Brain Structure and Function (2019) 224:2199–2211
https://doi.org/10.1007/s00429-019-01902-z

ORIGINAL ARTICLE

The neural correlates of auditory-verbal short-term memory: a voxel-based lesion-symptom mapping study on 103 patients after glioma removal

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Received: 1 December 2018 / Accepted: 1 June 2019 / Published online: 8 June 2019

Abstract

The relationship between verbal-auditory short-term memory (STM) and language is an open area of debate and contrasting hypotheses have been proposed, suggesting either that STM would strongly rely on language-related processes, or that it depends on a dedicated system related to language, but independent from it. In this study we examined 103 patients undergoing surgery for glioma resection in the left or right hemisphere, and we conducted a VLSM analysis on their behavioral performance on auditory-verbal STM, as well as on more general verbal and nonverbal tasks. The aim was to investigate whether the anatomical correlates of auditory-verbal STM were part of the language system or they were spatially segregated from it. VLSM results showed that digit span scores were linked to lesions in both the left supramarginal gyrus and superior-posterior temporal areas, as reported in the literature on patients with a selective deficit of auditory-verbal STM. Conversely, other verbal tasks involved areas only partly overlapping with those found for digit span, with repetition being affected by lesions in more anterior regions in the parietal, temporal, and frontal lobes, and word comprehension by lesions in a network including cortical and subcortical pathways in the temporal lobe. The present results, thus, show that auditory-verbal STM neural correlates are only partially overlapping with those supporting comprehension and production: while the left posterior–superior temporal cortex, involved in speech perception, takes part in both functions, the left supramarginal gyrus has a consistent and specific role only in STM, supporting the hypothesis of interacting but segregated networks.

Keywords Auditory-verbal short-term memory · Supramarginal gyrus · Forward digit span · VLSM

Introduction

Auditory-verbal or phonological short-term memory (STM) has been extensively investigated both from a functional and from an anatomical point of view. Several cognitive models of this function have been proposed, but certainly the most popular one is the phonological loop incorporated in the Baddeley and Hitch (1974)'s working memory model,

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00429-019-01902-z) contains supplementary material, which is available to authorized users.

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which distinguishes between a phonological input store and an articulatory process of rehearsal, which is capable of refreshing the memory trace, preventing its decay (Baddeley 1990). An impairment of the phonological loop is expected to produce a selective STM syndrome, characterized by a reduced verbal span for all strings of unrelated auditory-verbal items not due to perceptive or production deficits. This model also assumes specific neural correlates for auditory-verbal STM, that are derived from anatomo-clinical studies in brain-damaged patients (see Vallar and Papagno 2002; Shallice and Papagno 2019, for reviews), neuroimaging studies with positron emission tomography (Awh et al. 1995; Paulesu et al. 1993; but see Poeppel 1996) and fMRI (Henson et al. 2000), and repetitive transcranial magnetic stimulation experiments (Romero et al. 2006). Evidence from such different methodologies converge in supporting the hypothesis that the phonological short-term storage and the rehearsal process depend on the activity of two discrete regions in the left hemisphere: the inferior parietal lobule (more specifically, the supramarginal gyrus, Brodmann's area BA 40, but also the angular gyrus, BA 39, see for example Newhart et al. 2012; Vallar et al. 1997; Warrington et al. 1971) and the inferior frontal operculum (BA 44 and BA 6, but also BA 45), respectively.

Moreover, Papagno et al. (2017) suggested a possible mapping of the phonological loop that includes the arcuate fascicle (AF). This white matter bundle might be central since it consists of different segments connecting crucial regions: indeed, the long segment connects Wernicke's area, where the phonological analysis occurs, directly to Broca's area; the anterior segment of the AF indirect pathway, also considered as the third segment of the superior longitudinal fasciculus (SLF-III), conveys information from the supramarginal gyrus (the neural correlate of the phonological short-term store) to Broca's area, whereas the posterior segment of the AF indirect pathway transfers the output of Wernicke's area to the phonological short-term store in the supramarginal gyrus (Fig. 1).

The Baddeley and Hitch's model, however, has encountered several criticisms. In particular, it has been proposed that verbal STM could be an emergent property of language due to a temporary activation of the linguistic network (Martin and Saffran 1997). This account implies, from an anatomical point of view, that the same areas involved in speech processing should be relevant for verbal STM tasks. Indeed, neuroimaging studies are being increasingly used to support a related position (see e.g., D'Esposito and Postle 2015). For instance, Koenigs et al. (2011) suggest that verbal STM may not rely on a dedicated short-term storage buffer, but simply reflects the temporary activation of the same long-term representations of speech sounds that are used to comprehend and generate speech. If verbal STM reflects the temporary activation of long-term representations of speech sounds, we should expect that its neural correlates might simply overlap with those implicated in speech sounds processing. Accordingly, Koenigs et al. (2011) found that patients with damage to the inferior frontal and posterior temporal regions were impaired on digit span, as well as on tests requiring the production and/or comprehension of language.

More recently, a study on epileptic patients (Zamora et al. 2016) suggested an involvement of the lateral temporal cortex in active rehearsal, a result that contradicts the current literature on the neural correlates of the rehearsal process (see Vallar and Papagno 2002) and concerns a particular type of population (intractable temporal lobe epilepsy). Additional evidence has been provided by Leff et al. (2009) who demonstrated a superior temporal cortex involvement in a voxel-based morphometry study on stroke patients. It has to be noted, however, that the median time after stroke

