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Mechanisms of Verbal Fluency Impairment in Stroke: Insights From "Strategic Indices" Derived From a Study of 337 Patients

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ABSTRACT

Verbal fluency provides a unique index of the functional architecture of control functions because it reflects the interactions between executive processes and lower-level language processes. However, an evaluation of the number of correct words alone does not enable one to determine precisely which processes are impaired. This study investigates post-stroke fluency impairments, focusing on previously unexplored indices and their neuroanatomical correlates using voxel-based lesion symptom mapping (VLSM). In total, 337 patients and 851 controls performed letter and semantic fluency tests. Analyses included overall performance (correct responses) and strategic indices (errors, time course, frequency, switches, and cluster size). Stroke patients produced fewer correct responses, more rule-breaking errors, fewer words after 15″, fewer infrequent words, fewer switches, and smaller clusters in letter fluency. Switching was strongly associated with letter fluency, while clustering was more related to semantic fluency. VLSM identified left-hemisphere structures, particularly frontal tracts (e.g., anterior thalamic and frontostriatal tracts), associated with switching, and a smaller set of left-hemisphere structures linked to clustering.

Conceptually, the findings suggest stroke-related fluency disorders primarily arise from impairments in executive strategic search, as indicated by switching impairments, with weaker impairment on lexicosemantic abilities. The rarity of rule-breaking and perseverative errors indicates that inhibition and working memory deficits do not significantly contribute to poor fluency. The patients' production of infrequent words and fluency worsened over time, although the precise contributions of the three core processes to these additional changes require further investigation. Our results highlight the importance of detailed fluency evaluations in stroke patients for optimized rehabilitation.

Abbreviations: AAL, Automatic Anatomical Labelling; ANOVA, analysis of variance; ATP, anterior thalamic projection; BA, Brodmann area; BNT, Boston Naming Test; CST, corticospinal tract; FST, frontostriatal tract; FAT, frontal aslant tract; GREFEX, *Groupe de réflexion sur l'évaluation des fonctions exécutives*; IFOF, inferior fronto-occipital fasciculus; L, left; Let, letter; MANOVA, multivariate analysis of variance; MMSEadj, the Mini-Mental State Examination score after adjustment for the educational level; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; mVLSM, multivariate voxel-wise lesion symptom mapping; NIHSS, National Institutes of Health Stroke Scale; R, right; Sem, semantic; TMTA, Trail Making Test part A; UF, uncinate fasciculus; VSLM, voxel-based lesion symptom mapping; WMH, white matter hyperintensity.

1 | Introduction

Fluency tests are widely used to examine language and executive functions owing to their simple, quick administration and high sensitivity to the presence of brain diseases (Godefroy et al. 2018; Henry, Crawford, and Phillips 2004; Henry and Crawford 2004). These tests require the subject to produce as many words meeting a given criterion (semantic or phonemic) as possible in a limited amount of time usually one or 2 minutes. The most commonly used verbal fluency performance index is the number of correct answers (i.e., the total number of words produced excluding errors) (Cardebat et al. 1990; Roussel and Godefroy 2008). Although it is widely acknowledged that verbal fluency tasks involve both linguistic and executive processes (Godefroy et al. 2018), the latter's respective contributions and interactions have not been fully characterized. These enduring uncertainties have clinical and conceptual implications. From a clinical point of view, the interpretation of an abnormally low number of correct responses prevents practitioners from precisely determining which processes are impaired and which are spared. From a conceptual point of view, a verbal fluency task provides a unique opportunity to determine the functional architecture of control functions, by revealing the interactions between executive processes and lower-level (e.g., language) processes.

According to a recently validated model of the functional architecture of verbal fluency (Godefroy et al. 2023), fluency production involves three types of processes operating in common: (i) linguistic processes, namely semantic and output lexicophonological processes (common to externally triggered oral expressions, such as those involved in the naming task), (ii) a general attentional activation process that optimizes processing speed (purposely assessed in a simple non-verbal task like the Trail Making Test part A, TMT A), and (iii) a strategic (i.e., cue-based, unusual) search process (Godefroy et al. 2023). This model has been cross-validated in a study of bilingual Lebanese people (which argues in favor of the involvement of a single, centralized strategic search process, regardless of the language or the level of fluency) (Kassir et al. 2023) and in a study of more than 2000 multicultural stroke patients from the MetaVCI map consortium (Weaver et al. 2021) (which confirms the involvement of the three above-mentioned sets of processes) (Godefroy et al. 2024).

With a view to determining the level of impairment, several experts have suggested that the indices derived from verbal fluency tasks can provide mechanistic insights into the underlying cognitive impairment (Thiele, Quinting, and Stenneken 2016; Troyer, Moscovitch, and Winocur 1997). These include rule-breaking errors, word repetitions, the time course of word production, word production frequency, and word production clustering, as detailed below. Rule-breaking errors have been reported in stroke patients, usually interpreted in terms of an impairment in monitoring and inhibition and associated with left frontomesial lesions (Cipolotti et al. 2020; Jansson, Ortiz, and Barreto 2020). The repetition of words (also called perseveration) is typically attributed to an impairment in working memory (Itaguchi et al. 2022). However, the few studies to have measured the number of repetitions in stroke patients found no difference versus controls (Cipolotti et al. 2020; Faroqi-Shah and Milman 2018; Szepietowska and Kuzaka 2021). The time course of word production is characterized by a lower percentage of late production (i.e., in the last 45 or 30″) by controls and even more so by stroke patients (Bose, Wood, and Kiran 2017; Kim et al. 2011; Pagliarin et al. 2021). The ability to produce infrequent words remains rarely assessed: it was reportedly impaired in 28 stroke patients (Faroqi-Shah and Milman 2018). Given that infrequent words are more difficult to activate, this impairment might primarily reflects difficulties in lexical access (Faroqi-Shah and Milman 2018), as also suggested by research on bilinguals (Kassir et al. 2023). Lastly, the decomposition of word production into clusters (corresponding to consecutive words with the same two first letters or within the same semantic subcategories) and switches (corresponding to shifts between subcategories) has provided valuable insights. The mean cluster size is considered to mainly reflect language abilities (Bose et al. 2022; Faroqi-Shah and Milman 2018; Troyer et al. 1998), whereas the number of switches would mainly reflect executive abilities (Bose, Wood, and Kiran 2017; Bose et al. 2022; Troyer, Moscovitch, and Winocur 1997). Most studies of stroke patients have consistently reported a lower number of switches in both letter fluency (Babulal 2016; Bose et al. 2022; Faroqi-Shah and Milman 2018; Patra, Bose, and Marinis 2020; Sarno et al. 2005) and semantic fluency (Babulal 2016; Bose, Wood, and Kiran 2017; Bose et al. 2022; Kiran, Balachandran, and Lucas 2014; Patra, Bose, and Marinis 2020; Troyer et al. 1998), whereas lower cluster size was observed in only one out of four studies in letter fluency (Babulal 2016) and in two out of five studies in semantic fluency (Bose, Wood, and Kiran 2017; Kiran, Balachandran, and Lucas 2014). Lastly, one research group reported a prominent impairment in switching in individuals with frontal lesions and reduced cluster size for semantic fluency in those with left temporal lesions only (Troyer et al. 1998).

