Stroke

CLINICAL AND POPULATION SCIENCES

Texture Features of Magnetic Resonance Images Predict Poststroke Cognitive Impairment: Validation in a Multicenter Study

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BACKGROUND: Imaging features derived from T1-weighted (T1w) images texture analysis were shown to be potential markers of poststroke cognitive impairment, with better sensitivity than atrophy measurement. However, in magnetic resonance images, the signal distribution is subject to variations and can limit transferability of the method between centers. This study examined the reliability of texture features against imaging settings using data from different centers.

METHODS: Data were collected from 327 patients within the Stroke and Cognition Consortium from centers in France, Germany, Australia, and the United Kingdom. T1w images were preprocessed to normalize the signal intensities and then texture features, including first- and second-order statistics, were measured in the hippocampus and the entorhinal cortex. Differences between the data led to the use of 2 methods of analysis. First, a machine learning modeling, using random forest, was used to build a poststroke cognitive impairment prediction model using one dataset and this was validated on another dataset as external unseen data. Second, the predictive ability of the texture features was examined in the 2 remaining datasets by ANCOVA with false discovery rate correction for multiple comparisons.

RESULTS: The prediction model had a mean accuracy of 90% for individual classification of patients in the learning base while for the validation base it was ≈ 77%. ANCOVA showed significant differences, in all datasets, for the kurtosis and inverse difference moment texture features when measured in patients with cognitive impairment and those without.

CONCLUSIONS: These results suggest that texture features obtained from routine clinical MR images are robust early predictors of poststroke cognitive impairment and can be combined with other demographic and clinical predictors to build an accurate prediction model.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrophy ■ demography ■ hippocampus ■ machine learning ■ magnetic resonance imagingx

Poststroke cognitive impairment (PSCI) is one of the most common causes of dependency after stroke.[1] Its predictive diagnosis may allow the stratification of high-risk patients and the early initiation of care strategies. However, the clinical determinants and underlying mechanisms of PSCI are still not understood. Research has to date identified several risk factors including older age, sex, low level of education, stroke severity, risk factors for cerebrovascular disease, and previous pathology.[2,3,4] In a study involving diverse ethno-regional groups from the Stroke and Cognition Consortium (STROKOG), Lo et al[5] confirmed the high prevalence of PSCI in diverse stroke populations. In the 3146 stroke patients examined, 44% were impaired in global cognition. They also reported that diabetes mellitus and a history of stroke were strongly associated with poorer cognitive function.

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Nonstandard Abbreviations and Acronyms

DEDEMAS	Determinants of Dementia After Stroke
IDM	inverse difference moment
MRI	magnetic resonance imaging
PSCI	poststroke cognitive impairment
SSS	Sydney Stroke Study
STROKDEM	Study of Factors Influencing Poststroke Dementia
STROKOG	Stroke and Cognition Consortium

Casolla et al[6] reviewed the biological and imaging predictors of cognitive impairment after stroke and reported that the most consistent predictors were global atrophy and medial temporal lobe atrophy. However, the dynamics of atrophy may be long and therefore may be measurable only at advanced stages. In a previous study that included clinical and experimental material,[7] magnetic resonance imaging (MRI) texture features were investigated as early markers of PSCI. On the clinical side, the study showed that these features, computed on T1-weighted (T1-w) images, had a higher sensitivity than volumetric measures in separating patients with cognitive impairment from those without. In the preclinical part of the study, imaging investigations and histological measurements conducted on rats with middle cerebral artery occlusion, which stimulated an ischemic stroke, revealed that some of these imaging features were correlated with neural density.

Texture features allow the quantification of subtle signal variations in a whole image or a region of interest, based on different statistical measures taking into account the signal distribution and voxels neighborhood. They were reported with the potential to discover hidden information that is inaccessible with single-parameter approaches, such as volume and shape, and may reflect genomic, cellular, and metabolic information.[8] They are thought to reflect the tissular changes related to the disease progression.

However, in MR images, the signal distribution is subject to variations due to magnetic field in-homogeneities and image encoding. This can limit the transferability of these features between MRI centers.[9] The primary aim of this study was to examine the reliability of these features against imaging settings and qualities using different study cohorts from the STROKOG consortium. Machine learning modeling using these imaging features is investigated to build robust PSCI prediction models.

METHODS

Data Availability Statement

Readers seeking access to the data used in this study are advised to contact the corresponding author.