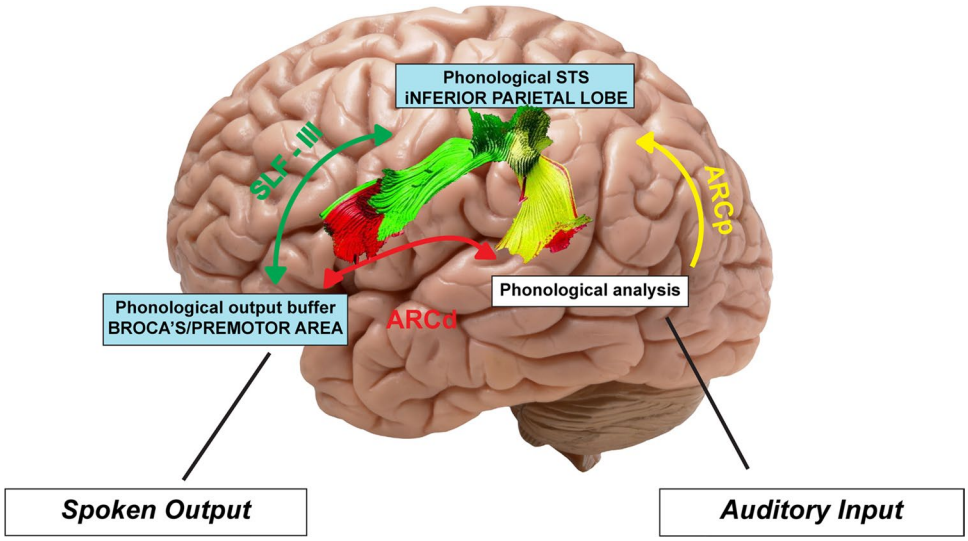

Fig. 1 Schematic mapping of the phonological loop with relevant cortical regions and subcortical pathways. ARCp = posterior branch of the arcuate fasciculus (in yellow); ARCd = direct segment of the arcuate fasciculus (in red); SLF-III = third branch of the superior longitudinal fasciculus, or anterior branch of the arcuate fasciculus (in green). Adapted from Papagno et al. (2017)

of patients included in this study was 35 months, a period during which reorganization could have taken place.

Therefore, the still unanswered question is whether the STM syndrome could arise from weakened speech perception due to lesions of the lateral superior temporal cortex, as suggested for example by Buchsbaum et al. (2011), or whether it depends from a system bound to language but separable from it.

To shed light on this issue, we investigated the cognitive performance on digit span and other verbal tasks in a large series of patients who underwent surgery for glioma removal in the fronto-parieto-temporal region. A voxel-based lesion-symptom mapping (VLSM) approach was used to verify possible links between task performance and specific brain regions. Post-surgery volumes of interest (VOIs) and behavioral scores on auditory-verbal STM, and other cognitive verbal and nonverbal tasks were analyzed. If we consider studies suggesting that auditory-verbal STM emerges from the interface of a fronto-temporal sensory motor circuit that supports speech perception and production (for a review see Buchsbaum and D'Esposito 2019), then we would expect an involvement of this region in verbal STM tasks. Similarly, Koenigs et al. (2011) suggest that "verbal STM may simply reflect the temporal activation of the same long-term representations of speech sounds that are used to comprehend and generate normal speech". Accordingly, they found that patients with either frontal inferior or posterior temporal areas had a low digit span but also an impaired production or comprehension of language. A similar anatomical result is reported by Leff et al. (2009). Conversely, were auditory-verbal STM and language separable, even though interacting, systems, only a partial overlap of cortical areas should be found in the VLSM analysis.

Materials and methods

Participants

A hundred and three patients (57 male, mean age 42.7, SD 13.13, range 15–74; mean education 13.42 years, SD 3.63, range 5–23), were included in the study. Thirty-eight patients underwent surgical resection in the right hemisphere (RH), while 65 in the left hemisphere (LH). All but six patients were right-handed (Oldfield 1971). fMRI pre-surgical scanning using a word generation and a picture-naming task (Papagno et al. 2011) revealed left lateralization of language in all patients but one, who showed moderate right lateralization. Forty-four patients had a high-grade glioma (HGG; RH: 12, LH: 32), 47 a low-grade glioma (LGG; RH: 17, LH: 30) and 12 an evolving low-grade glioma (ELGG; RH: 9, LH: 3), according to the World Health Organization classification (see Tab. S1 for demographic and clinical information). No differences were present between RH and LH patients in tumor volume [$t(70) = 1.27$, $p = .2$], age [$t(101) = .19$, $p = .85$], or educational level [$t(101) = .97$, $p = .33$]. The study was approved by the local ethical committee, and all participants gave their written informed consent before participating, in accordance with the Declaration of Helsinki.

Neuropsychological assessment

Before and after surgery (± 7 days), patients were submitted to a neuropsychological assessment that included Attentional Matrices, Raven Coloured Progressive Matrices (CPM), Corsi span (Orsini et al. 1987), and several verbal tasks, such as Verbal Fluency on phonemic and semantic cue (Papagno et al. 2012), Rey Auditory Verbal Learning Task (RAVLT), in its immediate and delayed recall version (Carlesimo et al. 1996), word comprehension and word, nonword, and sentence repetition (from the BADA, Miceli et al. 1994). Object and action naming of picture, as well as the Token Test (De Renzi and Faglioni 1978), were also administered, but those data are not reported here since they have been published in Pisoni et al. (2018) on the same group of patients but six. Half of the patients received also a syntactic comprehension task (Cecchetto et al. 2012).

Auditory-verbal short-term memory tasks

To test auditory-verbal STM, the forward digit span (Orsini et al. 1987), and the backward digit span (Monaco et al. 2013) were administered. The procedure was as following: the experimenter read, at the rate of one digit per second, a sequence of digits to the patient, who was instructed to immediately repeat it in the same order of presentation (forward version), or in the reversed order (backward version). If a string was correctly reported, the experimenter increased the sequence length by one digit, until the patient was unable to report at least one sequence of that length out of two, or correctly repeated a nine-digit sequence. The span was scored as the length of the longest correctly reported sequence, separately for forward and backward versions.

Data analysis

Behavioral performance

Analyses were performed with the statistical software SPSS (version 24; Armonk, NY: IBM Corp). We analyzed span and additional language tasks, to verify whether their neural correlates are totally overlapped, and nonverbal abilities,

such as attention, visuo-spatial span, and nonverbal intelligence, to verify the selectivity of our results, namely the fact that performance was not generally impaired in all tasks after brain damage/surgery.

Corrected scores at the neuropsychological tests of interest, namely the Attentional Matrices, Raven Colored Progressive Matrices, Rey Auditory Verbal Learning task, Verbal Fluency on phonemic and semantic cue, word comprehension, word, nonword and sentence repetition, and Forward and Backward Digit Span as well as Corsi Span were analyzed by means of mixed time (pre- and post-surgery) by hemisphere (left and right) ANOVAs. Post-hoc tests were run on estimated marginal means, applying Bonferroni correction for multiple comparisons.

