Erschien zuerst in: NeuroImage 20 (2003) 657–666 www.elsevier.com/locate/ynimg

# Temporal dynamics of linguistic processes are reorganized in aphasics' cortex: an EEG mapping study

Alessandro Angrilli,[a,b,c,*] Thomas Elbert,[c] Stefano Cusumano,[d] Luciano Stegagno,[a] and Brigitte Rockstroh[c]

[a] *Department of General Psychology, University of Padova, Padova, Italy*
[b] *CNR Institute of Neuroscience, Center on Aging, Padova, Italy*
[c] *Fachgruppe Psychologie, University of Konstanz, Konstanz, Germany*
[d] *Department of Neurology, Regional Hospital of Treviso, Treviso, Italy*

Received 16 January 2003; revised 1 July 2003; accepted 1 July 2003

**Abstract**

Brain lesions are known to elicit reorganization of function in representational cortex. Using linguistic function as an example, we show that (a) injury-related reorganization may also be observed in language-related cortex and (b) this reorganization not only appears in cortical space but also in the dynamic flow of activity. The present study investigated cortical reorganization in a group of 10 nonfluent aphasics who demonstrated partial recovery of linguistic functions. Compared with controls, linguistic functions were organized in an atypical manner, both in terms of spatial structures involved and in the time course of the linguistic processes, from word reading to late stages of word encoding in working memory. For this purpose, event-related potentials were recorded in a two-stimulus design comprising phonological and semantic tasks. Subjects were asked to judge whether two words, separated by a 2-s interval, rhymed (phonological task) or were semantically associated. During word reading of the phonological task, controls showed negativity/activation over occipital sites, whereas patients displayed negativity at left-medial orbitofrontal locations anterior to the common sites of lesion. During the subsequent 2-s interval associated with word encoding, the two groups showed a reversed pattern: significant left–right anterior asymmetry prevailed in controls, whereas lateralization was absent in patients. Aphasics displayed maximum positivity/inhibition over the left frontal regions, at the typical site of lesion. Compared with controls, patients exhibited significant disinhibition (decreased positivity) of right frontal areas and greater activation of left temporal sites. These results suggest that the concept of language plasticity should include, in addition to spatial aspects of linguistic reorganization, the reorganized temporal dynamics associated with recovery of impaired functions.


*Keywords:* Aphasia; Brain plasticity; Cortical reorganization; Language; Phonological encoding; Semantic processing; ERPs; EEG

## Introduction

Research on brain system plasticity focuses on alterations of functional organization, i.e., reorganization in representational cortex. In humans, several experiments have demonstrated functional reorganization of somatosensory areas in healthy subjects—e.g., string players—with highly specialized use of hands (Elbert et al., 1995), in Braille readers (Sterr et al., 1998), and also in patients, e.g., affected by focal hand dystonia (Elbert et al., 1998) or amputees suffering from phantom limb pain (Elbert et al., 1994; Flor et al., 1995). In the human brain, motor (Stefan et al., 2000) and parietal cortices (Bavelier et al., 2001) have also shown capacity for plastic changes. Compared with sensory and motor functioning, higher level processes such as those involved in language perception and production have been shown to involve neural networks relatively more widespread in the cortex, mainly within the left hemisphere, but also in subcortical structures and right cerebral cortex (Cabeza and Nyberg, 1997; Fiez and Petersen, 1998; Pulvermüller, 1998).

Recently, several investigations have been performed in

* Corresponding author. Department of General Psychology, Via Venezia 8, 35131 Padova, Italy. Fax: +39-049-8276600.
*E-mail address:* alessandro.angrilli@unipd.it (A. Angrilli).

1053-8119/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S1053-8119(03)00395-1

order to clarify whether and how cortical reorganization occurs in aphasic patients. Imaging of cerebral blood flow using PET and, less frequently, fMRI, has demonstrated reorganization of linguistic function both within the left hemisphere (Karbe et al., 1998; Warburton et al., 1999), also in the proximity of the damaged area (Belin et al., 1996), and in the right hemisphere, in regions more or less homologous with those damaged in the left hemisphere (Buckner et al., 1996; Calvert et al., 2000 fMRI; Cappa et al., 1997; Gold and Kertesz, 2000; Lazar et al., 2000; Müller et al., 1999a, 1999b; Musso et al., 1999; Ohyama et al., 1996; Weiller et al., 1995). In most of these investigations, language-related activity has been found in both hemispheres, although the relative contribution of one hemisphere over the other and the location of language-activated areas was quite variable across studies.

