Behavioral and Neurofunctional Changes Over Time in Healthy and Aphasic Subjects
A PET Language Activation Study

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Background and Purpose—Follow-up neuroimaging studies of aphasia never addressed a comparison between aphasic and healthy subjects. Investigation of changes over time in healthy subjects during language tasks seems a prerequisite before interpretation of longitudinal changes in aphasic patients.

Methods—Six healthy subjects and 8 aphasic patients were PET scanned twice (PET1 and PET2) at a 1-year interval during a word generation task. Using SPM99, language-rest main effect was compared at PET1 and PET2 in each group, whereas group effect was assessed at each session. Correlations were analyzed in each group between performance indexes and changes in regional cerebral blood flow (rCBF) between the 2 sessions.

Results—Language performances were improved in both groups. rCBF decreased from PET1 to PET2 in the healthy group and increased in the aphasic group in perisylvian regions bilaterally. Correlations between performance and rCBF changes across sessions were similar in the 2 groups; positive correlations involved superior temporal cortices bilaterally, and negative correlations concerned superior frontal and medial temporal regions.

Conclusions—Increased perisylvian activation over time probably reflects improved performance at the expenses of cognitive effort in aphasic patients. Decreased activation in different neural systems suggests a familiarization effect with reduced emotional load. (Stroke. 2003;34:2900-2907.)

Key Words: follow-up studies ■ language ■ stroke ■ tomography, emission computed
topography of lesions was prerolandic in 2 cases, postrolandic in 2 cases, and subcortical in 4 cases (Table 1 and Figure 1).

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 generation and 2 verb generation tasks in which subjects had to produce semantically related words of the same lexical category as binaurally presented stimuli (20 items per run, 1 item every 6 seconds). The same stimuli were used in the 2 PET sessions. Responses were recorded in both groups, and performances were obtained as accuracy scores. Reaction times (RTs), ie, latencies of correct verbal responses, were considered only in the healthy group because latencies were exceedingly long in patients.

Data Acquisition
Subjects were scanned with their 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 SPM 99. 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 Tournoux13 and smoothed with a 12-mm gaussian filter.

Statistical Design
PET images from all subjects were scaled to an overall cerebral blood flow (CBF) grand mean of 50 mL · 100 g⁻¹ · min⁻¹. Analysis of covariance, with global activity as a confounding covariate, was performed on a pixel-by-pixel basis. Appropriate contrasts tested in each group 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 >50 voxels). Factorial 2×2 analyses were further effected to assess (1) in each group the test-retest effect, ie, (language2−rest2)−(language1−rest1) and vice versa, and (2) at each session the group effect, ie, [(language1−rest1)aphasics−(language1−rest1)healthy] and [(language1−rest1)healthy−(language1−rest1)aphasics], and likewise at session 2 (significance threshold, P<0.05; cluster extent >50 voxels). These compound contrasts were
assessed with an inclusive mask consisting of the second term of the subtractions.

Correlations were performed in each group between performance (number of hits in patients, RTs in healthy subjects as parametric variable in SPM design) and changes in regional CBF (rCBF) as assessed between the 2 sessions by test-retest compound contrasts (significant threshold, \(P<0.001\); cluster extent >100).

Results

Language Tasks
High and stable accuracy scores (PET1, 71.8/80±5.8; PET2, 72.1/80±5.6; nonsignificant difference) were observed in healthy control subjects. Improvement at T2 was found for both groups in terms of reaction time for healthy subjects (PET1, 2.38±0.41 seconds; PET2, 2.04±0.26 seconds; paired t test, \(P<0.007\)) and response accuracy for aphasic patients (PET1, 41.6/80±15.6 hits; PET2, 51.1/80±15.0 hits; paired t test, \(P<0.01\)).

At T2, all healthy subjects exhibited near-ceiling accuracy scores and shorter RTs while not producing systematically the same items as those given at T1. Six aphasic patients showed increased accuracy scores (from 10 to 22 hits more at PET2); the remaining 2 patients were stable (−1 hit). No correlation was found between performance and time after stroke at any stage.