Data

Data were collected from the STROKOG members who agreed to participate in the study and who had the required data available at their recruitment. Patients were required to have a T1-w MRI acquisition at baseline or up to 6 months poststroke, with sufficient quality for accurate segmentation of gray matter nuclei and cortical parcellation, and a follow-up cognitive assessment up to 12 months poststroke (see Table 1 for detailed imaging parameters). The study excluded participants with preexisting dementia.

The current work included data drawn from the STROKDEM (Study of Factors Influencing Posttroke Dementia)[10] and 3 studies from the STROKOG consortium, including the DEDEMAS (Determinants of Dementia After Stroke) cohort from Germany,[11] the SSS (Sydney Stroke Study) from Australia,[12] and STRATEGIC from the United Kingdom.[13] Four other studies from Hong Kong, Korea, and Singapore contributed data; however, the MR images did not pass quality control and were excluded from the analyses. Images were required to have slice thickness <5 mm to allow accurate brain structures segmentation.

Ethics approval for all studies was granted by the local institutional review boards. Table 1 summarizes the characteristics of the databases included.

Texture Features Calculation

Brain segmentation and parcellation were applied to extract the main gray matter nuclei. For these purposes, Freesurfer software version 6.2 (https://surfer.nmr.mgh.harvard.edu) with a cross-sectional pipeline[14,15] was used. Among the processing steps included in this pipeline, intensity normalization was applied. This dealt with signal variation and in-homogeneities, and was based on the method proposed by Dale et al.[16] It assumed that the highest intensity tissue on each slice would be white matter and as a first step it centered the mean white matter intensity at a desired value. The remaining bias field was then corrected by automatically detecting a set of control points which were determined to be in the white matter. The method was successfully tested using data from a variety of scanners and MRI protocols.

Starting from the normalized images, and based on the early results reported by Delattre et al[17] showing that the hippocampus and entorhinal cortex are impacted by cognitive impairment in patients with stroke, these 2 structures were considered in regions of interest-based texture measurements. Two sets of texture features were computed: (1) first-order statistics, which quantified the signal distribution in the defined regions. These included the mean and SD of grayscale levels, as well as kurtosis and skewness that quantify the signal distribution asymmetry; (2) second-order metrics derived from the co-occurrence matrix. This matrix was built by measuring pair-wise dependencies between grayscale values of adjacent voxels. Seven features were extracted from this matrix: (1) homogeneity (also called angular second moment); (2) contrast; (3) entropy; (4) correlation; (5) variance (also called sum of squares); (6) sum average; and (7) inverse difference moment (IDM). Features were computed for each structure on the left and right hemisphere separately and then averaged.

A detailed description of the process of texture features generation is given in Table S1 and summarized in Figure 1. This figure depicts a coronal T1w MR slice with the delineation