Compared with PET and fMRI research, fewer studies have used EEG or evoked potentials for locating inter- or intrahemispheric reorganization of language in patients after recovery. A number of recent ERP studies found significant differences in linguistic processing (lexical, semantic, and syntactic) between aphasics and controls (Friederici et al., 1999; Hagoort et al., 1996; Swaab et al., 1997). Another set of studies used electrophysiological methods to locate linguistic activation in aphasics: some studies pointed to greater activation of right hemisphere in aphasics (Moore, 1986; Selinger et al., 1989; Thomas et al., 1997), but there is also evidence of left frontal (Cohen et al., 2001; Thomas et al., 1997) and temporal (Dobel et al., 2002) cortex activation in these patients.

The partial inconsistency of the results obtained so far probably depends on the heterogeneity of the patients studied, the extent and location of their lesions, and the variety of experimental designs, tasks, and stimuli used. Nevertheless, part of this inconsistency may be due to the fact that different cortical maps are dynamically activated by specific functional features (e.g., lexical, semantic, syntactic, phonological) of linguistic stimuli which follow one another across time. With brain-imaging methods such as PET and fMRI, many cortical regions seem to be simultaneously coactivated, whereas instead they may infact be activated sequentially (Elbert and Keil, 2000). There is currently evidence of phenomena of dynamic cortical reorganization in which different somatosensory maps may be dynamically switched and modulated (Braun et al., 2000, 2002).

The main innovation of the present study is an attempt to measure both spatial aspects of cortical plasticity and the temporal dimension of the reorganizational processes associated with the functional recovery of language in aphasics. We hypothesized the existence of spatial reorganization of linguistic processes in aphasics' cortex, depending on the different temporal phases of linguistic processes. In particular, we tried to distinguish the cortical networks activated by word reading (the early stage of word processing) from networks involved in verbal working memory and phonological/semantic word elaboration (late stage). The use of evoked potentials and their high time resolution was therefore mandatory to test the above hypothesis.

The second aim of the present experiment was to overcome some methodological limits of past investigations. A number of contrivances were adopted. First, in order to control the phenotypic variability of patients' lesions, a relatively homogenous sample of nonfluent Broca aphasics was selected. Second, to avoid psychophysical and word-category systematic effects, the same sample of linguistic stimuli was used in different tasks. We have shown in previous cross-linguistic validation that the same words activate different neural networks, depending on the task in which they are used (Angrilli et al., 2000; Elbert et al., 1999). Third, the adoption of an eye artifact modeling method termed MSEC (Berg and Scherg, 1991, 1994) yielded more precise and reliable scalp mapping of electrical brain activity, which avoided the typical underestimation of frontal lobe activity produced by standard eye movement correction methods.

## Methods

### *Subjects*

Ten aphasic patients (nine men, one woman, mean age $50.3 \pm 17.8$ years, 10.8 years of education on average) were recruited from the Regional Hospital of Treviso, Italy. The average time since the lesion was 19.4 months (range: 4–46 months; see Table 1 for details).

In the acute phase, patients had been classified on the basis of CT/MRI documentation of the lesion and neurological symptoms, and had been diagnosed as nonfluent aphasics. All patients had left-hemispheric lesions which included cortical or subcortical areas around the left frontal operculum: Broca's area (Brodmann areas 44 and 45), and the lateral portion of premotor and motor cortex (areas 6 and 4), insula, basal ganglia, anterior portion of the temporal lobe (Table 1). The map of the common site of lesion is displayed in Fig. 1a. For all patients, the orbitofrontal and most dorsolateral prefrontal cortices, the parietal and posterior temporal areas were not damaged (Fig. 1a). Prior to the experiment, patients were tested for linguistic deficits with the Aachen Aphasie test validated in Italian (Luzzatti et al., 1987, 1994). As Table 1 shows, most patients demonstrated no or very mild deficits at the time of the experiment, indicating substantial recovery of language.

Ten healthy volunteers matched for sex, age (mean age: 56.7), and educational level (mean education: 11.8 years) served as controls. All subjects were 100% right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). All participants gave their informed consent to the study. Experimental procedures were approved by the local Ethics Committee.