Despite the significant value of these indices (rule-breaking errors, repetition, time course, lexical frequency, switch number, and cluster size, collectively referred to henceforth as "strategic indices"), two main questions remain unanswered. Firstly, in stroke patients, the pattern of impairments in all the strategic indexes and thus the level of impairment accounting for fluency deficit have not been systematically studied. Thus, it remains difficult to determine which mechanism primarily accounts for the impaired fluency observed in stroke. Second, the structure of the strategic indexes has not been examined in detail. Although a few studies suggest that the switch number and cluster size were associated with frontal/temporal lesions (Haugrud et al. 2012; Hirshorn and Thompson-Schill 2006; Troyer et al. 1998), these findings were not confirmed by the only available VLSM study (Davidson et al. 2008). To better document the pattern of stroke-related impairments in strategic verbal fluency indices and thus to examine the influence of lesion location, we compared a substantial control population with the large GRECogVASC cohort (Godefroy et al. 2012) of patients with documented, imaging-specified lesion characteristics and detailed analyses of verbal fluency. The objectives of the present study were to (i) more accurately describe the linguistic and executive processes involved in verbal fluency in stroke patients and (ii) identify their lesion determinants by applying a previously validated multivariate voxel-wise lesion symptom mapping (mVLSM) analysis (Arnoux et al. 2018).

2 | Materials and Methods

2.1 | Population

The GRECogVASC study's cross-sectional design and main results (NCT01339195) have been reported elsewhere (Barbay et al. 2018; Godefroy et al. 2012). Briefly, the study documented the prevalence of poststroke neurocognitive disorder in 49.5% of the stroke patients in the GRECogVASC cohort and found that 80% of the affected individuals had mild cognitive impairment (Barbay et al. 2018). We included French-speaking patients aged between 40 and 81, hospitalized for acute cerebral infarct or hemorrhage with initial positive imaging and an available informant. Patients with previously diagnosed conditions affecting cognition, other than a previous stroke, were excluded. The main exclusion criteria were as follows: neurological conditions (mental retardation, dementia, epilepsy, severe traumatic brain injury, Parkinson's disease, multiple sclerosis, brain tumor, or brain radiotherapy), systemic conditions (chronic alcoholism, substance addiction, liver, kidney, or respiratory failure, and paraneoplastic syndrome and treatments that affect cognition, other than stable dosage levels of an anxiolytic or serotoninergic antidepressant), a previous diagnosis of a psychiatric condition (schizophrenia or major psychiatric disorders requiring admission to a specialist hospital ward for > 2 days), or conditions that preclude cognitive assessment (illiteracy, severe sensory or motor impairments, alertness disorder), comorbid conditions associated with a life expectancy < 2 years, contraindication to MRI, pregnancy, legal guardianship, or lack of written informed consent. Aphasia, hemineglect, and prior stroke were not exclusion criteria.

The study was approved by the regional investigational review board (*Comité de Protection de Personnes Nord-Ouest II*, Amiens, France; reference: 2010/25).

The present study focused on the subgroup of patients ($n = 337$) who had both magnetic resonance imaging (MRI) data and written verbal fluency data available, recorded at Amiens University Medical Center (Amiens, France). The demographic, clinical, and imaging characteristics of the included patients (Table 1) were typical of a hospital-based stroke population, most of whom had experienced a non-severe ischemic stroke (Online Supplement 1, Table 1).

The normative data came from 851 healthy controls with available data on written fluency (Roussel and Godefroy 2016): mean ± SD age: 62.35 ± 11.3; females: 63%; right-handed: 92.6%; educational level 1 (≤ 8 years of full-time education): 26%;

TABLE 1 | Demographic, clinical, neuropsychological and imaging characteristics of patients at 6 months ($n = 337$).

Demographic characteristics	Age	63.95 ± 10.5
	Female sex (%)	39.2
	Right-handedness (%)	90.5
	Educational level 1/2/3* (%)	39.2/41.5/19.3
Cause of stroke	Ischemia/haemorrhage (%)	92/8
Clinical characteristics at 6 months	NIHSS score	1.45 ± 2.39
	Rankin grade 0/1/2/3/4 (%)	20.5/23.1/22.3/27.6/6.5
	Depressive symptoms (%)	29.7
	Anxiety (%)	31.8
Neuropsychological characteristics	$MMSE_{adj}$ score	26.7 ± 3.05
	MoCA score	23.06 ± 4.9
	Processing speed (TMTA)	−1.04 ± 1.49
	Naming (BNT)	−0.93 ± 1.36
Imaging characteristics	Normalized brain volume (ml)	1273.9 ± 116.7
	Normalized lesion volume (ml)	7.8 ± 22.5
	WMH Fazekas score 0/1/2/3 (%)	19.3/46.6/25.8/8.3
	Number of microbleeds	0.63 ± 2.99
	Hippocampal atrophy score	1.95 ± 1.8
	Hemosiderosis (%)	2.1

Note: Expressed as a percentage (%) or mean ± standard deviation (SD).
*Level 1: schooling years ≤ 8, level 2: schooling years > 8 and ≤ 11, level 3: schooling years ≥ 12.
BNT, Boston Naming Test; MMSEadj, Mini-Mental State Examination score after adjustment for educational level; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; TMTA, Trail Making Test part A; WMH, white matter hyperintensities.

educational level 2 (>8 and ≤11 years of full-time education): 37.1%; educational level 3 (≥12 years of full-time education): 36.9%; $MMSE_{adj}$ (Mini-Mental State Examination score adjusted for educational level): 28.6 ± 1.45.

2.2 | General Procedure

2.2.1 | Neuropsychological Assessments

Cognitive abilities were assessed using the previously described and normalized French adaptation of the National Institute of Neurological Disorders and Stroke—Canadian Stroke Network comprehensive battery (Barbay et al. 2018; Roussel and Godefroy 2016) (Online Supplement 1, Table 2), 6 months after the stroke (chronic phase). Lexicophonological output processes were assessed using the 34-item Boston Naming Test (BNT). Processing speed was purposely assessed with a visuomotor test: the TMT A (Godefroy et al. 2012). Performance was analyzed using a validated framework (Godefroy et al. 2014) for the interpretation of normative cognitive data from 1003 healthy volunteers; it provided z scores adjusted for demographic factors (age and educational level).

2.2.2 | Verbal Fluency Measurements and Indices

We analyzed the results of two verbal fluency tests performed in one minute (Roussel and Godefroy 2016): a letter test and a semantic test.

In the letter fluency test, all the words produced had to begin with the letter "p". In French, the distinction between letter and phonological fluency is necessary because some letters are associated with several phonemes (e.g., the letter "p" is associated with/p/and/f/, such as in "parapluie" ["umbrella"] and "pharmacie" ["pharmacy"]).

In the semantic fluency test, all the words produced had to belong to the animal category.

The tests were always performed in the same order, and the examiner noted down each word produced for further analysis. In line with the *Groupe de réflexion sur l'évaluation des fonctions exécutives* (GREFEX) instructions (Godefroy et al. 2010, 2023; Roussel and Godefroy 2008), participants were instructed not to say proper nouns, previously generated words with a different suffix only (e.g., "pomme" and "pommier" ["apple" and "apple tree"]) and nonwords and not to repeat words.

The total number of correct words produced in one minute was counted. We excluded rule-breaking errors (i.e., the production of proper nouns—e.g., "Paris", words not beginning with the letter "p"—e.g., "tomate" ["tomatoes"], or words not belonging to animal category—e.g., "dress"), repetitions (e.g., "dog, [...], dog"), derived words, and supra-ordinates (i.e., if the subject says "bird, blackbird, pigeon, sparrow", for example, the supra-ordinate "bird" is not counted in the total number of correct words).

