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RESEARCH ARTICLE

Lesion-symptom mapping of language impairments in people with brain tumours: The influence of linguistic stimuli

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Abstract

People with tumours in specific brain sites might face difficulties in tasks with different linguistic material. Previous lesion-symptom mapping studies (VLSM) demonstrated that people with tumours in posterior temporal regions have more severe linguistic impairments. However, to the best of our knowledge, preoperative performance and lesion location on tasks with different linguistic stimuli have not been examined. In the present study, we performed VLSM on 52 people with left gliomas to examine whether tumour distribution differs depending on the tasks of the Aachen Aphasia Test. The VLSM analysis revealed that single-word production (*e.g.* object naming) was associated with the inferior parietal lobe and that compound and sentence production were additionally associated with posterior temporal gyri. Word repetition was affected in people with tumours in inferior parietal areas, whereas sentence repetition was the only task to be associated with frontal regions. Subcortically, word and sentence production were found to be affected in people with tumours reaching the arcuate fasciculus, and compound production was primarily associated with tumours affecting the inferior longitudinal and inferior fronto-occipital fasciculus. Our work shows that tasks with linguistic stimuli other than single-word naming (*e.g.* compound and sentence production) relate to additional cortical and subcortical brain areas. At a clinical level, we show that tasks that target the same processes (*e.g.* repetition) can have different neural correlates depending on the linguistic stimuli used. Also, we highlight the importance of left temporoparietal areas.

KEYWORDS
cognition, glioma, language, tumour, VLSM

INTRODUCTION

Brain tumours that are located mainly in the left hemisphere and are classified as 'language eloquent' can induce language deficits (Bilotta et al., 2014). It is estimated that after the resection of a language eloquent brain tumour about 25%–50% of patients will experience aphasia (Davie et al., 2009). Unlike the post-operative condition, preoperative language difficulties have been reported to be mild by early studies on language abilities of people with brain tumours (Miceli et al., 1981; Whittle et al., 1998). However, to the best of our knowledge, patients' preoperative performance and lesion distribution on linguistic tasks with different linguistic material has not yet been examined. Hence, the present study aims at filling in this gap by performing lesion-symptom mapping for tasks with different linguistic stimuli in a sample of people with left perisylvian gliomas.

Language processing in people with and without tumours: task influence and brain loci

In recent years, the language abilities of people with brain tumours have received much attention (Mooijman et al., 2021; Rofes, Mandonnet, et al., 2017; Satoer et al., 2013). Tasks and assessments at the sentence and at the word level have been employed. Satoer et al. (2013) reported that during preoperative spontaneous speech individuals with brain tumours produced more incomplete sentences and had shorter mean length of utterance than a matched control group. However, even though people with brain tumours report word finding problems, single-word object naming tasks are not always sensitive enough to detect any preoperative difficulties (Mooijman et al., 2021). More importantly, the numbers of patients that are classified as 'impaired' seem to differ according to the linguistic modality and the linguistic stimuli used in each neurosurgical centre. For example, Brownsett et al. (2019) investigated the chronic postoperative language performance after left glioma resection. The authors reported that while 8% of their sample was impaired in object naming, 54% faced difficulties in action naming. Also, reading of simple words identified 19% of the patients as impaired, but reading of morphologically complex words reported a slightly higher 23% below the cut-off (Brownsett et al., 2019). During a comparison of spontaneous speech and formal assessment methods, Rofes et al. (2018) highlighted that even though both object naming and spontaneous speech assessment evaluate word retrieval abilities, spontaneous speech tasks require additional grammatical and memory processes. Therefore, previous work demonstrates that different tasks pose varying demands and assess different linguistic processes that may be impaired in people with brain tumours.

The question that arises is whether the different processing demands posed by different linguistic stimuli translate to distinct neural correlates. For example, both word and sentence production tasks evaluate the same language modality, namely production. Both words and sentences assess semantic, phonological and articulatory processes. However, in this example, syntax (*e.g.* subject-verb agreement, gender marking, argument structure) can only be assessed by using sentence production (Rofes et al., 2018). Additionally, as sentences are longer utterances compared to single words, an added complexity might also arise from phonological processes [see Lauro et al., (2010) for effects of sentence length on the phonological loop]. On the same basis, object naming (*e.g. car*) and compound naming (*e.g. mailbox*) assess semantic access, phonological and articulatory processes. However, given that compounds undergo decomposition (*i.e. mail* + *box*) and are compiled by two independent words and meanings, they have been shown to pose additional morphological and semantic demands compared to single words (Semenza et al., 2011; Semenza & Mondini, 2010).

Differences at the neural level between the processing of single words, compounds and sentences have received much attention. Imaging studies have demonstrated that in the healthy brain the reading of sentences compared with that of single words evokes higher activation in the left IFG, middle temporal and posterior temporal/temporoparietal areas (Xu et al., 2005). Even though word processing engages semantic knowledge, work on sentence processing has highlighted that tasks with single words do not assess grammatical knowledge (Friederici, 2018; Friederici et al., 2003). Grammatical features seem to be left lateralized, mainly processed in inferior frontal and posterior temporal regions (Friederici, 2011, 2018; Matchin & Hickok, 2020). Regarding the neural signatures of compounds compared with words, these also seem to be represented more in left frontal as well as posterior temporal cortical areas (Forgács et al., 2012). Lesions that lead to Broca's or Wernicke's aphasia have also manifested in increased impairments with compounds compared to lesions that lead to anomic aphasia (Semenza et al., 2011). Therefore, neuroimaging and aphasiological work suggests that tasks with different linguistic stimuli might be associated with distinct cortical and subcortical brain regions. This bears the question whether this is the case also for individuals with brain tumours.