MRI acquisition and VLSM

MRI was performed post-operatively on a 3 Tesla MR scanner (Siemens Verio, Erlangen, Germany). Standard MR evaluation for morphological characterization of lesions included axial T2-weighted TSE sequence (TR/TE 3000/85 ms; field of view (FOV), 230 mm; 22 slices; section thickness, 5/1-mm gap; matrix, 512 × 512; SENSE factor, 1.5), axial 3D-FLAIR sequence (TR/TE 10 000/110 ms; FOV, 230 mm; 120 slices; section thickness, 1.5/0-mm gap; matrix, 224 × 256; SENSE factor, 2) and postcontrast T1-weighted inversion recovery sequence (TR/TE 2000/10 ms; FOV, 230 mm; 22 slices; section thickness, 5/1-mm gap; matrix, 400 × 512; SENSE factor, 1.5). Lesion volume was calculated with semi-automatic segmentation with the region of interest analysis with iPlan Cranial 3.0 software suite (Brainlab, Feldkirchen, Germany). FLAIR hyperintense and gadolinium-enhanced signal abnormalities were included in the lesion load for low-grade and high-grade gliomas, respectively, and then reported in cm^3. The extent of resection (EOR) was measured on pre- and post-operative MR performed after surgery, and classified as previously reported (EOR = [(pre-operative volume − post-operative volume)/pre-operative volume)] × 100 (Smith et al. 2008). Individual lesion mapping was manually performed by two independent judges (GM and AP) who drew over the lesion boundaries, on each relevant post-surgery T1-weighted inversion recovery sequence MRI axial slice, a VOI in MRIcron software (www.mricro.com/mricron). All voxels with altered signal, i.e., the regions removed by surgical procedure and adjacent edema when present (Pisoni et al. 2018; Mattavelli et al. 2019) were included in the VOIs, which were then smoothed in the three planes with a Gaussian filter and inspected by a skilled neurologist (CP) and neurosurgeon (MR). Finally, lesion maps and patients' MRIs were normalized to an MNI T1 template in SPM8 (Ashburner and Friston 1999) with no use of cost function masking or unified segmentation.

Voxel-based lesion-symptom mapping (VLSM) was performed with the NPM software, included in the MRIcron package (Version 2011). Post-surgery VOIs and behavioral scores on the considered neuropsychological tests were analyzed. As in Pisoni et al. (2018) and Mattavelli et al. (2019), post-surgery performance was analyzed, with the aim of linking the actual brain damage with patients' cognitive abilities at the time-point when images were acquired. Before surgery, indeed, some areas inside the lesion can be functionally active; therefore, mapping a pre-surgery lesion does not guarantee that we are mapping an inactive region (Karnath and Steinbach 2011), while analyzing acute behavioral scores and acute structural imaging allows examining the link between patients' cognitive abilities and brain lesions at the post-surgery time-point. This excludes the possible functional reorganization occurring in chronic patients (Karnath and Rennig 2017), although plastic changes related to the disease process could have occurred prior to surgery (Duffau et al. 2002). Voxel-by-voxel analysis was performed by means of *t* tests (Campanella et al. 2014; Pisoni et al. 2018; Mattavelli et al. 2019) only in those voxels damaged in at least 5% of the patients (7109,137 voxels) with a statistical threshold of $p = 0.05$ applying a FWE permutation threshold based on 1000 permutations.

Results

Behavioral results

Neuropsychological assessment

The neuropsychological assessment highlighted a general decrease in performance after surgery (see Table 1 for mean neuropsychological scores and Table 2 for analyses results), as the main effect of time was significant in each ANOVA performed on the selected tests. We will consider digit span, and other verbal and nonverbal tasks separately.

Digit span forward and backward On digit span forward, 5 LH and 2 RH patients scored below the cutoff of 3.75 at the pre-surgery evaluation, while post-surgery the number of impaired patients was 18 for LH and 5 for RH participants. In the Time by Hemisphere ANOVA, the main effect of Time was significant [$F(1,101) = 24.92$; $p < .001$; partial $\eta^2 = .2$], with patients scoring better pre- (mean score = 5.4; SD = 1) than post-surgery (mean score = 4.75; SD = 1.3), while the main effect of Hemisphere was not significant [$F(1,101) = 3.68$; $p = .16$; partial $\eta^2 = .02$]. Critically, the Time-by-Hemisphere interaction resulted significant [$F(1,101) = 6.78$; $p = .011$; partial $\eta^2 = .06$]: as highlighted by post hoc comparisons, while RH patients did not sig-

Table 1 Results of the neuropsychological assessment

Test	RBD patients			LBD patients		
	No patients	Mean	SD	No patients	Mean	SD
RAVLT immediate						
Pre-surgery	36	36.96	9.50	65	34.04	8.17
Post-surgery	36	31.09	10.56	65	17.75	11.88
RAVLT delayed						
Pre-surgery	36	7.11	3.13	65	6.40	3.18
Post-surgery	36	5.43	3.15	65	2.29	2.77
Verbal fluency (phonemic cue)						
Pre-surgery	35	29.17	8.15	65	29.60	11.50
Post-surgery	35	23.06	11.62	65	15.05	11.43
Verbal fluency (semantic cue)						
Pre-surgery	35	38.26	9.55	65	38.92	10.61
Post-surgery	35	32.89	8.54	65	24.26	14.71
Word repetition						
Pre-surgery	36	35.81	1.167	66	35.98	0.120
Post-surgery	36	35.36	2.758	66	33.73	6.420
Nonword repetition						
Pre-surgery	36	34.64	1.533	66	34.70	1.040
Post-surgery	36	34.53	1.748	66	32.77	6.000
Word comprehension						
Pre-surgery	37	47.83	0.571	65	47.94	0.427
Post-surgery	37	47.73	1.353	65	46.21	4.58
Sentence repetition						
Pre-surgery	36	19.56	2.667	66	19.88	0.670
Post-surgery	36	19.19	3.429	66	17.48	4.660
Attentional matrices						
Pre-surgery	37	47.82	7.74	66	47.76	6.97
Post-surgery	37	40.59	9.68	66	37.78	14.33
CPM						
Pre-surgery	36	29.28	4.05	64	30.26	4.00
Post-surgery	36	26.44	4.07	64	27.59	4.86
Corsi span						
Pre-surgery	36	4.85	0.82	65	4.68	0.84
Post-surgery	36	3.93	0.96	65	4.09	1.07

RAVLT rey auditory verbal learning test, *CPM* colored progressive matrices

nificantly decrease after surgery (5.37 vs 5.1; $p = .14$), LH patients did (5.43 vs 4.44; $p < .001$; see Fig. 2a). Before surgery, LH and RH patients did not differ ($p = .78$) while they did after ($p = .019$).