Table 1
Patients' demographic data along with lesion location, Token and Comprehension subtests as indexes of verbal impairment

| Patient | Sex | Age | Education (years) | Onset lesion (months) | Token test | Compr. test | Lesion location in left hemisphere |
|---|---|---|---|---|---|---|---|
| 01-MR | M | 67 | 13 | 19 | 5 | 113 | Temporal lobe/basal ganglia stroke |
| 02-BO | M | 59 | 13 | 46 | 0 | 120 | Frontal area stroke |
| 03-VM | M | 44 | 6 | 36 | 14 | 100 | Capsular hemorrhagia |
| 04-BD | F | 40 | 8 | 6 | 20 | 104 | Temporal lobe stroke |
| 05-LB | M | 56 | 5 | 11 | 20 | 110 | Insula/sylvian area stroke |
| 06-CG | M | 64 | 10 | 5 | 3 | 105 | Insula/sylvian area stroke |
| 07-FR | M | 58 | 13 | 24 | 22 | 109 | Insular frontal stroke |
| 08-ML | M | 71 | 11 | 4 | 5 | 117 | Basal ganglia hemorrhagic stroke |
| 09-CM | M | 18 | 11 | 8 | 21 | 115 | Temporal/frontal head trauma |
| 10-BM | M | 26 | 13 | 35 | 16 | 112 | Temporal/frontal stroke |

*Note*. The Token Test is representative of general language impairment: a rating below 8 indicates no deficit, between 8 and 22 slight deficit, between 23 and 40 moderate deficit, above 40 severe deficit. For Comprehension subtest a rating between 108 and 120 indicates no deficit, between 92 and 107 slight deficit.

### *Apparatus and physiological recordings*

EEGs were measured from 26 tin electrodes: 19 electrodes were placed on an elastic cap (ElectroCap) according to the International 10–20 system (Jasper, 1958), and the other 7 were placed on mastoids (M1, M2), below each eye (Io1, Io2), on the two external canthi (F9, F10), and on the nasion (Nz). Cz was used as reference. Data were stored using a DC-MES 32 channel system. Amplitude resolution was 0.1 $\mu$V. Bandwidth ranged from DC to 30 Hz (6 dB/octave). Sampling rate was set at 100 Hz.

### *Stimuli, tasks, and procedure*

Stimuli consisted of bi- or trisyllabic Italian content words with an average frequency in written language, selected from a frequency dictionary of 5000 written Italian words (Bortolini et al., 1972).

Words were presented one by one, with an interstimulus interval of 2 s. The first word (S1) was presented for 1 sec, the second word (S2) was presented until the subject pressed a button, but not for longer than 5 s (Fig. 2a). Stimuli were associated with two tasks in separated blocks: the same words being presented as S1, although in different randomized order. In the rhyming task, selected to induce phonological encoding, subjects had to decide, upon S2 presentation, whether the word pairs rhymed (e.g., cat–hat) or not (e.g., cat–hut). In the semantic task, subjects had to decide whether the second word (S2) was semantically related to the first (e.g., wood–tree). Subjects pressed a button with the left index or left middle finger to indicate

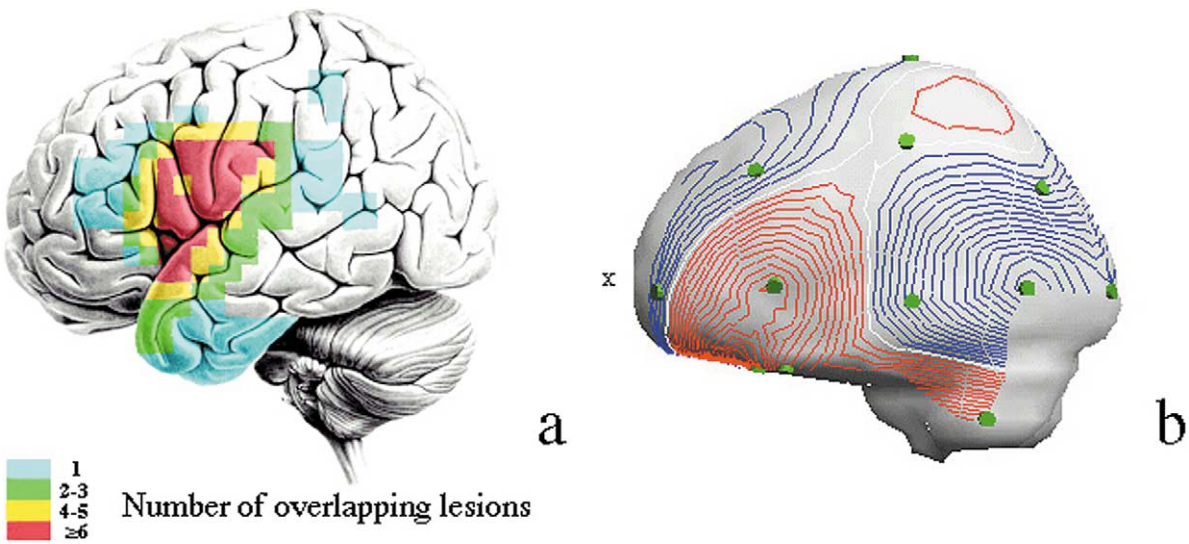



Fig. 1. Map of average cortical lesions of aphasics (a) in comparison with projection of aphasics' scalp electrical activity on cortex of a standard brain model (b). F7 electrode corresponds to left frontal opercular area (Broca's area) which was damaged in most aphasics. Electrical potentials refers to the 2-s interstimulus interval measured during rhyming task (see also Fig. 3b). The color code in the lesion map (a) indicates lesion density, that is, areas with one lesion (sky), 2 to 3 lesions (green), 4 to 5 lesions (yellow), and more than 6 lesions (red).

