The Influence of Stroke Location on Cognitive and Mood Impairment. A Voxel-Based Lesion-Symptom Mapping Study

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Background and purpose: The role of stroke location as a determinant of mood and cognitive symptoms is still a matter of debate. The aim of this study was to identify the predictive value of ischemic stroke location, on a voxel basis, for mood and cognitive outcome. *Materials and methods:* A prospective monocentric study including patients with a supratentorial ischemic stroke was conducted. A 3 Tesla brain MRI was performed at baseline. Mood and cognition were assessed using Hospital Anxiety and Depression scale (HAD), apathy inventory (AI), and Montreal Cognitive Assessment scale subscores, performed at 3 months poststroke. Statistical maps of ischemic stroke location associated with 3 months mood and cognitive scores were obtained using a voxel-based lesion-symptom mapping approach (Brunner and Munzel test). Significant voxels (false discovery rate [FDR] corrected-$P < .01$) were identified using the standard Montreal Neurological Institute-152 space template. *Results:* Two hundred and sixty-five nonsevere stroke patients were included (64% men, mean age 66 ± 14, median National Institute of Health Stroke Score 3, interquartile range 2-6). Ischemic stroke location was not associated with HAD or AI scores. Language, abstraction, and delayed recall performances were mainly associated with left-side hemispheric lesions. Lesions in both hemispheres were associated with lower performances in visuospatial and executive functions, naming, attention, and orientation. *Conclusion:* Ischemic stroke location does not predict mood outcome at 3 months but is a determinant of cognitive outcome in specific domains.

Key Words: Ischemic stroke—cognition—MoCA subscores—mood—brain mapping—magnetic resonance imaging

Introduction

Mood disorders and cognitive impairment represent the main clinical expressions of the so-called "invisible" poststroke handicap. While large infarct volume, widespread leukoaraiosis, or brain atrophy have been associated with their occurrence,[1-3] the role of stroke location is still uncertain.[3] Indeed, limited date are available about the potential role of precise stroke location, beside the classical associations between aphasia and left side lesions, neglect and right

Abbreviations: VLSM, voxel-based lesion-symptom mapping; MoCA, Montreal Cognitive Assessment; NIHSS, National Institute of Health Stroke Score; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; HAD-A (-D), Hospital Anxiety And Depression-anxiety (-Depression); AI, apathy inventory; MNI, Montreal Neurological Institute; FDR, false discovery rate; SD, standard deviation; IQR, interquartile range

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side lesions, visual agnosia, and amnesia with posterior lesions.[4] This issue can be address by using a voxel-based lesion-symptom mapping (VLSM) approach, a method providing the evaluation of each individual voxel for potential relationship with a given clinical symptom.[5] This approach has the advantage to analyse all brain parenchyma on a voxel-by-voxel basis, without grouping patients by lesion site or clinical score cut-off. With this method, the influence of ischemic stroke location on global cognitive functions, assessed by the Montreal Cognitive Assessment (MoCA) scale, has been reported, on top of clinical determinants.[6] However, whether stroke location is differentially relevant in terms of specific cognitive domain and in terms of mood outcome is still an open question, and heterogeneous results have been published during the last decade.[7-10]

The aim of the present study was to apply VLSM analysis to a prospective cohort of ischemic stroke patients, in order to evaluate the predictive value of stroke location for poststroke anxiety, depression, apathy, and cognitive subdomains assessment measured at 3 months.

Materials and Methods

Study Population

Data were gathered from the "Brain Before Stroke" study,[6] a prospective and monocentric study conducted at the Bordeaux University Hospital. The study was accepted by the regional ethical board (CPP-2012/19 2012-A00190-43) and all patients or their legal representative provided a written informed consent. Inclusion criteria were an age over 18 years old, a diagnosis of supratentorial ischemic stroke confirmed on a brain MRI performed between 24 and 72 hours from symptoms onset (baseline), and a National Institute of Health Stroke Score (NIHSS) comprised between 1 and 25. Patients with prestroke history of dementia or psychiatric disorder matching to axis 1 DSM-IV criteria,[11] severe poststroke aphasia impeding mood and cognitive assessment, life threatening disease, MRI contraindication, and non-native French speakers were excluded.