Table 1. Summary of the Data Collected

	STROKDEM	DEDEMAS	Sydney Stroke Study	STRATEGIC
N	160	56	68	43
Country	France	Germany	Australia	United Kingdom
Age, y	64.09±13	70.25±7.97	72.01±8.74	69.47±8.37
Sex (F/M)	100/60	16/40	28/40	10/33
Education, y	11.17±3.70	(>12 y) Y (24)/N (32)	10.51±3.26	14.23±3.60
Stroke classification	Ischemic=150, hemorrhagic=10	Ischemic=54, hemorrhagic=2	Ischemic	Ischemic
Stroke severity	NIHSS 1 (0–2)	NIHSS 2 (1–4)	ESS 94 (40–100)	…
Hypertension (Y/N)	95/65	45/11	43/23	25/18
Diabetes (Y/N)	24/136	5/51	7/59, NA for 1 patient	7/36
Current smoker (Y/N)	36/124	8/48	…	21/22
Prior stroke (Y/N)	14/146	4/52	11/53, NA for 4 patients	…
MoCA (baseline)	25.78±3.52	25.76±2.67	…	26.20±3.07
MMSE (baseline)	27.65±2.78	27.70±2.24	…	…
Cognitive follow-up				
Time	6-mo poststroke	6-mo poststroke	1-y poststroke	1-y poststroke
MoCA	26.07±3.56	25.03±2.97	…	26.94±3.0
MMSE	27.92±2.38	28.80±1.42	28.51±1.76	…
Impairment (Y/N)	75/85	11/45	11/57	13/30
Imaging				
Time	Within first wk poststroke	Within first wk poststroke	3 mo poststroke	3–6 mo poststroke
Parameters	3T MRI systems (PHILIPS Healthcare, Best, Netherlands) with an 8-channel sensitivity encoding (SENSE) head coil. 3D T1-weighted images were acquired in the sagittal plane with 1 mm^2 isotropic pixel size, repetition time=7.2 ms, echo time=3.3 ms, flip angle=9°, field of view=240×256 mm^2; acquisition matrix=256×256; slice thickness=1 mm and 176 continuous slices.	3T MRI system, Siemens Magnetom Verio, 32-channel head coil. 3D T1-weighted images were acquired in the sagittal plane with 1 mm^2 isotropic voxel size, repetition time=2500 ms, echo time=4.37 ms, acquisition matrix=256×256; slice thickness=1 mm and 192 continuous slices.	1.5 T Signa GE scanner (GE Systems, Milwaukee). 1.5-mm thick T1-weighted contiguous coronal sections through whole brain using a FSPGR sequence and 3D acquisition (repetition time=14.3 ms, echo time=5.4 ms, field of view=250×250 mm^2, in plane resolution 0.977×0.977 mm^2).	3T MR scanner (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom). T1-weighted images MPRAGE sequence with repetition time=7.31 ms, echo time=3.02 ms and a flip angle of 11°. Sagittal plane with field of view=270×270 mm, matrix size=256×256 voxels, and slice thickness and gap of 1.2 mm.

Values shown are n, or mean±SD. DEDEMAS indicates Determinants of Dementia After Stroke; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MPRAGE indicates magnetization-prepared rapid acquisition gradient echo; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and STROKDEM, Study of Factors Influencing Poststroke Dementia.

of the hippocampus and the entorhinal cortex and shows the extraction of the gray values in each region and finally the texture features calculation.

Analyses. Previous work harmonized and standardized the neuropsychological tests and scores between the different studies involved in STROKOG (see Lo et al[5] for a detailed description of the procedures). Overall, cognitive function was assessed by administering an extensive battery of neuropsychological tests, classified into 5 cognitive domains (memory, executive function, attention, language, and visuospatial ability). For each patient, a test-specific *z*-score was calculated based on normative data adjusted for age, sex, and education.[10] A summary domain-specific *z*-score was obtained by standardizing and averaging the test-specific *z*-scores in each domain and a cutoff was applied to define cognitive impairment.

With regards to imaging, there is currently no standard protocol and disparities exist between the images in different aspects, including scanners and acquisition parameters. Most importantly, differences exist in patient profiles, the severity of the stroke, and the temporality of MR acquisitions since the index stroke. As it is assumed that textural features are sensitive to cognitive impairment and its progression and are the reflection of underlying tissue modifications, a single analytical framework would not be suitable for all the collected data. Among the 4 studies included in this work, STROKDEM and DEDEMAS have very similar designs and both recruited patients with mild stroke, while the other 2, SSS and STRATEGIC, had their own designs and differed mainly in the time of MRI acquisition (see Table 1). Consequently, 2 statistical analysis frameworks were applied.

Differential Diagnosis of PSCI: STROKDEM and DEDEMAS. In these studies, the first full neuropsychological evaluation was performed 6 months (M6) after the event and classified the patients into 2 groups, those with intact