With reference to the digit span backward, analyses were run on 101 patents, since two patients did not complete the task after surgery. Pre-surgery 9 LH and 3 RH patients scored below the cutoff of 2.66 while post-surgery 32 LH and 13 RH did. Time-by-Hemisphere ANOVA highlighted only a main significant effect of Time [$F(1,99) = 36.7$; $p < .001$; partial $\eta^2 = .27$], since patients performed worse post- (mean score = 2.9; SD = 1.1) than pre-surgery (mean score = 3.7; SD = 1). The main effect of Hemisphere [$F(1,99) = 1.7$; $p = .19$; partial $\eta^2 = .02$], as well as the Time-by-Hemisphere interaction [$F(1,99) = 2.6$; $p = .1$; partial $\eta^2 = .03$], were not significant (see Fig. 2b).

Additional verbal tasks Concerning the specific effects of lesion site, the main effect of Hemisphere resulted significant for language-related tasks (i.e., verbal fluency, RAVLT immediate and delayed test, and word comprehension), with RH patients performing better than LH ones. Critically, performance on language-related tasks decreased significantly for LH patients as compared to RH ones, being the Hemisphere-by-Time interaction significant for the immediate and delayed RAVLT, word com-

Table 2 ANOVAs results for verbal tests

Test	*df*	*F*	*p*	Partial η^2
RAVLT immediate				
Time	1, 99	102,813	< .000	0.509
Hemisphere	1, 99	20,360	< .001	0.170
Time × hemisphere	1, 99	22,780	< .001	0.187
RAVLT delayed				
Time	1, 99	74,220	< .001	0.428
Hemisphere	1, 99	12,910	< .001	0.115
Time × hemisphere	1, 99	13,080	.001	0.117
Verbal fluency (phonemic cue)				
Time	1, 98	60,980	< .001	0.384
Hemisphere	1, 98	4040	.047	0.040
Time × hemisphere	1, 98	10,170	.002	0.094
Verbal fluency (semantic cue)				
Time	1, 97	58,920	< .001	0.370
Hemisphere	1, 97	3710	.057	0.036
Time × hemisphere	1, 97	12,670	.001	0.114
Word repetition				
Time	1, 100	6120	.015	0.058
Hemisphere	1, 100	1530	.22	0.015
Time × hemisphere	1, 100	2750	.10	0.027
Nonword repetition				
Time	1, 100	3890	.05	0.037
Hemisphere	1, 100	2470	.119	0.024
Time × hemisphere	1, 100	3090	.082	0.030
Sentence repetition				
Time	1, 100	12,960	< .001	0.115
Hemisphere	1, 100	1570	.21	0.015
Time × hemisphere	1, 100	7060	.009	0.066
Word comprehension				
Time	1, 100	5560	.02	0.053
Hemisphere	1, 100	4370	.032	0.032
Time × hemisphere	1, 100	3270	.039	0.039

prehension, sentence repetition and for verbal fluency on both phonemic and semantic cue.

Nonverbal tasks Concerning the Corsi span, behavioral and VLSM analyses were run on 101 patients because two patients did not perform it after surgery. Before surgery, 3 LH and 2 RH patients scored below the cutoff of 3.5, while post-surgery 10 LH and 8 RH patients were impaired. The Time by Hemisphere ANOVA showed only a significant main effect of Time, with lower post-surgery (mean score = 4.01; SD = 1) than pre-surgery scores (mean score = 4.77; SD = .8). The main effect of Hemisphere and the Time-by-Hemisphere interaction was not significant.

On Attentional Matrices, there was a significant Hemisphere-by-Time effect, as LH patients' performance decreased to a higher degree as compared to RH ones after surgery. No difference between hemispheres was found for Colored Progressive Matrices (see Table 3).

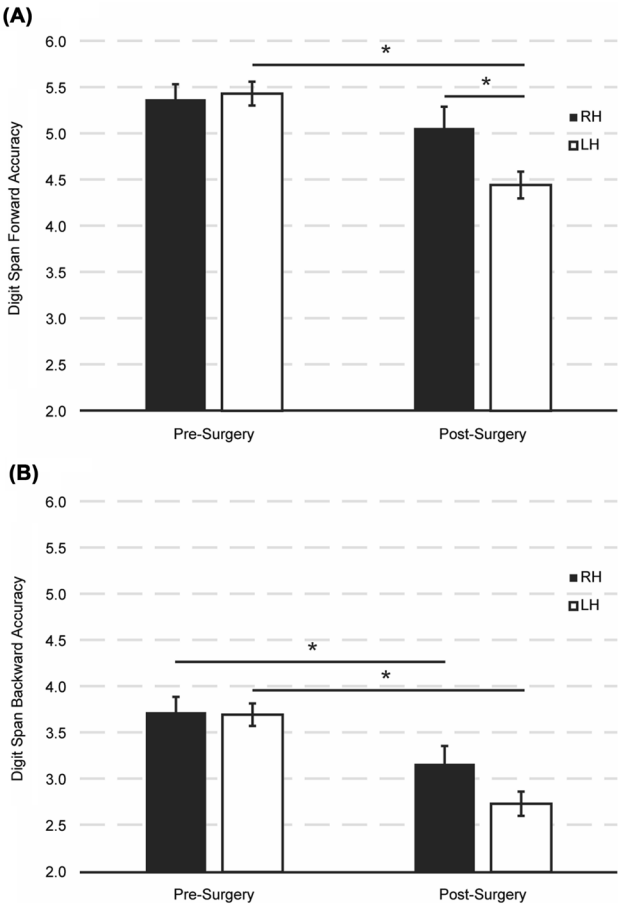

Fig. 2 Performance of right (LH) and left hemisphere (RH) patients on digit span forward (**a**) and digit span backward (**b**) tasks. Vertical bars represent ± 1 MSE; asterisks highlight significant results

Table 3 ANOVA results for the selected nonverbal tasks

Attentional matrices				
Time	1, 101	74,200	< .001	0.420
Hemisphere	1, 101	2670	.105	0.260
Time × hemisphere	1, 101	6020	.016	0.560
CPM				
Time	1, 98	48,520	< .001	0.331
Hemisphere	1, 98	1730	.19	0.017
Time × hemisphere	1, 98	0315	.83	0.000
Corsi span				
Time	1, 99	26,380	< .001	0.320
Hemisphere	1, 99	0000	.99	0.000
Time × hemisphere	1, 99	2160	.14	0.020

