Recovery of Neglect After Right Hemispheric Damage

H$_2^{15}$O Positron Emission Tomographic Activation Study

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Background: The neural correlates of recovery of unilateral neglect (ULN), as well as of other consequences of focal brain damage, are largely unknown. Functional neuroimaging methods (in particular, positron emission tomography [PET]) can be applied to the in vivo study of recovery mechanisms in neurologic patients.

Objective: To evaluate the functional cerebral correlates of recovery from ULN in patients with right-sided lesions, with the use of a PET activation paradigm.

Methods: Study of 3 patients with cerebrovascular lesions that involved corticosubcortical (patient 1) or subcortical (patients 2 and 3) areas of the right hemisphere. Unilateral neglect was tested twice, before and after completion of a 2-month rehabilitation program, after which all 3 patients showed considerable improvement. Similarly, 2 PET examinations were performed, before and after recovery, during the performance of a visuospatial task requiring the patients to detect and respond to visual targets moving on a computer screen from the right to the left visual hemifield (experimental condition). The cerebral activation was compared with a baseline task in which subjects responded to a black dot flashing in a fixed position of the right hemifield.

Results: The brain areas activated by the performance of the visuospatial task before and after recovery were compared. In all 3 patients, the regions notably more active after recovery were almost exclusively found in right-sided cortical areas and largely overlapped with those observed in a group of 4 normal subjects performing the same task. Other areas, which have been shown to be involved in attentional and oculomotor tasks in other PET studies, were also activated in patients with ULN.

Conclusions: The behavioral recovery of ULN in these patients with predominantly subcortical lesions is mainly associated with cerebral activations in cortical regions similar to those observed in normal subjects. There is some evidence of functional reorganization in individual subjects, which involves other areas related to space representation and exploration.

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The syndrome of unilateral neglect (ULN) is characterized by an impairment of space exploration and cognition, relative to the hemispace contralateral to the side of the hemispheric damage. The disorder is most frequent and severe after right hemispheric lesions. While a considerable degree of spontaneous improvement is usually observed in the first weeks after the acute lesion (usually a stroke), more subtle manifestations are persistent and are amenable to rehabilitation training.

The neural correlates of both spontaneous and rehabilitation-induced recuperation of ULN, as well as of other consequences of focal neurologic damage, are largely unknown. Functional neuroimaging methods (in particular, positron emission tomography [PET]) have been shown to provide relevant contributions to the in vivo study of recovery mechanisms in neurologic patients. Two different approaches have been used: measurement of regional cerebral perfusion or metabolism at rest, before and after recovery, or activation studies in which the measurement of brain perfusion is performed while the recovered patients are engaged in the actual performance of a task.

In the former case, the observed changes in perfusion or metabolism have been correlated with the behavioral modifications measured in patients who have undergone neuropsychological testing. In 6 patients with aphasia and 2 patients with hemineglect and subcortical lesions, a spontaneous recovery was associated with a notable improvement of cortical perfusion, ipsilateral to the lesion, as measured with single photon emission computed tomography. Using fludeoxyglucose F 18 and PET, improvements of visual field defects were correlated with metabolic changes in 2 successive observations of patients with occipital lesions. Similar results were reported in a patient with alexia, in whom a correlation was found between

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SUBJECTS AND METHODS

SUBJECTS

All of the subjects gave their written informed consent prior to participation. The protocol was approved by the Local Ethical Committee.

Three male patients with a unilateral right ischemic lesion were studied. Their ages were 61, 58, and 68 years (patients 1, 2, and 3, respectively). All 3 patients showed moderate to severe spatial hemineglect, assessed with a neuropsychological battery of tests. None of the patients showed signs of mental deterioration or had a history of mental illness. Individual clinical data are reported in Table 1.

In each patient, a 1.5-T magnetic resonance imaging scan (Magnetom 63SP, Siemens, Herlangen, Germany), performed prior to the PET examination, showed the following lesions. In patient 1, there was a large ischemic corticosubcortical lesion involving the right basal ganglia, the internal capsule, the opercular portion of the frontal lobe, and the middle and superior temporal gyri. The lesion extended to the white matter at the level of the parieto-temporo-occipital junction. In patient 2, there was a subcortical ischemic lesion extending from the right posterior and lateral thalamus to the parieto-occipital and frontoparietal white matter. In patient 3, there was a subcortical ischemic lesion, extending from the right anterior frontal to the parieto-temporo-occipital white matter.

All of the patients were examined twice. The first behavioral and PET studies were performed after 2.5, 4, and 11 months from the onset of stroke, respectively. The second PET study was performed within the week after the end of the rehabilitative treatment, which continued for 40 daily sessions (5 every week).