Clinical Assessment

Demographic characteristics, NIHSS, and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[12] were recorded at baseline. IQCODE was performed with a relative of the patient, to detect prestroke cognitive decline. Mood outcome was evaluated at 3 months during a medical hospital visit, using patient self-evaluations. The Hospital Anxiety and Depression scale (HAD)[13] included 7 questions for the measurement of anxiety on 21 points (HAD-A), and 7 other questions for

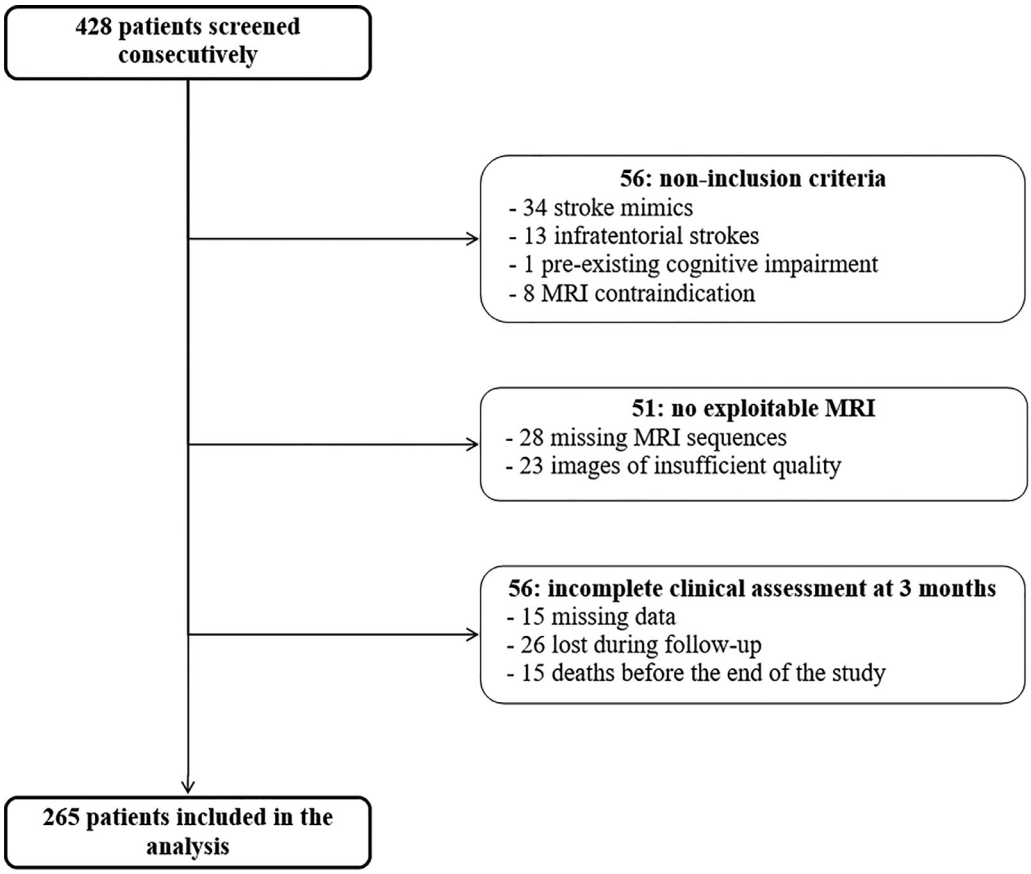

Figure 1. *Patient flow chart.*

depression on 21 points (HAD-D). The patient version of apathy inventory (AI)[14] explored the frequency and severity of 3 dimensions of apathy: emotional blunting (12 points), lack of initiative (12 points), and lack of interest (12 points). Cognitive subdomains were evaluated at 3 months during the same medical visit, by a trained research assistant blinded to baseline MRI. The MoCA subscores scale[15] were used, exploring visuospatial and executive functions (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), delayed recall (5 points), and orientation (6 points).