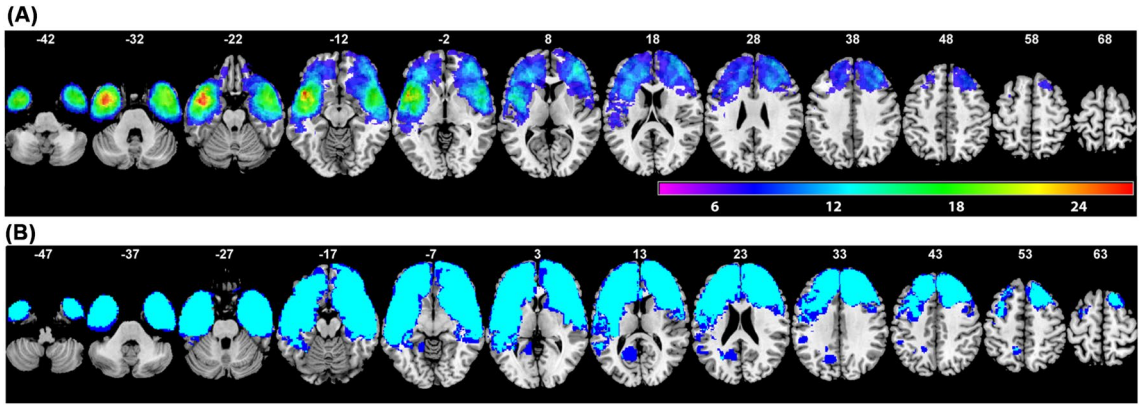

Fig. 3 **a** Lesion overlap of the 103 patients; **b** power maps for the forward (blue, 103 patients) and backward (light blue, 101 patients) digit span highlighting areas with power = .8

Table 4 VLSM results for the digit span forward

Area	$N > 0$	Max X	Max Y	Max Z
Left superior temporal	560	− 52	− 28	20
Left Rolandic operculum	111	− 50	− 28	21
Left supramarginal	106	− 56	− 26	20

VLSM results

Digit span tasks

Figure 3a displays the lesion overlap of the 103 patients. The maximum lesion overlap was in the fronto-temporo-insular regions. Regions with a statistical power of .8 in the VLSM analyses on forward and backward digit tasks are represented in Fig. 3b.

Only digit span forward showed a significant left-sided lesion–behavior correlation (forward: max t test: 5.67; Z score threshold = 4.68). In particular, forward digit span performance was significantly associated to a large lesion site, including the rolandic operculum, the left superior temporal gyrus, and the supramarginal gyrus (See Table 4 and Fig. 4).

Additional verbal tasks

Concerning verbal fluency, lesions in voxels of the left middle and inferior temporal gyri, middle and superior temporal pole, fusiform gyrus, amygdala, hippocampus and parahippocampal gyrus, as well as the uncinate fasciculus, significantly impaired performance in verbal fluency on semantic cue (Max t test 5,68; Z score threshold = 4.28; see Fig. 5 and Table 5). Conversely, verbal fluency on phonemic cue was significantly impaired after damage to the left insula, putamen, superior temporal pole and external capsule (Max t test 4.41; Z score threshold = 3.87; see Fig. 5 and Table 6).

Word comprehension scores were significantly linked to lesions in left temporal cortical and subcortical regions (Max t test: 6.19; Z score threshold = 5.1; see Fig. 6 and Table 7) involving the inferior, middle and superior temporal gyri, middle temporal pole, fusiform gyrus, putamen, and the external capsule.

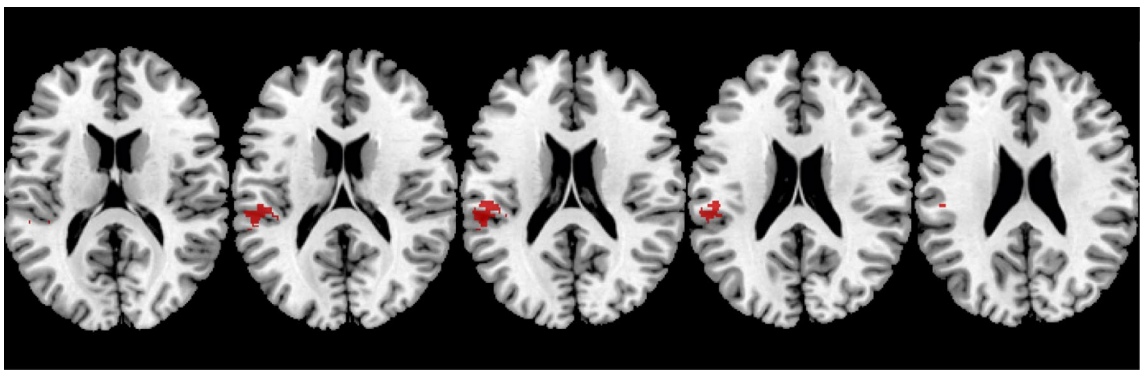

Fig. 4 VLSM maps for the forward digit span

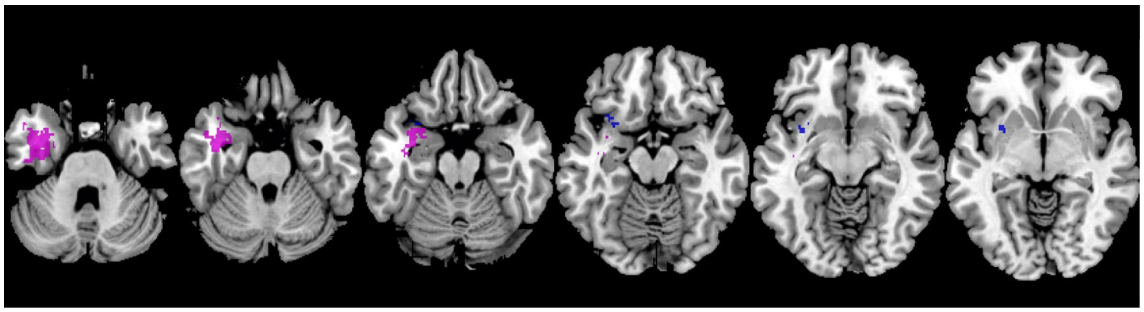

Fig. 5 VLSM maps for verbal fluency on semantic (in purple) and on phonemic (in blue) cue

Table 5 VLSM results for verbal fluency on semantic cue

Area	$N>0$	Max X	Max Y	Max Z
Left inferior temporal	1254	− 42	− 4	− 27
Left fusiform	723	− 37	− 7	− 31
Left middle temporal	278	− 42	− 2	− 27
Left superior temporal pole	257	− 31	5	− 19
Left parahippocampal	215	− 28	− 8	− 29
Left amygdala	177	− 31	4	− 19
Left middle temporal pole	152	− 30	7	− 36
Left hippocampus	95	− 33	− 4	− 27
Left uncinate fasciculus	18	− 32	0	− 20