VLSM in people with language eloquent brain tumours

Voxel-based lesion-symptom mapping (VLSM) is a method used to identify and connect linguistic scores with damaged regions in the brain of individuals with neuropathologies (Bates et al., 2003). For people with brain tumours, at the cortical level the left superior and middle temporal gyri have been connected with tasks that assess language comprehension (Banerjee et al., 2015; Fekonja et al., 2019). At the subcortical level, pathways such as the inferior fronto-occipital fasciculus (IFOF), the posterior part of the arcuate fasciculus (AF), the inferior longitudinal fasciculus (ILF) and the superior longitudinal fasciculus have been associated with decreased performance in receptive language tasks (Banerjee et al., 2015; Fekonja et al., 2019). Unlike comprehension, tasks of language production have not yielded such clear-cut-associated brain loci. Regarding task differences, naming of actions in isolation has been connected with inferior parietal and middle frontal regions, whereas naming of objects has been associated with damage to temporo-occipital areas (Tomasino et al., 2019). However, the majority of prior VLSM studies on the language abilities of individuals with brain tumours highlight the surprising absence of predictive frontal areas in naming tasks (Banerjee et al., 2015; Fekonja et al., 2019). Previous VLSM work has allowed us to draw connections between damaged cortical and subcortical areas for object and action naming as well as language modality (*i.e.* comprehension vs. production tasks). Nevertheless, the distribution of brain tumours in relation to tasks with different linguistic stimuli (*e.g.* single words vs. compounds vs. sentences) has not yet been examined.

The present study

We employed VLSM to investigate the relationship between tumour location and performance on linguistic tasks with (1) simple words (*e.g. car*), (2) compounds (*e.g. mailbox*) and (3) sentences (*e.g. The woman is washing the kettle*). Taking into account that patients with varying lesion profiles can be impaired in different tasks and stimuli, we aimed at answering the following questions:

1. Are different lesion foci associated with varying performance on tasks with single words versus compounds versus sentences? In other words, are neural correlates associated with different linguistic material used in tasks?
2. Also, does the lesion distribution differ according to task modality (*i.e.* auditory and reading comprehension, production, repetition)?

Based on previous evidence (*e.g.* Banerjee et al., 2015; Fekonja et al., 2019; Tomasino et al., 2019) we hypothesized that if indeed sentences and compound words require additional linguistic processes compared to single words, then we might see different lesion distributions according to type of linguistic stimulus (*i.e.* single word, compound, sentence). However, given that aforementioned VLSM studies have not identified separate regions to be affected for production compared with comprehension, we do not expect different lesion location according to task modality (*i.e.* production, comprehension).

METHODS

Patient sample

Fifty-two patients with brain tumours (mean age = 49.8, SD = 15.5, male = 29, female = 23) were included in the current retrospective study. All individuals were native German speakers and right-handed according to self-reports and their scores on the Edinburgh Handedness Inventory (Oldfield, 1971). All participants had a left hemisphere glioma. Tumour grade at the time of assessment was as follows: grade 2 (29% = 15), grade 3 (17% = 9), grade 4 (54% = 28). The biggest lesion overlap of the cohort appears in the left temporal and frontal lobes, but overall, most left perisylvian regions were affected (Figure 1). The average tumour size was 28.41 cm^3 with an interquartile range of 13.25–43.85 cm^3. All participants signed an informed consent before they participated in the study, which was conducted according to the guidelines of the Declaration of Helsinki.

Language assessment

The Aachen Aphasia Test (AAT; Huber et al., 1984) was administered to every participant. It is a standardized test that is commonly used to evaluate post-stroke aphasia severity in German-speaking patients. Scores below 90% are considered impaired and individuals are classified into groups of 'mild', 'moderate' and 'severe aphasia' depending on their overall score. It constitutes of parts that target reading comprehension, auditory comprehension, repetition and spoken language production. These parts of the AAT are divided into subtests each of which evaluate these domains at the word and at the sentence level. Specifically, reading and auditory comprehension consist of picture-matching tasks for word and sentence stimuli, while language production is assessed with naming tasks for simple words, compound words, and sentences. For example, the black-and-white image of a table elicits the production of the word

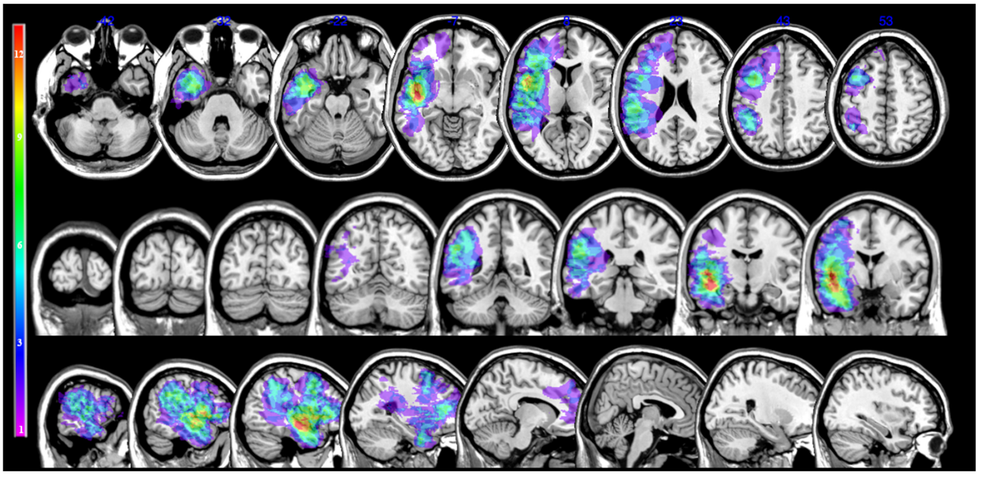

FIGURE 1 Lesion overlay for all 52 patients. Warmer colours indicate a higher number of patients with a given voxel lesioned. The numbers above the axial slices show the axial slice position in MNI space.

