[−2.32, 6.93]	3.83	Posterior ITG	6.93	10075	−61	−31	−18
					Fusiform	3.96	73	−28	−25	−22
		Yes	[−1.98, 6.93]	3.83	Posterior ITG	6.93	9930	−61	−31	−18
					Fusiform	3.96	93	−28	−25	−22
	Infiltration maps (resolution: 0.898 × 0.898 × 6 mm)									
	13064	No	[−2.40, 5.22]		No clusters survive					
		Yes	[−2.60, 5.06]		No clusters survive					
Resid-PS	Cavity maps (resolution: 1 × 1 × 1 mm)									
	288644	No	[−2.06, 6.13]		No clusters survive					
		Yes	[1.68, 6.12]		No clusters survive					
	19601	No	[1.47, 5.60]		No clusters survive					
		Yes	[1.61, 5.01]		No clusters survive					

Note that anatomical localization of significant brain structures is based on the Johns Hopkins University Atlas (JHU).

$t(103) = 3.17$, $P = 0.002$; Resid-anomia: $\beta = 0.63$, $t(72) = 3.83$, $P = 0.0003$]. Other predictors were not significant after Bonferroni correction.

Note that the model generated for Resid-PS was not significant.

Combined effect of surgical resections and lesion infiltrations in lexical retrieval impairments

Previous analyses assess in an independent manner the role of surgical resections and white matter disconnections (due to lesion infiltration in white matter tracts) in lexical retrieval impairments. To gauge the combined effect of resections and infiltrations in the long-term maintenance of these impairments, we ran a last analysis based on the results obtained using voxelwise and tractwise lesion-deficit analyses. Specifically, we sought to know whether taking into consideration ILF infiltration volume and posterior ITG volume loss together could allow us to better predict the lack of recovery after surgery. However, because the significant area revealed by VLSM extends to some extent beyond the posterior ITG (i.e. ventral middle temporal gyrus, anterior ITG and fusiform), it was also useful to consider the bulk of significant voxels as a whole.

As a first step, we computed the resection volumes of posterior ITG by overlapping the individual surgical cavities and the posterior ITG as anatomically defined in the JHU atlas. Then, we computed the overlap between the individual areas of resection and the bulk of significant voxels from the VLSM analyses.

In the first series of models, we computed a linear regression using ITG resection volume as a predictor. Next, we added ILF infiltration volume as a second predictor and assessed the change in the variance explained by the model. Then we ran the analyses again by adding ILF resection volume as a last predictor. Indeed, contrary to the majority of white matter tracts, the left ILF is sometimes surgically removed, but only in its anterior part (Ius *et al.*, 2011; Herbet *et al.*, 2016). The resection volume of the left ILF was computed following the same method described above. The statistical analyses were only performed on Resid-Anomia and Resid-TRs.

