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ORIGINAL COMMUNICATION

Architecture and anatomy of executive processes: evidence from verbal fluency and Trail Making Test in 2009 stroke patients

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Abstract

Objectives The few voxel-wise lesion-symptom mapping (VLSM) studies aimed at identifying the anatomy of executive function are limited by the absence of a model and by small populations. Using Trail Making Test (TMT) and verbal fluency and a model of their architectures, our objective was to identify the key structures underlying two major executive processes, set-shifting and strategic word search.

Methods We applied a validated VLSM analysis to harmonized cognitive and imaging data from 2009 ischemic stroke patients as a part of the Meta VCI Map consortium. All contrast analyses used an adjusted threshold with 2000 Freedman–Lane permutations ($p \leq 0.05$).

Results The TMT parts A and B were associated with structures involved in visual-spatial processing, the motor system, the frontal lobes, and their subcortical connections. Set-shifting depended on the left dorsomedial frontal region. Both semantic and phonemic fluency tests depended on verbal output abilities and processing speed with similar slopes in different languages. The strategic search process depended on Broca's area, F2 and related tracts, temporal and deep regions. Lastly, the lesion map of set-shifting did not overlap with those of strategic word search processes.

Interpretation Our results identify the anatomical substrates of two main executive processes, revealing that they represent only a specific subpart of previously reported structures. Finally, our results indicate that executive functions depend on several specific, anatomically separable executive processes mainly operating in various parts of the frontal lobes.

Keywords Stroke · Infarct · Mild cognitive impairment · Dementia · Executive functions · Lesion-symptom mapping

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Introduction

Action speed and executive functions make critical contributions to adaptive processes and human activities, and are often significantly impaired in brain diseases [1]. These higher order processes influence lower level automatic cognitive processes, enabling them to cope with non-routine situations [2] and to improve efficiency in routine situations [3]. In clinical practice, these functions are typically assessed using the well-known Trail Making Test (TMT) parts A and B (TMTA: joining numbers in ascending order; TMTB: joining numbers and letters alternately, i.e., set-shifting) and verbal fluency tests (giving as many names of a given category as possible in a set time) [3, 4]. These tests involve the executive process per se (i.e., set-shifting for TMTB and lexical–semantic strategic search for verbal fluency), but also 'peripheral' processes (visual-spatial–motor processes for TMT; lexical–semantic linguistic processes for verbal fluency) (supplement Table 1). Identifying the specific anatomy of executive processes, therefore, requires a model of their functional organization, specifying the links between executive and peripheral processes and their measures. Translating this model into lesion-symptom mapping (LSM) analysis makes it possible to adjust executive test performance for peripheral processes, and thus identify the specific anatomy of executive processes.

Recently, voxel-wise LSM (VLSM) studies have shown that performance in these tests depends on many brain regions. TMTB performance has been examined in six VLSM studies attributing performance to variable lesions in the frontoparietal region and deep left hemisphere [5–9], although these results are subject to debate [6, 10, 11]. The adjustment for peripheral sensorimotor processes has been performed in only three studies [5, 8, 9], which concluded that different left-hemisphere structures were involved: the rostral anterior cingulate gyrus [9], the insula [5], the external capsule and the corona radiata [8]. VLSM studies of verbal fluency tests have demonstrated the role of left-side lesions of the inferior frontal gyrus (F3), striatum, thalamus, insula, temporopolar region, and a large number of tracts [9, 12–18]. The two studies that controlled for language abilities reported contrasted results with extensive left-hemisphere damage [9] or a failure to identify a region specifically associated with the strategic word search process [12].

Overall these controversial results are probably due to the lack of adjustment for peripheral processes in many studies and the limited sample size of several studies resulting in variable coverage of key structures. Thus, the brain areas dedicated to task-specific control processes (i.e., set-shifting in the TMTB, and strategic searching in a verbal fluency task) have not been identified. Moreover, it remains unclear whether the brain areas dedicated to these specific control processes overlap, which would be expected if a single amodal control system underlies executive functions [2]. This second point is fundamental because it determines the functional architecture of executive functions.

By taking advantage of the very large multicenter dataset produced by the MetaVCI map consortium [19] with a harmonized cognitive assessment [4, 20], the objective of the present study was to identify the brain structures dedicated to two major executive processes, set-shifting and strategic word search, based on the structures subtending performance in the TMT and verbal fluency tests and to describe their interrelationships.

Methods

Population

We performed a large-scale lesion-symptom mapping study of pooled and harmonized individual patient data (brain imaging and cognitive assessments) from the Meta VCI Map consortium [19]. As reported previously [19], the Meta VCI Map multicenter dataset consists of individual data from cohorts of patients with ischemic stroke, with infarct segmentation data on acute MRI (diffusion-weighted imaging [DWI] or T2-weighted fluid-attenuated inversion recovery [FLAIR]) showing the symptomatic infarcts, and cognitive assessment data recorded within 15 months of the index stroke (including at least one measure of demographically adjusted TMT and verbal fluency, for the purposes of the present study). Five cohorts (Bundang VCI [21], Hallym VCI [21, 22], GRECogVASC-infarct subgroup [23], PRO-CRAS [24], and STROKDEM [25]) met these criteria for the present study (supplemental Fig. 1). Along with the data on TMT performance (completion time and, if available, the error rate) and semantic and phonemic fluencies, we analyzed data on confrontation naming, if available. We then excluded patients with missing data for age and educational level. All data were previously pooled, anonymized, and processed in a previous multicenter study [19] by the Utrecht coordinating center. The present analyses were performed at the study's coordinating center (Picardie Jules Verne University; Amiens, France). The ethical and institutional approvals required by local regulations had been obtained for all Meta VCI Map cohorts.

