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ORIGINAL COMMUNICATION

Aphasia outcome: the interactions between initial severity, lesion size and location

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Abstract

Objectives The outcome of aphasia at 3 months is variable in patients with moderate/severe stroke. The aim was to predict 3-month aphasia outcome using prediction models including initial severity in addition to the interaction between lesion size and location at the acute phase.

Methods Patients with post-stroke aphasia (assessed by the Aphasia Rapid Test at day 7-ART D7) and MRI performed at day 1 were enrolled ($n=73$). Good outcome at 3-months was defined by an Aphasia Handicap Score of 0–2. Each infarct lesion was overlapped with an area of interest in the left temporo-parietal region to compute an intersection index (proportion of the critical region damaged by the infarct). We tested ART D7, age, lesion volume, and intersection index as well as a combined variable lesion volume*intersection in a univariate analysis. Then, we performed a multivariate analysis to investigate which variables were independent predictors of good outcome.

Results ART at D7, infarct volume, and the intersection index were univariate predictors of good outcome. In the multivariate analysis, ART D7 and "volume ≥ 50 ml or intersection index ≥ 20%" correctly classified 89% of the patients ($p<0.0001$). When added to the model, the interaction between both variables was significant indicating that the impact of the size or site variable depends on the initial severity of aphasia.

Conclusion In patients with initially severe aphasia, large infarct size or critical damage in left temporoparietal junction is associated with poor language outcome at 3 months.

Keywords Aphasia · Magnetic resonance imaging · Prognosis

Introduction

Early prediction of language outcome remains challenging in aphasic stroke patients. Simple and robust prognosis models are important for patients and their relatives but also for improving the stratification of patients in language therapeutic trials during the first 3 months post stroke, corresponding to the "spontaneous" recovery period. To date, the best predictor of outcome is the initial severity of aphasia [1–9], whereas other patient-related predictors (age, education…) are more debated [10, 11]. However, while initially mild aphasias consistently recover, outcome is less predictable in more severe patients (see for example Fig 1 of Ref. [3]). Some studies [12, 13] have suggested that recovery is proportional to initial severity (about 70% of the maximum possible recovery), but this notion has been recently challenged on theoretical grounds [14, 15]. Lesion size and location are also related to language outcome [10–16]. The

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arcuate fasciculus and more broadly the white matter of the left temporo-parietal junction and the adjacent cortex are considered as critical regions for language outcome [17–22]. One recent study reported a multivariate prognostic model of aphasia outcome that included initial severity as well as the lesion size and location [23]. In this study, which also included non-aphasic stroke patients, the best single predictor of language outcome was initial severity of aphasia, yet overall prediction improved with lesion size and education with an additional 13% of variance explained by the site of the lesion with left temporo-parieto-occipital white matter lesions predicting worse outcome.

We have previously reported that the Aphasia Rapid Test (ART), a simple bed-site assessment of aphasia severity, can predict 3-months language outcome with high accuracy [8]. These findings have also been replicated in Portuguese [24]. In the present study, our aims were to confirm the predictive value of the ART at day 7 post-stroke onset (ART D7) for language outcome at 3 months post-stroke and investigate if prediction could be improved by the lesion size and location (involving the left temporo-parietal junction) determined on acute routine magnetic resonance imaging (MRI) in a population of aphasic patients.

Materials and methods

Patients

We enrolled 73 patients admitted to the stroke unit of the Pitié-Salpêtrière Hospital who consecutively met the following criteria: (1) ischemic stroke in the left middle cerebral artery (MCA) territory, (2) persistent aphasia at day 1 post stroke (≥ 1 point in the language items of the NIHSS), (3) age ≥ 18 years, (4) MRI performed at 1–2 days post stroke and suitable for spatial normalization, (5) no severe white matter lesions (Fazekas score < 3), (6) an available ART score at day 7 post-stroke and Aphasia Handicap Score (AHS) at 3 months post-stroke.

These patients constituted a subset of 262 patients with acute left MCA infarct and initial aphasia hospitalized between 2011 and 2015. One hundred and six of these patients had no follow-up at 3 months (34/106 had died). Another 83 patients were not included because of missing MRI at 24–48 h or missing ART D7. Fifteen of the 73 included patients were previously reported in Ref. [18] and 14 others in Ref. [8].