We also counted the number of repetitions and the number of rule-breaking errors produced by the participants.

The time course of word production was analyzed by computing the percentage of correct words produced in the first 15″, between 16 and 30″, between 31 and 45″, and between 46 and 60″.

Lexical frequency was assessed using the Lexis 3.83 database (New and Pallier 2020) (Online Supplement 2). We first computed the lexical frequency for all words produced by the 851 controls (a total of more than 35,000 productions and 1935 different words) for the two types of fluency. We then subdivided the lexical frequency of the 1935 words into a low-frequency tercile, a medium-frequency tercile, and a high-frequency tercile. Using these normative data, we determined the percentage of infrequent words (i.e., those in Tercile 1) for each subject.

Clustering and switching indices were calculated according to the method published by Troyer, Moscovitch, and Winocur (1997). Clustering is defined as the mean cluster size, which is the total cluster size divided by the number of clusters. For letter fluency, clusters were made up of phonologically related words (e.g., words beginning with the same first two letters: "panier, parapluie, partir" ["basket, umbrella, leave"]), distinguished by a vowel sound: "poule, pull" ["hen", "sweater"], forming a rhyme: "pommier, poirier" ["apple tree", "pear tree"], or a homonym when the words were explicitly distinguished by the patient or spelled out: "porc, port" ["pig", "port"]. When adapting these clustering criteria to the French language, we decided not to take accents into account. For semantic fluency, clusters were made up of animals of the same subcategory (e.g., from the same environment: "cow, horse, pig" for farm animals and animals for human use; "cat, dog" for pets; and animals of the same zoological category: birds, cattle, or insects). Some clusters related to particularities of the French language prompted us to add the following criteria: animals that are linked in common representations (e.g., "elephant" and "mouse") and animals that are linked in popular fables or songs (e.g., "wolf, fox, chicken"). If several clusters overlapped, only the largest cluster was considered. Switching corresponds to the number of transitions between clusters. Repetitions and errors were included in the determination of clusters and switches, as these provide details of the course of lexical retrieval during the verbal fluency tasks (Troyer, Moscovitch, and Winocur 1997). Coding was performed by one primary rater and one secondary rater, in compliance with a detailed procedure for scoring cluster size and switches (Troyer, Moscovitch, and Winocur 1997). The interrater reliability for clustering and switching measurements calculated for the 366 first participants was excellent, as judged by the intraclass correlation coefficients (ICC) (letter fluency; clustering: ICC = 0.998, $p < 0.0001$, switching: ICC = 0.996, $p < 0.0001$; semantic fluency; clustering: ICC = 0.946, $p < 0.0001$, switching: ICC = 0.965, $p < 0.0001$).

Thus, seven measures were obtained for each fluency test: (i) the total number of correct words, (ii) the number of rule-breaking errors, (iii) the number of repetitions, (iv) the percentages of words produced between 0–15″, 16–30″, 31–45″, and 46–60″, (v) the percentage of infrequent words, (vi) the number of switches, and (vii) the mean cluster size.

2.3 | Imaging and Voxel-Wise Lesion Symptom Mapping

2.3.1 | MRI Acquisition

MRI data were acquired 6 months after stroke using a 3T machine (SIGNA HDXt, General Electric Medical Systems) equipped with an eight-channel head coil. Five sequences were recorded for each patient, and four were used in the present analysis: (i) a 3D high-resolution coronal oblique T1-weighted sequence (3D-T1) inversion-recovery ultrafast gradient echo with magnetization preparation; repetition time/echo time (TR/TE) = 11.4/5.4 ms, slice thickness = 1.0 mm, no interslice gap, flip angle: 15°; (ii) a fluid-attenuated inversion recovery (FLAIR) sequence: repetition time/echo time/inversion time (TR/TE/TI) = 9002/153.5/2250 ms, slice thickness = 5 mm, no gap; (iii) T2*-weighted gradient echo imaging sequences: TR/TE = 460/13 ms, slice thickness = 5 mm, no gap; (iv) a coronal T2 fast spin echo sequence: TR/TE = 4400, TE = 100 ms, slice thickness = 5 mm, no gap.

2.3.2 | Visual Analysis of Imaging Data

2.3.2.1 | Stroke Lesions. The presence, type, number, and volume of cerebral infarcts and hemorrhages were evaluated with 3D-T1, FLAIR, and T2* sequences, in accordance with a previously reported method (Godefroy et al. 1998) and using the Standards For Reporting Vascular Changes on Neuroimaging (STRIVE) criteria (Wardlaw et al. 2013). A stroke lesion was defined as cavitation with a diameter greater than 4 mm, with no evidence of other causes, such as perivascular dilatation (Godefroy et al. 1998; Wardlaw et al. 2013). Lesions were defined by reference to the initial post-stroke MRI data, and especially those from the diffusion-weighted imaging and T2* sequences. Multiple stroke lesions were defined as lesions that did not coalesce on at least one slice, whatever their age.

2.3.2.2 | White Matter Hyperintensities (WMHs) and Microbleeds. WMHs and microbleeds were identified according to the STRIVE criteria (Wardlaw et al. 2013). Microbleeds were defined as small (diameter < 10 mm) areas of signal void with associated blooming on T2*-weighted MRI. Hemosiderosis was defined according to Charidimou's criteria (Charidimou et al. 2015). WMHs were segmented using the LST lesion prediction algorithm for SPM12 (P. Schmidt et al. 2019), as previously validated in stroke (Lawson et al. 2024). This analysis provided WMH volumes.

2.3.2.3 | Medial Temporal Lobe Atrophy. Medial temporal lobe atrophy was evaluated using the Scheltens score (Scheltens et al. 1992) for 3D-T1 coronal sequences (total score = left + right hippocampal scores).

2.3.3 | MRI Normalization and Segmentation

The stroke lesions (defined as cavitation on a T1 sequence) related to the index stroke and (if applicable) the previous or recurrent stroke were analyzed and segmented according to a previously described method (Arnoux et al. 2018). Trained investigators segmented the lesions manually on native 3D-T1 MRI datasets using Mricron software (v1.0.20190902), according to a previously validated and reliable method (Arnoux et al. 2017). The lesion masks and MRI datasets were normalized against the MNI152 atlas by using the Clinical Master toolbox and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) (Rorden et al. 2012). This procedure automatically segmented the brain tissues, which were then used to compute the total normalized brain volume using SPM12 (Arnoux et al. 2018). The quality of brain and mask normalization was validated visually and by checking the sample's homogeneity with the CAT12 toolbox (Gaser et al. 2024).

2.3.4 | Determination of Lesioned Structures

Lesion maps (generated using both Mricron and the automated procedure in NiiStatV9) were loaded into NiiStatV9 (Rorden, Karnath, and Bonilha 2007) to determine the involved structures using the Automatic Anatomical Labelling (AAL) (Tzourio-Mazoyer et al. 2002) and NatbrainLab (Catani and Thiebaut de Schotten 2008) atlases.

2.3.5 | VLSM Analysis

The method used for VLSM has been validated previously (Arnoux et al. 2018) and has been used for the identification of lesion associated with poor verbal fluency (Godefroy et al. 2023). The first bivariate step corresponded to conventional VLSM (Bates et al. 2003) and was followed by an mVLSM analysis (Arnoux et al. 2018; Puy et al. 2018). This analysis was performed without including the lesion volume as a covariate; it has already been established that (i) the most accurate anatomic determinations using the VLSM method are independent of the lesion volume, and (ii) the lesion volume's contribution should be assessed in multivariate analyses (mVLSM) (Arnoux et al. 2018; Godefroy et al. 2024; Puy et al. 2018). The VLSM analyses were restricted to the indices that contributed most to fluency performance i.e., the number of switches and the mean cluster size for both letter and semantic fluencies.