Imaging Protocol

A 3 Tesla MRI: Milwaukee, Wisconsin (General Electrics Medical Systems Discovery MR750 W) was performed at baseline. The sequences used for the present study were as follows: diffusion-weighted imaging (DWI) b1000 (echo time/repetition time 82.3/9000, field-of-view 24×24 cm^2, matrix 128×128, thickness slice 4 mm, gap between slices 0.5 mm), and 3D T1 weighted imaging (WI, echo time/repetition time/inversion time 3.3/8.6/450, flip angle 12°, field-of-view 24×24 cm^2, matrix 256×256, thickness slice 1 mm).

Imaging Processing and Statistical Analysis

Ischemic stroke lesions were segmented on DWI, since it has been suggested that baseline DWI correlated well with final infarct volume.[16] A semi-automatic segmentation tool available on 3D Slicer 4.3.1 software was used. The mask of each segmented ischemic lesion, which defined ischemic stroke location, was coregistered with DWI and the native 3D T1-WI sequences, before being superimposed on a standard framework, the Montreal Neurological Institute (MNI), using the Statistical Parametric Mapping 8 software available on MATLAB (R2012b). The relationship between ischemic stroke location, mood, and cognitive scores was evaluated on a voxel-by-voxel basis by a VLSM approach, using the nonparametric mapping toolbox of MRIcron 4.8.2014: University of South Carolina, South Carolina, United States.[17]

Three months HAD-A, HAD-D, AI, and MoCA subscores were analysed in each voxel by the Brunner and Munzel test. Damaged voxels were voxels included in the mask of ischemic stroke lesions segmented previously. Significant voxels were damaged voxels wherein scores were significantly lower than in nondamaged voxels. For appropriate use of Brunner and Munzel statistics, only voxels damaged in at least 10 subjects were tested.[18] The significance threshold was set at .01 after multiple comparisons (false discovery rate). Statistical Z-score maps were generated. An elevated Z-score meant that the ischemic stroke location was significantly and robustly associated with worse performances at 3 months in the corresponding clinical score. The standard MNI-152 space template was used to identify MNI coordinates of significant clusters of voxels, for at least 50 contiguous voxels.

Results

Participants and Cognitive Performances

Two hundred and sixty-five patients displayed complete clinical and imaging evaluations (64% men, mean age 66 ± SD 14). The flow chart is detailed in Fig 1. Demographic data and results of neuropsychological evaluations at 3 months are described in Table 1. The median NIHSS at baseline was 3 (interquartile range [IQR] 2-6).

Table 1. *Demographic, clinical, and radiological data of all participants*

	N = 265
Demographic data	
Age, mean (SD)	66 (14)
Male, n (%)	171 (64)
Right-handed, n (%)	182 (92)
Vascular risk factors, n (%)	
Hypertension	125 (47)
Diabetes mellitus	45 (17)
Hypercholesterolemia	106 (40)
Current smoking	64 (24)
IQCODE at baseline, mean (SD)	3 (0.6)
NIHSS at baseline, median (IQR)	3 (2-6)
Modified Rankin scale at 3 mo, n (%)	
0, 1, 2	216 (81)
≥3	51 (19)
Total MoCA/30 at 3 mo, median (IQR)	24 (21-27)
Visuospatial and executive functions/5	4 (3-5)
Naming/3	3 (3-3)
Attention/6	5 (4-6)
Language/3	2 (2-3)
Abstraction/2	2 (1-2)
Delayed recall/5	3 (2-4)
Orientation/6	6 (6-6)
HAD at 3 mo, median (IQR)	
HAD-A/21	6 (3-8)
HAD-D/21	3 (1-6)
AI/36 at 3 months, median (IQR)	0 (0-6)
Stroke characteristics: hemisphere side and arterial territory, n (%)	
Right side	124 (47)
Left side	126 (47)
Right and left side	17 (6)
Middle cerebral artery	202 (69)
Anterior cerebral artery	27 (9)
Posterior cerebral artery	53 (18)
Anterior choroid artery	11 (4)
Stroke volume (cm^3), median (IQR)	12.1 (2.2-36.5)

AI, apathy inventory; HAD-A (-D), Hospital Anxiety and Depression scale-Anxiety (-Depression); IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; N, total number; n, a sample of the total number; NIHSS, National Institute of Health Stroke Score; SD, standard deviation.