Four normal adults composed the normal controls. They were studied once using the same PET activation procedure.

NEUROPSYCHOLOGICAL ASSESSMENT

The 3 patients were examined for the spatial hemineglect with a battery of 5 tests that comprised Line Cancellation,13 Letter Cancellation,14 Wundt-Jastrow Area Illusion Test,17 Sentence Reading Test,2 and the test for Personal Neglect.18 The 3 patients scored below the cutoff scores in all 5 of the tests for hemineglect. The functional neurologic impairment was assessed by the Barthel Index.19 The raw scores of the neglect battery tests were transformed into a z score that was taken as a global index of the hemineglect impairment.

REHABILITATION TRAINING FOR HEMINEGLECT

The 3 patients were submitted to a cognitive treatment specifically developed for hemineglect that relatively improves hemispatial disorders with stable effects up to 1 year over time5 and is considerably more effective than a non-specific cognitive stimulation in a randomized group study.20 The treatment consisted of 4 different procedures.

Visual-Scanning Training

The patient had to detect digits appearing in sequence on a large screen (2×3 m) in 48 different positions. In the early sessions, the digits were presented in a linear sequence and the patient had to press a keypad and read each stimulus aloud as quickly as possible. As the patient’s scanning abilities improved, nonlinear and less predictable presentation sequences were used. Both response time and number of omissions were recorded.

Reading and Copying Training

Newspaper headlines and handwritten sentences were presented to the patient, who read and copied them. Words and sentences had different degrees of linguistic and/or perceptual complexity (eg, sentence length, size of written material).

Copying of Line Drawings on a Dot Matrix

In this procedure, drawings made by solid lines connecting dots were presented on the left side; patients were required to copy them on a matrix on their right side. The number of dots (from 4–20) and lines was progressively increased.

Figure Description

Black-and-white pictures were shown to the patient who was required to describe them in detail. Increasing difficulty was represented by more elements to be described in the scene.

In all procedures, verbal and visual cues were provided during the early training stages and were progressively reduced when the patient’s exploration increased. Throughout training, the level of difficulty was consistently adjusted to the individual patient’s performance. Training was given 5 times a week, and each session lasted approximately 1 hour. The total duration was 40 sessions administered for 8 consecutive weeks.

PET PROCEDURES

Patients 1 and 2 and normal controls were studied with a PET scan (GE-Advance, General Electric Medical System, Milwaukee, Wis) with collimating septa retracted. The system has 18 rings that allow 35 transaxial images to be obtained with a slice thickness of 4.25 mm covering an axial field of view of 15.2 cm. Transmission data were acquired using a pair of rotating pin sources filled with germanium 68 (370 MBq per pin). A filtered back-projection algorithm was employed for image reconstruction, on a
emission computed tomography steady-state techniques is the lack of a direct correlation between regional functional changes and specific behavior. Activation studies seem to be more adequate for a fine-grained correlation of modifications in the pattern of cerebral activation and behavioral recovery. Findings from 2-dimensional regional cerebral blood flow (rCBF) studies provided early evidence for the involvement of undamaged areas in language and hemineglect recovery, measuring the variation of rCBF in a test-retest paradigm while the patients were performing specific cognitive tasks.9-12
More recently, 2 PET activation studies have been performed in patients who had recovered from motor impairments, and in recovered patients with Wernicke aphasia. These studies have reported an extensive functional reorganization and an important participation of regions in the contralateral, undamaged hemisphere.

In this study, we designed a PET activation paradigm to evaluate the brain's functional correlates of recovery from ULN in patients with right-sided lesions. We measured rCBF changes during the execution of a visuospatial task before and after rehabilitation training administered for a period of 2 months between the 2 PET measurements.

**RESULTS**

**BEHAVIORAL MEASUREMENTS**

All 3 patients showed a considerable improvement between the first and the second examination both in the raw scores of the 5 measures of neglect as well as in the global evaluation [z scores; Table 1]. This improvement was consistent with the qualitative observation by the cognitive therapist at the beginning and at the end of the treatment.

She noted patients' increased awareness of the hemispatial disorders, as witnessed by their attempts at exploring the contralateral side, with the development of specific strategies, for example, looking for the left border before reading. Furthermore, at the end of the treatment all 3 patients showed an improved capacity to deal with the spatial problems of everyday living. However, all of them still took more time in performing actions in the left side of the space, particularly in a complex context.

Table 1 shows the neurologic recovery of the 3 patients. Patients 1 and 3 improved from a severe to a moderate disability; patient 2 from a severe to a mild disability.