Cognitive and imaging assessments

The cognitive assessment comprised the country-specific adaptation of the NINDS-Canadian Stroke Network

harmonization standards battery [4]. The TMTB used numbers and letters (Roman or Korean letters depending on the country) [22–24, 24, 25]. The TMTA involves visuospatial search, visual identification, visuomotor processes, and sustained attention; in addition, the TMTB involves rapid switching between number and letter series. The semantic fluency test used the category "animals", while the phonemic fluency test used items with a frequency matched to that in the harmonization standards battery [22, 24]. The Boston naming test was available in four cohorts (Bundang VCI and Hallym VCI [21, 22], GRECogVASC [23, 26], and PROCRAS [24]). Performance analysis was based on a validated method [27] that provides Z scores adjusted for age and education (i.e., adjusted for demographics). These analyses were carried out by the investigators of each cohort, using norms of each country.

Lesion-symptom mapping

Using previously validated methods [19, 28, 29], VLSM was performed on voxels lesioned in at least four patients. The data were analyzed using NiiStatV9 (https://www.nitrc.org/projects/niistat/), running with Matlab R2018b (https://in.mathworks.com/products/matlab.html) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Analyses were computed using the general linear model.

First, we analyzed demographically adjusted performance (Z scores) in all tests. The dependent variables were Z scores of completion times for parts A and B of the TMT, and semantic and phonemic fluencies. The naming score was analyzed as a guide to structures associated with verbal output and is described in the online supplement (Supplement Fig. 3 and Table 3). The threshold was adjusted using the false discovery rate and $p < 0.001$ was considered statistically significant. The potential effect of the time interval between MRI and cognitive assessment on VLSM results was addressed by two sets of analyses (Supplement results 2.2.) which yielded negative results, thus indicating that the time interval and its variation between subjects did not account for our findings.

Second, additional subtraction contrast analyses were used to identify structures associated with executive processes, set-shifting, and strategic word search (Supplement Table 2). Using NiiStat, all the contrast analyses used an adjusted threshold with 2000 Freedman–Lane permutations and $p \leq 0.05$. Set-shifting (i.e., the process required to switch between digit and letter series in a time-constrained task) was analyzed by subtracting the TMTA completion time from the TMTB completion time in VLSM analysis. A sensitivity analysis was performed using an ANOVA with the test part (TMTA, TMTB) as the within-subject factor and the

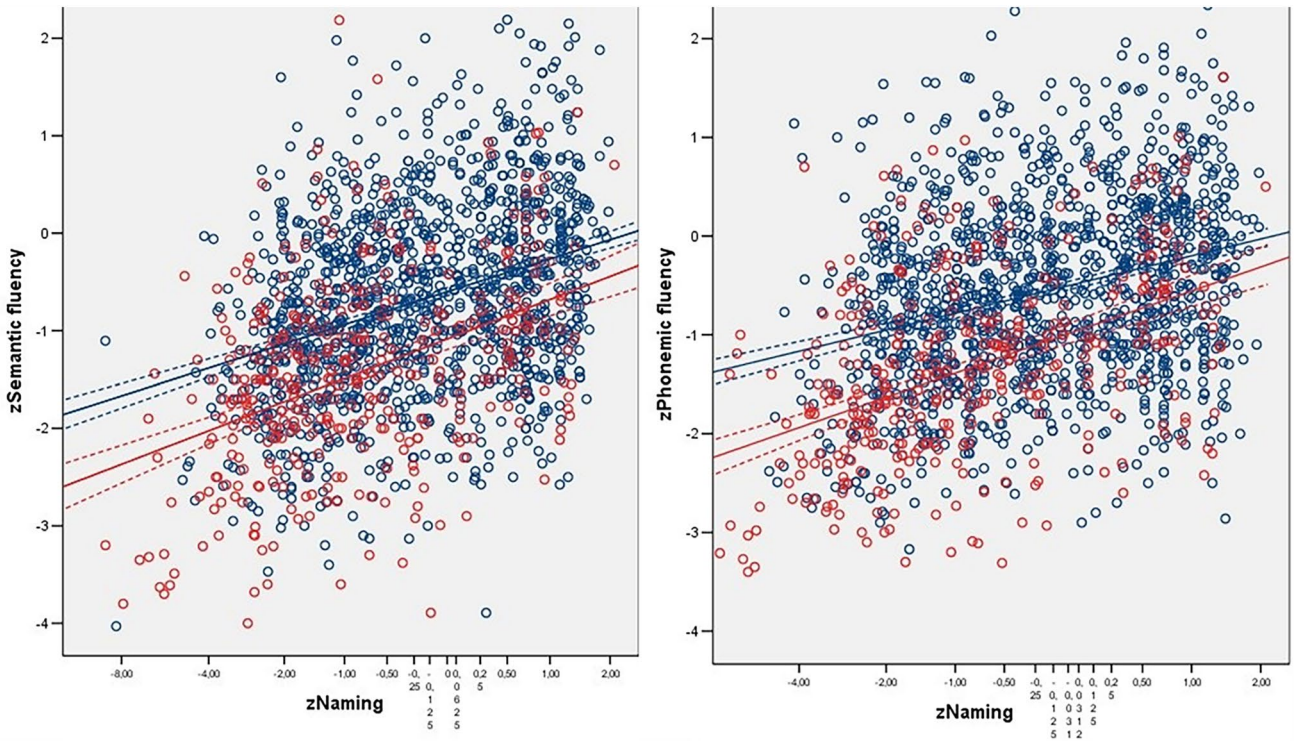

Fig. 1 Associations (Z scores) between semantic fluency and naming (left) and between phonemic fluency (right) and naming, as a function of the speed (blue: normal; red: impaired) in the TMTA. Notice that fluency production is closely related to naming abilities and processing speed

presence (present, absent) of a lesion in the TMTB–TMTA contrast map as the between-subject factor.