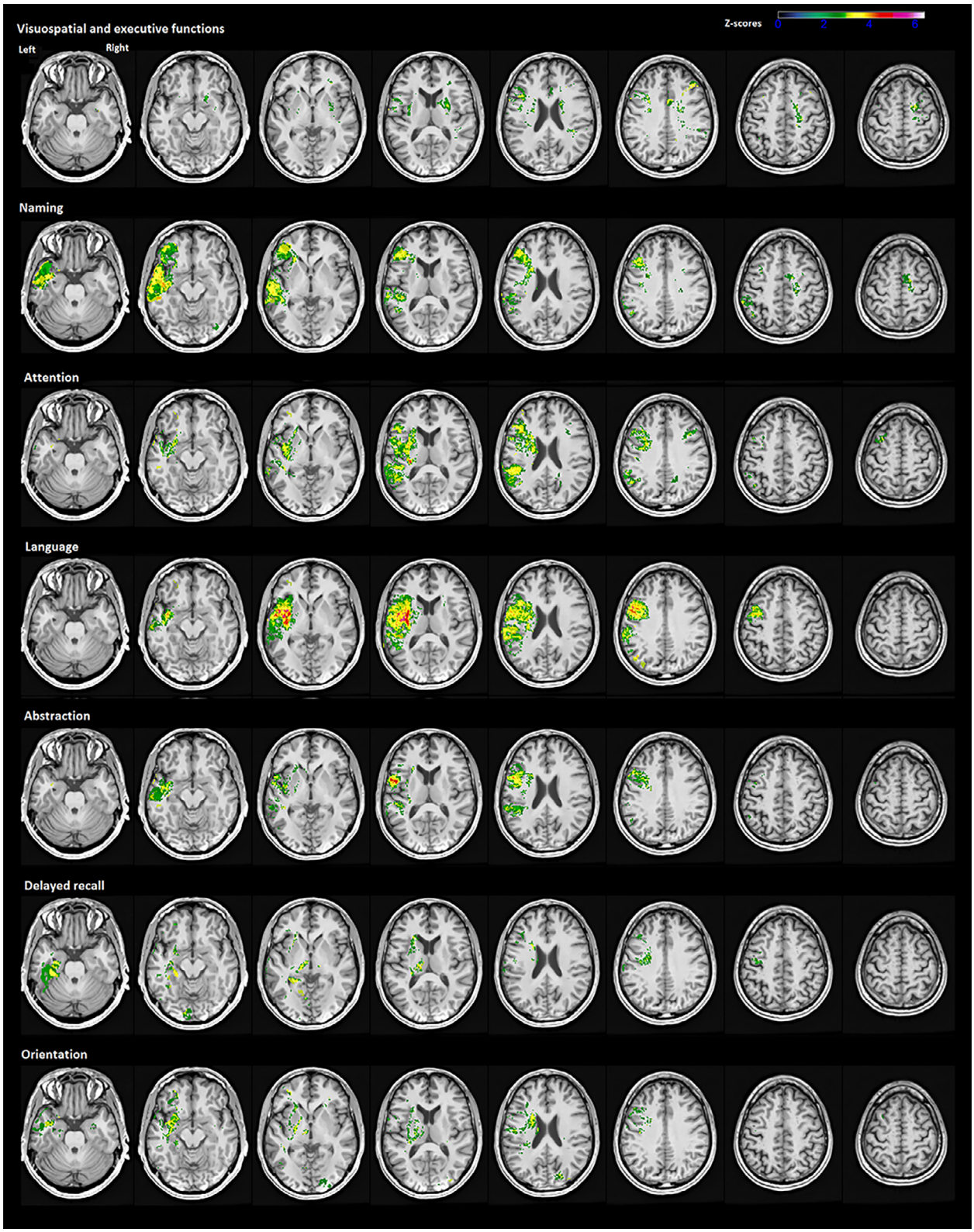

Figure 2. *MoCA subscores related to ischemic stroke location (VLSM analysis). Color range represents values of Z-scores thresholded for multiple comparisons (P < .01 FDR). Voxels in red color are damaged voxels in which MoCA subscores are the most impaired compared with nondamaged voxels. Images are presented in neurological orientation (left is on the left side).* Abbreviations: *MoCA, Montreal Cognitive Assessment; VLSM, voxel-based lesion-symptom mapping; FDR, false discovery rate. (Color version of figure is available online.)*

Ischemic stroke lesions involved both right (47%) and left (47%) side hemispheres. At 3 months, median HAD, AI, and MoCA scores were respectively 10 (IQR 6-14), 0 (IQR 0-6), and 24 (IQR 21-27).

Relationship between Ischemic Stroke Location and Clinical Scores

No significant association was observed between ischemic stroke location and HAD-A, HAD-D, and AI. Conversely, several locations of ischemic stroke were associated with MoCA subscores at 3 months (Fig 2). Only left-side hemispheric lesions were associated with performances in language, abstraction, and delayed recall. Performances in visuospatial and executive functions, naming, attention, and orientation subdomains were predominantly associated with left-side hemispheric lesions, and to a lesser extent with right-side hemispheric lesions. Cerebral gyri associated with MoCA subscores are described in Table 2.

Discussion

The main result of this study is that, in a population of patients with a recent ischemic supratentorial stroke, ischemic lesion location does not predict the severity of poststroke affective symptoms while it contributes to predict specific cognitive domains outcome.

