Subcortical Aphasia
A Longitudinal PET Study

Xavier de Boissezon, MD; Jean-François Démonet, MD, PhD; Michèle Puel, MD; Nathalie Marie, MA; Gaëlle Raboyeau, MA; Jean-François Albucher, MD; François Chollet, MD; Dominique Cardebat, PhD

Background and Purpose—Very few neuroimaging studies have focused on follow-up of subcortical aphasia. Here, overt language production tasks were used to correlate regional cerebral blood flow (rCBF) changes and language performance in patients with vascular subcortical lesions.

Methods—Seven aphasic patients were scanned twice with positron emission tomography (PET) at 1-year interval during a word-generation task. Using SPM2, Language-Rest contrast at PET1 was correlated to language performance and to time-lag from stroke. The same contrast was performed at PET2 and session effect (PET2–PET1) was correlated with performance improvement.

Results—At PET1, correlation between rCBF and delay from stroke involved mainly ventral regions of the left temporal cortex and mesial frontal cortex. Correlations between rCBF and performance showed predominantly left dorsal regions in the frontal, temporal, and parietal lobes, but also the left ventral temporal cortex. One year apart, language performance improved and rCBF increased in perisylvian regions bilaterally. Best performers at PET2 showed an increase of activity in left ventral temporal cortex as well as in right middle temporal gyrus.

Conclusions—On follow-up, expected language improvement and increase of activation in the classical language areas and their counterparts were observed. Moreover, all correlational analyses both at PET1 and on follow-up implicated the anterior part of the left inferior temporal gyrus, suggesting a disconnection between the superior and inferior parts of the left temporal cortex and a specific role for this region in lexical semantic processing. (Stroke. 2005;36:1467-1473.)

Key Words: aphasia ■ stroke ■ tomography, emission, computed

The specific roles of subcortical structures in language are still controversial. It seems quite clear that the basal ganglia have some function in motor processing, including articulation, and that the thalamus plays a role in other language functions including verbal memory.

In stroke patients, several mechanisms have been invoked to explain how such subcortical lesions can lead to aphasia: for some authors, these areas play a direct role in language1,2; for others, they do not, but the subcortical lesion create a diachisis, functional de-afferentation of a remote cortical area connected with damaged subcortical pathways3 or nuclei.4,5 At last, language impairment can be linked to the hypoperfusion of cortical structures caused by stenosis or occlusion of a large cerebral vessel responsible at the same time of the subcortical infarct.6–8

Very few functional imaging studies have followed-up groups of patients with aphasia caused by subcortical lesions. Heiss9 relates a longitudinal positron emission tomography (PET) study using a covert repetition task and involving nine patients with subcortical aphasia. In terms of performance, this group compared with patients with frontal or temporal lesions was the best at initial examination and improved significantly at follow-up, without or with only minimal disturbance. The 2 notable changes in PET results from baseline (2 weeks after onset) to follow-up (8 weeks after onset) were the disappearance of a right inferior frontal gyrus activation and the emergence of activation in the left superior temporal gyrus. Similar language recovery and PET pattern of changes were observed in the frontal group. In sum, these authors emphasized the critical role of the latter region for good recovery in patients who did not present a structural lesion in the left temporal cortex.

Our study concerned patients with strictly subcortical lesion (2 thalamic and 5 nonthalamic) who were studied longitudinally with PET using an overt language task (word generation) 1 year apart.

Two lines of results were investigated here. First, we addressed whether the time lag between stroke and PET study would affect language activation pattern as subcortical aphasia tends to recover more quickly than cortical aphasia.10 In a
second part, we investigated the relationships between changes in PET activation and changes in performance over the first year after stroke.

Subjects and Methods

**Patients**

Seven French-speaking, right-handed aphasic patients (7 men; mean age: 52.4±13) met the following inclusion criteria: left single strictly subcortical stroke and preserved ability to understand task instructions. Exclusion criteria were severe aphasia, neuropsychiatric disease, and confluent leukoariosis. Patients were studied twice (first PET session planned 2 months \(\pm 35\) days on average after stroke; the second one, 1 year after the first PET session \(\pm 1.4\)). Aphasia was assessed twice using the Montreal–Toulouse Aphasia Battery.\(^{11}\) The topography of lesions was strictly subcortical, thalamic in 2 cases, and more extended in the 5 other cases involving putamen (4 cases), pallidum (2), caudate nucleus (4), external capsule (5), and anterior part of the internal capsule (2) (Table 1 and Figure 1). One patient had a pacemaker and could not be MRI scanned.