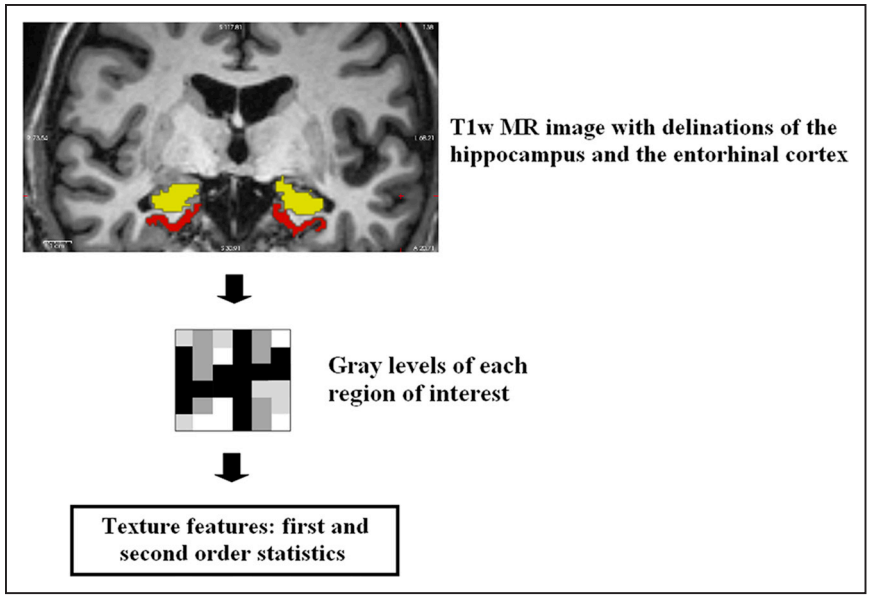

Figure 1. Texture features measurement process.
MR indicates magnetic resonance.

cognition and those with cognitive impairment. Data from the 2 cohorts were already combined in a previous study where a pooled analysis revealed that early cognitive testing by baseline Montreal Cognitive Assessment (MoCA; test administered within the first week poststroke) can predict long-term cognitive outcome, functional outcome, and mortality after stroke.[18] In terms of MRI acquisitions, the first exploration was done within the first week poststroke. Differences between the images concerned only the scanners and sequence parameters. The similarity between the 2 studies, combined with the substantial size of the datasets (n=160 for STROKDEM and n=56 for DEDEMAS) made the configuration suitable for setting up a machine learning study aimed at testing the ability of the texture features to differentiate patients with cognitive impairment from those with intact cognition. Consequently, baseline data from STROKDEM were used to train a random forest (RF) model for predicting cognitive status at M6 and data from DEDEMAS were used for testing. This algorithm appears as one of the most suitable algorithms to handle this kind of situations where the target variable to be predicted is binary. Compared with other methods as Support Vector Machines (SVM), it presents the advantage of including a features selection step. The RF algorithm employs a parallel structured ensemble tree-based method that uses bagging to aggregate multiple decision tree classifiers to select the best features and combine them optimally. In a first investigation[7] done on the STROKDEM data, it was demonstrated that texture features are predictors of cognitive status independently of age and sex. These variables were already reported as risk factors for poststroke cognitive impairment. Therefore, to have a complete model, the RF algorithm was run by considering the imaging features, age, sex, and baseline MoCA score. A 5-fold cross-validation was used to obtain unbiased estimates of the classification error. The dataset was randomly split into 5-fold without duplication: 4-folds were used to train the model, and the fifth fold was the testing set. The global validation approach consisted of repeating the 5-fold validation 10 times. After RF model optimization (feature selection and combination), sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve were calculated as evaluation scores for each of the 10 derived models. Overall classification performance was expressed as mean±SD of each score.

The final model was derived by considering the entire data from STROKDEM as learning data and the obtained model was blindly applied to the DEDEMAS data. Before this testing, each selected variable was tested separately in this dataset using the appropriate test according to the variable type and distribution (Student *t* test or Mann-Whitney *U* test for continuous variables in the case of a normal distribution or not, respectively, and Chi^2 test for binary and categorical variables). The model was applied, and as for the learning base, the performances were measured using the same scores as previously.

Guidelines for the development of machine learning models as proposed by Luo et al[19] were followed for the development described in this section. Please report to the checklists in Figures S1 and S2 as well as Table S2 through S6.

Predictive Abilities of Texture Features: SSS and STRATEGIC. For these studies, MR images were acquired 3 to 6 months after the stroke (3 months for SSS and 3–6 months for STRATEGIC), and the first global cognitive assessment was performed ≈ 1 year after the stroke, classifying the patients as cognitively intact or with cognitive impairment. Texture features were tested between the 2 patient groups to examine their predictive abilities. ANCOVA with the 2 main risk factors age and sex as covariates was used. For all analyses, significance was fixed at $P<0.05$ and was corrected using the false discovery rate for multiple testing and comparisons.

RESULTS

Differential Prediction of Cognitive Impairment

Performance on the Learning Base: STROKDEM

The cross-validation process using data from STROKDEM showed stability in performance through the 5-fold validation process. Accuracy was 0.90±0.05,

sensitivity was 0.92±0.04, specificity was 0.93±0.02, and the area under the receiver operating characteristic curve was 0.90±0.03.