Table 6 VLSM results for verbal fluency on phonemic cue

Area	$N>0$	Max X	Max Y	Max Z
Left insula	151	− 35	9	− 8
Left putamen	42	− 29	6	− 7
Left superior temporal pole	20	− 35	12	− 20
Left external capsule	16	− 32	4	− 8

In the case of word immediate and delayed recall, a significant involvement of several regions in the left hemisphere was found, namely the inferior and middle temporal gyri, superior and middle temporal pole, hippocampus and parahippocampal gyri, fusiform gyrus, amygdala and fornix, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and external capsule (immediate recall: Max t test: 6.67; Z score threshold = 4.11; see Fig. 7, blue map and Table 8; delayed recall: Max t test: 5.51; Z score threshold = 3.63; see Fig. 7 purple map and Table 9).

Finally, word, nonword and sentence repetition scores were significantly related to lesions in the inferior frontal gyrus and, to a lesser extent, parietal areas (Max t test: words = 10.26, threshold = 5.27; nonwords = 8.21, threshold = 5.3; sentences = 7.25, threshold = 5.61; see Fig. 8 and Table 10). Specifically, a significant correlation was found between lesions in the left postcentral gyrus, Rolandic operculum, superior temporal and supramarginal gyrus, and lower scores at repetition tests. Critically, these regions are only partly overlapping with those related to digit span impairment, being the latter more posterior (See Fig. S1).

Nonverbal tasks

VLSM analysis showed no significant correlation between brain damage and performance on the Corsi span. Similarly, there was no link between brain lesions and cognitive performance for the Colored Progressive Matrices and Attentional Matrices.

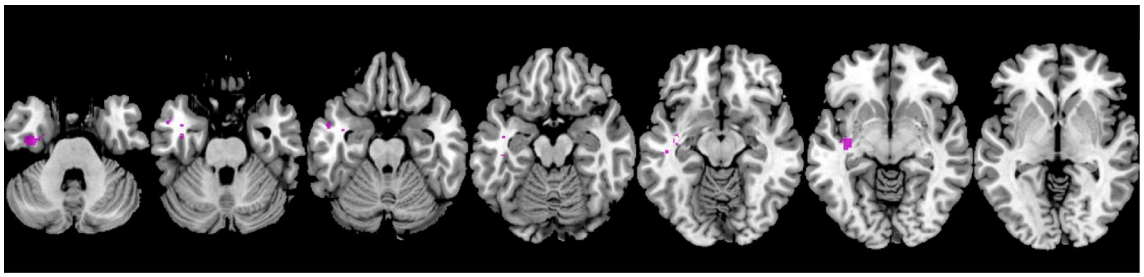

Fig. 6 VLSM maps for the word comprehension task

Table 7 *VLSM results for word comprehension*

Area	*N* > 0	Max *X*	Max *Y*	Max *Z*
Left fusiform	321	− 28	− 12	− 29
Left inferior temporal	213	− 43	− 15	− 35
Left middle temporal	153	− 50	− 23	− 12
Left superior temporal	32	− 40	− 11	− 8
Left putamen	28	− 35	− 15	− 7
Left middle temporal pole	22	− 47	9	− 31
Left hippocampus	21	− 37	− 16	− 11
Left external capsule	15	− 36	− 14	− 8

Discussion

In this study, we examined 103 patients who underwent surgery for glioma resection in the left or right hemisphere and we conducted VLSM analyses on their behavioral performance on digit span, word comprehension, repetition and production, and nonverbal tests. The aim was to verify whether the anatomical correlates of auditory-verbal STM, and in particular of the phonological input buffer, are the same as for the language system, as assumed by strong language-related accounts of auditory-verbal STM (see for example Buchsbaum and D'Esposito 2008; Koenigs et al. 2011), or auditory-verbal STM has specific neural correlates, only partially overlapping with the language network, as suggested by models that consider auditory-verbal STM related but independent from language (see Shallice and Papagno 2019 for a review).

Crucially, forward digit span scores were linked to lesions in both the left supramarginal gyrus and superior temporal areas, as reported in the literature on patients with a selective deficit of auditory-verbal STM mainly with a vascular (but not exclusively) lesion (see Vallar and Papagno 2002, for a review). Similarly, patients with logopenic variant of primary progressive aphasia show an impaired verbal span, no improvement with a pointing procedure and no phonological similarity effect; in those patients, atrophy or decreased blood flow is consistently found in the posterior portion of

Table 8 VLSM results for immediate verbal recall

Area	*N* > 0	Max *X*	Max *Y*	Max *Z*
Left inferior temporal	5995	− 42	− 4	− 27
Left middle temporal	2561	− 42	− 2	− 27
Left superior temporal pole	2449	− 38	7	− 23
Left fusiform	1953	− 33	0	− 34
Left middle temporal pole	1629	− 30	7	− 36
Left insula	1216	− 36	2	− 12
Left superior temporal	776	− 50	2	− 14
Left hippocampus	548	− 34	− 4	− 27
Left parahippocampal	531	− 32	0	− 31
Left amygdala	425	− 29	0	− 23
Left putamen	157	− 31	4	− 7
Left external capsule	89	− 30	4	− 6
Left uncinate fasciculus	45	− 34	2	− 18
Left fornix	20	− 32	− 6	− 18
Left IFL/IFOF	16	− 40	− 12	− 16

ILF inferior longitudinal fasciculus, *IFOF* inferior fronto-occipital fasciculus

Table 9 VLSM for delayed verbal recall

Area	*N* > 0	Max *X*	Max *Y*	Max *Z*
Left inferior temporal	5656	− 42	− 4	− 27
Left superior temporal pole	2982	− 38	7	− 23
Left middle temporal	2212	− 42	− 2	− 27
Left fusiform	2040	− 37	− 4	− 31
Left middle temporal pole	1857	− 30	7	− 36
Left parahippocampal	907	− 32	0	− 31
Left amygdala	458	− 31	0	− 24
Left hippocampus	426	− 34	− 4	− 27
Left insula	395	− 45	11	− 11
Left superior temporal	376	− 50	2	− 14
Left inferior frontal (opercularis)	59	− 51	14	0
Left inferior frontal (orbitalis)	36	− 48	17	− 8
Left uncinate fasciculus	35	− 34	2	− 20
Left fornix	13	− 32	− 6	− 18