All subjects gave written informed consent before participation. The regional ethics committee approved the protocol, in accordance with the Declaration of Helsinki.

**PET Paradigm**

Each PET study consisted of 6 consecutive scans under 2 conditions (ABBBBA). A was rest condition and B was language condition, including 4 runs of 2 noun–noun generation and 2 verb–verb generation tasks. Subjects were instructed to produce semantically related words belonging to the grammatical category of the target stimulus (20 items per run, 1 item every 6 seconds). The same stimuli, presented binaurally, were used in the 2 PET sessions. Responses were tape-recorded. The semantic relationship between stimuli and responses was scored by 2 independent judges and only congruent judgments were considered. The number of hits was computed and errors were classified as no response, grammatical error (eg, verb instead of noun), or semantic errors.

**Data Acquisition**

Subjects were scanned with eyes closed in a darkened room. The head was immobilized and head position was aligned transaxially to...
the orbitomeatal line with a laser beam and controlled before each acquisition. Measurements of regional distribution of radioactivity were performed with an ECAT HR+ (Siemens) PET camera with full-volume acquisition (planes, 63; thickness, 2.4 mm, axial field-of-view, 158 mm; resolution ~4.2 mm in all directions). The duration of each scan was 120 seconds; ~6 mCi of H2O15 was administered. Each experimental condition was started ~15 seconds before data acquisition and continued until scan completion.

Data Analysis
Data were analyzed with SPM2. Images were realigned and coregistered with the mean image calculated from the whole set of PET images. Images were then transformed into the standard space of the Montreal Neurological Institute MRI template, which is based on the atlas of Talairach and Tournoux12 and smoothed with a 12-mm Gaussian filter.

Statistical Design
PET images from all subjects were scaled to on overall cerebral blood flow (CBF) grand mean of 50 mL·100g−1·min−1. Analysis of covariance, with global activity as a confounding covariate, was performed on a pixel-by-pixel basis. Appropriate contrasts tested the main effect of language task against the “rest” condition at the 2 sessions PET1 and PET2 (significance threshold P<0.001, uncorrected; cluster extent >100 voxels). No comparison between noun tasks and verb tasks were made because of reduced statistical power. Factorial 2x2 analyses were further effected to assess the test-retest effect, ie, [Language2–Rest2] – [Language1–Rest1] and vice versa (P<0.001, uncorrected; cluster extent >100 voxels). These compound contrasts were tested with an inclusive mask consisting in the second term of the subtractions.

Correlations were performed between time lag from stroke to PET1 (in days) as parametric variable in SPM design and changes in regional CBF (rCBF) between rest and activation at PET1 [Language1–Rest1] to identify areas where activation increased over time after subcortical stroke (P<0.01; cluster extent >100). Correlations were also performed between performance at PET1 (number of hits) and changes in rCBF between rest and activation at PET1 [Language1–Rest1] to determine areas of activation associated with correct naming (P<0.01; cluster extent >50). Correlations were performed between performance (number of hits as parametric variable in SPM design) and changes in rCBF as assessed between the 2 sessions by the test-retest compound contrast [Language2–Rest2] – [Language1–Rest1] to identify areas of activation associated with improved performance (P<0.01, cluster extent >20).

Because of the small number of observations and the non-Gaussian distribution of data, the statistical validity of correlations observed at maximum peaks was further assessed using non parametric correlation test (Spearman rank test) with a threshold at P<0.05. Peaks of maximum statistical differences were considered only when coordinates were located in cortical areas, ie, outside of vascular subcortical lesions.

Results

Language Tasks
Improvement at PET2 was found for response accuracy (PET1: 43.7/80±15.2, PET2: 53.6/80±11.6, Wilcoxon test, P<0.05). Five patients showed increased accuracy scores from 10 to 22 hits more at PET2), 1 patient remained stable (1 hit more at PET2), and 1 patient worsened at PET2 (patient 6 had 9 hits less at PET2). Errors at both sessions consisted mainly of absence of response and to a lesser extent grammatical errors; no semantic errors were observed whatever the session.

No correlation was observed between performance at PET1 and time elapsed from stroke to PET1 (Spearman ρ 0.643, P=0.12).