PET Results

Main Contrasts
In healthy subjects, the language-rest contrast showed at PET1 bilateral activations located mainly in temporal and frontal areas (right BAs, 20, 47, 46/45, 6; left BAs, 38, 42), along with clusters in the right thalamus and both cerebellar hemispheres, while no activation was found at PET2 at the same threshold (\(P<0.001\)) with minor activation in the superior temporal cortices bilaterally (BAs, 22, 38) and the left cerebellum for lower threshold (\(P<0.01\), cluster extent >25).

In aphasic patients, follow-up revealed at PET2 BA, including frontal (right BAs, 9, 11, 6, 47; left BAs, 46/9, 11, 24), temporal (BA, 21 bilaterally), right insular, and cerebellar/mesencephalic areas bilaterally. Very limited activation, restricted to the superior posterior temporal regions bilaterally (left BA, 22; right BA, 21; \(P<0.001\)), was observed at PET1 (see Table 2).

In each group, the magnitude of CBF changes was assessed in the maxima of activated clusters at each session. Typical values observed from PET1 to PET2 were 7% to 9% of increase in patients; decreases of similar amplitude were seen in healthy subjects.

Session Effects in Each Group
These findings were confirmed by compound contrasts [(language PET1−rest PET1)−(language PET2−rest PET2)]. In healthy subjects (Figure 2a), bilateral activations were ob-

### Table 2. Areas Activated During the 2 Sessions in Both Groups

<table>
<thead>
<tr>
<th>Anatomic Areas</th>
<th>T1</th>
<th>T2</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(k) x y z</td>
<td>Z</td>
<td>(k) x y z</td>
<td>Z</td>
</tr>
<tr>
<td>R BA 9</td>
<td>203 28 30</td>
<td>−10 4.34</td>
<td>268 36 54</td>
<td>30 4.91</td>
</tr>
<tr>
<td>R BA 11</td>
<td>119 36 22</td>
<td>12 3.58</td>
<td>211 20 26</td>
<td>−16 4.04</td>
</tr>
<tr>
<td>R BA 47/11</td>
<td>63 38 −6</td>
<td>32 4.35</td>
<td>118 28 44</td>
<td>−14 3.90</td>
</tr>
<tr>
<td>L BA 9/46</td>
<td>158 −56 10</td>
<td>−18 5.14</td>
<td>148 −34 46</td>
<td>24 4.73</td>
</tr>
<tr>
<td>L BA 11</td>
<td>926 −68 22</td>
<td>8 6.54</td>
<td>181 −24 48</td>
<td>−18 3.96</td>
</tr>
<tr>
<td>L BA 24</td>
<td>364 74 −34</td>
<td>8 3.32</td>
<td>165 −8 16 34</td>
<td>5.65</td>
</tr>
<tr>
<td>R anterior SMA</td>
<td>206 60 20</td>
<td>−10 3.23</td>
<td>493 10 8</td>
<td>52 6.17</td>
</tr>
<tr>
<td>R BA 47</td>
<td>2249 56 20</td>
<td>−22 6.73</td>
<td>3957 62 −36</td>
<td>2 9.24</td>
</tr>
<tr>
<td>R BA 20</td>
<td>230 6 −18</td>
<td>−6 4.03</td>
<td>70 16 −18</td>
<td>−4 4.17</td>
</tr>
<tr>
<td>R thalamus</td>
<td>206 −32 44</td>
<td>−28 4.11</td>
<td>1603 10 −62</td>
<td>−16 5.74</td>
</tr>
<tr>
<td>L cerebellum</td>
<td>194 30 −10</td>
<td>18 5.32</td>
<td>68 38 44</td>
<td>−22 5.71</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>647 14 −64</td>
<td>−22 5.71</td>
<td>674 14 −64</td>
<td>−22 5.71</td>
</tr>
</tbody>
</table>
served (posterior temporal BA, 21 bilaterally; right temporal pole BA, 38; right inferior frontal BAs, 45 and 47, right cerebellar, top mesencephalon), whereas no activation was found in the patient group.