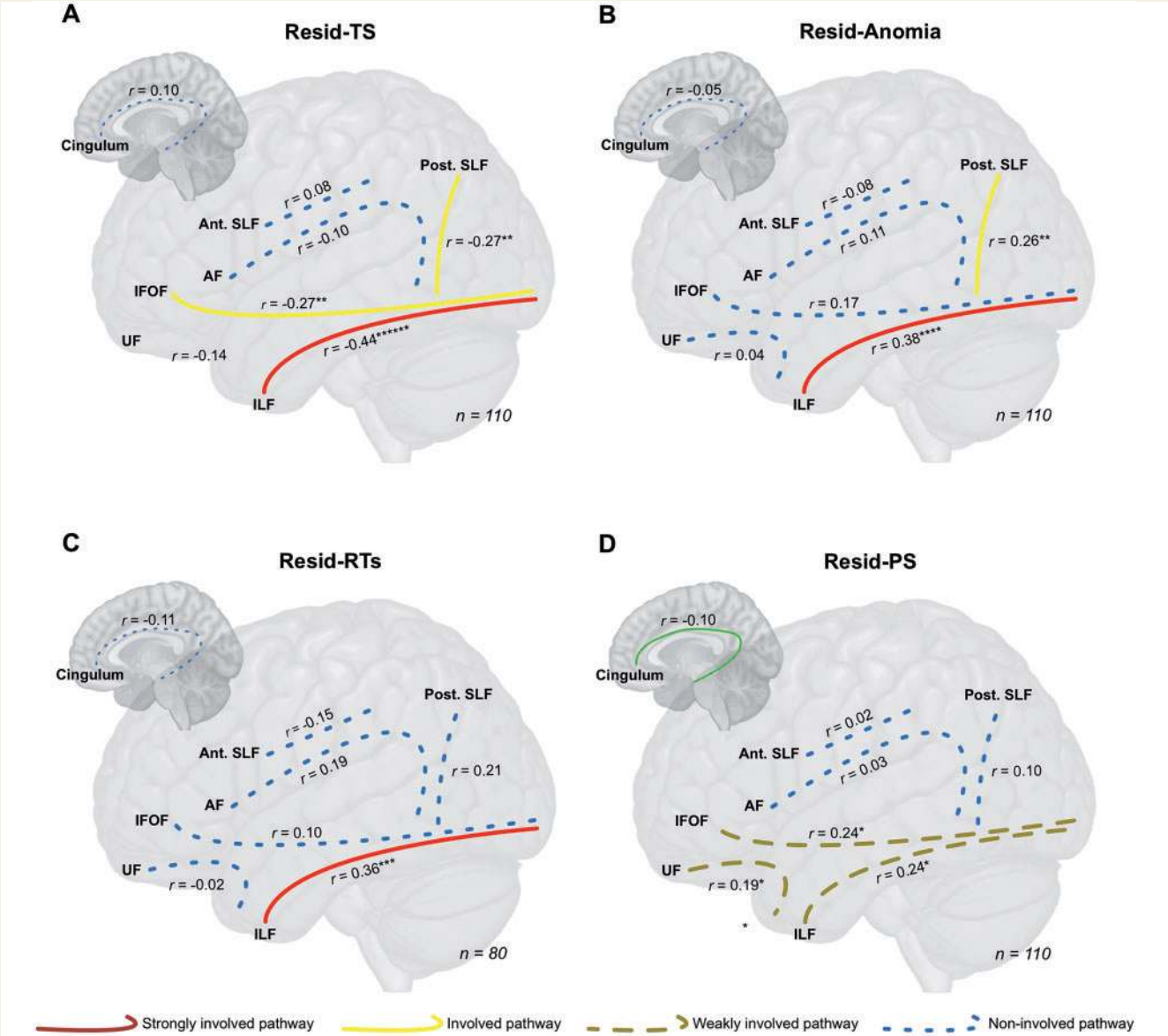

Figure 4 General overview of correlation analyses. (**A**) Correlations performed between Resid-TS and volume of lesion infiltration in white matter tracts. (**B**) Correlations performed between Resid-PS and volume of lesion infiltration in white matter tracts. (**C**) Correlations performed between Resid-Anomia and volume of lesion infiltration in white matter tracts. (**D**) Correlations performed between Resid-TRs and volume of lesion infiltration in white matter tracts. The blue colour (dotted line) means that no associations were found (non-involved pathway). The green colour (dashed line) means that an association was found but it did not survive the Bonferroni correction (weakly involved pathway). The yellow colour (solid line) means that a low association was found (involved pathway). The red colour (solid line) means that a strong association was found (strongly involved pathway). AF = arcuate fasciculus; cing = cingulum; UF = uncinate fasciculus. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$; $^{******}P < 0.000001$.