**PET FUNCTIONAL ANATOMY**

**Normal Controls**

The leftward visual exploration compared with baseline showed bilateral activations in the superior parietal lobule/precuneus (Broadmann area [Ba] 7) and superior occipital gyrus (Ba 19). In addition, activation foci were found in the right parieto-temporo-occipital junction (Ba 39/19) and the left cuneus (Ba 18/19) (see Table 2 for stereotactic coordinates and z scores; also see the Figure).

Patients With ULN

Comparison of Experimental and Baseline Tasks in Studies 1 and 2. The stereotactic coordinates and the corresponding z scores of the activated areas are reported in Table 3. In the first study, patient 1 showed left inferior frontal (Ba 47) and right parahippocampal (Ba 35) activations. In the second PET study, right-sided regions, ie, the superior (Ba 7) and inferior parietal lobule

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**Table 1. Clinical Synopsis**

<table>
<thead>
<tr>
<th>Patient No./ Age, y/Sex</th>
<th>Onset to 1st Examination, mo</th>
<th>Line Cancellation (0-21)</th>
<th>Letter Cancellation (0-104)</th>
<th>WJ (20-0)</th>
<th>Sentence Reading (0-6)</th>
<th>Personal Neglect (0-6)</th>
<th>Overall z Scores</th>
<th>Barthel Index (0-100)</th>
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<tr>
<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<td>6</td>
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<tr>
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<td>103</td>
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<td>19</td>
<td>89</td>
<td>9</td>
<td>0</td>
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*WJ indicates Wundt-Jastrow Area Illusion Test; Pre, prerecovery; and Post, postrecovery. The numbers in parentheses represent the range of scores on each test. Incorrect responses are reported for the Personal Neglect Scale and for the WJ, the other values indicate the number of correct responses. None of these patients had a visual field defect.

**Table 2. Regional Activations During the Visual Search Task in Normal Controls**

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<tr>
<th></th>
<th>Left</th>
<th>Right</th>
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<tr>
<td></td>
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<tr>
<td>---</td>
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</tr>
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<td>Superior occipital gyrus</td>
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<td>−14</td>
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<td>.</td>
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<tr>
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<td>−14</td>
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<td></td>
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<td></td>
<td>18</td>
<td>−8</td>
</tr>
</tbody>
</table>

*Ba indicates Broadmann area; ellipses, the absence of activation in these areas.*

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(Ba 40) and the junction between the fusiform and the inferior temporal gyrus (Ba 37/19), were activated. On the left side, activation foci were found in the cuneus (Ba 18), inferior frontal gyrus (Ba 46), and cerebellum.

In patient 2, no notable activations were seen during the first examination. In the second study, we found right-sided activations in the dorsal frontal gyrus (Ba 6), superior parietal lobule (area 7), parieto-occipital junction (Ba 39/19), and parahippocampal gyrus (Ba 28). On the left side notable activations were present in the parieto-occipital junction (39/19), cuneus (Ba 18), inferior and middle frontal gyri (Ba 45,46, 8), and in the inferior occipital gyrus (Ba 18).

In patient 3, results from the first examination showed activation of the left cuneus (BA 18) and in the precuneus bilaterally (BA 7). In the follow-up study there were areas of activation in the right superior occipital gyrus and precuneus (Ba 19/7), in the right parieto-temporo-occipital junction (Ba 19/39) and in the right middle occipital gyrus (Ba 18/19).

Task by Experimental Session Interactions: Areas of Greater Activations in the Second Studies. The stereotactic coordinates and the corresponding z scores of the areas in which significant interactions were found are reported in Table 4 and the Figure.

In patient 1, 3 right-sided areas showed considerably greater activation in the second session: the superior and inferior parietal lobules (Ba 7 and 40), and the junction between the fusiform and inferior temporal gyri (Ba 37/19), a region that, in normal controls, approached our criteria for significance in a very similar location (stereotactic coordinates: x = 56; y = -56; z = -12; z score, 2.7). One left-sided area of greater activation in the second session was seen in the cuneus (Ba 18). A positive task by session interaction was also seen in the left cerebellar hemisphere.

In patient 2, 4 right-sided areas showed considerably greater activation in the second session: the superior parietal lobule (Ba 7), the parieto-occipital junction (Ba 39/19), the middle frontal gyrus (Ba 8), and the parahippocampal gyrus (Ba 28). A single left-sided interaction was observed in the left inferior frontal gyrus (Ba 46).