their decisions. Each task included 80 trials/word-pairs. In both tasks, 50% matches (rhyme–nonrhyme, semantic relation–no relation) were randomly interspersed with 50% mismatch trials. The order of the tasks was randomly varied across subjects.

*Data analysis*

Performance measures were error rates and mean reaction times, determined for each subject and compared between tasks and groups. EEGs were recorded continuously in the DC mode with Cz as recording reference, and stored for off-line analysis. Data were off-line rereferenced to the average reference, and epoched into 15-s intervals, including 1 s before and 14 s after S1. A linear detrend was performed on each epoch and each channel to eliminate slow DC shifts. A 100-ms baseline preceding S1 was subtracted from the whole trial epoch. Data were transformed into average reference. Single trials were corrected for eye movement artifacts, vertical and horizontal movements, and blinking, according to Berg and Scherg (1991, 1994). Each trial was then visually inspected for any remaining artifacts which were rejected. Among the trials rejected during this step there were also the incorrect trials (overall 38% of trials were rejected from controls and 46% from aphasics including both artifact and incorrect trials).

After eye movement correction, all accepted trials were averaged for each task and for each subject. Two epochs entered the statistical comparison: the first covered the average potential during the 300- to 1000-ms interval of S1 presentation. The second epoch (interval 1000–3000 ms), which corresponded to the language-related contingent negative variation (CNV) (Angrilli et al., 2000), included the mean potential measured during the 2-s interval between S1 and S2. In agreement with the literature on slow evoked potentials and CNV (Angrilli et al., 2000; Birbaumer et al., 1990; Rockstroh et al., 1989) negativity was interpreted as an index of relative cortical activation and positivity as correlated with relative inhibition.

Electrodes were clustered into four groups/regions-of-interest to perform statistics with two spatial factors of two levels each: antero-posterior asymmetry and laterality (Angrilli et al., 2000). Each quadrant comprised 5 electrodes (Fig. 2b): anterior left (AxLx: Io1, Fp1, F3, F7, F9), anterior right (AxRx: Io2, Fp2, F4, F8, F10), posterior left (PxLx: T3, P3, M1, T5, O1), and posterior right (PxRx: T4, P4, M2, T6, O2). Although orbitofrontal electrodes (Fp1, Fp2, F9, F10, Nz, Io1, Io2) are typically used to detect or correct eye movements, after applying the MSEC correction method of Berg and Scherg (1991, 1994), these electrodes become active, free of artifact, cortical sites.

For each time window, the ANOVA included the following variables: Group (two levels: Controls vs Aphasics), Task (two levels: Rhyming vs Semantic), AP asymmetry (Anterior–Posterior Asymmetry, two levels: Anterior vs Posterior), and Laterality (two levels: Left vs Right side). Post hoc comparisons were computed using Newman–Keuls tests.

Specific statistical comparisons (Stevens, 1990) between the two groups were performed on single-electrode activity through Student's $t$ test for independent samples, with $P$ set a priori at 0.002, corresponding to a two-tailed absolute threshold $t(18) = 3.60$ (Stevens, 1990).

Patients' lesion maps were obtained by the method described by Damasio and Damasio (1989), starting from individual CT or MRI scans. Individual CT/MRI scans were mapped by an expert neurologist onto standard templates (ranging from A1 to A5 scan slope) using criteria described by Damasio and Damasio (1989). The template sets were then matched with the lateral view of a left-hemisphere figure. The lateral view was overlapped with a grid of 23 × 30 lines (690 squares), and for each square the number of patients with a corresponding lesion was computed (this number could range from 0 to 10). The color code, blue, green, yellow, red indicates an increasing number of patients with a lesion in the coded area (see Fig. 1a).