Stability was also observed in the selected features. The final model optimized using the whole data was built using texture features kurtosis and IDM from the entorhinal cortex, and kurtosis and entropy from the hippocampus, age and MoCA score.

Performance on the Testing Base: DEDEMAS

Pair-wise comparison of texture features between the 2 patient groups showed significant differences: IDM (P=0.009) and kurtosis (P=0.01), measured in the entorhinal cortex and kurtosis in the hippocampus (P=0.003). The entropy feature measured in the hippocampus did not show any significant differences after false discovery rate correction (P=0.06). Figure 2 shows the results of these comparisons.

When this optimized model was applied to the testing base, the performance was 0.76 for accuracy, 0.78 for specificity, 0.74 for sensitivity, and 0.77 for the area under the receiver operating characteristic curve.

Texture Features in SSS and STRATEGIC Databases

The results of ANCOVA of the texture features between the patients diagnosed with cognitive impairment and those without are summarized in Tables 2 and 3, respectively. There was a significant difference in texture features kurtosis and IDM between the patients in the 2 datasets.

DISCUSSION

Main Outcomes

This study aimed to confirm texture parameters, measured in the hippocampus and entorhinal cortex, from baseline structural MR images (T1-w) as potential predictors of cognitive impairment in the months after a stroke. For this purpose, data from 4 cohorts were collected and 2 analytic approaches were employed to deal with the heterogeneities of data, mainly in terms of temporalities of acquisitions. The first analysis built a prediction model by combining texture features and other predictors from demographic and clinical data. The model was trained on data from the STROKDEM cohort (n=160) and showed an overall accurate prediction of around 90%. When the derived model was applied to the testing data from DEDEMAS cohort (n=56), overall accuracy was ≈ 76%. The second analysis used the other 2 cohorts, SSS (n=68) and STRATEGIC (n=43), and showed significant differences in texture features, independent of age and sex. These were measured on images acquired within the first 6 months after the stroke, in patients with cognitive impairment and those without, as evaluated 1-year poststroke.

Texture Features as an Alternative to Volumetry

Imaging features were widely investigated as predictors of poststroke cognitive impairment. The main outcomes are stroke features, white-matter hyperintensities and cerebral atrophy.[4] Thus, larger strokes were associated with higher likelihood of cognitive dysfunction[20] while more extensive white-matter hyperintensities were described in patients with cognitive deficits poststroke.[21]

Brain atrophy is probably the most robust predictor that was consistent across studies.[6] However, the reported patterns of atrophy differed and several regions were highlighted as being impacted: the hippocampus,[22,23] the amygdala,[24] the thalamus,[25] and cortical regions.[7,6] Furthermore, cerebral atrophy in mild cognitive impairment was reported as a slow process[26]: mean atrophy rates were for the whole brain 0.46%/year, for the hippocampus 1.35%/year, and for the entorhinal cortex 1.13%/year. Furthermore, the dynamics of cortical and hippocampal atrophy in Alzheimer Disease were reported with nonlinear behaviors.[27] More globally for all these predictors, to the best of our knowledge, none of them was examined at the patient-individual level to establish the sensitivity and specificity in differential diagnosis.

Texture features, derived from a texture analytic approach, are able to detect the structural changes related to the atrophy process with a higher sensitivity than volumetry.[7,28] They were investigated in several clinical conditions. In neuro-radiology, the method was initially applied in neuro-oncology with promising results for the prediction of treatment outcomes.[29] More recently, there has been a growing number of studies in neurodegenerative and neurological diseases with clinical applications in differential diagnosis[30,31,32,33] and prediction of cognitive evolution.[34,35]

Normalization to Ensure Reliability

Because texture analysis is based on the detection of inter-voxel statistical patterns, variations in absolute levels of gray-level intensity of images acquired from different scanners may pose a challenge to multicenter data and impact reproducibility. Ta et al[9] assessed the intrasite and inter-site reliability of the method, applied on different brain structures using multicenter data acquired with harmonized MR sequence parameters, and demonstrated good reproducibility. However, the reliability when the MR protocols are not standardized is still unknown. The main issue for generalization of the method proposed in the current study is the