Regarding fluency performance, phonemic fluency minus semantic fluency contrast analysis was used to determine whether or not some structures were specifically associated with a given fluency test. The identification of brain structures associated with strategic word search was based on our previously validated model of the functional architecture of verbal fluency [12, 30]. This model posits that fluency production involves three main types of process operating in common: (1) linguistic processes, namely semantic and output lexico-phonological processes (common to externally triggered oral expression, such as those involved in the naming task), (2) a general attentional activation process that accelerates processing speed (which is purposely assessed using a simple non-verbal task, the TMTA), and (3) a strategic (i.e., cue-based, unusual) search process [12, 30]. The main advantage of this model is that the key structures underlying the strategic search process can be identified by a VLSM analysis of fluency production with a contrast analysis subtracting structures associated with naming and processing speed. The validity of this model in this multi-ethnic population was first verified (Supplement 2.1): it showed that fluency production depends on verbal output abilities and processing speed (Fig. 1), with strikingly similar slopes in different languages (Supplement Fig. 2). Then structures associated with strategic word search were examined using two subtraction contrast analyses ([phonemic fluency]–[TMTAt and naming], [semantic fluency]–[TMTAt and naming]). A sensitivity analysis was performed using two ANOVAs (semantic word search, phonemic word search) with the test as a within-subject factor (naming, TMTA and semantic fluency for semantic word searching; naming, TMTA and phonemic fluency for phonemic word searching) and the presence (present, absent) of a lesion in the semantic or phonemic contrast maps as the between-subject factor.

Statistical analyses

All statistical analyses were performed using SAS® software (version 9.4, SAS Institute, Cary, NC). The threshold for statistical significance was set to $p \leq 0.05$, unless otherwise indicated.

Results

Characteristics of the study population

We included 2009 patients (Table 1) from the 5 cohorts (Bundang VCI: $n = 758$, GRECogVASC-infarct: $n = 296$, Hallym VCI: $n = 643$, PROCRAS: $n = 175$, STROKEDEM: $n = 137$) which are detailed in Supplement Table 2. The patients' demographic and clinical characteristics (Table 1; Supplement Table 2) were typical of a hospital-based stroke population. Pre-stroke cognitive impairment (defined as an Informant Questionnaire on Cognitive Decline score > 3.38 [31]) was observed in 18.9% of the participants. Most of the imaging data were recorded in the first 2 weeks after the stroke. DWI was used most frequently for infarct segmentation. The cognitive assessment was usually performed 2 to 6 months after the stroke. The infarct distribution (Fig. 2) was similar in the two hemispheres, with a high level of brain lesion coverage: 1,556,726 of the 1,817,478 voxels (85.6%) in the Montreal Neurological Institute template were damaged in 4 or more patients. and were therefore included in the analyses. Only the distal part of the anterior cerebral artery territories, the posterobasal part of temporal lobes, the midbrain and the medulla oblongata

Table 1 Clinical characteristics of the study population (expressed as the percentage (%) or the mean ± standard deviation)

	Total
N	2009
Age	67.1 ± 11.4
Males (%)	53.5
Right-handedness (%)	95.4
Educational level (%) (1/2/3/4)	27/18.6/38.5/15.9
Europa/Korea (%)	30.3/69.7
Arterial hypertension (%)	67.0
Hypercholesterolemia (%)	40.1
Diabetes/overweight (%)	28.7/16.8
Active smoking (%)	24.3
Atrial fibrillation (%)	14.6
Prior stroke/TIA (%)	12.2/3.1
IQCODE	3.27 ± 0.5
NIHSS at admission	3.82 ± 4.4
Imaging: time after stroke (days)	7.7 ± 47.4
Infarct segmentation: DWI/FLAIR (%)	89.5/10.5
Lesion volume (cm^3)	14.53 ± 37.19
Cognitive assessment (day)	117 ± 90
TMTA completion time Z score	− 0.807 ± 2.005
TMTB completion time Z score	− 1.057 ± 2.029
Naming Z score	− 0.720 ± 1.553
Semantic fluency Z score	− 0.953 ± 1.100
Phonemic fluency Z score	− 0.789 ± 1.047

Education: 1 = less than high school completion; 2 = high school completion; 3 = technical college diploma; 4 = university degree and above

TIA transient ischemic attack, *IQCODE* Informant Questionnaire on Cognitive Decline, *NIHSS* National Institute of Health Stroke Scale, *DWI* diffusion-weighted imaging, *FLAIR* fluid-attenuated inversion recovery *TMT* Trail Making Test

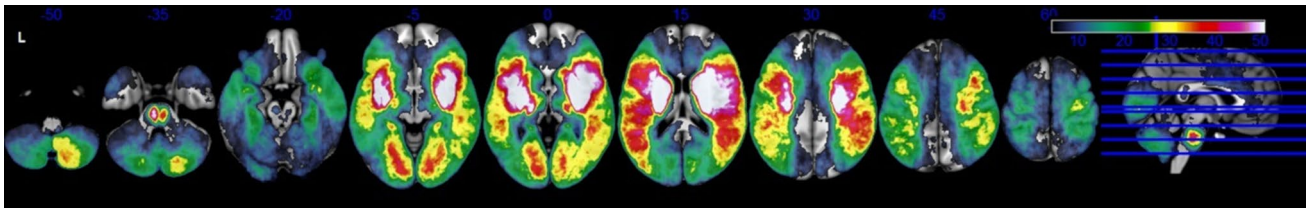

Fig. 2 Lesion overlap in at least 4 of the 2009 patients (left-side structures are shown on the left of the figure)

could not be included in the analyses, due to damage observed in fewer than four patients. Furthermore, the lesion distribution was not significantly associated with age or educational level ($p > 0.05$ for both).

VLSM analyses

The TMT

The demographically adjusted test completion time The completion times for the TMTA and TMTB were associated with a very large number of structures (Fig. 3a; Table 2; Supplement Table 3); the latter were characterized by slight overall right prominence (52.7% of the significant voxels) for the TMTA and left prominence for the TMTB (64.7% of the significant voxels). The TMTA and TMTB both involved regions underlying visual-spatial processing (the occipital, temporal and parietal lobes, the optic radiations and their connections, including the inferior longitudinal fasciculus (ILF) and the inferior occipitofrontal fasciculus (IOFF)), the motor system (precentral, corticospinal, and internal capsule), the frontal lobes (three frontal lateral gyri and, for the TMTB, the dorsomedial area) and their subcortical connections (the frontostriatal and thalamofrontal tracts).