'*Tisch*/table', whereas the picture of a fridge elicits the German compound '*Kühlschrank*/fridge'. Images that depict situations, require the production of declarative sentences. The black-and-white picture of a woman washing a kettle, elicits the sentence '*Die Frau putzt die Kanne*/The woman is washing the kettle'. Within the same clinical neuropsychological assessment, cognitive functions were assessed using the German version of the DemTect (Kessler et al., 2000), a standardized test used to assess mild cognitive impairment.

Imaging, tumour masking and normalization

Imaging data were collected using a Siemens Skyra 3-Tesla magnetic resonance scanner. Anatomical contrast-enhanced T1 MPRAGE (TR = 2300, TE = 2.32, TI = 900 ms, 9° flip angle, 256 × 256 matrix, 1 mm isotropic voxels, 192 slices) and T2-weighted (FLAIR) images were acquired for each patient. T1 (for high-grade tumours) and T2-weighted/FLAIR images (for low grade tumours) were used to perform semi-automatic lesion segmentation using ITK-snap (Yushkevich et al., 2006) according to Yushkevich and Gerig (2017) and Fekonja et al. (2019). All anatomical images and masked lesions were then registered to the Montreal Neurological Institute 152 (MNI) space using FSL (https://fsl.fmrib.ox.ac.uk/fsl/) and the script *lesion_norm_fsl.sh* that performs both linear and non-linear registrations. For optimal results, prior to registration, we skull-stripped the anatomical images using *optiBET.sh* (Jenkinson et al., 2012; Smith, 2002). Figure 1 shows the lesion overlap of our patient sample in MNI space.

Statistical analysis and VLSM

To control whether besides tumour location and size, there was other potential demographic information that affected task performance, we conducted the following: a two-sample *t*-test to appraise potential performance differences between males and females, and linear regressions to evaluate potential performance differences across different tumour grades and ages.

To assess the relationship between performance on language tasks and voxel-wise lesions, we used VLSM (Bates et al., 2003). VLSM was performed using the NiiStat toolbox (https://www.nitrc.org/projects/niistat) with MATLAB version R2020b (MathWorks). The analysis used generalized linear models to create statistical parametric maps including lesion size as a covariate. Voxel-wise comparisons were performed in voxels with a minimum of two patients with lesion overlap. To account for multiple comparisons, all analyses were accounted for false discovery rate (FDR) correction and results were thresholded at $p < .05$. To determine the localization of significant voxel clusters, we used MRIcron (Rorden & Brett, 2001) and overlayed thresholded voxels on cortical and subcortical atlas templates. For cortical regions, we used the AAL template (Tzourio-Mazoyer et al., 2002), whereas for subcortical fibres we used the Natbrainlab white matter atlas (Catani & de Schotten, 2008).

RESULTS

Overall AAT scores and influence of demographic and tumour factors

Approximately 27% of our sample was diagnosed with aphasia ($n = 14$), whereas 73% ($n = 38$) did not face preoperative language difficulties according to the overall scores of the AAT. To examine the influence of demographic and tumour factors, a multiple linear regression was carried out to test whether age and tumour grade predicted performance on the AAT language battery. To check whether an interaction between the two predictors was necessary, the base model without interaction (*AAT_score ~ age + tumour grade*) was compared using ANOVA to a model with interaction between the two predictors (*AAT_score ~ age * tumour grade*). The result of the ANOVA indicated that the model with interaction was not significantly better than the model without interaction ($F = 2.008$, $p = .145$). Hence, we proceeded using the base model without interaction. Results of the linear model indicated that *age* was a significant predictor of AAT score (β = 1.052, p = .049), whereas *tumour grades III* and *IV* did not have an effect on AAT scores (grade III: β = 1.048, p = .97; grade IV: β = .988, p = .098). To evaluate the potential effect of sex differences, we compared the overall AAT scores of males and females (t = −.401, p = .69).

Our VLSM analysis indicated significant voxel clusters for language production tasks as well as repetition tasks. However, no voxels survived FDR correction for tasks of reading and auditory comprehension.

Language production: object naming versus compounds versus sentences

During object naming, 14 (27%) out of 52 patients had scores below 90% accuracy. For compound naming, 21 participants (40%) scored below 90%, whereas for sentences this number was 19 people (36.5%).