2.3.5.1 | Conventional VLSM Analysis. The lesion overlap map for the 337 patients is presented in Figure 1. Analyses were performed using NiiStatV9 (https://www.nitrc.org/projects/niistat/), running on Matlab R2018b (https://in.mathworks.com/products/matlab.html) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The adjusted threshold ($p = 0.05$) was computed using 2000 permutations.

The locations of significant clusters within brain structures (hereafter referred to as "significant structures") were determined using the AALCAT atlas (Catani and Thiebaut de Schotten 2008; Tzourio-Mazoyer et al. 2002) with a probability threshold > 0.85; the latter has been found to be more appropriate (Aubignat et al. 2023) for the frontostriatal tract (FST), anterior thalamic projections (ATPs), and frontal aslant tract (FAT). We used an automated in-house MATLAB procedure to automatically determine the lesion volume for each cluster in each patient (e.g., patient 1's lesion included 20 voxels from the cluster located in the right insula). The individual volumes for each cluster were used as an independent variable in the mVLSM analysis.

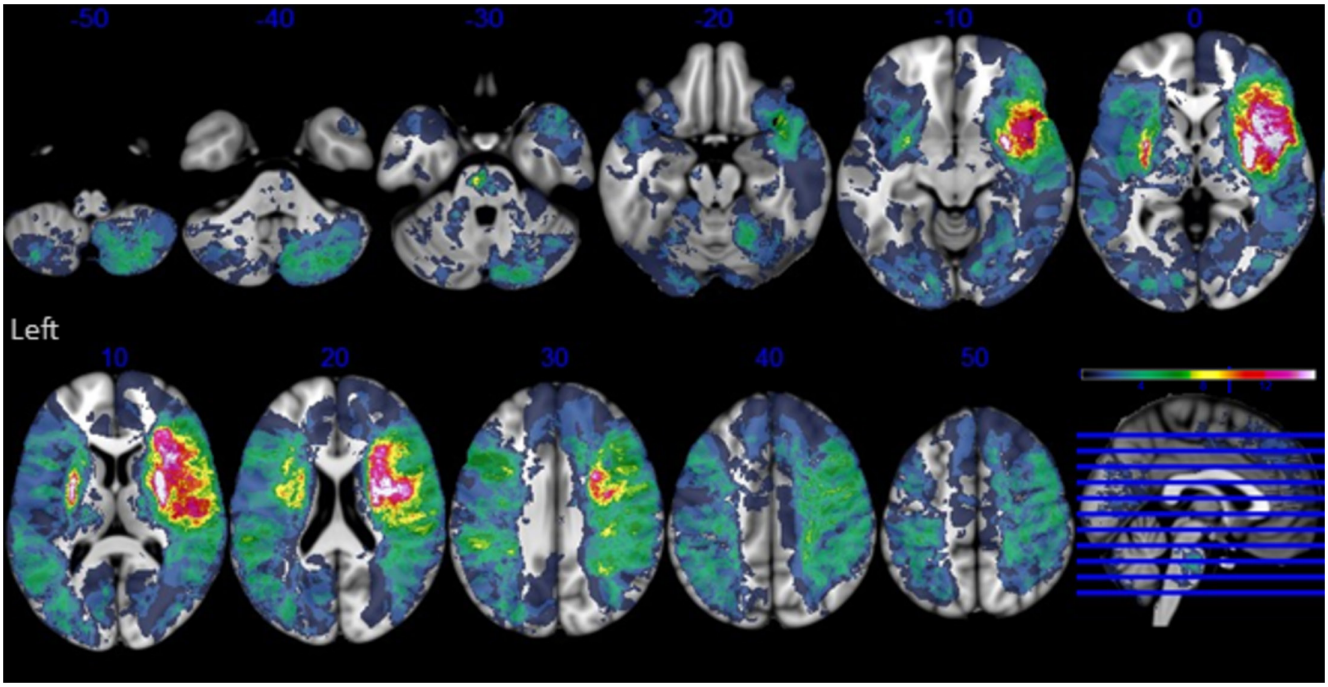

FIGURE 1 | Lesion overlay maps for the whole study population of stroke patients ($n = 337$). In each image of the brain, the left hemisphere is shown on the left side.

2.3.5.2 | mVLSM Analysis. To reduce bias in the mass-univariate analysis (especially bias due to false positives and Type 1 error) (Arnoux et al. 2018), we performed a multivariate analysis in two steps: (i) a bivariate step, using Pearson correlation coefficients, and (ii) stepwise linear regression analysis (Godefroy et al. 1998); this approach has been found to improve the accuracy of VLSM results (Arnoux et al. 2018; Puy et al. 2018). The correlation analysis examined the association between performance and the following general volumetric measures: normalized brain volume, lesion volume, and WMH volume. In the multivariate step, any volumetric measures (normalized brain volume, lesion volume, and WMH volume) found to be significant in the correlation analysis and the structures found to be significant in the VLSM analysis were fed into a stepwise linear regression (one regression per strategic index).

2.3.6 | Statistical Analysis

After appropriate data transformation, the strategic fluency indices influenced by demographic factors (the number of words, the number of switches, and the mean cluster size) were adjusted for age and educational level when appropriate, according to a previously validated method (Godefroy et al. 2014). A lower Z-score corresponds to worse performance.

The patients' levels of performance were compared with those of controls in a repeated-measures multivariate analysis of variance (MANOVA), and effect size was assessed using η^2. Firstly, the number of correct words was compared in a repeated-measures MANOVA with group (patients, controls) as the between-subject factor and fluency (letter, semantic) as the within-subject factor. Secondly and thirdly, the groups were compared with regard to the number of rule-breaking errors and the number of repetitions in two separate repeated-measures MANOVAs (one with the number of rule-breaking errors and the other with repetitions as dependent variable) with group (patients, controls) as the between-subject factor and fluency (letter, semantic) as the within-subject factor. Fourthly, the groups were compared with regard to the percentage of correct words generated in the four-time intervals (0–15″, 16–30″, 31–45″, and 46–60″) in a repeated-measures MANOVA with group (patients, controls) as the between-subject factor and fluency (letter, semantic) and time interval (0–15″, 16–30″, 31–45″, and 46–60″) as within-subject factors. Fifthly, the groups were compared with regard to the percentage of infrequent words in a repeated-measures MANOVA with group (patients, controls) as the between-subject factor and fluency (letter, semantic) as the within-subject factor. Sixth and seventh, the groups were compared with regard to switching and clustering indices in two repeated-measures analysis of variance (ANOVA) (number of switches, mean cluster size) with group (patients, controls) as the between-subject factor and fluency (letter, semantic) as the within-subject factor. These MANOVAs were followed by post hoc contrast analyses.

We also examined how these strategic fluency indices contributed to fluency performance in all participants, using two stepwise linear regression analysis with the fluency Z-score as the dependent variable (first regression analysis: letter fluency; second regression analysis: semantic fluency). Given the previously demonstrated role of the oral output language and processing speed in fluency (Godefroy et al. 2023, 2024; Kassir et al. 2023), the z-scores for the BNT and TMT A were first entered into the regression. Next, the strategic fluency indices that were found to be impaired in stroke patients (the number of rule-breaking errors, production in 16–60″, the percentage of infrequent words, the number of switches, and the mean cluster size) were selected in a stepwise process.