## Results

Performance (error rates in matching word pairs, and reaction times) indicated slower responses in aphasics (mean: 1426 ms) than in controls (mean: 1010 ms; Group: $F(1,18) = 4.86$, $P < 0.04$). In both groups, reaction times were longer for the semantic (1326 ms) than for the rhyming (1110 ms) task ($F(1,18) = 35.09$, $P < 0.0001$). Patients made more errors (mean: 19.76%) than controls (mean: 4.87%) in both tasks (Group, $F(1,18) = 9.50$, $P < 0.006$). For both performance measures, the interaction Group x Task was not significant ($F(1,18) < 1$).

Fig. 3 illustrates ERP spline interpolated maps of controls and aphasics during the 1-s first word presentation. In controls, the first epoch (300–1000 ms) of word processing was characterized by negativity over posterior occipital areas (Figs. 3a and c), which was slightly left-lateralized for rhyming and right-lateralized for the semantic task. In contrast, aphasics produced negativity over left orbitofrontal cortex (Fig. 3b) during rhyming and a left posterior negative shift during the semantic task (Fig. 3d). This pattern was indicated by the significant four-way interaction Group × Task × AP asymmetry × Laterality ($F(1,18) = 5.90$, $P < 0.03$; Figs 3e and f).

For rhyming, post hoc analyses confirmed group differences: greater negativity at left frontal locations in aphasics ($P < 0.01$, Fig. 3e) and greater negativity at posterior areas in controls with respect to aphasics ($P < 0.05$). For the semantic task, groups differed significantly at posterior sites (Fig. 3f, right side): controls displayed greater negativity at right than left hemisphere, whereas patients showed reversed lateralization, with greater positivity than controls at right posterior locations ($P < 0.05$).

The slow potentials which develop during the 2-s epoch

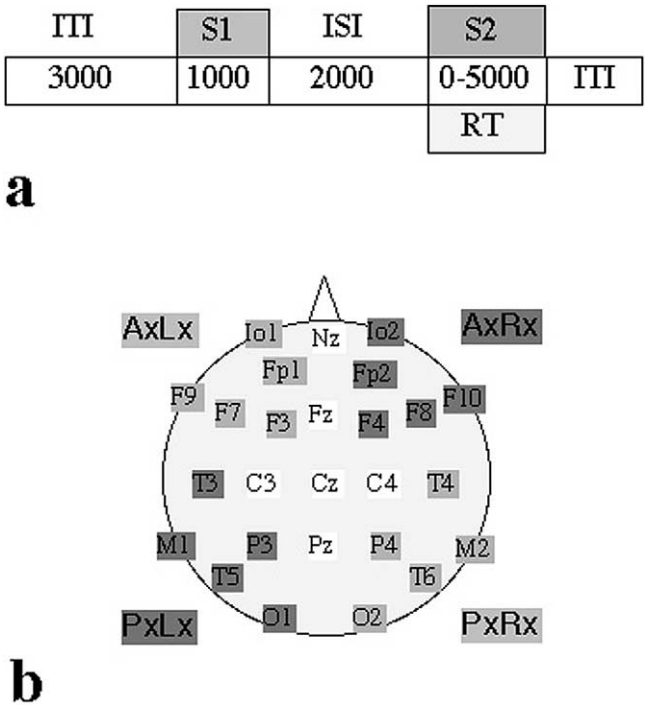



Fig. 2. (a) Organization of the experimental trial. Duration indicated in ms. ITI, intertrial interval; ISI, interstimulus interval. (b) Clustering of electrodes in four quadrants: Anterior Left (AxLx), Anterior Right (AxRx), Posterior Left (PxLx), Posterior Right (PxRx).

between S1 and S2 represent activation of areas involved in task-dependent word encoding. More left-hemispheric negativity was found in controls on the rhyming task and more right posterior negativity on the semantic task (Figs. 4a and c). Aphasics again revealed a different pattern with relative positivity over left frontal and relative negativity over left posterior regions on both tasks (Figs. 4b and d).

The Group × AP asymmetry × Laterality interaction ($F(1,18) = 4.47$, $P < 0.05$; Fig. 4e) revealed greater negativity at posterior than anterior sites in aphasics' left hemisphere ($P < 0.05$) whereas controls exhibited a highly significant negative shift at right posterior compared with anterior sites ($P < 0.004$). The Group × Task × Laterality interaction ($F(1,18) = 13.27$, $P < 0.002$; Fig. 4f) confirmed that rhyming evoked strong left-hemispheric negativity in controls ($P < 0.001$, left–right comparison) whereas there was no evidence for lateralized activation in aphasics. This group difference in hemispheric laterality was partly due to a larger positive shift in aphasics' left hemisphere and partly to reduced positivity of their right hemisphere ($P < 0.02$).