Structures specific for set-shifting: the TMTB minus TMTA contrast analysis The contrast analysis revealed small foci of 626 voxels specifically associated with the TMTB (Fig. 4; Table 2). The voxels were mainly located in the left dorsomedial frontal region, involving the subgenual and pregenual anterior cingulate gyrus (Brodmann area [BA] 24), the adjacent areas (BA 32 and the superior part of BA 11), the adjacent corpus callosum, and the frontostriatal tract.

The sensitivity analysis (Fig. 4.) showed (1) a significant effect of lesion within this contrast map ($p = 0.003$) due to an overall slowing in lesioned patients (lesion present: -1.29 ± 0.16; lesion absent: -0.81 ± 0.05), (2) a significant effect ($p = 0.0001$) of the test part, due to a slower time in the TMTB (-1.39 ± 0.09) than in the TMTA (-0.704 ± 0.87), and (3) most importantly, a significant lesion × test part interaction ($p = 0.0001$), related to the expected disproportionate slowing in the TMTB by lesioned patients.

Phonemic and semantic fluency tests

Demographically adjusted fluency production Both fluency tests were associated with many structures in the left hemisphere (Fig. 2b; Table 3; Supplement Table 5), including the three frontal lateral gyri (F1, F2, and F3) and their frontostriatal, thalamofrontal, and aslant tracts; the temporal lateral gyri (T1, T2, and T3, especially the polar part); the parietal lobe (the inferior and superior lobuli, and the precuneus); central regions (including the rolandic operculum and the corticospinal tract); and the insula. The deep lesions mainly involved the striatum, thalamus, corpus callosum, and many tracts (including the arcuate, uncinate, ILF, and IOFF).

We checked the three tasks with a strong linguistic component (naming and both fluency tests) in the 1836 right-handed patients: these checks gave similar results (data not shown).

Structures specific for semantic and phonemic searching:

This analysis failed to find any structures differentially associated with fluencies.

Structures specific for strategic word search: fluency minus naming and TMTA contrast analysis The subtraction contrast VLSM analyses (Fig. 5; Table 3) revealed clusters of voxels specifically associated with fluency tests; the voxels were mainly located in Broca area (Brodmann area [BA] 44 and 45), F2 (BA 46) and related tracts (the uncinate, aslant, frontostriatal and thalamofrontal tracts), temporal regions (mainly centered on T1, and especially BA 22), and deep regions (the striatum, pallidum, thalamus, arcuate, corpus callosum, corticospinal and internal capsule, ILF, and IOFF).

The sensitivity analyses showed congruent results, with a disproportionate effect of the presence of a lesion within the contrast maps in each fluency test (Fig. 5). For the semantic word search, the significant effect of test ($p = 0.0001$) was due to worse performance for fluency (-1.007 ± 0.03) than in the TMTA (-0.878 ± 0.06) and naming (-0.694 ± 0.04); the lesion effect ($p = 0.0001$), to worse overall performance (present: -1.052 ± 0.06; absent: -0.667 ± 0.03). Most importantly, the lesion x test interaction ($p = 0.001$) was due to the disproportionate decrease in fluency (relative to the

Table 2 Main structures associated with Trail Making Test (TMT) performance (completion time) in a VLSM analysis (full results in supplement Table 3)

	TMTA completion time		TMTB completion time		TMTB–TMTA completion time contrast	
	Voxel (n)	Z	Voxel (n)	Z	Voxel (n)	*Z*
Threshold		*– 4.540*		*– 4.197*		*– 4.092*
Precentral_L	1784	– 5.530	548	– 4.511		
Precentral_R	828	– 5.872	148	– 4.736		
Frontal_Sup_L	244	– 5.430	65	– 4.554		
Frontal_Sup_R	768	– 5.279	365	– 4.718		
Frontal_Mid_L	3084	– 5.567	1243	– 4.549		
Frontal_Mid_R	158	– 5.228	131	– 4.695		
Frontal_Inf_Oper_L	321	– 5.190	418	– 4.462		
Frontal_Inf_Tri_L	142	– 5.190	247	– 4.409		
Supp_Motor_Area_R	48	– 5.250	50	– 4.000		
Frontal_Sup_Medial_L			197	– 4.025		
Cingulum_Ant_L			284	– 4.123	18	– 4.000
Cingulum_Mid_L			17	– 4.059		
Occipital_Sup_L	2719	– 5.696	1354	– 5.047		
Occipital_Mid_L	7486	– 5.872	8463	– 5.217		
Occipital_Mid_R	1420	– 5.137	1198	– 4.611		
Occipital_Inf_L	879	– 6.104	28	– 4.857		
Occipital_Inf_R	2395	– 5.405	3415	– 4.907		
Fusiform_R	13	– 5.077	182	– 4.462		
Parietal_Sup_L	173	– 5.150	2580	– 4.807		
Parietal_Sup_R	668	– 5.802	31	– 4.677		
Parietal_Inf_R	699	– 5.003	105	– 4.371		
Angular_L	35	– 5.086	1729	– 4.736		
Angular_R	1727	– 5.042	1900	– 4.703		
Temporal_Mid_L	42	– 5.024	2730	– 4.966		
Temporal_Mid_R	8298	– 5.056	12,065	– 4.852		
Temporal_Inf_R	1682	– 5.154	2247	– 5.052		
Cingulum_L			1090	– 4.517	614	– 4.337
Cingulum_R	32	– 5.156	196	– 4.444		
Corpus_Callosum_L	363	– 5.242	1624	– 4.740	245	– 4.306
Corpus_Callosum_R	65	– 5.215	374	– 4.588		
Cortico_Spinal_L	977	– 5.428	1681	– 4.667	19	– 4.263
Cortico_Spinal_R	324	– 5.293	638	– 4.820		
Inf_Long_Fasc_L	403	– 5.998	3127	– 4.888		
Inf_Long_Fasc_R	844	– 5.039	1303	– 4.699		
Inf OFFasc_L	75	– 5.453	835	– 4.680		
Inf OFFasc_R	73	– 5.137	115	– 4.548		
Optic_Radiations_L	82	– 5.841	467	– 4.955		
Optic_Radiations_R	257	– 5.023	103	– 4.544		
Uncinate_L	528	– 5.674	2681	– 5.348	15	– 4.733
Ant Thalamic Proj*_L	1402	– 5.464	1743	– 4.590		
Ant Thalamic Proj_R	2228	– 5.793	1265	– 4.644		
Frontal Aslant Tract_L	3077	– 5.628	1993	– 4.626		
Frontal Aslant Tract_R	731	– 5.309	669	– 4.580		
Fronto_Striatal_L	3288	– 5.509	4421	– 4.705	56	– 4.839
Fronto_Striatal_R	1905	– 5.625	1270	– 4.677	21	– 4.238