For object naming, the VLSM analysis indicated 654 voxels that survived the threshold. These voxels were located mainly in inferior parietal grey and white matter regions (Figure 2; mean z = −4.02). The main part of the significant voxel clusters was located subcortically (92.2% white matter correlates, 7.8% grey

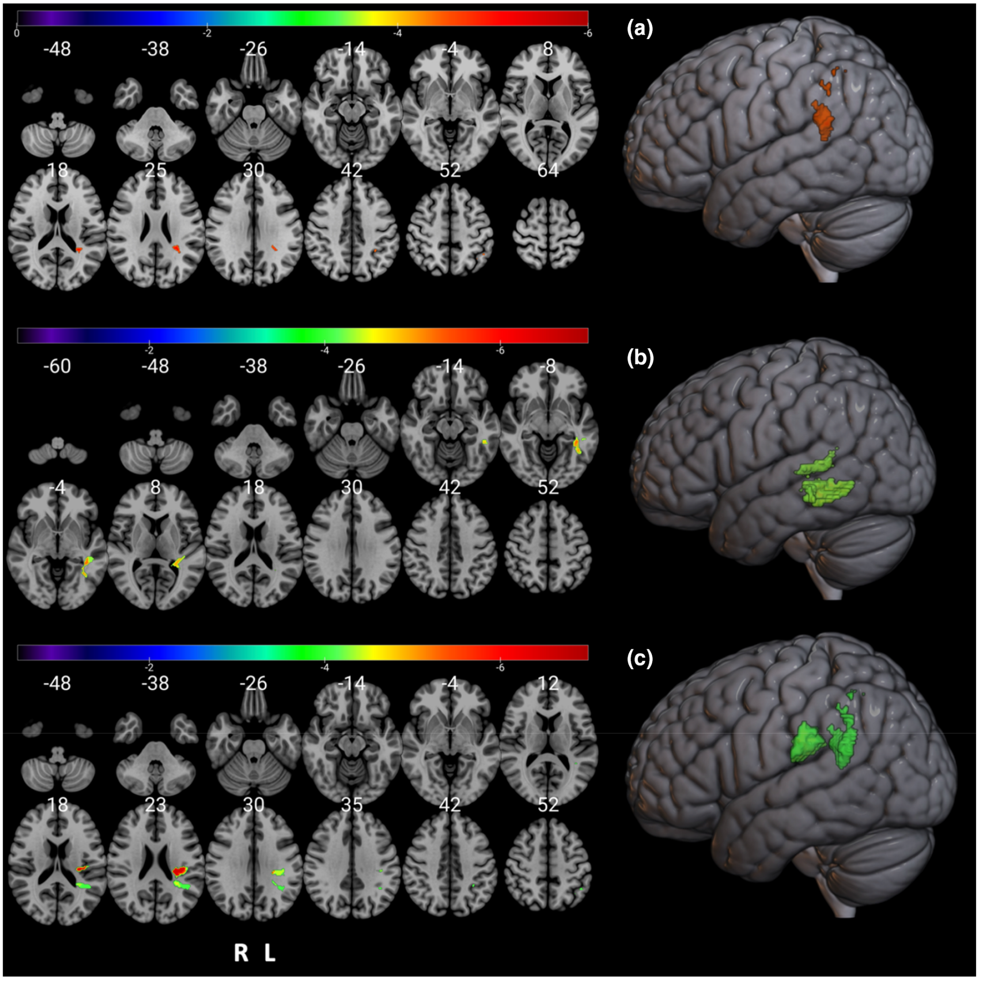

FIGURE 2 VLSM maps of FDR corrected z-scores for the following AAT tasks: object naming (a), compound naming (b) and sentence production (c). The significant clusters are in MNI space and projected onto the Colin27 template provided by MRIcroGL (Rorden & Brett, 2001). Axial slices are displayed according to the radiological convention, and numbers are indicated above each slice (R: Right; L: Left).

TABLE 1 Numbers and percentages of overlapping voxels for object, compound and sentence production for each region of the AAL atlas (Tzourio-Mazoyer et al., 2002)

AAL index	Region name	Number of overlapping voxels	Percentage of overlapping voxels
Object naming			
61	Parietal_Inf_L	51	7.8
Compound naming			
37	Hippocampus_L	32	1.4
39	ParaHippocampal_L	23	1.0
55	Fusiform_L	100	4.5
81	Temporal_Sup_L	19	1
85	Temporal_Mid_L	53	2.4
89	Temporal_Inf_L	421	19
Sentence production			
17	Rolandic_Oper_L	385	8
29	Insula_L	358	7.3
61	Parietal_Inf_L	143	3
63	SupraMarginal_L	11	.2
65	Angular_L	224	4.6
85	Temporal_Mid_L	180	3.8

matter correlates). Atlas localization showed that the only grey matter correlate was the inferior parietal lobe (7.8% of all significant voxels), whereas subcortically the largest overlap was with the cortico-spinal tract (46%), followed by the left optic radiations (16.8%), the internal capsule (8.7%), the cortico-ponto cerebellar tract (8.2%), the posterior segment of the AF (6%), the corpus callosum (4.1%) and the long and anterior segment of the AF (1.3% and 1.1% respectively).

VLSM analysis for compound production revealed 2.225 voxels that survived threshold (Figure 2; mean $z = -3.94$). These voxels were located inferior to object naming clusters, encompassing mainly the posterior inferior temporal gyrus (approximately 19% of total voxels), the posterior middle temporal gyrus (2.4%), the fusiform area (4.5%), and to a lesser extent the posterior superior temporal gyrus, the hippocampus, the parahippocampal gyrus and the inferior occipital cortex (all below 1.5% of total voxels). For subcortical regions, our atlas analysis showed that the cluster overlapped mainly with the ILF (33.5%), the left optic radiations (approximately 9%), the internal capsule and corpus callosum (7.4% and 7.5% respectively) as well as the IFOF (6.7%). Additionally, the long and posterior segment of the AF as well as the cortico-ponto cerebellar tract were associated with performance on compound production (below 3%).