TABLE 2 | Verbal fluency indices.

	Letter fluency		Semantic fluency	
	Patients	**Controls**	**Patients**	**Controls**
Nb of words (z-score)	−0.847 ± 0.05*	−0.026 ± 0.03	−1.002 ± 0.05*	−0.038 ± 0.03
Nb of rule-breaking errors (n)	0.110 ± 0.02*	0.072 ± 0.01	0.047 ± 0.01*	0.030 ± 0.01
Nb of repetitions (n)	0.141 ± 0.03*	0.239 ± 0.02	0.228 ± 0.03*	0.279 ± 0.02
Production 0–15 s (%)	41.9 ± 0.6*	38.8 ± 0.4	39.8 ± 0.5*	37.3 ± 0.3
Production 16–60 s (%)	58.1 ± 0.6*	61.2 ± 0.4	60.1 ± 0.5*	62.6 ± 0.3
Production of infrequent words (%)	11.76 ± 0.6*	13.51 ± 0.4	6.37 ± 0.4*	7.92 ± 0.2
Nb of switches (z-score)	−0.732 ± 0.05*	−0.012 ± 0.03	−0.773 ± 0.05*	−0.009 ± 0.03
Mean cluster size (z-score)	−0.122 ± 0.06*	0.007 ± 0.04	0.084 ± 0.06	0.007 ± 0.04

Note: Expressed as the mean (n) or z-score or percentage (%) ± standard deviation. Nb, number; s, second.
*$p < 0.05$.

Statistical analyses were performed using SAS (version 7.15) and R (version 3.6.3) (R Core Team 2013). The threshold for statistical significance was set to $p < 0.05$, unless otherwise indicated.

3 | Results

3.1 | Behavioural Analysis

3.1.1 | Measurements of Verbal Fluency

3.1.1.1 | The Number of Words. The adjusted z-scores for the number of correct words were lower ($p < 0.0001$, $\eta^2 = 0.200$) in patients (−0.925 ± 0.04) than in controls (−0.032 ± 0.03) and tended to be lower ($p = 0.062$, $\eta^2 = 0.003$) for semantic fluency (−0.520 ± 0.03) than for letter fluency (−0.437 ± 0.03). The semantic fluency was worse in patients (group x fluency: $p = 0.040$, $\eta^2 = 0.003$) (Table 2).

To sum up, this analysis showed that patients exhibit lower fluency, which was prominent for semantic fluency.

3.1.1.2 | The Number of Errors. The number of rule-breaking errors was higher ($p = 0.02$, $\eta^2 = 0.004$) in patients (0.079 ± 0.01) than in controls (0.051 ± 0.01) and higher ($p < 0.0001$, $\eta^2 = 0.017$) for letter fluency (0.091 ± 0.01) than for semantic fluency (0.039 ± 0.01; group x fluency: $p = 0.3$).

The repetition rate was higher ($p = 0.002$, $\eta^2 = 0.008$) in controls (0.259 ± 0.01) than in patients (0.185 ± 0.02) and higher for semantic fluency (0.254 ± 0.02; $p = 0.024$, $\eta^2 = 0.004$) than for letter fluency (0.190 ± 0.02; group x fluency: $p = 0.3$).

To sum up, these analyses showed that patients produced more rule-breaking errors and fewer repetitions.

3.1.1.3 | Time Course. The time course of fluency production did not differ from one group to another ($p = 0.4$) or as a function of the type of fluency ($p = 0.6$). The effect of the time interval was significant ($p < 0.0001$, $\eta^2 = 0.560$), due to a greater proportion of production in the first 15″ (39.8% ± 0.3) than in other time intervals (16–30″: 23.9% ± 0.2, 31–45″: 19% ± 0.2, 46–60″: 17.2% ± 0.3; $p < 0.0001$ for all) (Figure 2). The fluency x time interval interaction ($p < 0.0001$, $\eta^2 = 0.011$) was due to lower production after 15″ for letter fluency (Letter: 0–15″: 40.7% ± 0.4, 16–30″: 23.9% ± 0.3, 31–45″: 18.8% ± 0.3, 46–60″: 16.7% ± 0.4; Semantic: 0–15″: 38.9% ± 0.4, 16–30″: 24.1% ± 0.3, 31–45″: 19.2% ± 0.3, 46–60″: 17.7% ± 0.3; $p < 0.0001$ for all). Lastly, the group x time interval interaction ($p < 0.0001$, $\eta^2 = 0.021$) was due to lower production by patients after 15″ (Patients: 0–15″: 41.6% ± 0.5, 16–30″: 23.2% ± 0.4, 31–45″: 18.7% ± 0.4, 46–60″: 16.5% ± 0.4; Controls: 0–15″: 38.2% ± 0.4, 16–30″: 24.8% ± 0.3, 31–45″: 19.4% ± 0.3, 46–60″: 17.8% ± 0.3; $p < 0.0001$ for all) (Figure 2) (group x fluency: $p = 0.6$; group x fluency x time interval: $p = 0.5$).

To check that the patients' fluency production in the first 15″ was indeed impaired (despite the higher proportion of productions in this time interval), we performed an additional ANOVA of the number of corrects responses produced between 0 and 15 s, with group (patients, controls) as the between-subject factor and fluency (letter, semantic) as the within-subject factor. This analysis confirmed that patients were impaired ($p < 0.0001$, $\eta^2 = 0.08$) in the first 15″ (patients: 4.5 ± 0.05; controls: 5.7 ± 0.07).

To sum up, these analyses showed that the patients' word production worsened as the test went on and was especially poor after the first 15″.

3.1.1.4 | Production of Infrequent Words. The infrequent word production rate was lower ($p < 0.0001$, $\eta^2 = 0.013$) in patients (9.03% ± 0.4) than in controls (10.7% ± 0.2) and lower ($p < 0.0001$, $\eta^2 = 0.147$) for semantic fluency (7.1% ± 0.2) than for letter fluency (12.6% ± 0.3) (group x fluency: $p = 0.8$).

To sum up, patients produced less infrequent words than controls.

3.1.1.5 | Switching and Clustering. The adjusted z scores for switching were lower ($p < 0.0001$, $\eta^2 = 0.153$) in patients (−0.753 ± 0.04) than in controls (−0.010 ± 0.03). There was no effect of fluency ($p = 0.602$) (group x fluency interaction: $p = 0.541$).