Regarding Resid-Anomia, the obtained model confirmed that posterior ITG damage is a strong predictor of lexical retrieval impairments [$R^2 = 0.24$, $F(1,108) = 34.57$, $P < 0.0000001$]. Adding ILF infiltration volume as a second predictor significantly increased the predictive power of the model ($R^2_{change} = 0.047$, $F_{change} = 7.10$, $P = 0.009$), contrary to ILF resection volume ($R^2_{change} = 0.012$, $F_{change} = 1.81$, $P = 0.18$).

We observed the same type of results when Resid-TRs was considered [$R^2 = 0.23$, $F(1,78) = 24.16$, $P = 0.000005$]. Adding ILF infiltration volume as a second predictor significantly increased the predictive value of the model ($R^2_{change} = 0.049$, $F_{change} = 5.27$, $P = 0.025$), contrary to ILF resection volume ($R^2_{change} = 0.00005$, $F_{change} = 0.006$, $P = 0.93$).

In the second series of models, we repeated again the analyses using the measurement of overlap between individual areas of resection and the bulk of significant voxels (measurement of overlap) from VLSM analyses instead of posterior ITG resection volume.

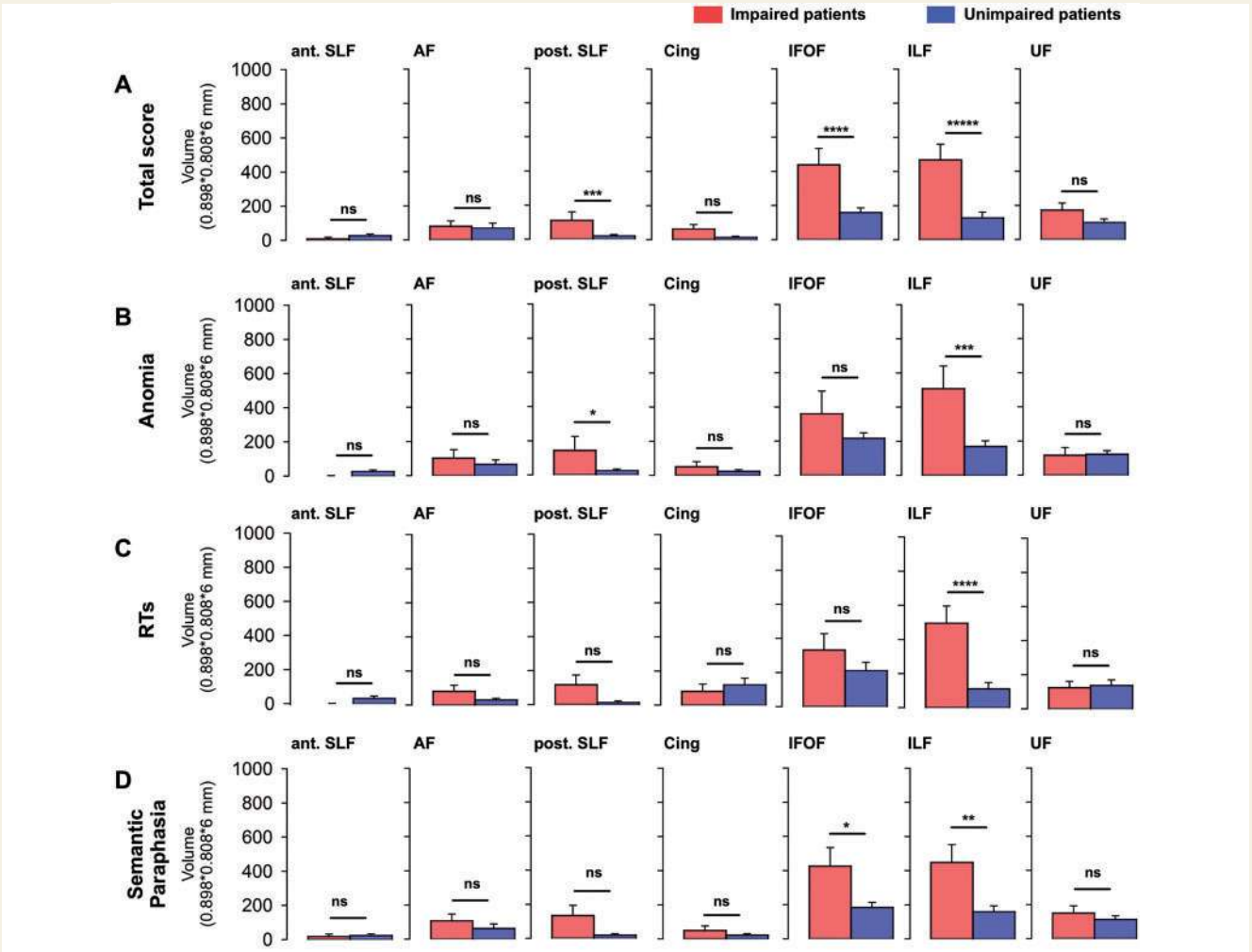

Figure 5 ANCOVA results. (**A**) Group difference for total score (TS) on the naming task after controlling for age, educational level and chronicity. (**B**) Group difference for anomia after controlling for age, educational level, chronicity and semantic paraphasia. (**C**) Group difference for response times (RTs) after controlling for age, educational level, chronicity and semantic paraphasia. (**D**) Group difference for semantic paraphasia (SP) after controlling for age, educational level and chronicity. AF = arcuate fasciculus; cing = cingulum; UF = uncinate fasciculus; $^{*}P < 0.05$; $^{***}P < 0.005$; $^{****}P < 0.001$; $^{*****}P < 0.0001$.

For Resid-Anomia, the obtained model indicated that measurement of overlap was a predictor of lexical retrieval impairments but less powerful that posterior ITG damage [$R^2 = 0.10$, $F(1,108) = 12.21$, $P = 0.0007$]. Adding ILF infiltration volume significantly increased the predictive value of the model ($R^2_{change} = 0.08$, $F_{change} = 10.55$, $P = 0.0015$), contrary to ILF resection volume ($R^2_{change} = 0.01$, $F_{change} = 1.39$, $P = 0.24$).