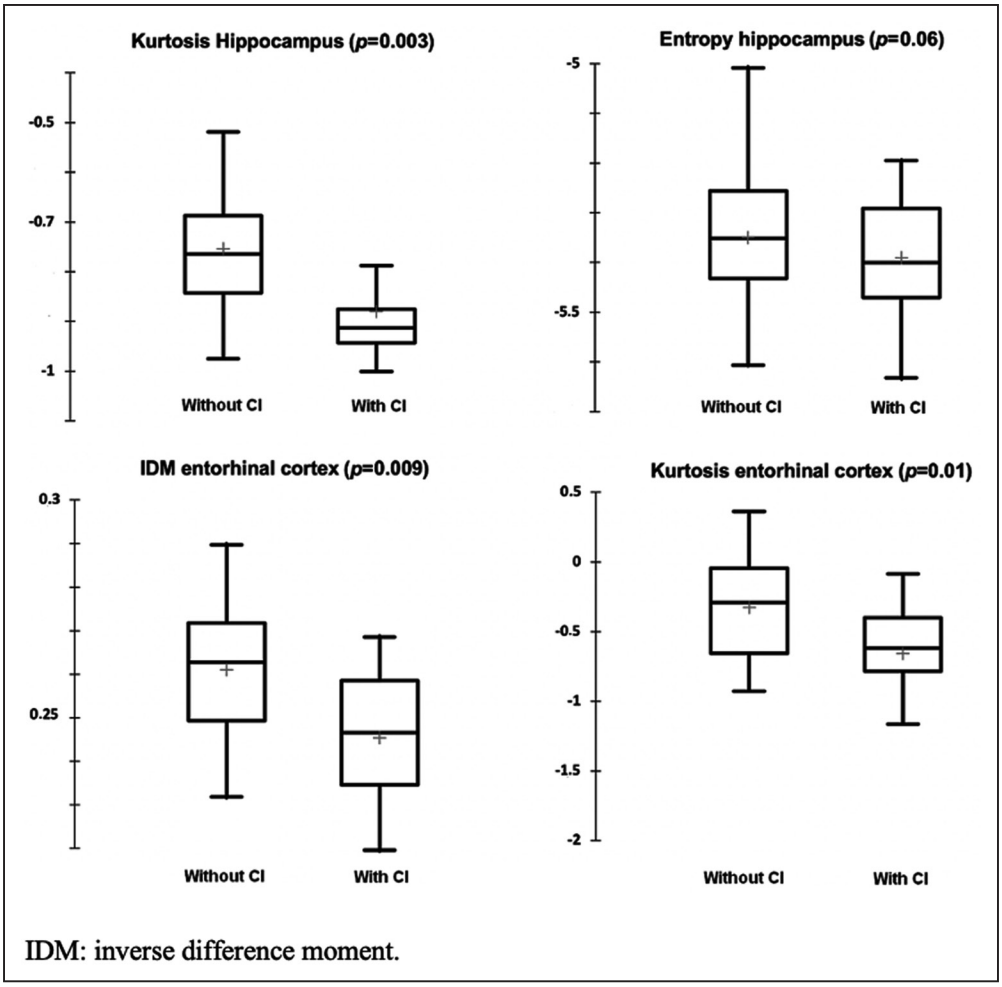

Figure 2. Comparison of the distribution of texture features predictors (optimized in the STROKDEM [Study of Factors Influencing Poststroke Dementia] cohort) between patients with cognitive impairment (CI) and those without in the DEDEMAS (Determinants of Dementia After Stroke) cohort.
IDM indicates inverse difference moment.

signal changes on MR images acquired from the same scanner and from different scanners when differences concern hardware, including constructor, coil type, and field strength.

T1-w images are typically affected by magnetic susceptibility artifacts and field in-homogeneities leading to variations in both intensity and contrast across the images. To deal with this problem, a normalization step was applied before extracting the texture features. Normalization of MRI intensity values has been shown to reduce the effect of varying acquisition parameters and to reduce classification errors in multicenter datasets.[36] Several generic algorithms exist for this processing, such as intensity scaling, histogram stretching, contrast stretch normalization, histogram normalization and histogram equalization, but there is currently no gold standard approach. More importantly, normalization should not affect the sensitivity of the texture parameters to disease pathology. In a study by Loizou et al,[37] the authors compared the effect of some of these methods on texture features measured on T2w images of multiple sclerosis and showed that the features were affected differently by the normalization process. In the current study, the applied method is not a generic method from image processing but it is suitable to brain imaging since it is based on centering the mean white matter intensities.[16] This process made the intensity values comparable between the images and scanners, but the sensitivity regarding the disease should be investigated further.