Our sentence production VLSM analysis showed the biggest cluster of significant voxels with 4885 voxels surviving the FDR corrected threshold (Figure 2; mean $z = -3.52$). The clusters for sentence production were distributed more superior and anterior to previous tasks. Specifically, the main correlates of sentence production were also subcortical (73% of all significant voxels) rather than cortical (27%). At the cortical level, approximately 7.9% of total voxels overlapped with the left rolandic operculum and 7.3% with the insula. Fewer voxels (4.6%) were connected with the AnG, the posterior MTG (3.7%) and the superior parietal lobule (3%). The subcortical analysis revealed that 21.4% of voxels were located in the posterior segment of the AF whereas 16.4% in the anterior segment of the AF, with 15.7% of the voxels being in the left cortico-spinal tract and 11.4% in the long segment of the AF. Less than 5% of the voxels also overlapped with the internal capsule, optic radiations, and the cortico-ponto cerebellar tract. Tables 1 and 2 list percentages of total voxel overlap as well as raw voxel count for each production task according to the AAL (Tzourio-Mazoyer et al., 2002) and NatBrainLab (Catani & de Schotten, 2008) atlas respectively (see also Figure 3).

TABLE 2 Numbers and percentages of overlapping voxels for object, compound and sentence production for each tract of the NatBrainLab atlas (Catani & de Schotten, 2008)

NatBrainLab index	Region name	Number of overlapping voxels	Percentage of overlapping voxels
Object naming			
2	Arcuate_Anterior_Segment_Left	7	1.1
3	Long_Segment_Left	9	1.4
4	Arcuate_Posterior_Segment_Left	38	5.8
6	Corpus_Callosum_Left	27	4.1
7	Cortico_Ponto_Cerebellum_Left	54	8.3
8	Cortico_Spinal_Left	301	46
13	Internal_Capsule_Left	57	8.7
14	Optic_Radiations_Left	110	16.8
Compound naming			
3	Long_Segment_Left	10	.5
4	Arcuate_Posterior_Segment_Left	37	1.7
6	Corpus_Callosum_Left	167	7.5
7	Cortico_Ponto_Cerebellum_Left	11	.5
8	Cortico_Spinal_Left	62	2.8
9	Fornix_Left	25	1.1
11	Inferior_Longitudinal_Fasciculus_Left	746	33.5
12	Inferior_Occipito_Frontal_Fasciculus_Left	148	6.7
13	Internal_Capsule_Left	164	7.4
14	Optic_Radiations_Left	199	9
Sentence production			
2	Arcuate_Anterior_Segment_Left	803	16.4
3	Long_Segment_Left	554	11.3
4	Arcuate_Posterior_Segment_Left	1044	21.5
7	Cortico_Ponto_Cerebellum_Left	127	2.6
8	Cortico_Spinal_Left	766	15.7
13	Internal_Capsule_Left	149	3.1
14	Optic_Radiations_Left	116	2.5

Repetition: words versus sentences

On the behavioural level, for both word and sentence repetition 13.5% ($n = 7$) of participants scored below 90% accuracy.

The VLSM analysis for word repetition revealed 8.404 significant voxels (Figure 4; mean $z = -3.60$). Unlike production tasks, the clusters associated with word repetition were split between cortical (50.2%) and subcortical regions (49.8%). The main cortical areas affected were the rolandic operculum (12% of total voxels), the SMG (11.7%), the superior parietal cortex (9.3%) and the posterior STG (7.5%). Less than 5% of voxels additionally overlapped with the insula, the hippocampus and the postcentral gyrus. Important subcortical regions for word repetition clusters were the cortico-spinal tract (13.7%), the anterior segment of the AF (13%) and the long segment of the AF (7.1%). Additional subcortical regions that were connected with the voxel clusters were the left fornix, the internal capsule, the left corpus callosum and the left optic radiations (below 5% of total voxels).

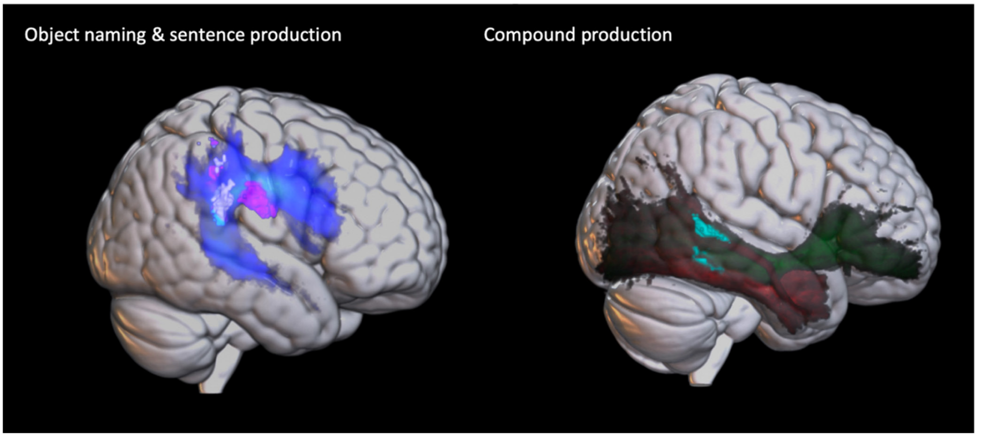

FIGURE 3 Example of tracts that overlap with clusters of object naming and sentence production (left panel) as well as compound production (right panel). Left panel: AF (blue), object and sentence production joint cluster (pink), voxels affecting only sentence production (white). Right panel: IFOF (green), ILF (red), compound production cluster (light blue). For better visualization of the voxel clusters, the figures are shown from the side of the right hemisphere.