For the opposite contrast (PET2 > PET1), no activation was found for the group of healthy subjects, whereas in aphasic patients (Figure 2b), frontal (BAs, 11, 9, 6 bilaterally; left BA, 24), parietal (right BA, 3), and temporal (BAs, 21/22 bilaterally) activation was observed, as well as a cluster in the cerebellar vermis (Table 1).

**Group Effects in Each Session**

At PET1, the compound contrast [(language1 − rest1)_{healthy} − (language1 − rest1)_{aphasic}] revealed higher rCBF increase in healthy subjects than in patients that corresponded to a bilateral pattern including temporal (BAs, 38 and 22/42 bilaterally; right BA, 37), right inferior frontal (BA, 47), upper mesencephalic, hemispheric cerebellar, and right insular areas. The reverse comparison (aphasic > healthy) was nil.

At PET2, the appropriate compound contrasts revealed significant changes in the “aphasic > healthy” only. The corresponding pattern was bilateral and involved temporal

**(left BA, 21/22/20/38; right BA, 21), frontal (right BA, 4/6, 9/46, 11/47; supplementary motor area, left BAs, 6, 24, 10/47), upper mesencephalic, and right cerebellar right areas.**

**Correlations Between Longitudinal Changes in rCBF and Longitudinal Changes in Performance**

**Healthy Subjects**

Improvement in RTs in the language task was quantified in each subject as the difference RT1 − RT2 > 0 because improved performance corresponded to shorter RT. We then performed correlation analyses between RT improvement and rCBF changes between PET1 and PET2 as assessed by compound contrasts, ie, (language2 − rest2) − (language1 − rest1) > 0 for positive correlations and (language1 − rest1) − (language2 − rest2) > 0 for negative correlations.

Positive correlations between rCBF and RT changes were found in posterior superior temporal regions, BA 22, bilaterally, and right BA 42. These correlations mean that best performers at T2 showed an increase in activity in such regions (Figure 3a).

Negative correlations between rCBF and RT changes were found in the right BA 31 (precuneus/posterior cingulate), amygdala/hippocampal (BA 34), and left superior lateral frontal (BAs 8 and 10) and lateral extrastriate cortex (BA 18). These correlations mean that best performers at T2 showed a decrease in activity in such regions (Figure 3b).

**Patients**

Improvement of performance (number of hits) in the language task was quantified in each subject as the difference performance2 − performance1 > 0. We performed correlation analyses between performance improvement and rCBF changes between PET1 and PET2. As for healthy subjects, we used for positive correlations the (language2 − rest2) − (language1 − rest1) contrast and for negative correlations the (language1 − rest1) − (language2 − rest2) contrast.

Positive correlations between rCBF and performance changes were found in the BAs 22 bilaterally and the right cerebellar hemisphere. These correlations mean that best performers at T2 showed an increase in activity in such regions (Figure 3a).

Negative correlations between rCBF and performance changes were found in dorsal posterior visual regions (left BA 7, right BA 19), in the right superior lateral frontal cortex (BA 8), and in the left amygdala/hippocampus region (BA 34). These correlations mean that best performers at T2 showed a decrease in activity in such regions (Figure 3b).

**Discussion**

The performance improvement found in the group of aphasic patients was expected because of the well-known language recovery observed in the early post-stroke onset period,11 with a steep gradient in the first month after onset, that reaches a plateau between 6 and 12 months after onset.

Unexpected improvement was also observed in healthy subjects who exhibited shorter response latencies, whereas accuracy scores were high and stable over time. Two lines of interpretation can be proposed. In session 2, healthy subjects were accustomed to the PET environment and to
the language paradigm, and this feeling of familiarity allowed them to respond faster. Alternatively, memory processes such as priming effects might have intervened because subjects might have accurately remembered many task stimuli. Nevertheless, analysis of the response quality revealed that subjects did not tend to produce the same responses at the 2 sessions in terms of errors (which were rare) or hits.
The general pattern of activation we observed has been previously and repeatedly described for word generation tasks in healthy subjects (ie, bilateral frontal and temporal activation). Yet, contrasted follow-up patterns were found between our 2 groups.