Although reduced with respect to the first epoch, some relative activation of right-medial orbitofrontal electrodes during rhyming could still be observed in this late epoch in aphasics (Figs. 4b and 5; statistics computed on single electrode waveforms showed greater negativity in aphasics compared with controls at Fp2, Io2, Nz, $t(18) > 3.6$, $P < 0.002$, two-tailed).

To summarize the time course of the significant effects described above, the complete waveforms from aphasics and controls are displayed in Figs. 5 (rhyming task) and 6 (semantic task). All next mentioned effects at electrode site were significant with Student's $t(18) > 3.6$, $P < 0.002$, two-tailed. The central electrodes (C3, C4, Cz, Pz), which were not in the quadrant statistics, showed an unspecific (that is, task-independent) significantly greater negativity (CNV) in controls than in aphasics during the 2-s interstimulus interval in both tasks (Figs. 5 and 6).

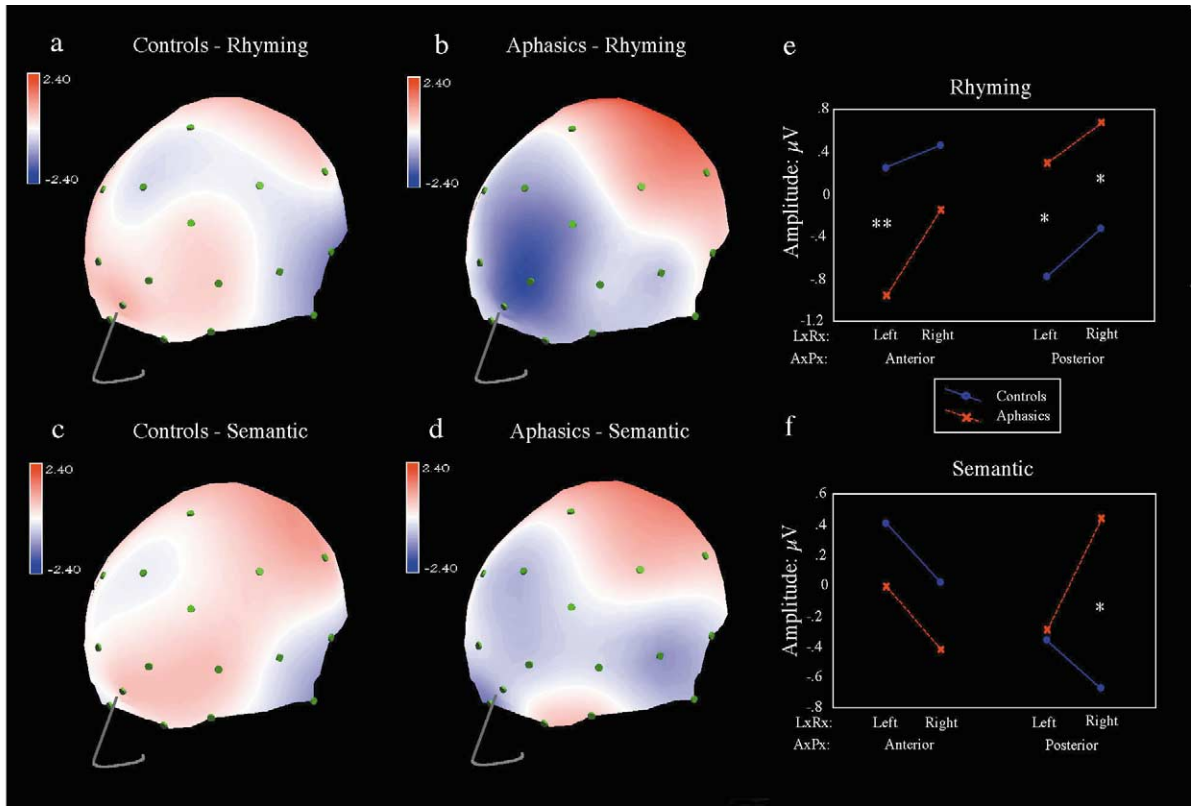
Aphasics showed greater negativity than controls over left orbitofrontal electrodes (see Fp1 in Fig. 5, but this effect was also significant at F3, F9, Nz) during the first epoch of rhyming. However, during the second epoch, characterized by word encoding in verbal working memory, controls showed a negative potential, while patients exhibited a peak of positivity at the left frontal electrode F7, extending to M1, i.e., in a region corresponding to the lesioned cortical area common to most aphasics (that is, frontal operculum—Broca's area, electrode F7, see Fig. 1a). On the semantic task, controls displayed a negativity peak over right temporoparietal sites (P4, T6), whereas patients had greater negativity at left temporal electrodes (M1, T3) (Fig. 6).