Table 2. *Labels of significant clusters of damaged voxels associated with MoCA subscores (>50 contiguous voxels, P < .01 FDR)*

			MNI coordinates			
MoCA subscores	Cluster labeling	Maximal Z-score	x	Y	z	Cluster size (voxels)
Visuospatial and executive functions	Left inferior frontal gyrus, pars opercularis	3.7	−39	8	22	1782
	Right frontal eye field	3.5	34	27	39	639
	Right supramarginalis gyrus	3.2	50	−36	28	184
	Right putamen	3.2	20	12	−12	57
Naming	Left insula	3.9	−45	2	−3	24,931
	Left angular gyrus	3	−45	−60	46	67
	Right associative visual cortex	2.7	38	−78	−16	64
Attention	Left primary motor cortex	5.3	−40	−12	15	18,738
	Left primary somatosensory cortex	3.6	−42	−22	36	85
	Left anterior prefrontal cortex	3	−28	45	−9	313
	Right inferior frontal gyrus, pars opercularis	3	33	14	30	174
	Right ventral posterior cingulate cortex	2.6	15	−52	32	362
	Right associative visual cortex	2.6	21	−62	20	63
Language	Left primary motor cortex	6.3	−50	−10	8	27,386
	Left angular gyrus	3.9	−45	−69	32	397
	Left caudate	3.9	−10	−2	15	122
	Left inferior frontal gyrus, pars orbitalis	3.6	−46	22	−15	52
Abstraction	Left inferior frontal gyrus, pars opercularis	4.9	−58	6	12	12,346
	Left temporopolar area	3	−57	8	−16	54
Delayed recall	Left parahippocampal gyrus	3.9	−34	−33	−20	2265
	Left thalamus	3.9	−15	−21	0	730
	Left associative visual cortex	3.4	−8	−92	−14	471
	Left middle temporal gyrus	3.4	−69	−26	−4	64
	Left dorsolateral prefrontal cortex	2.9	−38	32	22	88
	Left temporopolar area	2.7	−57	8	−16	54
	Left inferior frontal gyrus, pars orbitalis	2.5	−39	34	−8	59
Orientation	Right associative visual cortex	3.1	18	−98	4	367
	Left parahippocampal gyrus	3.5	−24	−27	−14	85
	Left hippocampus	2.7	−24	−12	−22	100
	Right anterior prefrontal cortex	2.7	27	44	−6	54

FDR, false discovery rate; MNI, Montreal Neurological Institute; MoCA, Montreal Cognitive Assessment.