The study was approved by the local ethics committee (Paris VI committee) and in agreement with French legislation informed consent was waived since assessing the severity of aphasia and imaging is part of standard care in stroke patients.

Language scoring

The initial severity of aphasia was assessed at day 7 post-stroke using the ART, which is a standardized bedside assessment to rate aphasia severity in stroke patients in less than 3 min [8]. The ART is a 26-point scale with higher scores indicating greater impairment. It is based on 6 items, consisting of simple comprehension tasks (rated from 0 to 5 points), word and sentence repetition (0–8 points), object naming (0–6 points), semantic fluency of animals (0–4 points), and dysarthria evaluation (0–3 points). Note that the repetition items represent 30% of the total score, whereas they represent only 13% (2/15) in the LAST, another validated rapid bedside assessment of aphasia [25]. The reproducibility, sensitivity, and high predictive value of the ART score have been published [8], and its external validation has recently been published in Portugal and in India [24, 26]. In chronic aphasic patients, ART scores have been reported to correlate with decreased fractional anisotropy in a critical area of the temporo-parietal white matter (TPWM) overlapping with the arcuate and inferior fronto-occipital fasciculi [18]. In our initial study, the ART score obtained at 1 week post stroke best predicted aphasia outcome and was, therefore, used in the present study [8].

The outcome of aphasia was assessed at 3 months post-stroke using the AHS [8]. The AHS is a five-point functional patient-orientated scoring system for disability in verbal communication similar to the modified Rankin Scale. 0 = normal communication, 1 = minor difficulties of language without disability (no impact on normal life), 2 = mild-language related disability (without restrictions in the autonomy of verbal communication in daily life), 3 = moderate language-related disability (restricted autonomy of verbal communication), 4 = severe language-related disability (lack of effective verbal communication), 5 = mutism or total loss of verbal expression and comprehension. A detailed description as well as the reproducibility and comparison with the Boston Diagnosis Aphasia Examination aphasia severity rating scale (ASRS) [27] is provided in the online resource 2 of Ref. [8]. Here, good outcome was defined as an AHS 0–2, which has a concordance of 95% with an ASRS 3–5.

Therefore, we evaluated patients with the ART, which is a standardized test, at the acute stage and the AHS as a functional test at 3 months [28]. This is analogous to assessing initial stroke severity, which is assessed with the NIHSS score and subacute/chronic outcome is assessed with the modified Rankin scale [29].

Magnetic resonance imaging (MRI) acquisition and DWI image processing

MRIs were performed 24–48 h post stroke using a 3 T whole-body MRI unit (General Electric, USA). DWI

sequences yielded a series of 256 × 256 axial scans (5-mm thickness, spin-echo multi-slice single-shot echo planar imaging) with a baseline T2 acquisition ($b = 0$ s/mm^2) and a b value of 1000 s/mm^2. Infarct volume was defined as abnormal hyper-intense regions observed on the DW images ($b = 1000$s/mm^2) and was measured using interactive manual outlining with the MRIcron software (http://www.mricro.com). The segmentation was performed by an experienced stroke clinician (SB) and verified by another (CR).

The next step consisted in calculating the percent overlap of each subject's lesion with a TPWM region-of-interest as defined in Ref. [18]. To this purpose, the diffusion image of each subject was normalized to MNI space using the Echo-planar imaging (EPI) template provided in SPM12 (http://www.fil.ion.ucl.ac.uk/spm) similar to previous studies [30, 31].

The lesion mask of each patient was then normalized by applying the respective transformation matrix. Each normalized image and mask were visually checked using a previously reported method for misregistration [31]. We then computed the intersection index given as the proportion of the TPWM critical area damaged by the infarct (Fig. 1).

