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Critical brain regions related to post-stroke aphasia severity identified by early diffusion imaging are not the same when predicting short- and long-term outcome

Chiara Zavanone[a,b,c,*], Yves Samson[a,b,d,e], Céline Arbizu[d,f], Sophie Dupont[a,b,c,e], Didier Dormont[a,b,e,g], Charlotte Rosso[a,d,e,h]

[a] Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, F-75013 Paris, France
[b] ARAMIS, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, ICM, F-75013 Paris, France
[c] APHP, Neurological Rehabilitation Unit, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[d] APHP, Urgences Cérébro-Vasculaires, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[e] UPMC Paris Sorbonne Université, Paris, France
[f] Centre des Maladies Cognitives et Comportementales, IM2A, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[g] APHP, Department of Neuroradiology, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[h] Control of Normal and Abnormal Movement: Physiopathology and Experimental Therapeutics, UPMC Paris 6, Inserm, U1127, CNRS, UMR 7225, Paris, France

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ABSTRACT

Objectives: To identify the critical brain regions associated with 7-days, 3 and 6-months aphasia severity using diffusion-weighted imaging (DWI) in acute post-stroke patients.
Materials and methods: We performed a voxel-based ADC (Apparent Diffusion Coefficient) analysis to identify the critical brain areas correlated with aphasia at the acute (7-days outcome) and chronic stages (3 and 6-months). The location of these areas was compared with the trajectory of the dorsal (the arcuate fasciculus) and the ventral language pathways (the inferior fronto-occipital and the uncinate fasciculi).
Results: Disconnections of the language fasciculi, which were correlated with aphasia outcome, were not the same for the 7-days outcome (disconnection of the ventral stream) and the chronic outcome (3 and 6 months) (disconnection of the dorsal and ventral streams).
Conclusion: Routine clinical images can be merged with atlases of anatomical connectivity to provide new insights about the relationship between the lesion location and aphasia severity.

1. Introduction

When considering aphasia prognosis research, at least two points are well established. Most of the spontaneous/speech therapy-induced recovery occurs during the first 3–6 months, and the initial severity of aphasia is the most important predictive factor for long-term outcome (El Hachioui et al., 2013; Laska, Hellblom, Murray, Kahan & Von Arbin, 2001; Pedersen, Jørgensen, Nakayama, Raaschou & Olsen, 1995). However, upon consideration of the initial severity as a predictor of outcome, it should be noted that in aphasic patients, the plot of initial *vs.* the chronic severity of aphasia has a triangular shape, with a complete or near complete recovery in patients who initially have mild aphasia and considerable variability in recovery for patients with moderate or severe aphasia (Pedersen, Vinter, & Olsen, 2004). One possible explanation for the difference in this trajectory of recovery, despite similar initial severities, is that the critical site of the brain involved in the initial severity of aphasia is different from the critical site that hampers the "recovery potential" (Ueno & Lambon Ralph, 2013). Little is known about the factors conditioning post-stroke aphasia outcome at the acute phase (Inatomi et al., 2008; Martins et al., 2017) and at the chronic phase (Watila & Balarabe, 2015). A recent study has shown that recovery in aphasic patients at one week post-stroke was not predictable on initial impairment, lesion volume, or age, which are the classical predictors of long-term outcome (Dunn et al., 2016). The complex interaction between structural damage and functional reorganization during the first week after stroke has yet to be elucidated. Thus, the early identification of brain areas related to acute or chronic aphasia outcome at the early stage could help in understanding the

* Corresponding author at: Neurological Rehabilitation Unit, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.
E-mail addresses: chiara.zavanone@aphp.fr (C. Zavanone), yves.samson@aphp.fr (Y. Samson), celine.arbizu@aphp.fr (C. Arbizu), sophie.dupont@aphp.fr (S. Dupont), didier.dormont@aphp.fr (D. Dormont), charlotte.rosso@aphp.fr (C. Rosso).

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Table 1
Characteristics of the included patients.

N°	Age	Gender	Educational level	Delay stroke/MRI (days)	ART 1	ART 7	ART M3	ART M6	Aphasia type day seven	Infarct volume (cm^3)
1	78	F	4	1	24	22	17	17	global	89.6
2	65	M	4	1	1	1	0	1	conduction	47.6
3	26	F	4	1	26	24	6	3	global	41.8
4	42	F	6	0	24	21	7	4	global	42
5	69	F	6	2	15	14	6	4	TMoA	26.1
6	74	M	6	1	24	24	11	8	Wernicke	83.5
7	78	M	3	1	4	3	4	2	Sub-cortical	9.8
8	47	M	4	2	25	18	6	7	global	174.5
9	20	F	3	2	1	1	0	0	anomia	10.9
10	66	F	2	1	1	0	0	0	unclassified	0.2
11	80	M	6	1	3	0	0	0	unclassified	0.2
12	57	M	3	2	1	0	0	0	anomia	23.6
13	44	F	6	2	26	25	7	3	global	70.4
14	71	M	1	1	26	8	4	5	MTA	11.2
15	53	M	3	1	3	3	0	0	conduction	7.2
16	60	F	5	1	10	7	3	1	TMoA	24
17	59	F	5	2	24	24	17	15	global	41.2
18	54	F	4	1	21	19	4	5	Broca	23.3
19	61	F	6	1	2	2	0	0	anomia	22.3
Mean	**58**	**–**	**4.3**	**1.26**	**13**	**11**	**4**	**4**	**–**	**39.1**
SD	**16**	**–**	**2.0**	**0.56**	**11**	**10**	**5**	**5**	**–**	**44.8**