L left, *R* right, *Inf* inferior, *Sup* superior, *orb* orbital, *oper* opercularis, *tri* triangular, *mid.* middle, *supp* supplementary, *CPCereb* corticopontocerebellar, *OFF* occipitofrontal fasciculus, *Proj* projection, *Ant* anterior, *Long* longitudinal, *Fasc* fasciculus, *proj* projection

Table 2 (continued) *thalamofrontal tract

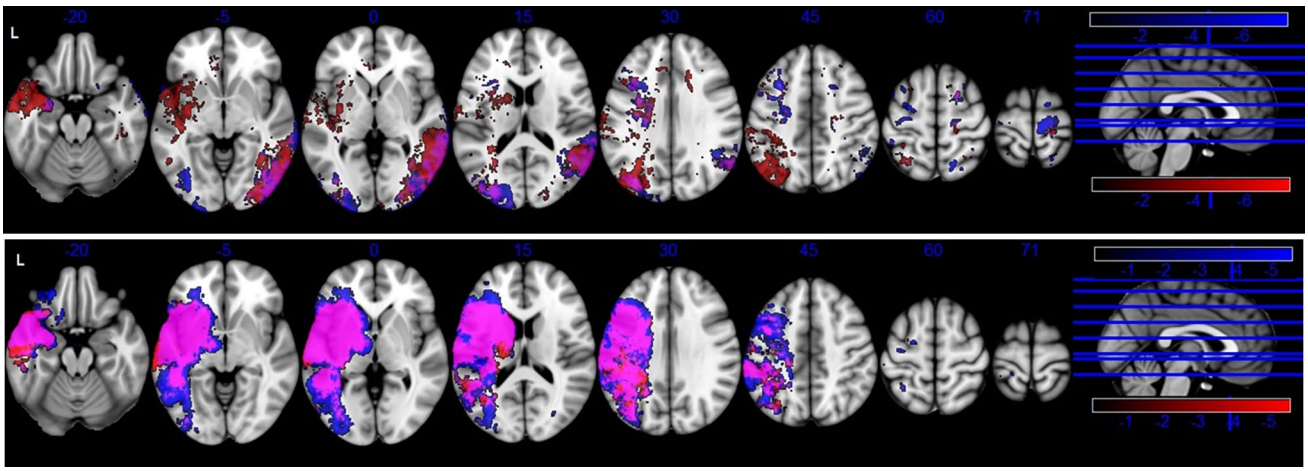

Fig. 3 A VLSM analysis of demographically adjusted scores (left-side structures are shown on the left of the figure). 3**a** (upper). The completion times in the TMTA (in blue) and TMTB (in red) (overlapping in purple). 3**b** (lower). Semantic fluency (in blue) and phonemic fluency (in red) (overlapping in purple). *TMT* Trail Making Test

two other tests) when a lesion was present in the semantic contrast maps. For the phonemic word search, the significant effect of test ($p = 0.0001$) was due to worse performance for fluency (-0.760 ± 0.04) than for naming (-0.478 ± 0.05; TMTA: -0.752 ± 0.07). The lesion effect was not significant (lesion present: -0.736 ± 0.07; absent: -0.591 ± 0.04 $p = 0.07$). Most importantly, the lesion × test interaction ($p = 0.0001$) was due to the disproportionate decrease in fluency (relative to the two other tests; $p < 0.05$ for both) when a lesion was present in the phonemic contrast maps.

Lastly, the maps for set-shifting did not overlap with those for strategic word search processes (Figs. 4 and 5).

Discussion

This study of a very large, multi-ethnic meta-cohort with a harmonized battery was designed to reveal the anatomical substrates of two major executive processes, set-shifting and strategic word search, assessed using the two most commonly used executive tests and to investigate the functional architecture of control processes.

Our results extend previous findings [5–9, 32] and show that the TMT completion time is associated with a very large number of structures in both hemispheres. The TMT's anatomical substrate included regions involved in visuospatial processing (the occipital, temporal, and parietal lobes, optic radiations, and their connections, such as the ILF and the IOFF) and required for visual scanning, reading, and visuomotor guidance [33]. The substrate also involved the motor structures (the precentral, corticospinal, and internal capsule) needed to quickly draw connecting lines. Lastly, the substrate included some of the frontal lateral regions (F1, F2, F3) and their subcortical connections (the frontostriatal and thalamofrontal tracts); these are all especially involved in the temporary maintenance of information [34, 35] and processing speed [33, 36, 37]. Our anatomical findings show that the attentional component needed to accelerate TMT completion [5–9, 32] cannot be identified from the completion time because it also reflects many sensorimotor components [3, 33, 38]. Interestingly, the regions associated with TMTA completion time included the right frontostriatal and orbital parts of F3, which have been previously associated with motor speed and sustained alertness, respectively [33]. The large size of the TMT anatomical substrate explains why it is highly vulnerable to brain lesions in general [3] and stroke in particular [20, 23, 39]. According to the subtraction contrast analysis, the anatomical substrate of set-shifting mainly depended on the left dorsomedial frontal region and especially the subgenual and pregenual anterior cingulate gyrus (BA 24) and adjacent areas (BA 32 and the superior part of BA 11). This result is at odds with the previously reported role of the insula, external capsule, center semiovale, and parietal lesions [5–7, 9–11]. Given the large population size in our study, this discrepancy cannot be attributed to insufficient power. Our finding is congruent with the known role of the pregenual anterior cingulate gyrus in the suppression of automatic actions and the control of voluntary action, which require the coordination of processes associated with sustained attention and motor timing [40, 41]. Thus, our result indicates that disproportionate slowing for TMTB (relative