In healthy subjects at PET2, decreased albeit stable activation resembled a phenomenon described in studies of test-retest effects in motor16 or visual17 experiments. This decrease was interpreted mainly as a habituation effect leading to reduced attentional load and stress. Despite the dearth of such studies in the language domain, similar results were described by Raichle et al18 in the same task that we used, although over much shorter interval and after intensive learning, and interpreted as a general practice effect.

Conversely, in aphasic patients, increased activation was found at PET2 in bilateral frontal and temporal territories that belonged to the pattern observed at T1 in healthy subjects with no novel areas activated over time. This increase is congruent with the few functional imaging studies reporting follow-up data in aphasic patients.19 These effects were viewed as a regression of functional depression induced by the lesion in the first stage of evolution in both the perilesional areas and remote territories in the right hemisphere. However, our results relied on activation minus rest contrasts at each session and could not be directly interpreted as such.

Another complementary line of interpretation relates to cognitive efforts made by patients to better achieve the task that induce an increase in activity in several regions bilaterally. Nevertheless, language recovery was associated with left-sided activation, whereas the functional significance of such enhanced activities in the right-sided regions remained poorly understood. According to Heiss et al,1 good recovery of language was observed in patients with sparing of the left posterior superior temporal region in which increase of activity was observed on follow-up. In contrast, both poor recovery and activation restricted to right-sided regions were found in their group of patients with a left temporal lesion. In a patient (patient 5) who demonstrated a good recovery, with 10 items more on session 2, the left superior temporal region was damaged, but this lesion was restricted to its anterior part and did not include the key region identified by Heiss et al. Conversely, the 2 patients who did not recover suffered from lesions in the left frontal area, a region pertaining to the activated network in healthy subjects. These findings suggest that the left frontal region plays a special role in word generation, as shown by Buckner et al.

The above discussion emphasizes follow-up changes, namely rCBF decreases in healthy subjects and rCBF increases in patients that were observed on average in each of these groups. However, such effects do not preclude that a relationship may exist in each group between changes in rCBF and performance improvement. For example, an increase in rCBF activity may be correlated to performance improvement (which we called positive correlations), even in healthy subjects, although in regions different from those showing significant decreased activation. The same applies to the aphasic patients in whom some regions that do not pertain to the pattern of rCBF increase at T2 may show decreased activation correlated with improved language performance (which we called negative correlations).

In both aphasic and healthy subjects, positive correlations were found in the posterior superior temporal regions bilaterally. The left superior posterior temporal region pertains to the classic pattern of activation during word generation18 and is associated with semantically driven lexical search.20 Although possibly involved in voice perception during speech production,21 the right superior posterior temporal region has been found to be activated in studies of lexical semantic processing in both healthy22 and aphasic subjects.23,24 Better scores in patients probably indicate more efficient lexical search in session 2; the same applies to healthy subjects because their responses, although faster, were not stereotyped.

The negative correlations might reflect differences in attentional demand and/or level of anxiety. Indeed, in healthy subjects, CBF reductions in right posterior cingulate, amygdala/hippocampal, left superior frontal (BA 8), and extrastriate areas were strongly correlated with improved performance. Simpson et al23 interpreted CBF reductions in the amygdala and BAs 8/9 in the frontal cortex during a practiced word generation task as “a dynamic interplay between cognitive task and emotion.” The functional significance of signal changes in posterior cingulate and precuneus regions (BAs 7/31) during cognitive experiments remains unclear. However, Shulman et al24 found that BAs 7/31 showed increase activity in unfocused state of attention while their activity decreased in task-focused state.