For Resid-RT, the results were different. Measurement of overlap was a very strong predictor of lexical retrieval impairments [$R^2 = 0.42$, $F(1,108) = 56.20$, $P = 0.0000001$]. Adding ILF infiltration as a second predictor did not contribute to increase the predictive value of the model ($R^2_{change} = 0.0047$, $F_{change} = 0.49$, $P = 0.48$), contrary to ILF resection volume ($R^2_{change} = 0.047$, $F_{change} = 6.80$, $P = 0.011$). The contribution of ILF resection volume was, however, in the opposed direction than that expected.

Taken as a whole, these results suggest that Resid-Anomia is better predicted by the combined effect of posterior ITG volume and ILF infiltration volume while Resid-RTs is better predicted by the bulk of significant voxels from VLSM analyses.

Discussion

Lexical retrieval impairments are commonly observed after damage of the left hemisphere, and can severely impact interpersonal communication and delay the return to a normal socio-professional life. Furthermore, they often constitute the lasting language deficit in patients with good functional outcomes, irrespective to the type of aphasia primarily observed. Understanding their precise neuroanatomical underpinnings is therefore a critical step for a better

management of patients in general. Our study has a number of substantial strengths compared to other previous studies: (i) data were not processed in raw format allowing us to have more specific measures of lexical retrieval; (ii) lexical access time, which along with anomia, a valuable measure of lexical retrieval, was also considered; and (iii) behavioural data were processed in a manner enabling us to gauge the combined effect of surgical resections and postoperative residual lesion infiltrations (mainly located along axonal connectivity) in the long-term maintenance of residual lexical retrieval impairments.