Regarding sentence repetition, the VLSM analysis indicated that 11.592 significant voxels survived FDR correction. Unlike word repetition, the biggest number of voxels was located cortically (69.1% of total surviving voxels), whereas 30.9% of voxels were located subcortically. Our atlas analysis showed that the majority of cortical voxels overlapped with the ventral postcentral (29.5% of total voxels) and precentral gyrus (21.3%), followed by the rolandic operculum (7.5%) and the insula (4.1%). Further frontal areas such as the posterior MFG, posterior IFG also overlapped with the clusters for less than 4%. Affected subcortical tracts comprised the anterior segment of the AF (13.1% of surviving voxels), followed by the cortico-spinal tract (8.7%) and the long segment of the AF (6.4%). The internal capsule and the cortico-ponto cerebellar tract were both implicated less than 2%. Tables 3 and 4 show percentages of affected cortical regions and subcortical tracts alongside raw voxel numbers according to the AAL (Tzourio-Mazoyer et al., 2002) and NatBrainLab (Catani & de Schotten, 2008) atlases (see also Figure 4).

DISCUSSION

The present study investigated whether tumour sites differ according to performance of tasks with different linguistic stimuli. Within tasks that assess the same modality and similarly to previous studies, our VLSM analysis demonstrated that production of single words (*i.e.* object naming) was associated mainly with inferior parietal cortical regions and the anterior and main segments of the AF. Adding to previous literature, however, sentence production was mainly connected with voxels of the posterior part of the AF and at the cortical level the insula and the posterior temporal lobe. Compound production was exclusively associated with posterior temporal areas and constituted the only task that was connected with the ILF and IFOF. Tasks evaluating repetition also had different correlates for words and sentences. Even though word repetition was mainly associated with temporoparietal cortical and subcortical regions, sentence repetition was the only task to be connected with areas of the left IFG. Regarding task modality (*i.e.* production vs. repetition), we also observed different neural correlates. Production tasks had exclusively posterior correlates with many overlapping regions with repetition tasks. However, the differences lied in the involvement of ventral motor and sensory areas as well as posterior frontal areas in repetition processes.

TABLE 3 Numbers and percentages of overlapping voxels for word and sentence repetition according to the AAL atlas (Tzourio-Mazoyer et al., 2002)

AAL index	Region name	Number of overlapping voxels	Percentage of overlapping voxels
Word repetition			
17	Rolandic_Oper_L	1007	12
29	Insula_L	374	4.5
37	Hippocampus_L	128	1.5
57	Postcentral_L	242	2.9
61	Parietal_Inf_L	778	9.3
63	SupraMarginal_L	984	11.7
79	Heschl_L	31	.4
81	Temporal_Sup_L	627	7.5
85	Temporal_Mid_L	36	.4
Sentence repetition			
1	Precentral_L	2473	21.3
7	Frontal_Mid_L	147	1.3
11	Frontal_Inf_Oper_L	297	2.6
13	Frontal_Inf_Tri_L	270	2.3
17	Rolandic_Oper_L	876	7.5
29	Insula_L	473	4.1
57	Postcentral_L	3426	29.5
12	SupraMarginal_L	31	.3
13	Caudate_L	17	.1
14	Temporal_Pole_Sup_L	13	.1

Cortical organization of production and repetition

Although studies on individuals with brain tumours are still scarce, evidence from post-stroke aphasia has connected lesions in left frontal regions with Broca's aphasia. For example, it has been reported that lesions in Broca's area result in impairments of sentence production and verb naming but also articulation programming (Lee & Thompson, 2004; Miceli et al., 1984; Mohr et al., 1978; Thompson et al., 2015; for a review see Hillis, 2007). Recently, however, the view that language production deficits result from circumscribed left IFG lesions has been challenged (Fekonja et al., 2021; Fridriksson et al., 2015; Gajardo-Vidal et al., 2021; Mandonnet & Duffau, 2021).

From a neurosurgical perspective, removal of Broca's area has also appeared to be feasible without resulting in aphasia and is the optimal approach for the resection of insular gliomas in some neurosurgical centres (Benzagmout et al., 2007; Duffau, 2009; Mandonnet & Duffau, 2021). Previous VLSM studies demonstrate that non-fluent aphasia does not result exclusively by lesions in Broca's area, but mainly in the posterior temporal lobe (Fridriksson et al., 2015). A large-scale study of 134 stroke survivors also indicated that contrary to previous expectations, language production impairments are not connected to IFG damage, but rather, damage of the AF (Gajardo-Vidal et al., 2021). Along these lines, our findings also do not indicate a connection between the left posterior IFG and lower performance in language production tasks for patients with brain tumours. In contrast, we showed that performance on production of words, sentences or compounds was connected rather with subcortical white matter tracts. Similarly to Fekonja et al. (2021) as well as Gajardo-Vidal et al. (2021), damage to the AF was connected with lower performance on sentence and word production, whereas the ILF was mainly associated with lower performance on compound production. Also, in-line with Fridriksson et al. (2015) and Fekonja et al. (2021), scores on

TABLE 4 Numbers and percentages of overlapping voxels for word and sentence repetition for each tract of the NatBrainLab atlas (Catani & de Schotten, 2008)