PET1 Results: Main Contrasts
The Language–Rest contrast showed at PET1 activations only for very low thresholds (P<0.05, k>50). Activations were located mainly in bilateral frontal and temporal (BAs 47, 21/22) regions and in the mesial part of the right cerebellum (Table 2).

Correlations at PET1
We performed correlation analysis between the delay elapsed from stroke to PET1 and rCBF at PET1. The correlation pattern involved ventral regions of the left temporal lobe and mesial frontal cortex, as well as the right temporal pole, the

| TABLE 2. Areas Activated in Main Contrasts and Compound Contrasts |
|---------------|---------------|---------------|
|               | T1            | T2            | T2–T1         |
|               | (P<0.05, k>50) | (P<0.001, k>100) | (P<0.001, k>100) |
|               | k | x | y | z | Z | k | x | y | z | Z | k | x | y | z | Z |
| L BAs 21/22   | 603 | -58 | -34 | 4 | 2.16 | 5416 | -68 | -36 | 4 | Inf | 440 | -68 | -36 | 4 | 5.87 |
| R BAs 21/22   | 508 | 58 | -40 | 14 | 2.63 | 3327 | 72 | -30 | 4 | 7.66 | 185 | 72 | -30 | 4 | 4.95 |
| L BA 32       | 211 | -8 | 18 | 36 | 7.43 |
| L BAs 13/47   | 298 | -34 | 26 | 0 | 4.75 |
| L BA 47       | 1964 | 18 | -66 | -22 | 6.31 | 103 | 18 | -66 | -22 | 4.50 |
| R BAs 6/32    | 425 | 10 | 6 | 54 | 6.03 |
| L BAs 10/46   | 237 | -34 | 44 | 20 | 5.77 |
| R BA 47       | 639 | 20 | 24 | -22 | 5.77 | 103 | 20 | 24 | -22 | 3.91 |
| L Cerebellum  | 699 | -24 | -66 | -34 | 5.76 |
| R BAs 10/46   | 262 | 36 | 52 | 24 | 5.26 |
| L BA 11       | 162 | -24 | 48 | -10 | 4.82 |
| R BAs 28/35   | 106 | 10 | -20 | -10 | 4.52 |
mesial occipital cortex, and the left cerebellum (Table 3a and Figure 2a). These correlations mean that the longer the time lag from stroke the larger the activation in such regions.

Besides correlation analyses were computed between language performance (number of hits) and rCBF at PET1. The correlation pattern involved predominantly left dorsal regions in the frontal, temporal, and superior parietal regions, but also in the left ventral temporal cortex, and in the right hemisphere, the posterior superior temporal cortex, and insula (Table 3b and Figure 2b). These correlations mean that best performers at PET1 showed the largest activation in these regions.

PET Results on Follow-up: Main Contrasts at PET2

By contrast to PET1, activation at PET2 was observed for the Language–Rest contrast for stringent threshold ($P<0.001$, $k>100$) in frontal and temporal regions bilaterally.

Session Effects

These findings were confirmed by the frontal and temporal activations observed in the compound contrast ([Language PET2–Rest PET2] – [Language PET1–Rest PET1]; Figure 3). No activation was found for the opposite contrast (PET1>PET2).

Correlations Between Longitudinal Changes in rCBF and Longitudinal Changes in Performance

We performed correlation analyses between improvement of performance (quantified in each patient as the difference $\text{perf2–perf1}<0$) and rCBF changes between PET2 and PET1. Correlations were only found in the left ventral temporal cortex, as well as in the right middle temporal gyrus and the right cerebellar hemisphere (Table 3c and Figure 2c). These correlations mean that best performers at T2 showed an increase of activity in such regions.

**Discussion**

The performance improvement found in our patients was expected because spontaneous recovery is usually observed in the course of vascular aphasia and particularly in subcortical aphasia.10 Nevertheless, the language recovery 1 year apart was not complete because the mean patients’ performance differed
Figure 3. Correlations (a) between rCBF at PET1 and number of days after onset, (b) between rCBF and performances at PET1, and (c) between longitudinal changes in rCBF and longitudinal changes in performances from PET1 to PET2. Left, Brain glass view for each correlation. Right, For the left ventral temporal cluster (BA 20), graphic representations of correlation between (a) number of days after onset and rCBF, (b) performance and rCBF at PET1, and (c) changes in performance and changes in rCBF from PET1 to PET2.
significantly \( (P<0.01) \) from the control subjects described in a previous study,\(^{13}\) although 2 patients showed performance at T2 comparable to those of control subjects.