First and foremost, it is worth reiterating that this study dealt with patients presenting with a DLGG. This neurological tumour is known to induce major functional neuroplasticity phenomena (Bonnetblanc *et al.*, 2006; Desmurget *et al.*, 2007) with, however, marked restriction in certain structures that have been recently mapped out (Ius *et al.*, 2011; Herbet *et al.*, 2016) (e.g. major part of white matter tracts, primary or unimodal areas and a restricted set of neural hubs). This has some important consequences for the interpretation of neuropsychological results: the identified structures in these patients can be clearly considered as forming a core system for the function under scrutiny but other (more plastic) structures (e.g. anterior temporal lobe, ATL) may also play a role in normal circumstances. This may be the reason why a relatively well-circumscribed set of structures was pinpointed in the context of this study while classical neuropsychological literature, mainly based on stroke patients in whom plasticity is clearly less efficient (Desmurget *et al.*, 2007), generally highlights a plethora of distributed areas potentially involved in lexical retrieval. It is also important to consider that language function was mapped in all patients during surgery: it follows that certain critical language nodes had been preserved and were consequently not represented in the distribution of resection cavities. This is the case, for example, of the more posterior part of the middle and the superior temporal gyri (Fig. 2) that generally remain to some extent functional despite lesion infiltration.

At the cortical level, we found that the mid-to-posterior ITG was strongly associated with both measures of lexical retrieval (Resid-Anomia and Resid-TRs). Historically, the posterior ITG was first associated with anomia by Charles Mills more than 100 years ago, who called it the 'naming center' (Mills and McConnell, 1895), which then was referred to as the language formulation area by Nielsen and FitzGibbon (1936). Pioneer studies in neurosurgical patients had already reported naming deficits following resection of basal and inferior temporal cortex (Penfield and Roberts, 1959), and cortical stimulation of these same structures is known to induce language dysfunction (Burnstine *et al.*, 1990), especially naming impairments (Luders *et al.*, 1991). In a case study, anomia was associated with damage to Brodmann area 37, including the more postero-superior part of the left ITG. More recent studies have emphasized the involvement of the left ITG in accessing word forms from semantic input (Binder *et al.*, 2009) and its major role in modality-independent lexical processing (Mummery *et al.*, 1999; Antonucci *et al.*, 2008; Race *et al.*, 2013; Sebastian *et al.*, 2014). Admittedly, however, the mid-to-posterior ITG is generally sparsely described in the current literature contrary to other prominent areas such as anterior temporal structures. Divergence in these findings can be easily explained considering that posterior ITG structures are poorly covered in large-scale neuropsychological studies (based generally on stroke patients).

Although the most significant associations were found in the mid-to-posterior ITG, other areas were also significantly associated with both measures of lexical retrieval, especially the posterior and ventral MTG. This is consistent with prior evidence that this brain structure may play a pivotal role in lexical retrieval (Indefrey and Levelt, 2004) and acts as a critical hub in the language network generally (Turken and Dronkers, 2011).

Our results are not, however, in complete agreement with those of Wilson *et al.* (2015) who studied, among other things, naming performances of neurosurgical patients operated on under local anaesthesia with intraoperative language mapping. Their VLSM analyses showed that postoperative naming scores were strongly associated with more anterior and basal areas (including the mid-to-anterior MTG, the mid-to-anterior ITG and part of the fusiform and para-hippocampal gyri) compared to the current study—even if some degree of overlap seems to exist especially at the level of the middle ITG. This discrepancy might be explained by the fact that semantic paraphasia was partialled out from both measures of lexical retrieval in our study explaining the more posterior localization. Other lines of explanation might, however, be invoked. First, patients recruited in the study of Wilson *et al.* (2015) were not homogeneous and presented with high-grade glioma in almost 50% of cases. Functional reorganization in these patients is less efficient due to the high growth of the tumour. Second, because the postoperative assessment was performed relatively early after surgery (1 month after), it is likely that the results would be slightly different if patients had been assessed in the chronic period.