In patient 3 the areas with increased activity after the treatment for hemineglect were all located in the right hemisphere: the superior occipital gyrus/precuneus (Ba 19/7), the parieto-occipito-temporal junction (Ba 19/39), and the middle occipital gyrus (Ba 18/19).

The aim of the present study was to characterize the brain activation pattern of recovered patients with ULN while performing a visuospatial exploration task. In these 3 patients, the behavioral improvement was associated with specific patterns of cerebral activation that included predominantly ipsilesional, right hemispheric areas. The activations observed in recovered patients were in similar locations to those found in normal controls performing the same task. The results from normal subjects delineate a network of cerebral areas that subserve the attentional mechanisms involved in locating visual stimuli in space. Comparable results have been reported in another PET study during a spatial exploration task without visual control in which activations of right cingulate, premotor, and posterior parietal areas were found. Given that the exploration task was performed with the right hand in the right hemispace, these results together with the present study confirm the right hemispheric dominance for spatial at-

The first row illustrates the location of the regional cerebral blood flow (rCBF) increases induced by the visual search task in the normal controls. Areas of significant rCBF increase have been plotted on average magnetic resonance images (MRIs) transformed into a stereotactic space. The activated areas (P < .001) are displayed in red/white. The second, third, and fourth rows illustrate the locations where patients with unilateral neglect showed significantly greater activation in the visual search task during the second experimental session as compared with the first session (P < .01; areas in red/white). These task-by-study interaction effects are superimposed on each patient’s individual MRI normalized to the stereotactic space. The second MRI slice of each row corresponds to the bicommissural plane. The MRI slices are 4 mm thick. The level of significance (expressed as z scores), stereotactic coordinates, and anatomical identification of activation foci and interaction effects are reported in Table 2 and Table 4.
At the first examination, the direct comparison of leftward visual exploration vs control condition showed limited or no similarity with the activation pattern observed in the normal controls. Patient 2 did not show any activated area. Similarly, in patients 1 and 3 during the same comparison before treatment, the activation was very scarce. Overall, these findings are not surprising, given the fact that the patients were either totally unable or reluctant to perform the exploratory task. During the second PET study, all patients showed activations of several brain regions in conjunction with recovery from neglect. The involvement of crucial structures in the right hemisphere, such as the inferior and superior parietal lobule and the parieto-occipito-temporal junction, was evident and further qualified by the formal task by experimental session interactions. This degree of overlap of the interaction effects is remarkable given the confounding effect of the different locations of the subcortical lesions of these patients.

Table 3. Regional Activations During the Visual Search Task in Patients With Unilateral Neglect

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<th>Ba</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z Score</th>
<th>x</th>
<th>y</th>
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</table>

*Ba indicates Broadmann area; ellipses, the absence of activation in these areas.*
In particular, the right superior parietal cortex and precuneus were considerably more active in the second study for all subjects. As discussed above, this brain structure seems involved in attentional shift.\textsuperscript{27,31} Another area of overlap in the interaction effects across subjects was the right parieto-occipital junction (patients 2 and 3). This structure may contribute to reinterpretation of visual images on the basis of signals from the oculomotor system\textsuperscript{32} and may be required to monitor gaze direction toward the visual stimuli appearing, as in the present task, in a predicted section of the space.\textsuperscript{33,34}

A noteworthy exception to the right-sided prevalence is the enhanced activity of the left inferior frontal gyrus in patient 2. While no formal interaction effect was seen in this area in the other patients, an activation for this region was evident for both patients 1 and 2 in the second study. A bilateral activation of this area has been described in normal subjects while performing spatial tasks with a short-term memory demand.\textsuperscript{35,36} The nature of the spatial task used in the present study may have engaged a working memory strategy to predict the location of the successive stimulus.

It should be noted that patient 2 was tested and observed a longer time after stroke (11 months instead of the 2.5 and 4 months for patients 3 and 1). At present it is difficult to know whether this temporal difference might have any meaningful relation with the present data.

\section*{Conclusions}

The rCBF changes induced by the experimental task, both in normal controls as well as in the patients with ULN in the second study, were confined to the cortical areas involved in reorienting the oculomotor behavior and the attention toward a stimulus appearing in a new spatial position.\textsuperscript{37}