Statistics

Descriptive statistics are provided as the median and interquartile range (IQR). First, ART at D7, infarct volume, the intersection index, age, gender, and the use of thrombolysis were evaluated using univariate analyses to determine their clinical relevance for good language outcome at 3 months post-stroke [odds ratios and 95% confidence intervals (95% CIs)]. For each significant predictor, we performed a ROC curve analysis (to obtain the accuracy, sensitivity, and specificity) and Spearman's coefficient to obtain the proportion of the variance of the 3-month good outcome explained by the predictors. Then, we ran several stepwise logistic regressions with the dichotomized AHS at 3 months post-stroke as the dependent variable. The independent variables were those found to be significant in the univariate analysis in addition to their interactions. Statistical analyses were performed with MedCalc (version 12.5.0, Belgium, 2013).

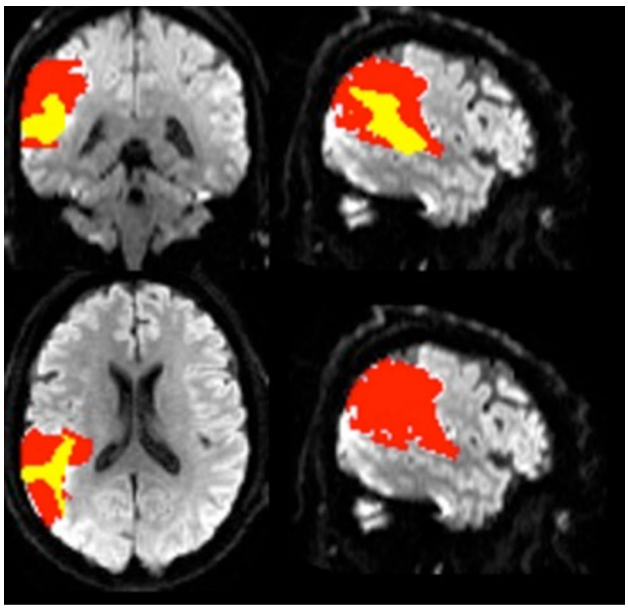

Fig. 1 Overlap of the left temporoparietal area of interest from (8) in yellow with the infarct mask in red, on the diffusion images (coronal, sagittal and axial views)

Results

Patients

Seventy-three patients were included in the study. Table 1 describes the characteristics of the patients. The probability map of infarct location covered most of the middle cerebral artery territory (Fig. 2). The infarct in most patients affected the basal ganglia and the insula/rolandic operculum areas.

Univariate prediction of good outcome

The ART at D7, infarct volume, and the intersection index were univariate predictors of good outcome at 3 months (AHS 0–2) (Table 2). Gender, age, and thrombolysis treatment were not significant.

The ART D7 explained 55.8% of the variance in 3-month good outcome ($p < 0.0001$) and correctly classified 84.9% of the patients (40/46 patients with good outcome, and 22/27 patients with poor outcome). The infarct volume explained 19.7% of the variance ($p = 0.001$) and correctly classified 42/46 patients with good outcome, and 12/27 patients with poor outcome. The intersection index explained 13.3% of the

Table 1 Baseline characteristics of the included patients

Population	$N = 73$ (%)	Median and IQR (25–75)
Female sex, *n* (%)	29 (40%)	
Age		63.7 (52.3–78)
NIHSS 24 h		8 (2.25–16.75)
NIHSS day 7		4.5 (1–11.75)
ART day 1		15 (3–23)
ART day 7		10 (1–20.25)
AHS 0–2, *n* (%)	47 (64.4%)	
Thrombolysis treatment, *n* (%)	49 (68%)	
Infarct volume on MRI (cm^3)		34.53 (16–70.38)