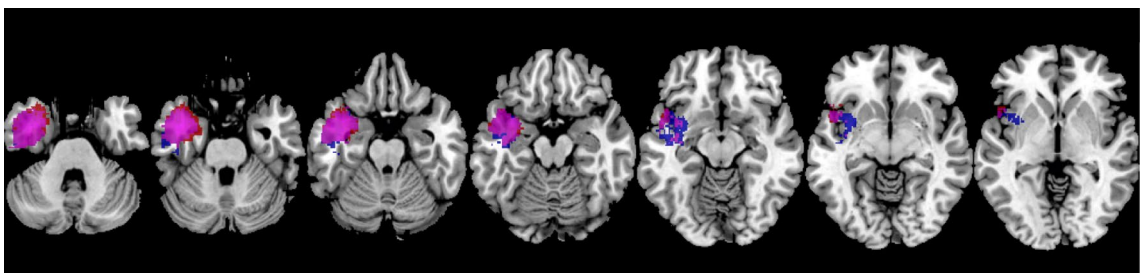

Fig. 7 VLSM maps for the immediate (blue) and delayed (purple) RAVLT tests

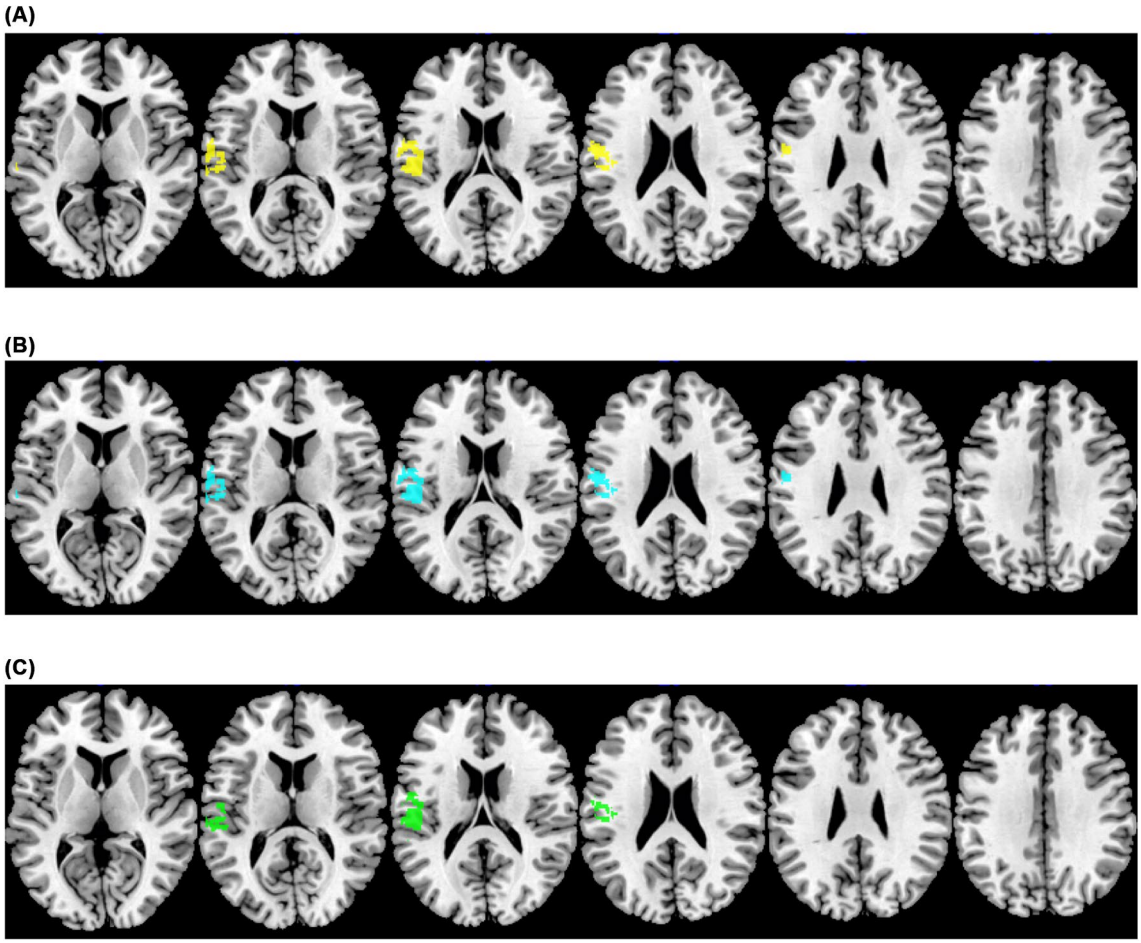

Fig. 8 VLSM maps for **a** word (in yellow), **b** nonword (in cyan) and **c** sentence (in green) repetition tasks

Table 10 VLSM results for word, nonword and sentence repetition

Area	$N>0$	Max X	Max Y	Max Z
Word repetition				
Left postcentral	1419	− 51	− 14	20
Left Rolandic operculum	913	− 48	− 16	20
Left superior temporal	507	− 62	− 27	9
Left supramarginal	265	− 63	− 23	15
Nonword repetition				
Left postcentral	1384	− 51	− 14	20
Left Rolandic operculum	885	− 48	− 16	20
Left superior temporal	503	− 62	− 27	9
Left supramarginal	265	− 63	− 23	15
Sentence repetition				
Left Rolandic operculum	762	− 48	− 16	20
Left superior temporal	721	− 55	− 38	18
Left postcentral	533	− 51	− 14	20
Left supramarginal	265	− 63	− 23	15

the left superior and middle temporal gyri and inferior parietal lobule (Gorno-Tempini et al. 2008). Our VLSM results clearly support a relevant role of the inferior parietal regions in auditory-verbal STM; word, nonword and sentence repetition, and crucially word comprehension, involved more anterior regions, partly overlapping with those found for digit span (see Fig. S1).