The predictive value of stroke location in poststroke mood disorders has been a debate for many decades.[10,19] Some studies suggested a higher risk in patients with lesions involving the left hemisphere,[7] the left dorsolateral prefrontal cortex,[20] or basal ganglia.[21] Our results, using 1 of the most accurate methodology available to date (VLSM) on a large sample of patients, suggest the absence of relationship between ischemic stroke location and poststroke affective symptoms. That is in accordance with the results of Gozzi et al,[22] who did not observe any association between damaged voxels and poststroke depression in a sample of mild ischemic strokes, using statistical parametric mapping. We can hypothesize that, rather than the location, the interruption of brain anatomical or functional networks involved in mood regulation contribute to poststroke affective disorders.[23] Moreover, dysregulation in noradrenalin, dopamine, and serotonin neuronal network after stroke might also influence the occurrence of affective and apathetic symptoms, as suggested by Hama et al.[21]

The role of ischemic stroke location on specific cognitive subdomains is in line with the current knowledge on the anatomofunctional role of brain structures in cognitive domains. Our results emphasize the role of fronto-temporo-insular locations, together with deep brain structures, such as the thalamus and basal ganglia.[24,25] Unsurprisingly, we observed the main role of left-side hemispheric lesions for most of the cognitive domains, predominantly those in the language field, while right-side hemispheric lesions were mainly associated with visuospatial and executive functions.[25]

Nevertheless, the results of this study should be interpreted cautiously due to some limits. First, they only apply to patients with minor to moderate ischemic strokes, as represented in our cohort. Obviously, patients with larger ischemic lesions encompassing many cognitive areas will have more diffuse and severe cognitive impairment. Second, the mood scores (HAD and AI) were low in our sample, thus the absence of severe mood impairment might participated to the absence of association between stroke location and mood outcome, albeit we had a large sample of patients. Third, only patients with supratentorial stroke were included, which did not allow us to evaluate the influence of cerebellar lesions on poststroke cognitive and affective disturbances. Indeed, the role of cerebellum has been suggested through the disruption of cerebello-cerebral connections.[26,27] Fourth, cognitive evaluations were limited to the MoCA, which is relatively rough compared to a full battery of neuropsychological tests. Nonetheless, MoCA is a short and well-tolerated test independently associated with poststroke cognitive impairment,[28,29] which can be carried out routinely. In addition, MoCA subdomains have been previously well-associated with more extensive cognitive batteries.[30] Fifth, patients with severe aphasia who were not able to achieve the tests were excluded. Neuropsychological assessment adapted to aphasic patients are now available, and such tests should be used in the future, so as not to miss the cognitive outcome of these patients.

Conclusion

Ischemic stroke location, in minor to moderate strokes, can predict cognitive outcome at 3 months in various domains, emphasizing the hypothesis of strategic lesion location in poststroke cognitive outcome. However, ischemic stroke location does not seem to predict affective and apathetic symptoms.

Conflict of Interest

Sagnier S., Munsch F., Bigourdan A., Debruxelles S., Poli M., Renou P., Olindo S., Rouanet F., Dousset V., Tourdias T., and Sibon I. declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and regional research committee (CPP-2012/19 2012-A00190-43), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study, or their legal representative.