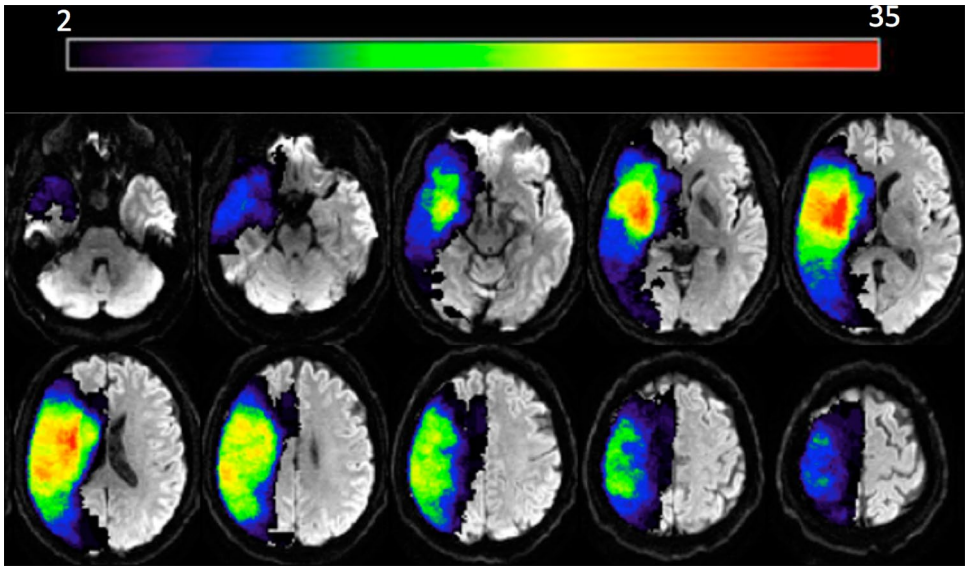

Fig. 2 Lesion probability maps from the patients overlaid on selected slices of the diffusion images in the MNI space. The color map reflects the percentage of lesioned voxels

Table 2 Predictive values for good outcome (AHS 0–2) at 3 months in the univariate analysis

	ART D7	Volume (cm^3)	Intersection (%)
OR (95% CI)	0.728 (0.628–0.845)	0.983 (0.972–0.994)	0.107 (0.022–0.502)
AUC	0.942 (0.861–0.983)	0.819 (0.711–0.899)	0.738 (0.623–0.833)
Cut-off	< 13	< 53 cm^3	< 20%
Sensitivity	84.8% (71.1–93.6)	87% (73.7–95.0)	84.8% (71.1–93.6)
Specificity	92.6% (75.7–98.9)	66.7% (46.0-83.4)	60.7% (40.6–78.5)
Accuracy	84.9%	74%	70.3%

OR odds ratio, *AUC* area under the curve

variance ($p = 0.002$) and correctly classified 41/46 patients with good outcome, and 11/27 patients with poor outcome.

We further tested the univariate predictive value of a combined variable, which represents the presence of either a large volume or either the damage to a critical area: volume ≥ 50 ml or intersection index ≥ 20%. Thirty-two patients (43.8%) had this profile. This combined variable classified correctly 80.8% of the patients (36/46 patients with good outcome, and 23/27 patients with poor outcome). The OR was 0.055 (95% CI 0.015–0.196, $p < 0.0001$).

Multivariate prediction of good outcome

In the stepwise logistic regression, we included as initial variables ART at D7, Volume (cm^3), intersection index (%), and the combined variable: "volume ≥ 50 cm^3 or intersection index ≥ 20%". It retained ART D7 with an OR of 0.744 (95% CI 0.636–0.871, $p < 0.0002$) and the combined variable "volume ≥ 50 ml or intersection index ≥ 20%" with an OR of 0.11 (95% CI 0.02–0.61, p: 0.01). The model correctly classified 89% of the patients (41/46 with good outcome and 24/27 with poor outcome), and explained 62.8% of the variance.

To investigate if the prognosis value of ART D7 depends on the location (intersection index) and size (volume) of the lesion, we created an interaction term: ART at D7 × "volume ≥ 50 ml or intersection index ≥ 20%". When added in the model, this interaction term was significant (OR 0.88, 95% CI 0.79–0.98, $p < 0.02$). This is graphically depicted on Fig. 3 which shows that the predictive positive values for good outcome is similar for small ART threshold values but decreased much faster with increasing ART threshold values in patients with volume ≥ 50 ml or intersection index ≥ 20%.