As stated, digit span forward was also linked to lesions in the superior temporal region. Critically, however, this area was mostly located in regions specific for auditory processing (i.e., A1, BA 41 and 42), likely due to span-presentation modality. Further evidence of a dissociation between language and auditory-verbal STM systems is that the subcortical pathways involved in word comprehension, including the left external capsule, were located in more ventral and anterior parts of the temporal lobe than the voxels found for digit span. Furthermore, when a more restrictive significance threshold was used for VLSM

results on the digit span scores, only the left supramarginal gyrus and, to a lesser extent, the left Rolandic operculum survived (See supplementary materials, Fig. S2 and Table S2). Finally, when adding in the VLSM as control variable word repetition, nonword repetition or word comprehension, results still show segregated regions in the temporoparietal areas, with more anterior voxels for language tasks and posterior ones for verbal short-term memory (see Fig S2, S3 and S4 in the supplementary materials). Therefore, our results show that the regions involved in auditory-verbal STM are distinct from those involved in language comprehension and production, and only partially overlapped with those involved in repetition. Specifically, only the left supramarginal gyrus has a consistent and specific role in auditory-verbal STM, as it has also been demonstrated by direct electrical stimulation in a series of 29 patients (Papagno et al. 2017).

Our findings differ from those reported by Leff et al. (2009), who advocate, in a voxel-based morphometry study on stroke patients, a role for the superior temporal cortex in auditory-verbal STM, with no involvement of the supramarginal gyrus. One reason accounting for this difference could be that, as already acknowledged, in Leff et al.'s study patients were tested in a chronic stage, and plastic changes could have occurred. In fact, when patients were tested within 48 h of stroke a crucial role of the supramarginal gyrus in verbal span has been demonstrated (Pettigrew and Hillis 2014). Moreover, in a recent fMRI study Yue et al. (2018) found that while the left superior temporal region was active in speech perception, it did not show load effect in auditory-verbal STM. By contrast, the left supramarginal region showed both effects. In addition, several single case studies consistently demonstrated a role of the inferior parietal lobule, and not necessarily an association with impairment of other language tests (see Shallice and Papagno 2019 for a review).

Finally, patients with conduction aphasia do not consistently show a reduced digit span (Damasio and Damasio 1980), possibly because single word repetition and digit span follow two distinct pathways through the arcuate fasciculus (Papagno et al. 2017).

Conversely, no significant result was found for the digit span backward. Critically, when VLSM was performed with a less conservative number of overlapping maps (3% of patients), a significant correlation with voxels in the left supramarginal gyrus was found. Backward digit span involves a control system that manipulates the buffer content. It is possible that, while the buffer has a clearly left-sided localized neural correlate, the control system depends on a more widespread, and potentially bilateral, frontal network. Indeed, this was the only task in which a consistent number of RH patients scored below the cutoff. If both frontal lobes are involved in working memory (see also Petrides et al. 1993), lesions in either hemisphere would produce similar behavioral outcomes, and thus VLSM would have failed in detecting this bilateral working memory network ("partial injury problem", Kinkingnéhun et al. 2007; Rorden et al. 2009). Furthermore, the lack of use of cost function masking or unified model to normalize the MRIs could introduce small displacement errors which can increase false negatives (Crinion et al. 2007).

Finally, we could not analyze the anatomical correlates of complex sentence comprehension, since a limited number of patients (53 patients, 27 with left brain damage) received this task, and none of them had lesions involving the supramarginal gyrus. However, we run a VLSM for the Token Test itself, and voxels in the posterior part of the left superior and middle temporal gyri as well as the angular and supramarginal gyri were correlated with impaired Token Test (see Pisoni et al. 2018); accordingly, it has been demonstrated that this task involves verbal STM (Vallar and Papagno 2002). Critically, residualizing digit span scores for the performance at the Token Test, VLSM reported a significant region in the temporoparietal areas (see Fig. S6). In the case of syntactically complex sentences, our expectation would have been to find an overlapping area in the supramarginal gyrus for syntactically complex sentences with a heavy load on memory; indeed, it has been demonstrated that verbal STM is necessary for processing center-embedded object-relative clauses (see Papagno and Cecchetto 2019 for a review).

Apart from the evidence concerning auditory-verbal STM, some side information emerged from this study. We will consider each of them separately.

First, behavioral neuropsychological results confirmed that surgery in the left hemisphere produces more cognitive consequences than resection performed in the right one, which is certainly relevant from a clinical point of view. Post-surgery impairment cannot be attributed to a general attentional deficit, since a few tests (Corsi span, Raven Colored Progressive Matrices) were not specifically impaired after left hemisphere resection; rather, this decline must depend on specific abilities implemented in the left hemisphere. One speculation could be that language mediates most of the cognitive functions, as already suggested, for example, for nonverbal reasoning (Newton and De Villiers 2007) and conceptual thinking, that are helped by internal verbalization. Indeed, the hypothesis has been raised that the left hemisphere is crucial for all intellectual tasks, verbal and nonverbal (De Renzi and Faglioni 1965).

Similarly, a second result was the lack of correlation between Corsi span performance and a specific lesion site in the right hemisphere. In fact, after surgery, more left brain-damaged patients than right brain-damaged ones were impaired, confirming that visuo-spatial span is not so clearly lateralized as digit span. This also suggests an

observation made during awake surgery (Papagno et al. 2017), and already highlighted by Hurlstone et al. (2014), namely that the left supramarginal gyrus seems to store order information independently from the type of material considered. Finally, we found significant voxels accounting for verbal fluency tasks in the left temporal region. Larger clusters involving the inferior, middle, and superior temporal lobe resulted for VLSM analysis of fluency on semantic cue, according to the hypothesis that the temporal cortex is critical for category-based word retrieval (Baldo et al. 2006). Differently, verbal fluency on phonemic cue has been related to the frontal cortex in previous studies (Henry and Crawford 2004; Baldo et al. 2006). Unexpectedly, we did not find significant clusters for phonemic fluency in the frontal cortex; however, previous studies reported impairments on verbal fluency on phonemic cue in patients with temporal damage, although to a lesser extent than semantic fluency (Henry and Crawford 2004). Furthermore, recent VLSM studies highlighted that a common neural substrate of phonemic and semantic fluency could be found in subcortical pathways, insula and in the left temporal cortex (Chouiter et al. 2016). Our results confirm these observations, supporting a role of the temporal cortex, as well as of the putamen and insula (Henry and Crawford 2004; Baldo et al. 2006), which are part of a "frontal" network.

In conclusion, this is the first study exploring the involvement of the supramarginal gyrus in auditory-verbal STM, with such a relevant number of patients, which is crucial to obtain reliable VLSM results. All data seem to converge on the assumption that auditory-verbal STM and language share partial common mechanisms, but the first relies on a specific network centered on the supramarginal gyrus.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was approved by the local ethical committee, and all participants gave their written informed consent before participating, in accordance with the Declaration of Helsinki.

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