Considering results obtained at PET1, the Language–Rest pattern showed very few activation at stringent threshold, in accordance with previous results.\(^{13,14}\)

The correlation analyses concerned delay from stroke, language performance, and rCBF changes. It is noteworthy that no significant correlation between performance and delay was found. This absence of correlation accounts for the dissimilarity of the patterns observed between rCBF and delay and, in other cases, between rCBF and language performance.

\( r\text{CBF}\times\text{delay} \) correlation concerned mainly a set of ventrally and rostrally localized areas in the temporal and frontal lobes showing decrease of activity in patients observed at earlier stage. This finding cannot be accounted for by vascular effect as areas involved in this pattern are dispatched throughout the territories of the 3 main cerebral arteries, whereas lesions were restricted to the sylvian territory in 5 patients. As a tentative interpretation, we suggest that this effect might rather relate to a functional diaschisis phenomenon\(^{15}\) affecting a left cortical–subcortical network involved in the lexical semantic dimensions of the language task we used. The observed correlation suggests that functional depression, present in patients observed at early stages, seems to vanish over time. This phenomenon would affect cortical territories shown in the correlation map and are interconnected by neural pathways such as the inferior longitudinal and inferior occipitofrontal fasciculi. This ventral network has been shown to be involved in lexical semantic processes,\(^{16}\) which were also involved in our language task.

\( r\text{CBF}\times\text{language performance} \) correlation showed, mainly in the left hemisphere, a very different pattern because it involved dorsally distributed regions in the temporal, frontal, and parietal lobes. These regions showed increased activation in patients who were the most successful in the word generation task. This effect concerned regions normally activated by word generation tasks, ie, superior temporal gyri and left inferior frontal cortex,\(^{17}\) as well as regions located upwards (superior parietal lobule, middle, and superior frontal gyrus) that may reflect earlier compensatory phenomena in the most effective patients.\(^{18}\)

It should be noted that although very contrasted in anatomical terms, the 2 described patterns shared a common region located in the anterior part of the left inferior temporal gyrus (Figure 2) whose functional significance is discussed here.

Concerning follow-up results, we observed an increase of activation for the Language–Rest contrast performed at PET2 as previously noted;\(^{13}\) this pattern concerned the classical language areas (superior temporal gyrus, inferior frontal gyrus) and the right-sided homologous areas. Lack of activation observed at earlier stage in perisylvian territories that recovers later pleads in favor of a hypoperfusion in the cortical sylvian territories at PET1 as described by Hillis et al\(^{19}\) at a very early stage.

Besides, correlation analysis between performance improvement and rCBF changes from PET1 to PET2 showed small clusters located in the right cerebellum, the right middle temporal gyrus, and the anterior part of the left inferior temporal gyrus. These regions showed increased activation at PET2 relative to PET1 in patients who presented the largest performance improvement over time. The right cerebellum and the right middle temporal gyrus were also involved in the similar analysis performed in our previous study\(^{13}\) and the similarity between patterns was even clearer at a lower threshold.

Although performed with few patients, the present study suggests the involvement of an additional region, the anterior part of the left inferior temporal gyrus (a part of the basal temporal language area) that was already pointed out in the described correlational analyses. This finding may reflect the disruption of subcortical pathways that interconnect this region and the left superior temporal gyrus.\(^{20}\) The role of the latter region in recovery from aphasia has been emphasized by Heiss et al.\(^{9,21}\) Sharp et al\(^{20}\) recently pointed to the functional role of a subregion of the basal temporal language area, located medially (fusiform gyrus) relative to the cluster we observed in the inferior temporal gyrus. These authors stressed the role of this region for semantic assignment in triplets of heard words in which subjects had to form associated pairs. In the present study, some task features were similar (semantic association for heard words) but others were different (lexical search, overt speech output). These differences might account for the involvement of neighboring territory within the basal language area in our study.

The present findings should be interpreted with caution because the word generation we used is a complex task; it involves various cognitive processes, encompassing the different levels of word production in accordance with Levelt model\(^{22}\) and lexical search strategies that refer to executive processes.

The small size of our patient group calls for further studies to support these findings and to specify the role for the anterior inferior temporal cortex in the compensatory mechanisms subserving recovery from subcortical aphasia.

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**References**

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