References

1. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009;8:1006-1018.
2. Robinson RG, Jorge RE. Post-stroke depression: a review. Am J Psychiatry 2016;173:221-231.
3. Wei N, Yong W, Li X, et al. Post-stroke depression and lesion location: a systematic review. J Neurol 2015;262:81-90.
4. Ferro JM. Hyperacute cognitive stroke syndromes. J Neurol 2001;248:841-849.
5. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. Nat Neurosci 2003;6:448-450.
6. Munsch F, Sagnier S, Asselineau J, et al. Stroke location is an independent predictor of cognitive outcome. Stroke 2016;47:66-73.
7. Castellanos-Pinedo F, Hernández-Pérez JM, Zurdo M, et al. Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. J Neuropsychiatry Clin Neurosci 2011;23:340-347.
8. Nys GMS, van Zandvoort MJE, van der Worp HB, et al. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. J Neurol Sci 2005;228:27-33.

9. Chen X, Duan L, Han Y, et al. Predictors for vascular cognitive impairment in stroke patients. BMC Neurol 2016;16:115.
10. Nickel A, Thomalla G. Post-stroke depression: impact of lesion location and methodological limitations-a topical review. Front Neurol 2017;8:498.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: Author.
12. Jorm AF. The informant questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr IPA 2004;16:275-293.
13. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. Acta Psychiatr Scand 1983;67:361-370.
14. Robert PH, Clairet S, Benoit M, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatry 2002;17:1099-1105.
15. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
16. Rivers CS, Wardlaw JM, Armitage PA, et al. Do acute diffusion- and perfusion-weighted MRI lesions identify final infarct volume in ischemic stroke? Stroke 2006;37:98-104.
17. Rorden C, Karnath H-O, Bonilha L. Improving lesion-symptom mapping. J Cogn Neurosci 2007;19:1081-1088.
18. Medina J, Kimberg DY, Chatterjee A, et al. Inappropriate usage of the Brunner-Munzel test in recent voxel-based lesion-symptom mapping studies. Neuropsychologia 2010;48:341-343.
19. Carson AJ, MacHale S, Allen K, et al. Depression after stroke and lesion location: a systematic review. Lancet 2000;356:122-126.
20. Grajny K, Pyata H, Spiegel K, et al. Depression symptoms in chronic left hemisphere stroke are related to dorsolateral prefrontal cortex damage. J Neuropsychiatry Clin Neurosci 2016;28:292-298.
21. Hama S, Murakami T, Yamashita H, et al. Neuroanatomic pathways associated with monoaminergic dysregulation after stroke. Int J Geriatr Psychiatry 2017;32:633-642.
22. Gozzi SA, Wood AG, Chen J, et al. Imaging predictors of poststroke depression: methodological factors in voxel-based analysis. BMJ Open 2014;4:e004948.
23. Lassalle-Lagadec S, Sibon I, Dilharreguy B, et al. Subacute default mode network dysfunction in the prediction of post-stroke depression severity. Radiology 2012;264:218-224.
24. Fuster JM. The prefrontal cortex—an update: time is of the essence. Neuron 2001;30:319-333.
25. Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000;12:1-47.
26. Baillieux H, De Smet HJ, Dobbeleir A, et al. Cognitive and affective disturbances following focal cerebellar damage in adults: a neuropsychological and SPECT study. Cortex 2010;46:869-879.
27. Kim NY, Lee SC, Shin J-C, et al. Voxel-based lesion symptom mapping analysis of depressive mood in patients with isolated cerebellar stroke: a pilot study. NeuroImage Clin 2017;13:39-45.
28. Salvadori E, Pasi M, Poggesi A, et al. Predictive value of MoCA in the acute phase of stroke on the diagnosis of mid-term cognitive impairment. J Neurol 2013;260:2220-2227.
29. Pendlebury ST, Markwick A, de Jager CA, et al. Differences in cognitive profile between TIA, stroke and elderly memory research subjects: a comparison of the MMSE and MoCA. Cerebrovasc Dis 2012;34:48-54.
30. Lam B, Middleton LE, Masellis M, et al. Criterion and convergent validity of the Montreal Cognitive Assessment with screening and standardized neuropsychological testing. J Am Geriatr Soc 2013;61:2181-2185.