These findings in patients with ULN point to a pattern of functional reorganization underlying recovery, which involves areas relevant to visuospatial orientation and predominantly located in the right hemisphere. These observations have implications for the issue of brain plasticity and rehabilitation in human adults. There is ample evidence in animal models that the adult brain can reorganize after a sensory peripheral deafferentation or after a cortical lesion, provided that a prolonged specific stimulation is applied.\textsuperscript{38,39} An increasing body of evidence is also becoming available in humans. Prolonged practice in performing a complex motor task has been shown to produce plastic changes in the motor cortex, and this reorganization persisted for several months.\textsuperscript{40} In a more normal context, the long practice of string players to use the left-hand fingers was shown to be associated with a permanent enlargement of the cortical representation in the contralateral somatosensory area, which was correlated with the number of years devoted to the musical activity.\textsuperscript{41} Similarly, persistent plastic changes in the representation of the phantom limb in the somatosensory cortex were observed in a group of amputees, and the amplitude of this reorganization was highly correlated with the intensity of pain sensation experienced by these patients.\textsuperscript{42} All these examples of brain plasticity, and particularly those dealing with complex learning, can account for a persistent functional readjustment following an appropriate training and for its association with a structural reorganization of the cerebral cortex.

\begin{table}
\centering
\caption{Task by Study Interactions in Neglect Patients: Areas of Greater Activations in Second Studies\textsuperscript{*}}
\begin{tabular}{|l|c|c|c|c|c|c|c|c|c|c|c|}
\hline
& & & & & & & & & & & \\
\hline
& \textbf{Ba} & \textbf{x} & \textbf{y} & \textbf{z} & \textbf{z Score} & \textbf{x} & \textbf{y} & \textbf{z} & \textbf{z Score} & \\
\hline

\textbf{Patient 1} & & & & & & & & & & \\
Superior parietal lobule/precuneus & 7 & -10 & -68 & 4 & 2.4 & 22 & -28 & 56 & 2.6 & \\
Inferior parietal lobule & 40 & -14 & -72 & 12 & 2.8 & 20 & -52 & 36 & 2.9 & \\
Cuneus & 18 & -10 & -68 & 4 & 2.4 & 36 & -40 & 40 & 3.1 & \\
Fusiform/Inferior temporal gyrus & 37/19 & -20 & -74 & -36 & 3.3 & 44 & -62 & -12 & 3.7 & \\
Cerebellum & -24 & -68 & -40 & 3.3 & 2 & 0 & -5 & 23 & 6 & 2.9 & \\
\hline

\textbf{Patient 2} & & & & & & & & & & \\
Superior parietal lobule/precuneus & 7 & 18 & -46 & 60 & 2.8 & & & & & \\
Middle frontal gyrus & 8 & 22 & -56 & 56 & 2.7 & & & & & \\
Parieto-occipital junction & 19/39 & 30 & -74 & 40 & 2.5 & & & & & \\
Inferior frontal gyrus & 46 & 38 & -74 & 36 & 3.0 & & & & & \\
Parahippocampal gyrus & 28 & 30 & -8 & -20 & 2.9 & & & & & \\
\hline

\textbf{Patient 3} & & & & & & & & & & \\
Superior occipital gyrus/precuneus & 19/7 & 30 & -82 & 40 & 3.3 & & & & & \\
Parieto-occipito-temporal junction & 19/39 & 44 & -80 & 24 & 3.2 & & & & & \\
Middle occipital gyrus & 18/19 & 34 & -78 & 32 & 3.0 & & & & & \\
\hline
\end{tabular}
\end{table}

*\textsuperscript{Ba} indicates Broadmann area; ellipses, the absence of activation in these areas.
cortex. A similar within-system effect was observed in a case of short-term recovery from left hemianesthesia induced by caloric vestibular stimulation. In that study, the brain areas modulated by vestibular stimulation (right insula and putamen) belonged to the neural system involved in touch perception. Whether the same constraints apply to the case of recovery of other cognitive functions, such as language, remains a matter for investigation.

The lack of a control group of patients who were not rehabilitated (which was skipped for ethical reasons) prevents a definite conclusion as to whether the observed behavioral improvements were due to the training, as suggested by 2 previous studies, or to spontaneous recovery.

With this caution, it might be speculated that the rehabilitation program used for these patients might facilitate a functional reorganization based on the recruitment of brain areas that are involved in the neural organization of activities, such as oculomotor exploration or spatial short-term memory, related to visual exploration. Yet, it is clear that there are limits to cerebral plasticity. The only areas that were observed in recovered patients, but not in normal subjects engaged in the same task, were mainly ipsilateral, ie, in the hemisphere dominant for spatial attention, and could be considered as functionally related, being involved in space representation and exploration.

Finally, a note of caution must be expressed as to the generality of these findings. Two of 3 patients in this study had exclusively subcortical lesions. It is thus unclear whether the role of the right hemisphere in mediating recovery can be generalized to all patients with ULN. The possible participation of contralesional structures needs to be investigated in a greater number of patients with cortical lesions.

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