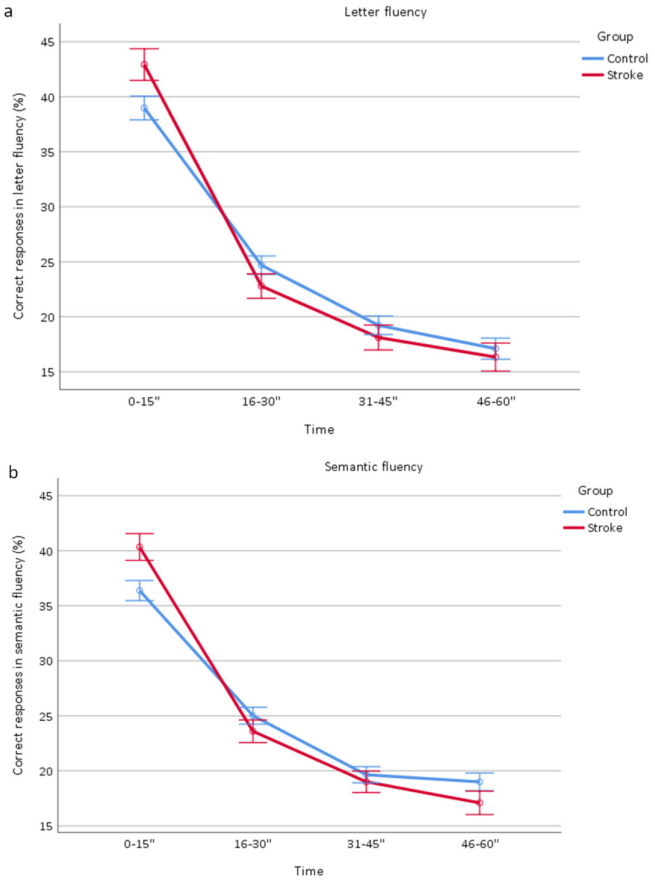

FIGURE 2 | The percentage of words produced as a function of time for (a) letter fluency and (b) semantic fluency. Words were produced by patients and controls. Time was divided into four intervals: 0–15″, 16–30″, 31–45″, and 46–60″.

The adjusted z scores for the mean cluster size were similar in the two groups ($p=0.6$), and were lower ($p=0.025$, $\eta^2=0.004$) for letter fluency (-0.058 ± 0.03) than for semantic fluency (0.046 ± 0.03). The mean cluster size was more impaired in patients for letter fluency (group x fluency interaction: $p=0.026$, $\eta^2=0.004$) (Table 2).

These analyses showed that relative to controls, patients performed fewer switches in semantic and letter fluencies and produced smaller clusters in letter fluency.

In summary, the group comparisons showed that patients exhibited poorer fluency in general and especially for the semantic fluency. This poor performance was associated with a higher rate of rule-breaking errors, a lower repetition rate, a lower percentage of production after 15″, less production of infrequent words, an overall decrease in switching, and a small mean cluster size for letter fluency.

3.1.2 | Contribution of Strategic Indices to Fluency Performance

3.1.2.1 | Letter Fluency. After controlling for naming and processing speed ($R^2=0.187$, $p<0.0001$), the regression analysis showed that switching ($R^2=0.470$, $p<0.0001$) and clustering ($R^2=0.196$, $p<0.0001$) were associated with letter fluency (model $R^2=0.853$, $p<0.0001$).

3.1.2.2 | Semantic Fluency. After controlling for naming and processing speed ($R^2=0.24$, $p<0.0001$), the regression analysis showed that switching ($R^2=0.188$, $p<0.0001$) and clustering ($R^2=0.316$, $p<0.0001$) were associated with semantic fluency (model $R^2=0.744$, $p<0.0001$).

To sum up, in addition to oral output processes and processing speed, switching and clustering accounted for a large proportion of the variance in fluency. Letter fluency was more strongly influenced by the number of switches, while semantic fluency was more influenced by the mean cluster size.

3.2 | The VLSM Analysis

3.2.1 | Conventional VLSM Analysis

The analysis of the switching and clustering indices revealed several structures, most of which were located in the left hemisphere. The number of switches (Figure 3a and Table 3) was mainly associated with the left insula, putamen, corticospinal tract (CST), uncinate fasciculus (UF), inferior fronto-occipital fasciculus (IFOF), FAT, and ATPs in both letter and semantic fluency tests. The mean cluster size (Figure 3b and Table 3) was mainly associated with the left putamen, UF, IFOF, FST, and FAT in both fluency tests. The frontosubcortical tracts (FST, FAT, and ATPs) contributed prominently to the number of switches (Table 3).

3.2.2 | mVLSM Analysis

The results of the correlation analysis indicated that the number of switches for both fluencies was associated with lesion volume (letter fluency: $R=-0.14$, $p=0.007$; semantic fluency: $R=-0.13$, $p=0.013$) and hippocampal atrophy (letter fluency: $R=-0.22$, $p<0.0001$; semantic fluency: $R=-0.14$, $p=0.01$). Furthermore, the number of switches for letter fluency was associated with brain volume ($R=0.23$, $p<0.0001$) and of the WMH volume ($R=-0.21$, $p<0.0001$).

A stepwise linear regression analysis showed that switching was associated with the left ATPs for both letter fluency ($R^2=0.063$, $p<0.0001$) and semantic fluency ($R^2=0.054$, $p<0.0001$). The proportion of the variance in clustering accounted for by the various structures was very low, and so the stepwise linear regression analysis was not performed.

4 | Discussion

Our present results not only confirmed the well-documented impairment in verbal fluency of stroke patients (Babulal 2016; Bose, Wood, and Kiran 2017; Bose et al. 2022; Faroqi-Shah and Milman 2018; Freire, Gagliardi, and dos Santos 2021; Godefroy et al. 2023, 2024; Henry and Crawford 2004; Kim et al. 2011; Roussel et al. 2016), but also indicated that various strategic indices can provide insights into the mechanisms that underlie