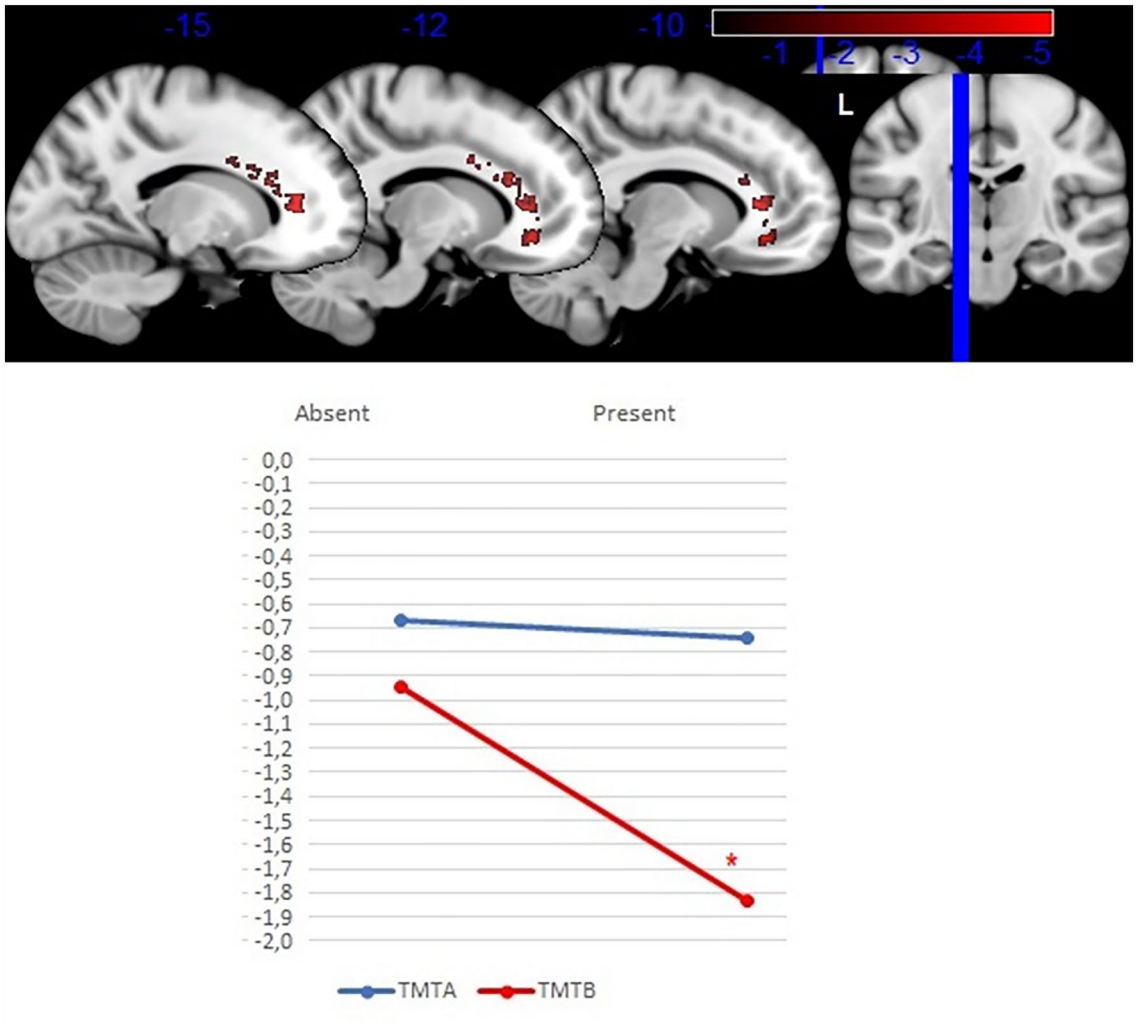

Fig. 4 Contrast analysis of the TMTB completion time minus the TMTA completion time: VLSM findings and sensitivity analysis of the lesion effect within this contrast map on TMT performance (Z score) showing the disproportionate effect of the lesion on TMTB (left-side structures are shown on the left of the figure). *TMT* Trail Making Test

to TMTA) indicates a lesion in the left pregenual anterior cingulate gyrus or its callosal connections.

Our present results also document the processes recruited during fluency tests and their anatomical substrates. The close relationships (with very similar slopes) between verbal fluency production, verbal output abilities (indexed by confrontation naming), and processing speed (indexed by the TMTA) in different ethnic groups confirm our previous findings in stroke patients [12] and monolingual and bilingual controls [12, 30]. These findings support our model that performance of a verbal fluency task involves three types of processes operating in common: (1) linguistic processes, namely semantic and output lexico-phonological processes, (2) a general attentional activation process that accelerates processing speed, and (3) a strategic (i.e., cue-based, unusual) search process [12]. The present results enable us to interpret the contrast of fluency minus both naming and processing speed in terms of the anatomy of strategic word search process. The anatomical substrates for the fluency tests both involved the left frontal lateral lobe and their tracts (frontostriatal, thalamofrontal, and aslant tracts), the temporal lobe (T1, T2, and T3 especially at the polar part), the parietal lobe (both inferior and superior lobulus, precuneus), the insula, and central regions (including rolandic operculum and corticospinal tract). The lesions of deep structures mainly involved the striatum, thalamus, corpus callosum, and various tracts (including the arcuate, uncinate, ILF, and IOFF). Our findings extend the results of previous VLSM studies highlighting left-side lesions in F3, the temporal and temporopolar regions, striatum, thalamus, insula, and a large number of white matter tracts [12–18]. Furthermore, the large cohort studied here enables us to document the

Table 3 Main structures associated with fluency tests in a VLSM analysis (full results in supplement Table 5)