In a network approach of cognitive dysfunction, efforts are now expected to disentangle the role of white matter disconnection in the occurrence of disorders (Corbetta *et al.*, 2015; Thiebaut de Schotten *et al.*, 2015). In the current study, we used a multilevel tractwise approach including correlations, ridge multiple regressions and group analyses. Results were convergent across these different approaches since disconnection of the left ILF (i.e. the residual lesion infiltration volume) was invariably pinpointed as a powerful predictor of lasting lexical retrieval impairments, suggesting the ILF to be a critical component of the lexical retrieval network. The posterior SLF was also pointed out in certain analyses highlighting the moderate but significant contribution of this white matter pathway in lexical retrieval.

Interestingly, the ILF provides connections between the occipital cortex, the posterior inferior temporal cortex/fusiform gyrus and the temporal pole (Catani *et al.*, 2002; Mandonnet *et al.*, 2007). In view of its pattern of connectivity, the ILF has been suggested to play a role in language processing (Von Der Heide *et al.*, 2013; Bajada *et al.*, 2015), especially semantic processing given its connections with the ATL, which is thought to be a multimodal semantic hub (Lambon Ralph *et al.*, 2010; Lambon Ralph, 2014), and is an integral part of current anatomo-functional models (Duffau *et al.*, 2013; Bajada *et al.*, 2015). However, compelling evidence of its participation in the language network in general, and in the lexical retrieval network in particular, is still scarce. Only a few studies have contributed in this sense. For example, resection of the left ILF has been linked to naming impairments in a recent case study (Shinoura *et al.*, 2010). In a large-scale neuropsychological study including stroke patients, lack of integrity of the left ILF as indexed by fractional anisotropy measurements was strongly correlated with deficit in oral picture naming (Han *et al.*, 2013). A significant association between fractional anisotropy values in this tract and lexical retrieval abilities in patients with the logopenic variant of primary progressive aphasia was also revealed in other works (Powers *et al.*, 2013; Tu *et al.*, 2015). Our results add strong support to the view that the left ILF plays a critical role in the network enabling it to link object representations to their lexical labels, as previously conjectured. In this respect, the contribution of the left ILF in language processing does not seem to be only partitioned to lexical retrieval abilities as it has been recently shown that direct electrostimulation or surgical removal of the posterior part of the left ILF can lead to pure alexia (Epelbaum *et al.*, 2008; Zemmoura *et al.*, 2015). As a consequence, consistent with the occipital connexions of this white matter tract, it appears that the ILF is especially solicited when the visual input is required. Further studies are needed to determine whether its contribution in the language network in general is modality-specific.

In a similar vein, the current findings do not exclude the possibility that the left ILF may also be involved in semantic processing. Indeed, we observed almost significant correlations between infiltration volume in the left ILF, but also in the left IFOF, and the regressed measure of semantic paraphasias. Patients with an abnormal rate of semantic paraphasias were also more likely to present with a larger infiltration volume in the ILF compared to others. Although these results are statistically low, they are nevertheless in agreement with prior evidence suggesting a possible role of this white matter tract in conveying semantic-related information (Agosta *et al.*, 2010).

The fact that disconnection of the left posterior SLF was also a moderate but still significant predictor of lexical retrieval in certain analyses is consistent in view of its cortical connections. This white matter tract is indeed known to connect the posterior ITG and the posterior MTG to the angular gyrus (Catani and Thiebaut de Schotten, 2008; Martino *et al.*, 2013; Martino and De Lucas, 2014)—a brain area known to be involved in lexico-semantic processing (Binder *et al.*, 2009) and pre-articulatory phonological processes regarding its rostral sector (Pillay *et al.*, 2014). As a consequence, it is likely that this white matter connectivity broadcasts critical information for lexical retrieval as shown in the context of this study.