As further confirmation of the functional alteration of phonological encoding (rhyming) found at lesioned site, in Fig. 1a the cortical surface of left hemisphere, corresponding to the average lesion of the patient group, showed a clear overlap with the peak of positivity (inhibition) measured over the scalp during rhyming and projected on to the cortical surface of a standard brain model (Fig. 1b).

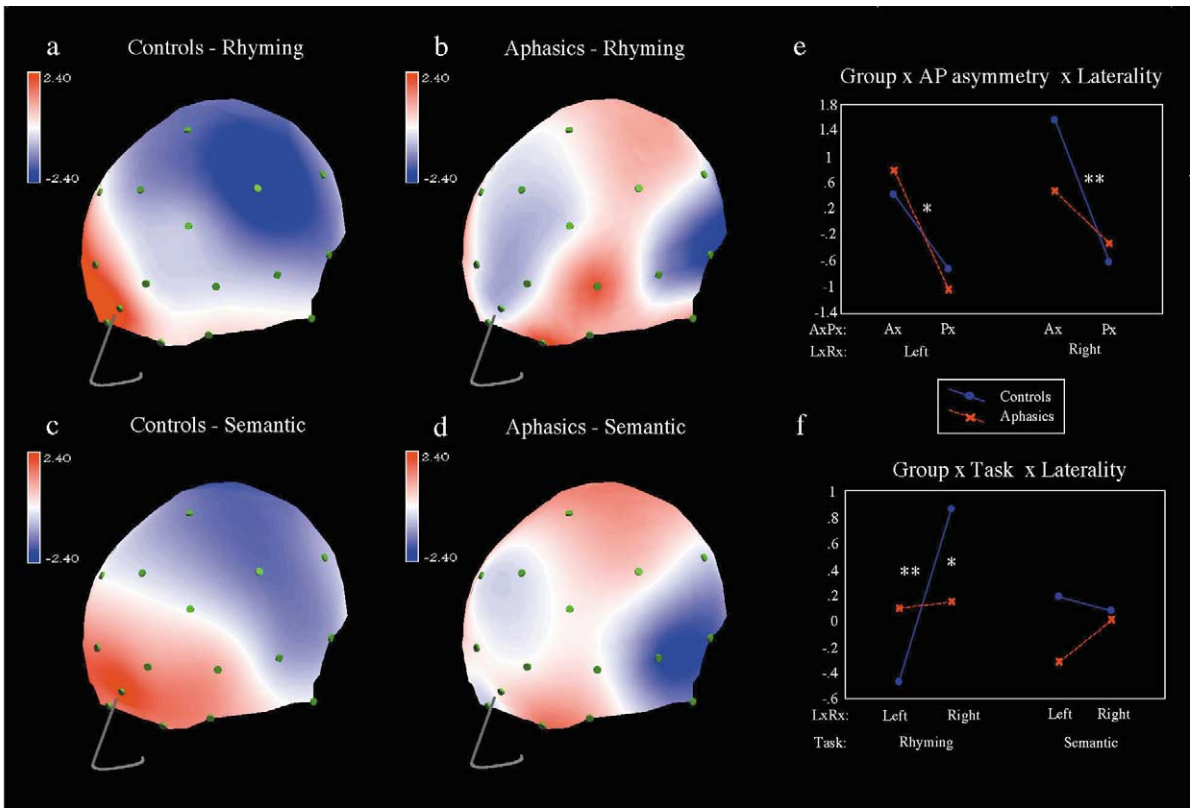
## Discussion

Two linguistic tasks were contrasted for their capacity to activate neural networks with different functional and neuroanatomical characteristics: a rhyming task was used to engage articulatory processes and phonological elaboration of the words which are known to activate Broca's area (Paulesu et al., 1993; Zatorre et al., 1992). It was expected that nonfluent aphasics would be relatively impaired on this task. ERPs were used to examine the cortical activation induced by these tasks, surface negativity being taken as indication of activation in underlying cortical networks and surface positivity as an indication of relative cortical inhibition (Angrilli et al., 2000; Birbaumer et al., 1990; Rockstroh et al., 1989).