Texture Features From Hippocampus and Entorhinal Cortex Across the Studies

In this study, once the image intensities were normalized, the method measured first order and second-order statistical features from the hippocampi and entorhinal cortex, because these structures are among the main structures involved in the occurrence of cognitive impairment.[38,39] In an evaluation of studies on texture analysis in mild cognitive impairment and Alzheimer disease by Won et al,[40] these authors reported that the hippocampus was the most frequently analyzed (46.2%) anatomic structure. These authors

Table 2. ANCOVA Results of Texture Features Comparisons Between Patients With Cognitive Impairment and Those Without in the Sydney Stroke Study

T1-w images texture features	Hippocampus			Entorhinal cortex		
	Patients with CI	Patients without CI	*P* value	Patients with CI	Patients without	*P* value
Mean	77.23±3.2	78.13±2.26	0.23	74.67±2.68	76.67±2.62	0.60
SD	9.82±1.26	10.92±1.24	0.13	9.52±1.56	9.81±1.31	0.17
Skewness	4.32±1.12	4.13±0.87	0.12	4.03±2.88	3.42±1.11	0.05
Kurtosis	−0.65±0.12	−0.40±0.06	0.001*	−0.44±0.10	01.02±0.09	0.004*
Homogeneity	328.42±80.18	334.75±80.0	0.25	320.40±88.8	332.08±68.8	0.38
Contrast	783.55±201.47	813.54±230.5	0.34	795.51±224.50	801.4±174.18	0.24
Correlation	−0.61±0.15	−0.65±0.20	0.27	−0.64±0.2	−0.67±0.28	0.15
SumA	68.21±8.68	65.76±9.31	0.25	69.08±9.31	67.61±8.69	0.38
SumV	434.78±60.7	480.98±75.2	0.07	526.91±107.9	575.86±123.20	0.03
Inverse difference moment	0.17±0.03	0.22±0.02	0.05	0.13±0.02	0.20±0.05	0.01*
Entropy	−5.60±0.21	−5.02±0.37	0.07	−5.94±0.24	−5.30±0.21	0.11

Values shown are n, or mean±SD. CI indicates cognitive impairment; and IDM, inverse difference moment.
*Significant *P* value after false discovery rate correction.

reported that the hippocampi were the most frequently analyzed (46.2%) anatomic structures. In poststroke cognitive impairment, our group discussed the implications of these structures using clinical data and animal models.[17] Other brain structures may also be involved when specific hypotheses are to be tested. Voxel wise analyses methods such as voxel-based morphometry can be applied to conduct whole brain analysis to identify these structures. The texture method could easily be extended to include these additional brain regions but additional data would be required to build accurate models taking into account all the features.

The first analysis in the current study aimed to test texture features sensitivity and specificity for the differential diagnosis and to validate them using external data. The similarities between the datasets STROKDEM and DEDEMAS provided an ideal framework for this test. Furthermore, the 2 cohorts shared their study design and recruited patients with the same profiles. In both cohorts, patients were predominantly diagnosed with mild stroke, with a National Institutes of Health Stroke Scale interquartile range of 0 to −2 in STROKDEM and 1 to −4 in DEDEMAS. On the imaging side, the acquisitions differed in constructor and sequence parameters (Table 1). Consequently, a model based on baseline data and predicting the cognitive state 6 months after the stroke was optimized on the STROKDEM data by selecting the most significant predictors. The model incorporated the texture features kurtosis and IDM from the entorhinal cortex, and kurtosis and entropy from the hippocampus, age, and baseline MoCA score. The model showed good prediction accuracy with a mean sensitivity of 92% and mean specificity of 93%. When it was applied to the DEDEMAS data, as external and unseen data, the results showed a sensitivity of 74% and specificity of

Table 3. ANCOVA Results of Texture Features Comparisons Between Patients With CI and Those Without in the STRATEGIC Study