Here we processed the data in a manner enabling us to obtain specific measures of lexical retrieval so that we were able to assign to the left mid-to-posterior ITG, and its underlying connections, a pivotal role in the retrieval of word form during the activity of picture naming. We may hypothesize that the mid-to-posterior ITG constitutes a critical crossroad in the lexical retrieval network, but also in the language network in general. Indeed, beyond the ILF and the posterior SLF, the mid-to-posterior ITG also receives strong connections from the arcuate fasciculus (Martino *et al.*, 2013; Bajada *et al.*, 2015; Sarubbo *et al.*, 2015), involved in the phonological encoding of lexical units, and the IFOF, involved in semantic control (Duffau *et al.*, 2013; Moritz-Gasser *et al.*, 2013; Mirman *et al.*, 2015), making it a convergence area (i.e. a structural hub) especially vulnerable, from a functional standpoint, in case of insult. Importantly, it has been recently shown that naming impairment severity in stroke patients was lesser not only if certain temporal areas, including the posterior ITG, were spared but also if they were still influential hubs in the remaining network (Gleichgerrcht *et al.*, 2015*b*). Moreover, remote physiological dysfunction of the posterior ITG in semantic dementia, without evidence of atrophy in this structure, has been shown to be associated with the most severe pattern of naming impairments (Mummery *et al.*, 1999), suggesting that deprivation of inputs in the posterior ITG is especially deleterious for naming.

A hypothesis developed in this study was that disconnection of white matter tracts could be a pathophysiological factor partly explaining the lack of recovery in the chronic phase in addition to cortical damage induced by cortical resection. Our results go in this direction as the predictive power of the generated models was significantly better when ILF infiltration volume was added as a predictor of lexical retrieval impairments, most notably regarding the regressed measure of anomia. Beyond confirming our previous observations in the social cognition domain (Herbet *et al.*, 2015*a*, *b*) and the interpretation according to which postoperative disconnection seems to impede the efficiency of recovery in glioma patients, we consider that such results have some important implications for the care of patients. For example, systematically assessing the amount of postoperative residual infiltrations in the left ILF may allow us to better predict language-related outcomes and to appropriately adjust language rehabilitation programmes.

Limitations

Our study has some notable limitations. The most significant is related to the lack of an effective semantic control

due to the retrospective nature of the study. Although data processing was designed to minimize the potential impact of semantic disturbances in the results and to obtain more specific measures of lexical retrieval in comparison to a global score in naming, the use of alternative semantic control tasks would have been useful to better control for. As a consequence, further studies using more sophisticated behavioural manipulations are needed to confirm the present findings. Second, as developed above, the subnetwork unmasked in this study must be considered as the critical, non-compensable part of the lexical retrieval network (strong plasticity in patients with glioma), and our findings have therefore to be integrated with the knowledge gained with other neuropsychological populations. Third, due to the typical spatial topography of DLGG, we were not able to study the involvement of most of the left parietal structures that are yet shown to have a role in lexical retrieval. This does not apply however to the fronto-parietal white matter connectivity that was appropriately covered even if the statistical power was lower compared to other more ventral tracts, necessitating taking the results with some caution. Last, it may be criticized on the ground that recruiting patients at different postoperative times may be a substantial bias when the study is about plasticity and functional recovery. However, although we certainly acknowledge this limitation, this variable was systematically controlled for and no effect was observed in all analyses. Other prospective studies should be planned by using a longitudinal design.

Conclusion

In brief, the current study delivers original insights into the core network sustaining lexical retrieval—with a clear demonstration that the left posterior ITG and its underlying connections, especially the left ILF, act as critical structures. Damage to this system mostly explains residual and lasting lexical retrieval impairments in glioma patients, and the conjunction of damage in both structures increases their severity, suggesting that postoperative lesion-related disconnection is a crucial pathophysiological mechanism. These findings have clinical implications: they may aid to better predict the occurrence of lexical retrieval deficits after surgery and to plan appropriate language rehabilitation strategies.

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