For aphasic patients, the pattern of negative correlations was not drastically different from that observed in healthy subjects and may be interpreted in the same way. Indeed, precuneus and BA 7 pertained to this pattern in both groups. Differences concerned the hippocampal/amygdala complex and the frontal BA 8 region in which mirror distributions were observed across groups (in patients, left hippocampal/amygdala complex and right frontal region). These differences might relate to the effects of left hemispheric damage in patients.

In conclusion, these findings were obtained in a small sample of subjects and should be considered cautiously. However, results underlined the interest of considering rCBF changes over time in both healthy subjects and aphasic patients in relation to performance. Apart from contrasted trends between groups, correlations between performance and CBF revealed similarities across groups, with improved lexical search associated with rCBF increase in temporal cortices and rCBF decrease in emotion-related brain regions.

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References
The plasticity of functional networks is an intriguing phenomenon that plays a role in learning and is important for recovery after brain damage. Activation studies by PET and functional MRI (fMRI) can be used to study neuroplasticity noninvasively and have opened new ways to understand the functional networks that play a role in learning and are important for the plasticity of functional networks. Cardebat et al.1 have used this concept to study activation of regional cerebral blood flow by PET during a word generation task in 8 stroke victims and compared the changes in the activation patterns in the chronic course with changes over time in healthy subjects. Whereas their data in the patient cohort add to longitudinal studies in poststroke aphasia, especially by extending the observation period over 1 year, the changes in activation patterns observed in healthy volunteers in relation to improved performance in language tasks are important as a basis for longitudinal studies in patients and indicate the ability of functional networks to minimize the workload for repeated and familiar tasks: It is the main finding of this study that with improved performance the extent of activation in normals is reduced, and the pattern is “normalized” in patients.

This study contributes important pieces to the puzzle of language performance and recovery after stroke, but it is quite difficult to compare the results with previous findings: The small group of patients included is rather heterogeneous with infarcts in different locations involving variable subcortical and cortical regions. Therefore, a correlation between extent of improvement and (re)activation pattern could not be obtained, which was reported previously.2 The patients were also studied rather late in the course after the stroke (first PET session ≈2 months, second PET session >12 months after the stroke) and some of the differences to other reports could well be due to this time factor as the observation period was in the subacute phase in other studies (8 patients, studied at 2 weeks and 6 months,3 23 patients, studied at 2 and 8 weeks4) when usually most of improvements of poststroke aphasia oc-
It is important to note that the present study again stresses the eminent role of the superior temporal gyrus for performance in language tasks in normals and for recovery of relevant language function after stroke.\textsuperscript{2,7,8} It is, however, still a matter of controversy if lateralized or bilateral involvement of this area is important for performance and recovery of speech: the majority of authors stress the superior role of the dominant left hemisphere,\textsuperscript{9,10} whereas the data presented show bilateral activation in normals and patients and thereby stress the importance of a bihemispheric network, in which the 2 hemispheres act as a unit with the right hemisphere aiding and sustaining speech processing and inhibiting unrelated activity.\textsuperscript{11} However, one still must consider that the role of the 2 hemispheres is differentiated with the left dominant regions more involved in complex and difficult tasks and in recovery of function to a high level, both of which could not be tested in the small cohorts.

In addition to positive correlations between performance and flow activations in superior temporal regions, Cardebat et al\textsuperscript{1} observed negative correlations between performance and flow in various regions, among others, in the left superior frontal cortex in healthy subjects and in the right superior frontal cortex in aphasic patients. This pattern of activation shows some similarity to that observed in patients with tumors in the dominant hemisphere, where the degree of lateralization of frontal activation to the right—a reversed speech dominance—was inversely related to language performance.\textsuperscript{12} Whereas the reduced activation in various regions might be related to changes in the emotional state with attention focused on task performance,\textsuperscript{13} the deactivation in some regions within the functional network might also be related to collateral inhibition by increased activity of specialized areas.\textsuperscript{10,14} The impact of the various activation patterns on the estimation of prognosis and recovery of poststroke aphasia, however, needs to be established in larger studies. The imaging protocols could also help to evaluate the efficacy of various rehabilitative therapies including adjuvant drug treatment.\textsuperscript{15}
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