To further investigate the interaction, we sorted the patients according to the median value of the ART D7. In the subgroup of 36 patients with ART D7 < 11, the combined variable (volume ≥ 50 ml or intersection index ≥ 20%) had no significant effect on outcome ($p = 0.19$). Conversely, in the subgroup of 37 patients with ART D7 ≥ 11, the combined variable had a significant impact on outcome ($p = 0.006$) with only 18% (4/22) of good outcome in patients with large volume or lesion of the critical area and 64% (7/11) good outcome in patients without.

We performed several supplementary analyses, as requested by reviewers the details of which can be found in a supplementary file. First, with a more conservative

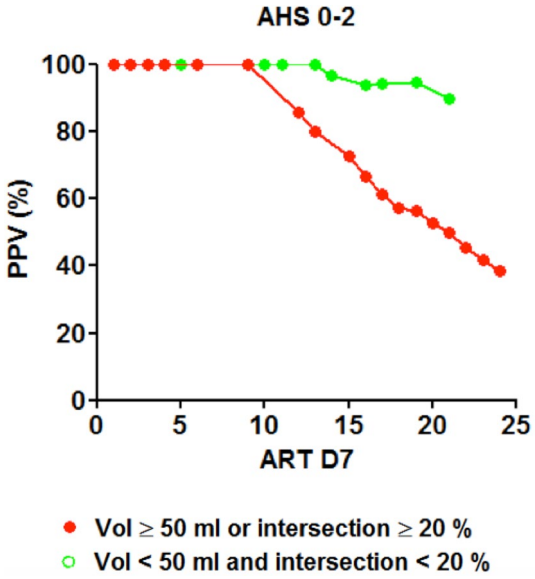

Fig. 3 Impact of size and site of stroke on the relationship between language outcome and initial aphasia severity. The plot represents the positive predictive value (PPV) for good outcome (AHS 0–2) as a function of ART values at day 7. The positive predictive values correspond to the ART values at day 7 above the threshold (*x*-axis). The red curve corresponds to the group of patients for whom the infarct volume is above 50 ml or the intersection index is above 20%. The green curve to the patients with infarct volume < 50 ml or with an intersection index below 20%

dependent variable: AHS 0–1 (no disability, i.e., "excellent outcome"). Second, we used the AHS as a continuous variable instead of a dichotomized 1. Finally, we showed the analysis without the 15 patients who were part of the sample used to define the ROI used for the intersection index in Ref. [18]. The results were very similar (see supplementary file).

Discussion

Our findings are consistent with a comprehensive review of the literature concluding that aphasia severity, lesion size, and lesion location are critical to post-stroke language recovery. The interesting findings here are (1) the change in the predictive value of initial severity on aphasia outcome according to lesion location and lesion size, and (2) the confirmation of the important role of the left temporo-parietal junction in aphasia outcome.

Univariate prediction of good outcome

The ART, which has been developed in the past few years, has been shown to be highly predictive of 3-months outcome [8, 32]. Here, the ART at D7 explained 55.8% of the variance and classified correctly 84.9% of the patients, providing an external validation of our initial findings [8]. Most of previous studies found that initial severity of aphasia explained 30–55% of the variance of outcome. For example, in Pedersen's studies, initial severity explained 47% and 50% of the 1-year outcome variance [3, 4]. Therefore, the ART is in the upper range of these predictions. This is perhaps because ART is strongly weighted for phonological items, which has been shown to be the most important for the early prediction of outcome [9, 33].

The infarct volume and the damage to the left temporo-parietal junction were determined on the DWI performed 24 h post stroke and were also predictive of outcome in univariate analyses. This is in line with the literature since size and infarct location are considered as critical to post-stroke aphasia recovery [10, 16]. Here, we found that the best cut-off for infarct volume was 52 ml. We are not aware of previous quantitative studies reporting thresholds for DWI lesion volumes related to aphasia outcome. Yet, Knopman et al. [34], reported that naming never recover when the CT infarct volume exceeded 60 ml [33]. Concerning the site of the lesion, several studies have shown that lesion load in the left posterior superior temporal gyrus and arcuate fasciculus are associated with poor naming and repetition recovery (see references in Ref. [19]). Here, we concentrate on a TPWM area, which has been identified in chronic stroke patients using voxel-based diffusion tensor imaging regression analysis. This area emerged as the single brain area associated with chronic aphasia severity [18]. It was small (15 cm^3) but fiber tracking showed that lesions to this region result in a combined disconnection of the dorsal and ventral language pathway. Similar findings have been reported by others [20]. In the present study, the occurrence of DWI abnormalities in this area was a univariate predictor of outcome, with a best cutoff value of 20% overlap.