	Semantic fluency	*Z*	Phonemic fluency	*Z*	Semantic fluency minus naming and TMTA contrast		Phonemic fluency minus naming and TMTA contrast	
	Voxel (*n*)		Voxel (*n*)		Voxel (*n*)	*Z*	Voxel (*n*)	*Z*
Threshold		− 3.789		− 4.276		− 3.789		− 4.276
Precentral_L	11,960	− 5.897	6807	− 5.083				
Frontal_Sup_L	523	− 4.868	93	− 4.484				
Frontal_Sup_Orb_L	564	− 5.220	135	− 5.133				
Frontal_Mid_L	15,295	− 5.731	5887	− 5.016				
Frontal_Mid_Orb_L	767	− 4.828	61	− 4.557				
Frontal_Inf_Oper_L	6988	− 6.498	6667	− 5.750	392	− 4.444	342	− 4.608
Frontal_Inf_Tri_L	12,731	− 5.977	8874	− 5.272	184	− 4.033	23	− 4.174
Frontal_Inf_Orb_L	4926	− 5.199	2491	− 4.925				
Rolandic_Oper_L	5381	− 6.457	4779	− 5.627	14	− 4.500	10	− 4.300
Insula_L	11,322	− 6.457	11,156	− 6.069	653	− 4.559	452	− 4.785
Postcentral_L	9268	− 5.622	6774	− 4.950				
Parietal_Sup_L	580	− 4.669	593	− 4.396				
Parietal_Inf_L	8254	− 5.088	7248	− 4.830				
SupraMarginal_L	5337	− 5.401	3881	− 4.860				
Angular_L	3055	− 4.976	1999	− 4.602				
Precuneus_L	40	− 4.775						
Caudate_L	3030	− 5.857	2262	− 5.729	317	− 4.984	753	− 5.122
Putamen_L	2495	− 6.576	2471	− 6.121	922	− 5.523	1547	− 4.827
Pallidum_L	667	− 6.529	647	− 6.091	276	− 5.018	396	− 4.864
Thalamus_L	1395	− 6.137	665	− 5.304	39	− 4.872		
Heschl_L	1590	− 6.099	1486	− 5.560	29	− 4.034	17	− 4.235
Temporal_Sup_L	13,808	− 5.812	11,647	− 5.604	135	− 4.067	122	− 4.582
Temporal_Pole_Sup_L	3501	− 5.851	4749	− 6.042				
Temporal_Mid_L	18,486	− 5.247	16,188	− 5.119			254	− 4.335
Temporal_Pole_Mid_L	559	− 4.925	1850	− 5.001				
Temporal_Inf_L	2265	− 4.924	650	− 4.589				
Ant _Commissure_L	86	2501	− 6.013	1953	282	− 4.770	307	− 4.762
Ant _Segment_L	933	− 6.395	807	− 5.191				
Arcuate_L	18,373	− 5.722	15,735	− 5.074				
Posterior_Segment_L	3018	− 5.408	2253	− 4.949				
Long_Segment_L	988	− 6.323	868	− 5.206				
Cingulum_L	564	− 4.699	233	− 4.494				
Corpus_Callosum_L	5265	− 5.199	2821	− 5.046	49	− 4.367	159	− 4.610
Inf_Long_Fasc_L	403	11,100	− 5.610	8106	15	− 4.000	78	− 4.744
Inf OF Fasc _L	75	6573	− 6.276	4926	848	− 5.163	1390	− 4.925
Uncinate_L	5289	− 6.151	5144	− 5.772	242	− 4.959	344	− 4.828
Optic_Radiations_L	3371	− 5.539	2084	− 5.358	43	− 4.442	435	− 4.777
CPCereb_L	25	850	− 5.533	630			64	− 4.188
Cortico_Spinal_L	12,905	− 5.870	9834	− 5.557	1173	− 5.599	2100	− 5.147
Internal_Capsule_L	3914	− 5.899	2881	− 5.515	848	− 5.163	1390	− 4.925
Ant Thalamic Proj*_L	1402	32,200	− 5.871	18,643	2331	− 5.174	3245	− 5.098
Frontal Aslant Tract_L	25,891	− 6.380	19,701	− 5.665	452	− 4.425	392	− 4.684
Fronto_Striatal_L	42,805	− 6.090	28,304	− 5.705	4742	− 5.249	6737	− 4.988

TMTA part A of the Trail Making Test, *L* left, *R* right, *Inf* inferior, *Sup* superior, *Orb* orbital, *Oper* opercularis, *Tri* triangular, *Mid.* middle, *Supp* supplementary, *CPCereb* corticopontocerebellar, *OFF* occipitofrontal fasciculus, *Proj* projection, *Ant* anterior, *Long* longitudinal, *Fasc* fasciculus

*thalamofrontal tract

Table 3 (continued)