Abbreviations: M, male; F, female; ART, Aphasia Rapid Test; ART 1 = 24 h post-stroke; ART 7 = 1 week post-stroke; ART M3 = 3 months post-stroke; ART M6 = 6 months post-stroke. TMoA: transcortical motor aphasia; MTA: mixed transcortical aphasia. Educational level was scored according to the French system [0: elementary school, 1: high school but dropped out before the junior certificate, 2: junior certificate (first certificate of general education), 3: high school but left before the high school diploma, 4: high school diploma, 5: university degree < 3 years, 6: university degree ≥ 3 years].

pathophysiology and dynamics of recovery.

We aimed to identify these critical brain regions using Apparent Diffusion Coefficient (ADC) maps derived from routine diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) obtained 24 h after stroke onset in aphasic patients. ADC abnormalities are a quantitative index and reflect the severity of ischemic damage at the acute phase.

We used a whole brain voxel-based analysis of the ADC maps obtained at 24 h to localize, without *a priori* anatomical assumptions, the regions correlated with aphasia severity at day 7 as well as 3 and 6 months post-stroke. We used routine clinical images and then merged them with connectome atlases of anatomical connectivity to provide new insights about the disconnections created by ischemic damage (Boes, Prasad & Liu, 2015; Corbetta et al., 2015).

We propose that the simultaneous disconnection of the dorsal phonological pathway and the ventral semantical pathway may hamper "compensatory" use of one pathway after damage in the other one. Indeed, converging evidence from neuroimaging studies and computational modelling suggests an organization of language in a dual dorsal–ventral brain network. At the acute phase of stroke, Kümmerer et al. (2013) provided evidence for the importance of the arcuate fasciculus fibers for repetition and of the ventral extreme capsule fibers for comprehension and thus stressed the differential contribution of each pathway. On the other hand, the neurocomputational model of Ueno's provides support to our hypothesis through a proposed synergetic mechanism (Ueno & Lambon Ralph, 2013). In this neurocomputational model, brain lesions were simulated by reducing both function and connectivity of the two network components. This model demonstrated that both streams contribute to some extent to each language task arguing for a 'graded division of labor'. Especially with regard to word repetition, the model makes use of both the ventral and dorsal stream to boost repetition performance of words. Thus, a strong interaction between both streams must be assumed (Weiller, Bormann, Saur, Musso & Rijntjes, 2011). This concept of a synergistic system rather than a segregated one is also supported by the observations made on chronic patients (Rolheiser, Stamatakis & Tyler, 2011).

2. Materials and methods

2.1. Subjects

Patients admitted to the stroke unit of Pitié-Salpêtrière Hospital were prospectively recruited according to the following criteria: (i) presence of their first-ever stroke in the left middle cerebral territory, (ii) age ≥18 years and < 85 years, (iii) French native speaker, (iv) persistent aphasia at day 1 post stroke (≥1 point in the language items of the Aphasia Rapid Test [ART]), (v) no contraindications for MRI, (vi) no severe white matter lesions (Fazekas score < 3) and (vii) right-handedness. As an index of aphasia global severity, we used the ART score (Azuar et al., 2013). The ART allows for the rapid evaluation of aphasia severity 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 a dysarthria evaluation (0–3 points). The final score ranges from 0 to 26 points, with higher scores indicating greater impairment. ART scores were recorded at the acute phase (at day 1 post stroke = ART 1; at day 7 post stroke = ART 7) and the chronic phase (at 3 months post stroke = ART M3; at 6 months post stroke = ART M6). A language evaluation by one trained speech therapist was also performed at the same endpoints as the ART scores at 3 and 6 months. The following tests were used: the Boston Diagnosis Aphasia Examination (BDAE) with the dedicated severity scale (BDAE SS) (Goodglass & Kaplan, 1983), the DO80 picture naming set (Deloche & Hannequin, 1997) and a literal fluency in two minutes (known as Cardebat's fluency) (Cardebat, Doyon, Puel, Goulet, & Joanette, 1990). The severity scale of the BDAE ranged from 0 to 5, with lower scores indicating higher impairments. Literal fluency was measured as the number of words beginning with the letter "p" that could be generated in 2 min, excluding proper nouns and different versions of the same word. Educational level was scored according to the French system [0: elementary school, 1: high school but dropped out before the junior certificate, 2: junior certificate (first certificate of general education), 3: high school but leaft before the high school diploma, 4: high school diploma, 5: university degree < 3 years, 6: university degree ≥3 years]. Nineteen patients were finally included in the study, as