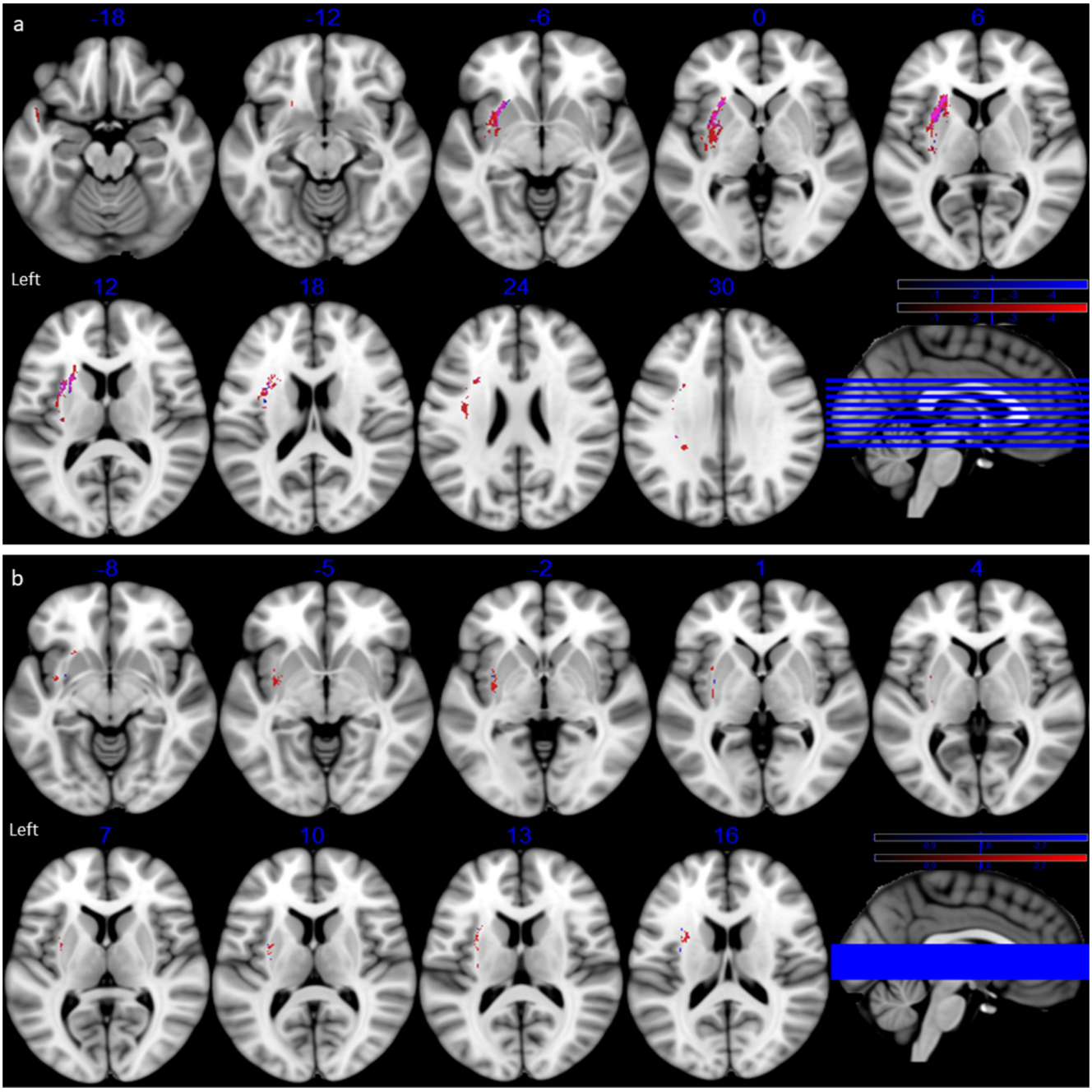

FIGURE 3 | The results of conventional VLSM. Voxels significantly associated with (a) switching and (b) clustering for letter fluency are shown in blue and those associated with semantic fluency are shown in red. Areas of overlap are shown in purple. The left hemisphere is on the left side of the figure. Only significant voxels are shown.

fluency impairment in this population; this should enable practitioners to provide a more reliable cognitive diagnosis.

4.1 | Behavioural Analysis

For both letter and semantic fluencies, the number of rule-breaking errors was higher for patients than for controls. This is consistent with previous findings and might reflect an impairment in the strategic search process and/or in the inhibition of irrelevant responses (Cipolotti et al. 2020; Jansson, Ortiz, and Barreto 2020). However, rule-breaking errors were infrequent and did not contribute to overall fluency performance in a stepwise regression analysis. This finding suggests that inhibition impairment is unlikely to account for the observed fluency deficits. This is expected for common causes of stroke, where inhibition impairments are infrequent (Godefroy et al. 2018; Roussel et al. 2016).

The number of repetitions was slightly lower among patients than among controls and, therefore, could not account for the former group's fluency impairment. This finding is in line with previous reports (Cipolotti et al. 2020; Faroqi-Shah and Milman 2018; Szepietowska and Kuzaka 2021) and suggests

TABLE 3 | Regions with voxels associated with clustering and/or switching in verbal fluency.

	Switch_let		Switch_sem		Cluster_let		Cluster_sem	
	Voxels	**Z**	**Voxels**	**Z**	**Voxels**	**Z**	**voxels**	**Z**
Voxel n/threshold	4638	−3.17	2364	−3.08	557	−2.66	84	−3.45
Voxels sum	9168		4827		1092		155	
Precentral_L	10	−3.100						
Insula_L	155	−3.819	34	−3.412				
Putamen_L	959	−3.616	485	−3.419	152	−3.000	29	−3.655
Pallidum_L	12	−3.333						
Temporal_pole_sup_L	28	−3.000						
Anterior_segment_L	11	−3.557						
Arcuate_L	104	−3.558	17	−3.000				
Long_segment_L	57	−3.719						
Uncinate_L	423	−3.742	243	−3.465	35	−3.000	2	−4.000
Inferior_occipito_frontal_L	1233	−3.826	841	−3.564	149	−3.000	19	−3.895
Cortico_spinal_L	520	−3.690	250	−3.368	29	−3.000		
Internal_capsule_L	79	−3.468	29	−3.069	27	−3.000		
Fronto_striatal_L	115	−3.450	18	−3.055	507	−3.000	76	−3.816
Fronto_striatal_R	3855	−3.696	2165	−3.459				
Frontal_aslant_tract_L	666	−3.564	226	−3.230	141	−3.000	16	−3.875
Anterior_thalamic_projections_L	885	−3.755	495	−3.404	47	−3.000		

Note: L, left; Let, letter; R, right, Sem, semantic.
The regions listed were selected in a multivariate analysis.

that stroke patients do not experience more difficulty in monitoring previously produced words and keeping them in memory (Faroqi-Shah and Milman 2018). Thus, the fluency deficit cannot be explained by an impairment in working memory; this is consistent with the general absence of a relationship between executive memory and working memory abilities in stroke (Roussel et al. 2012).

Our observation of a time-related decrement indicates that an impairment in fluency is already present at 15 s and worsens as time goes on. This corroborates the few earlier reports on stroke patients (Bose, Wood, and Kiran 2017; Kim et al. 2011; Pagliarin et al. 2021). The significance of this decrement over time remains debated, having been explored mainly in controls. Mayr and Kliegl's (2000) model features the constant involvement of executive processes responsible for initiating and sustaining word retrieval, with semantic processes becoming increasingly engaged as the task progresses. This gradual increase in the involvement of semantic processes is further underpinned by Raboutet et al.'s (2010) report of a rise over time in semantic indices (cluster size and semantic exploration index). In a third study, the decline in performance observed in bilinguals' non-dominant language (compared to their dominant language) was not attributed to executive control (which is independent of language), suggesting that lexicosemantic access (i.e., vocabulary) plays a primary role (Kassir et al. 2023). In contrast, two recent studies suggest that the time decrement is mainly driven by executive control (Bose et al. 2022; Michalko, Marko, and Riečanský 2023). One study (Bose et al. 2022) reported that the decrement in the proportion of correct responses over time was greater in monolinguals than bilinguals; the latter supposedly have better executive control. However, this interpretation has not been confirmed by measures of executive function. The second study (Michalko, Marko, and Riečanský 2023) found that the time-related decrement in fluency tests was associated with low typicality, low semantic similarity, and poor executive abilities (Stroop interference), suggesting that executive demand increases over time. However, processing speed was a confounding factor, as interference was measured by Stroop response time. Finally, a recent study conducted by our team using an interventional design (dual-task paradigm) found that phonological interference mainly affected the first time interval, whereas speed and flexibility interference primarily affected the last time interval (Dorchies et al. 2024). These results support the hypothesis that the phonological output lexicon plays a prominent role in early fluency production, while more demanding processes (i.e., executive functioning) become more involved in later stages of production.

We found that stroke patients produced fewer infrequent words. This is in line with a study of 28 aphasic patients (Faroqi-Shah and Milman 2018). Given that frequent words are easier to activate, the low production of infrequent words is interpreted as a

deficit in lexical access (i.e., a linguistic process) (Faroqi-Shah and Milman 2018).

The number of switches was lower in patients for both letter and semantic fluency tests, and the mean cluster size was slightly lower in patients for letter fluency only. Most studies on stroke patients have found that switching is impaired (Babulal 2016; Bose, Wood, and Kiran 2017; Bose et al. 2022; Faroqi-Shah and Milman 2018; Kiran, Balachandran, and Lucas 2014; Patra, Bose, and Marinis 2020; Sarno et al. 2005; Troyer et al. 1998). Conversely, clustering was reportedly impaired in only one out of four studies on letter fluency (Babulal 2016) and two out of five studies on semantic fluency (Bose, Wood, and Kiran 2017; Kiran, Balachandran, and Lucas 2014). Three studies found no clustering impairment (one on letter fluency only) (Troyer et al. 1998, temporal lesion group), one on semantic fluency only (Babulal 2016), and two on both fluency types (Bose et al. 2022; Troyer et al. 1998, frontal lesion group). Clustering might mainly reflect access to lexicophonological and/or lexical-semantic storage (i.e., linguistic processing), whereas it has been suggested that switching reflects cognitive flexibility (i.e., executive functioning) (Troyer, Moscovitch, and Winocur 1997).