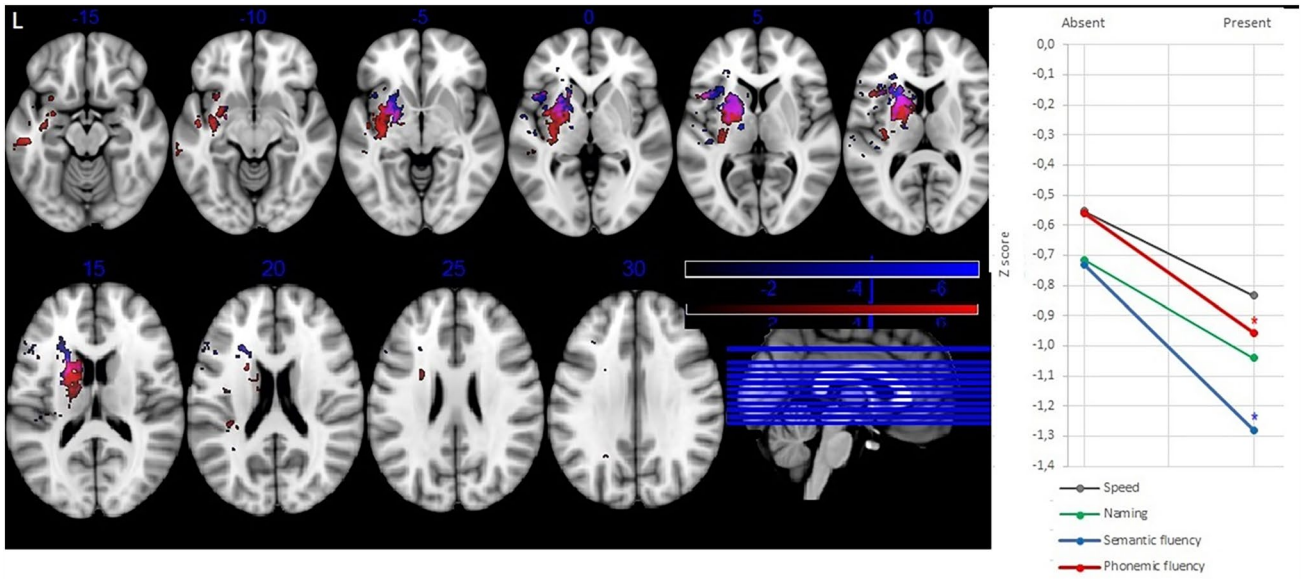

Fig. 5 Semantic fluency (in blue) and phonemic fluency (in red) minus naming and TMTA contrast: VLSM findings and sensitivity analysis of the lesion effect within this contrast map showing the disproportionate effect of the lesion on fluency (left-side structures are shown on the left of the figure). *TMT* Trail Making test

anatomical substrate of processes underlying the two fluency tests. The very similar anatomies for these two tests contrast with the previously reported prominent roles of F3 in phonemic fluency and temporal structures in semantic fluency [12, 14, 15, 18]. The prominent involvement of temporopolar structures in semantic fluency was expected, given their involvement in verbal semantic [12, 42]. Our present results showed that phonemic fluency is also associated with temporopolar structures. Further analyses of this topic between and within languages could be useful but are beyond the scope of this study. Our study is the first to describe the anatomical substrate of the strategic word search process, as our previous study of 358 patients failed to identify it. These findings strongly suggest that strategic lexical searching with both semantic and phonemic cues is performed by Broca's area and T1 and requires connecting tracts (the uncinate, aslant, frontostriatal, and thalamofrontal tracts).

Furthermore, our results have major implications for the functional architecture of executive functions. They indicate that control processes are anatomically separable from lower level processes (i.e., visuomotor processes for TMT, and verbal output for fluency) and this supports the hypothesis of separable executive processes [43]. Our results also show that (1) the anatomical substrates of the two executive processes (set-shifting and strategic word search) did not overlap, and therefore (2) executive functions depend on several specific, anatomically separable executive processes rather than a single amodal control system. This interpretation is consistent with previous reports of selective impairments in executive processes, as assessed with similar binary decision tasks [44–46]. The only previous study to generate VLSM maps for various executive tests in a smaller population with predominantly frontal lesions showed a slight overlap between perseverative errors in TMTB and modified card sorting test but not for phonemic fluency [9]. These congruent results indicate that executive functions depend on many specific, anatomically separable executive processes operating primarily in various parts of the frontal lobes.

Our study has several limitations. First, the executive function assessment involved two tests only and did not encompass other well-known tests. However, these two tests are known to capture most of the executive impairment due to stroke [39] and so were, thus, the only ones of this type included in the harmonized stroke battery [4]. Interestingly, the two tests also capture the most executive impairment due to Alzheimer's disease—another major cause of cognitive impairment [47–49]. Nevertheless, this limitation did not prevent us from finding non-overlapping anatomical substrates for executive processes, and therefore does not undermine the study's main conclusions. Second, the analyses focused on lesion effect and not on other imaging factors that also contribute to cognitive deficit, albeit to

a lower extent [29]. Third, the consortium pooled cohorts of patients with some differences in age and education, time interval of cognitive assessment and testing (due to language differences). However, this was controlled for by the use of age- and education-adjusted norms, by additional analyses excluding the role of time on VLSM results, and by additional analyses showing the striking similarities in the relationship between fluency and naming across countries. More importantly, these differences did not prevent important findings from being obtained. Fourth, cohort studies on post-stroke cognitive impairment tend to be selective. For example, patients who are most severely affected, such as severe aphasics or hemiplegic, are often underrepresented in more demanding research protocols. Fifth, cognitive trajectories after stroke differ between patients and may change over time. Therefore variation in timing of assessment might influence our results. Sixth, our pooled sample only includes Caucasian and Asian patients; thus, generalizability to other ethnicities remains undetermined.

Our study also has several strengths, including a very large population, the use of a normalized, harmonized assessment, and previously validated models of executive processes. This has enabled us to validate their functional architecture and identify the anatomical substrates of two main executive processes, revealing that they represent only a specific subpart of previously reported structures.

Appendix

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Author contributions OG, MR, FD, RK, and AA were responsible for study concept and design. OG and AA were responsible for VLSM analyses. OG, MR, FD, RK, and AA drafted the manuscript. All authors revised the manuscript critically for important intellectual content. All authors gave final approval for submission. Cohort-specific contributions: KJL, BJK, and HJB were responsible for the Bundang VCI cohort. HJB: data collection and data interpretation. BJK and KJL: data collection. JSL, ML, and KHY were responsible for the Hallym VCI cohort. JSL: data collection and data interpretation. ML and KHY: data collection. OG, MR. and AA were responsible for the GRECogVASC cohort, study design and data collection. HPA and PLMK were responsible for the PROCRAS cohort study design and data collection. RB, TD, RL were responsible for the STROKDEM cohort study design, data collection and analysis. NAW, JMB, GJB were responsible for the curation and harmonization of individual participant data in Meta VCI Map consortium (www.metavcimap.org).

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Data availability Data sharing is not applicable to this article as no new data were created in this study.

Declarations

Conflicts of interest Godefroy, NA Weaver, M Roussel, F Dorchies, R Kassir, JM Biesbroek, KJ Lee, HJ Bae, BJ Kim, HJBae, JS Lim, M Lee, KH Yu, H P Aben, P LM de Kort, R Bordet, R Lopes, T Dondaine, GJ Biessels, and A Aarabi: none related to this study.

Ethical standard The ethical and institutional approvals required by local regulations had been obtained for all Meta VCI Map cohorts.

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