NatBrainLab index	Region name	Number of overlapping voxels	Percentage of overlapping voxels
Word repetition			
2	Arcuate_Anterior_Segment_Left	1086	13
3	Long_Segment_Left	600	7.1
4	Arcuate_Posterior_Segment_Left	65	.7
6	Corpus_Callosum_Left	150	1.8
7	Cortico_Ponto_Cerebellum_Left	147	1.7
8	Cortico_Spinal_Left	1152	13.7
9	Fornix_Left	352	4.1
11	Inferior_Longitudinal_Fasciculus_Left	22	.3
13	Internal_Capsule_Left	329	3.9
14	Optic_Radiations_Left	294	3.5
Sentence repetition			
2	Arcuate_Anterior_Segment_Left	1519	13.1
3	Long_Segment_Left	744	6.4
6	Corpus_Callosum_Left	42	.4
7	Cortico_Ponto_Cerebellum_Left	85	.8
8	Cortico_Spinal_Left	1006	8.7
13	Internal_Capsule_Left	173	1.5

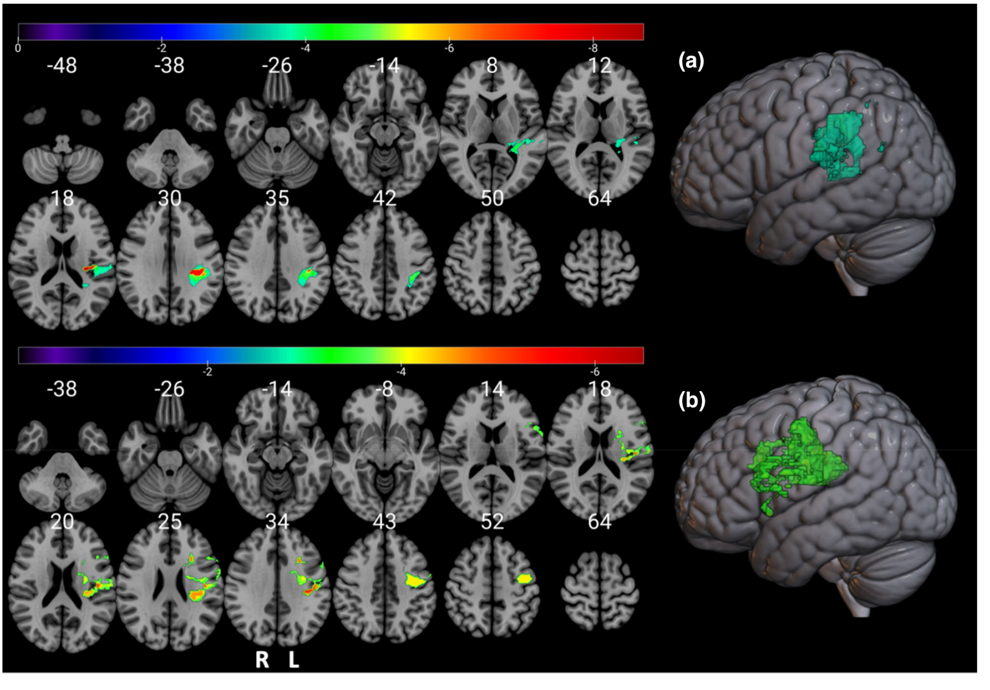

FIGURE 4 VLSM maps of FDR corrected z-scores for the following AAT tasks: word repetition (a) and sentence repetition (b). The significant clusters are in MNI space and projected onto the Colin27 template provided by MRIcroGL (Rorden & Brett, 2001). Axial slices are displayed according to the radiological convention, and numbers are indicated above each slice (R: Right; L: Left).

all three production tasks were correlated with posterior temporal and inferior parietal regions rather than the frontal cortex.

Regarding the correlates of the different linguistic material of the three production tasks, frontal lesions leading to agrammatic aphasia have been connected with impairments in verb rather than noun processing as well as sentence rather than word processing (Caramazza & Miceli, 1991; Miceli et al., 1984; Vanier & Caplan, 1989). Intraoperative stimulation, however, has failed to demonstrate such clear-cut distinctions during stimulations of the IFG at the group level (Corina et al., 2005; Rofes, Spena, et al., 2017; *cf.* Havas et al., 2015). Our findings do not support a clear distinction between object naming and sentence production in the IFG. The single frontal area that was associated with performance on sentence production rather than object naming was the left insula. Besides the inferior parietal lobe that was associated with both object and sentence production, the only additional area implicated in sentence rather than object production was the posterior middle temporal gyrus.

Regarding the role of the left insula in sentence production rather than word or compound production, it was initially hypothesized that this area is crucial for speech, with insular lesions leading to symptoms of apraxia of speech (Bates et al., 2003; Dronkers, 1996). Later meta-analyses also connected the region to speech processing, arguing that the insula acts as a preparatory interface before vocalization (Eickhoff et al., 2009; Oh et al., 2014). Our study validates these claims as in our data the insula was associated with performance for both sentence production as well as sentence and word repetition. This points towards the role of the insula in speech, especially when there is increased phonological load to be produced (*e.g.* sentences rather than words) or the focus of the task is more phonological rather than semantic (*e.g.* repetition vs. production).

The role of the posterior MTG in sentence processing has been extensively discussed. As the pMTG is considered part of Wernicke's area, several studies have indicated the region as crucial not only for sentence comprehension but also for sentence production (Fridriksson et al., 2018; Matchin et al., 2020; Matchin & Hickok, 2020; den Ouden et al., 2019; Tremblay & Dick, 2016). Interestingly, in the present study performance on compound production was also associated with the left posterior temporal lobe. The processing of compounds has been argued to demand greater combinatorial semantic processes, as the speaker is required to potentially combine two independent words into one (Graves et al., 2010). Hence, considering that posterior temporal regions have repeatedly been linked to lexico-semantic processes, tumours that mainly affect these regions might lead to increased difficulties in the processing of compound words (see also Semenza et al., 2011 for evidence from post-stroke aphasia).