T1-w images texture features	Hippocampus			Entorhinal cortex		
	Patients with CI	Patients without CI	*P* value	Patients with CI	Patients without	*P* value
Mean	75.11±3.98	74.57±1.9	0.80	72.33±2.65	75.07±1.98	0.70
SD	11.12±4.02	8.14±7.75	0.09	10.43±2.00	8.85±1.85	0.20
Skewness	5.62±0.88	7.02±0.55	0.08	4.23±0.95	3.75±1.35	0.52
Kurtosis	−0.80±0.12	−0.62±0.06	0.01*	−0.35±0.09	−0.95±0.11	0.009*
Homogeneity	320.20±75.3	338.50±83.2	0.22	310.40±78.72	340.63±38.9	0.35
Contrast	790.33±185.40	795.66±200.52	0.6	800.12±198.89	825.36±200.03	0.23
Correlation	−0.52±0.15	−0.63±0.06	0.07	−0.60±0.13	−0.72±0.35	0.10
SumA	60.11±7.88	65.75±8.91	0.22	65.12±10.11	69.37±9.01	0.45
SumV	422.52±55.1	455.78±85.32	0.15	520.69±99.98	540.74±83.59	0.40
Inverse difference moment	0.10±0.06	0.18±0.04	0.004*	0.19±0.07	0.27±0.02	0.003*
Entropy	−6.10±0.11	−5.22±0.68	0.01*	−5.00±0.32	−4.40±0.48	0.05

Values shown are n, or mean±SD. CI indicates cognitive impairment.
*Significant *P* value after false discovery rate correction.

78%. A higher performance was expected as the 2 datasets are identical; however, the small number of patients with cognitive impairment at the 6 month examination (11/56 patients) may explain these results. Interestingly, for the texture features, except for entropy in the hippocampus (P=0.06), the other selected features (kurtosis in the hippocampus and entorhinal cortex, and IDM in the entorhinal cortex) were statistically different between the 2 patient groups. In light of this analysis of the parametric distribution of the different models in the test cohort, one could conclude a larger validation dataset involving more data from this database will probably enhance the accuracy and get closer to that obtained on the learning base.

The second analysis was applied to 2 cohorts involving different ethno-regional groups, SSS and STRATEGIC. For these data, MR images were acquired within the first few months poststroke and cognitive evaluation was performed up to 1 year post-event and differed in many aspects such as the coil strength (Table 1). Given these differences, it did not appear appropriate to include these 2 cohorts as external data for validation of the previous model. On the other hand, the sample sizes were insufficient to build specific models. It is often recommended to have at least 10 entries in the dataset for each variable of the model. Therefore, the texture features were examined in each dataset for differences between patients with cognitive impairment at follow-up and those without. The results obtained showed that different features were significantly different between the 2 patient populations, independent of age and sex (Tables 2 and 3). It is interesting to observe that the texture features that were different were similar to those used for the prediction model developed in the first analysis. The feature kurtosis appeared to be a robust predictor across the datasets. From a statistical point of view, this parameter is a measure of the combined weight of the tails relative to the rest of the distribution of gray levels. It is thought to quantify signal asymmetry and, indirectly, changes reflecting biological alterations. In another context, where texture features were examined as early markers of cognitive worsening in Parkinson's disease, kurtosis and skewness were among the best predictors. Alternatively, in the preclinical part of our previous study on texture analysis and PSCI,[7] the texture features measured on T2-w images, which have a different distribution to T1-w images, showed that skewness (related to kurtosis in most cases) was among the texture features correlated with neural density. In preclinical studies, Colgan et al[41] showed that kurtosis of the hippocampus and thalamus was associated with tau burden in a mouse model of Alzheimer disease.

Limitations

These results taken together suggest that although the MR sequences were not harmonized for different aspects such as parameters and acquisition periods between the studies, the normalization step applied on the images ensured the reproducibility of the results and made texture features a robust predictor of poststroke cognitive status.

It is important to note that the methodology applied in this investigation was based on the categorical diagnosis of cognitive impairment, which involves the application of cutoff values for cognitive scores. This is a limitation of the study. Like dementia, continuous measurement of cognitive impairment and prediction of the cognitive scores using baseline texture features would make sense. This approach has not been adopted here for the reasons given above regarding data heterogeneity, but it is a recommendation for further studies.

Conclusions

A previous study showed that texture features are early markers of PSCI and have better sensitivity than atrophy measurement.[7] The current study provides new evidence about the reliability of the method. The data used were heterogeneous for many features such as patient profile, MR scanners, and T1-w sequence parameters. T1-w texture features are a marker that can be combined with other markers taken from demographics, clinical scores, biology, and multimodality imaging[6] to obtain the optimal predictive model.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S2
Tables S2–S6

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