Importantly, our stepwise regression analysis showed that clustering and switching were closely associated with fluency performance—even after accounting for the variance related to output lexicophonological processes (involved in the naming task) and processing speed. This could suggest that these indices reflect a latent variable corresponding to strategy, previously identified as the strategic search process in the model of Godefroy et al. (2023).

4.2 | VLSM Analysis

VLSM analyses showed that switching depends on a large number of structures, primarily frontal tracts such as the FST, FAT, and ATPs. mVLSM analysis identified the left ATPs in both letter and semantic fluency tests. Given the role of ATPs in the subcortical-frontal connection, this finding is in line with Troyer et al. (1998) and suggests that switching is strongly related to executive functioning. Previous studies have also reported that the left ATPs are associated with performance in both letter and semantic fluency (Cipolotti et al. 2020; Godefroy et al. 2023, 2024; Li et al. 2017), indicating that the two types of fluency share several strategic processes (Thye, Szaflarski, and Mirman 2021). Indeed, the left ATPs link the thalamus to the frontal lobe and are involved in both rapid access to sensory information and top-down modulation of early perceptual processes (Catani et al. 2012). These abilities seem essential for switching; in other words, awareness that the current subcategory will soon be exhausted and that it will be necessary to shift to another subcategory to continue generating correct words (Troyer et al. 1998). Clustering depends on fewer left hemisphere structures, as would be expected for stroke patients with a minor impairment. In our study, none of the temporal regions was associated with cluster size.

The association with lesions in the left UF suggests that the temporal lobe (BA38) is disconnected from the frontal lobe. The involvement of the left UF in semantic abilities and memory has been widely documented (Hagoort 2013; Harvey et al. 2013; Li et al. 2017), suggesting that clustering reflects underlying semantic and linguistic processes (Troyer, Moscovitch, and Winocur 1997). Our results are very similar to those of Troyer et al. (1998), who reported that lesions of the temporal lobe induced impairment in clustering in a semantic fluency test. According to Troyer et al. (1998) semantic fluency clustering might depend on access to (and the intactness of) semantic storage, whereas letter fluency clustering might depend on the ability to analyze the phonemic characteristics of words.

Our study had several limitations. Firstly, our analysis was based on indirect indices and not on specific measures of all processes. However, this was the only possible procedure; to the best of our knowledge, there is no way to measure the strategic search process directly. More generally, this is a significant challenge with control processes, which can only be measured indirectly through their influence on low-level processes. Secondly, there is little evidence to indicate that some of some indirect indices reflect executive or linguistic processes. This is especially the case for the time-related decrement and the production of infrequent words and, to a lesser extent, for switching and clustering. The present VLSM findings support the common interpretation of switching as an executive process because it mainly depended on fronto-subcortical tracts known to be involved in executive functions. However, a greater level of evidence is warranted and will require further research. Thirdly, our assessment of linguistic abilities was restricted to naming, and thus data on additional semantic and phonological abilities were not available for all patients. Fourthly, we did not formally assess inhibition, even though a higher rule-breaking error rate might be related to an impairment in this process (Cipolotti et al. 2020). Fifthly, the robustness of the mVLSM analysis will need to be analyzed in other study populations. Sixthly, the lesion distribution might not have sufficiently covered some regions known to be critical for semantic fluency (e.g. the left temporal pole, and the left angular gyrus). However, this does not constitute a major study limitation, as these regions were found to be associated with verbal fluency in a previous study of the same population (Godefroy et al. 2023). Lastly, the study was an association study—like other studies in this field. We are now considering whether to set up a study with a design that could provide a stronger level of evidence of a causal relationship (Dorchies et al. 2024).

Our study had several strengths. Firstly, the present study is the first to have assessed a large set of fluency indices in a very large sample of controls and stroke patients. This analysis should be powerful enough to detect patterns of impairment. Secondly, all the indices were adjusted for age and education when appropriate, which rules out associations related solely to demographic factors. Thirdly, our cluster determination was found to be very reliable. Lastly, our study was novel because only one other VLSM study investigated brain-behavior relationships associated with switching and clustering in patients with focal lesions (Davidson et al. 2008). However, the latter study was limited by its small, heterogeneous sample and found only an association between clustering and Broca's homologue region (BA44 and BA45) in the right hemisphere for both tasks (Davidson et al. 2008). Thus, our study is the only mVLSM study to investigate brain-behaviour relationships for linguistic and executive

fluency processes in a very large sample of controls and stroke patients.

5 | Conclusion

The present results provide a better understanding of fluency disorders in stroke. Previous research has shown that stroke-related fluency disorders are caused by a combination of impairments in three basic processes, namely processing speed, lexicophonological output, and strategic search process (Godefroy et al. 2023, 2024). The present use of strategic indexes demonstrates that other processes, such as inhibition (as indexed by rule-breaking errors) and working memory (as indexed by word repetition), contribute only slightly or not at all to fluency impairments in stroke. Furthermore, our findings confirm that lexicophonological processes significantly contribute to semantic fluency and the strategic search process significantly contributes to letter fluency. Additionally, our study highlights two other features of stroke-related fluency disorders, namely worsening over time and poor production of infrequent words; however, the contributions of the three processes to these features remain to be determined. From a clinical perspective, this work as a whole should help practitioners to more reliably identify the cause of verbal fluency impairments following a stroke, leading to more accurate cognitive diagnoses. This accuracy latter is essential for implementing rehabilitation that specifically targets the impaired processes. Conceptually, our results align with the prevailing interpretation that links switching to executive functioning (i.e., strategic search process), showing a significant contribution to the variance in fluency after controlling for oral output processes and processing speed, as well as an association with the left ATPs.

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Conflicts of Interest

Flore Dorchies, Ardalan Aarabi, Rania Kassir, Sandrine Wannepain and Martine Roussel report no disclosures. Claire Leclercq has received funding for travel and meetings from Sanofi Aventis, Biogen, Homeperf, Pfizer, Genzyme. Olivier Godefroy has served on scientific advisory boards (Novartis and Astra Zeneca) and has received funding for travel and meetings from Novartis, Lilly, Genzyme, Astrazeneca, Biogen, Teva, Pfizer, CSL-Behring, GSK, Boehringer-Ingelheim, Ipsen, Covidien, and Bristol-Myers Squibb.

Data Availability Statement

De-identified participant data and statistical codes used in this specific study can be shared for pooled studies: https://zenodo.org/record/7759957. However, the conditions of the study's approval by the investigational review board prevent public archiving of the full dataset. Readers seeking access to full data should contact the corresponding author (Olivier Godefroy) at the Department of Neurology, Jules Verne University of Picardy (Amiens, France). Access will be granted to named individuals in accordance with the ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data sharing agreement. The clinical trial identifier of the GRECogVASC study is NCT01339195 (https://clinicaltrials.gov/ct2/show/NCT01339195 and https://ichgcp.net/fr/clinical-trials-registry/NCT01339195).

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.