Subcortical correlates of production and repetition

Similarly to previous studies, we showed that for both production and repetition tasks the main correlates of poor performance were white-matter lesions (Fekonja et al., 2021; Tuncer et al., 2021). Additionally, we demonstrate that damage of different language tracts affects the performance for tasks with different linguistic material.

Even though object naming and sentence production were primarily associated with the three segments of the left AF, performance on compound production was primarily affected by lesions close to the ILF and IFOF. Considering that several intraoperative stimulation studies have largely connected the ILF and IFOF with semantic processes, the argument that compounds might require extra semantic load compared with simple words is reinforced (Duffau, 2005; Vigneau et al., 2006). In regard to the AF, although both object naming and sentence production were associated with the three tract segments, approximately 50% of the significant voxels for sentences were at the location of the AF. For object naming, this percentage was less than 10%. This discrepancy might relate to the linguistic functions of the AF. Besides articulatory processes, the AF has also been implicated in syntax (Friederici, 2018). As syntax is required for hierarchical and linear relations between words, it seems reasonable that damage to the AF would be more strongly associated with lower performance in sentential tasks.

Similarly to object naming and sentence production, lower performance in repetition tasks was also mainly associated with the AF. However, unlike sentence production, word and sentence repetition were mostly associated with the anterior and long segments of the AF (*cf.* highest sentence production overlap was with the posterior AF segment). These results are in line with intraoperative studies that report dysarthric and articulatory error induction when stimulating the long and anterior segments of the AF (Chang et al., 2015; Duffau et al., 2008; Sierpowska et al., 2017). However, in a study investigating the integrity of different AF segments in people with chronic post-stroke aphasia, both the main and posterior segments of the tract were correlated with both naming as well as repetition measures (Ivanova et al., 2021). It is challenging based solely on our findings to disentangle the potential varying contributions of the three AF segments. Nevertheless, given the importance of frontal regions for sensorimotor integration (*e.g.* supplementary motor area, primary motor cortex), it seems reasonable for the anterior and long segments of the AF to be mostly associated with performance on repetition tasks (Hickok et al., 2011).

Clinical significance

The present VLSM study demonstrated that lesions in different areas lead to variable performance in tasks that assess the same language modality but employ different linguistic material. This finding has important clinical implications, especially regarding the perioperative language assessment of patients with brain tumours. The implementation of sentence production tasks might be beneficial during the pre-, intra- and postoperative stage for people with tumours in left posterior temporal and inferior parietal areas. Although object naming is a sensitive and easily feasible task, the fact that linguistic stimuli with varying complexities and characteristics have different lesion correlates suggests that object naming should not be a uniform approach to language assessment. For example, this implies that two individuals with tumours in different cortical or subcortical regions might both have difficulties in language production. However, their impairments can only be captured by testing the production of specific linguistic structures rather than using one task to evaluate language production as a whole. For example, object naming does test the modality of production, but it does not test linguistic levels that are specific to sentences (*e.g.* syntax). Even though tailored perioperative protocols expand beyond object naming, few of them suggest intraoperative sentence production assessment and even fewer focus on compound production (Alves et al., 2021; De Witte et al., 2015; Ohlerth et al., 2020). This study could then act as a basis for choosing perioperative tasks as well as designing therapy protocols.

Limitations and future directions

The present study confirms previous VLSM findings for individuals with brain tumours (Banerjee et al., 2015; Fekonja et al., 2021) and highlights not only the lack of involvement of frontal regions but also the differential results for tasks with different linguistic stimuli. However, given the small sample size we opted for a low threshold for voxels entering the VLSM analysis (*i.e.* two patients). It should be highlighted that higher cut-off values produced similar, but less informative results with smaller and fewer significant clusters. In order for our results to be validated, studies with larger samples and higher cut-off values are needed. Another potential bias in our findings could be the choice of language battery. It is clinical practice in several neurosurgical departments in Germany to use the AAT for language assessment (Huber et al., 1984). Albeit a thorough language battery, the AAT was designed for assessment of post-stroke aphasia. This might render the AAT insensitive for people with tumour-induced aphasias that on average tend to show milder language deficits compared to patients with post-stroke aphasia (Duffau, 2014; Satoer et al., 2022). Notably, 73% of our sample was not diagnosed with aphasia based on the AAT. This could explain the lack of significant clusters in comprehension tasks. A prospective study could account for these limitations by implementing additional language tasks and more detailed assessments (*e.g.* Rofes, Spena, et al., 2017). Also, considering that different atlas selections would have resulted in different parcellations, it should be noted that our findings are atlas-dependent. Future work should expand the present study with a larger sample size (*e.g.* >60; Mirman et al., 2018) while evaluating the present findings with potentially more conservative multiple comparisons corrections. Additionally, studies of DES mapping should assess whether language tasks with different complexities have the potential to identify more language-relevant regions compared to the widely used task of object naming.

AUTHOR CONTRIBUTIONS

Lena Rybka: Data curation; project administration; writing – review and editing. **Jocelyn Lubbers:** Data curation; project administration; writing – review and editing. **Mehmet Salih Tuncer:** Conceptualization; formal analysis; investigation; methodology; software; writing – original draft; writing – review and editing. **Peter Vajkoczy:** Funding acquisition; writing – review and editing. **Adrià Rofes:** Conceptualization; supervision; writing – original draft; writing – review and editing. **Thomas Picht:** Conceptualization; funding acquisition; resources; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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