Imaging remained less powerful than initial clinical severity (ART) in predicting aphasia outcome since the infarct volume explained only 19.7% of the variance of the outcome and the damage to the critical area 13.3%. Interestingly, the "site or size" combined variable (volume ≥ 50 ml or intersection index ≥ 20%) explained 30.9% of the outcome variance, in line with the hypothesis that poor outcome may be either related to large left hemispheric lesions or damage to a critical site [11].

Multivariate prediction of outcome

The stepwise logistic regression retained ART at D7 and the combined "size or site" variable as independent predictors and the model correctly classified 89% of the patients. Another multimodality model combining age, initial severity, and functional MRI performed 12 days after stroke was able to correctly classified aphasia outcome in 86% of 21 patients [35]. However, to our knowledge, our model is the

first that shows that acute routine MRI combined with a measurement of initial aphasia severity improves the prediction of chronic aphasia outcome.

Interestingly, there was a significant interaction between ART D7 and the combined "site or size" variable, indicating that imaging findings did not have the same impact on outcome in patients with mild or more severe initial aphasia. For ART at D7 < 11, nearly all patients had good outcome regardless of imaging findings, whereas for ART D7 ≥ 11, the PPV for good outcome decreased much faster for patients with volume ≥ 50 ml or intersection index ≥ 20%. In other words, good outcome was statistically related to the "site or size" variable only in the patients with ART at D7 values above the median value. Patients with mild initial aphasia consistently show good recovery (see for example Fig 1 of Ref. [3]). One putative explanation is that patients with initially mild aphasia and large infarct or lesion to a critical area in the left hemisphere may have a premorbid bi-hemispheric (or less left lateralized) organization of language sufficient to achieve good outcome.

Limitations

First, this is a single center study based on data acquired during routine care. The missing data (especially MRI at 24–48 h and language assessment at 3 months) explained that we included only about one-third of the potentially eligible patients. On the other hand, we did not exclude severe aphasic patients since informed consent was waived. Second, the initial severity of aphasia was measured with the ART, which by definition does not capture the complexity of aphasia, due to its similarity to the NIHSS [36]. Because of its simplicity, however, it is reproducible, adapted to acute stroke patients, and can be performed by trained non-neurologists [8]. We did not control (nor reliably monitor) the amount of Speech and Language Therapy, which, nevertheless, is systematically given to our patients at least twice a week. Third, we only investigated the impact of the lesion of the TPWM area since it was the only area that correlated with chronic severity of aphasia in our previous DTI voxel-based study [18] but we acknowledge that other areas may be still critical for aphasia outcome [22, 23]. Fourth, our analyses are an in-sample analysis and should be confirmed by independent out-of-sample studies, as an external validation. We should therefore perhaps have used more consistently the word "explain" than the word "predict", but "predict" was sometime used to emphasize that the independent variables were obtained shortly after stroke: ART at day 7 and MRI at 24 h post stroke. Finally, we may have underestimated the stroke volume in the MNI normalised images since we did not use lesion masking in the process.

Conclusion

We confirmed that theinitial severity of aphasia is a good predictor of aphasia outcome at 3 months. In patients with moderate and severe aphasia, large size or significant lesions to the left temporoparietal junction improve the prediction of aphasia outcome. This result is an empirical support finding casting some doubt on the "proportional recovery rule" [12, 13]. Yet, nearly 40% of the variance remained unexplained and, therefore, potential targets for new pathophysiological and/or therapeutic trials.

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Compliance with ethical standards

Conflicts of interest The authors have none.

Patient consent and ethics The Pitié-Salpêtrière registry has approval by an ethics committee (Paris VI ethic committee). However and in accordance with French legislation, written informed consent from patients was waived, as it is a retrospective database implying only analysis of anonymized data collected prospectively as part of routine clinical care.

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