A large statistical difference between controls and aphasics was found at central electrodes (C3, Cz, C4, Pz), which were not included in ANOVA lateralization statistics. Controls displayed an overall greater negativity (CNV) at these sites than aphasics (Figs. 5 and 6). This group effect was equally present in both tasks; therefore it is probably related to a deficit of central–frontal motor cortex activity related to aphasics' motor impairment (they were still hemiplegic to some extent). Furthermore, this cortical unspecific deactivation may explain also the overall reduced efficiency of




3




4

Fig. 3. Maps rereferenced to average reference, representing mean potentials recorded in 300- to 1000-ms epoch, during S1 presentation. Spline maps of controls (a, c) and aphasics (b, d) during rhyming (a, b) and semantic tasks (c, d). Each map shows the head at left $\frac{3}{4}$ view. Right: the significant Group × Task × AP asymmetry × Laterality 4-way interaction is split into rhyming (e) and semantic data (f). Asterisks indicate significant post hoc tests.

Fig. 4. Spline maps, rereferenced to average reference, relative to mean potential measured in 1000- to 3000-ms epoch, during interstimulus interval. Maps of controls (a, c) and aphasics (b, d) during rhyming (a, b) and semantic tasks (c, d). Each map shows the head at left $\frac{3}{4}$ view. Right side: Group × AP asymmetry × Laterality (e) and Group × Task × Laterality (f) significant interactions. Asterisks indicate significant post hoc tests.

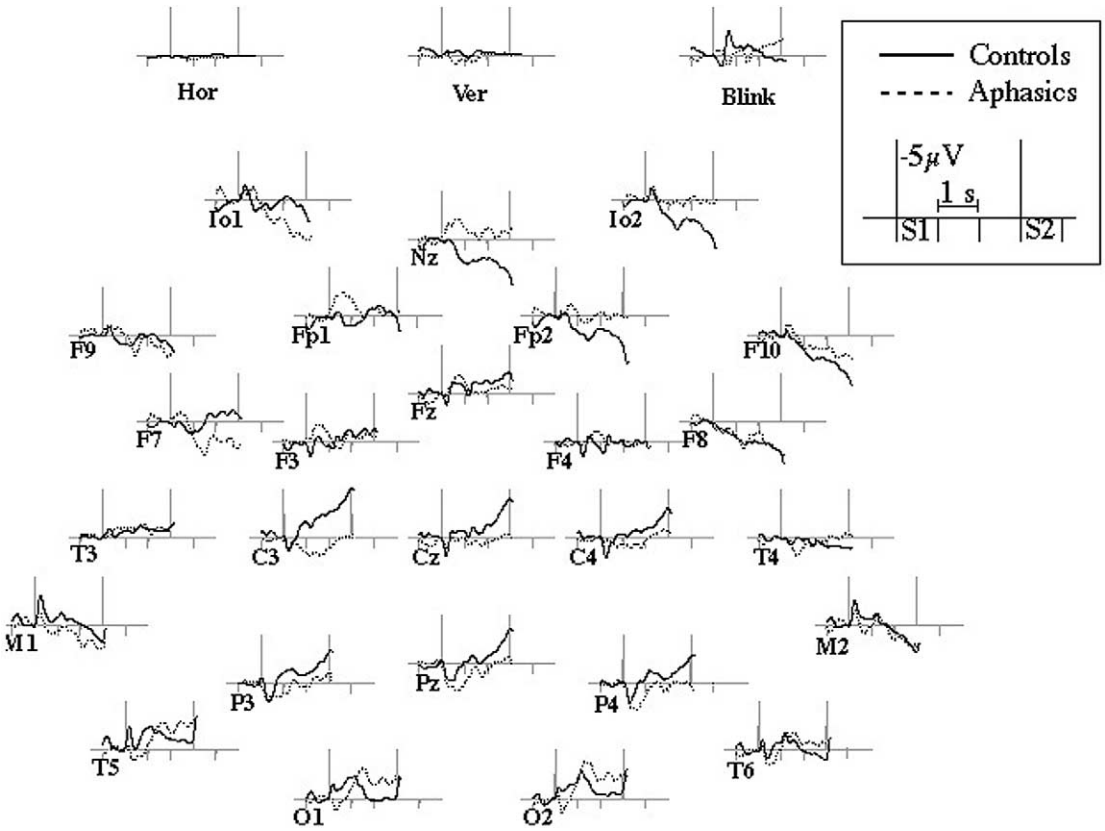



Fig. 5. Grandaverage waveforms of all electrodes showing time-courses of rhyming task in controls (solid line) versus aphasics (dashed line). Displayed activity includes 1-s baseline, 1-s S1 presentation, and 2-s interstimulus interval. Large vertical bars indicate onset of S1 and S2 and represent $-5$ $\mu$V amplitude. Negativity is displayed upside.

patients in linguistic tasks, since they made more errors and were on average slower than controls (other studies confirmed a general decrease in aphasics' behavioral efficiency, Cohen et al., 2001; Dobel et al., 2002). Thus, in the patients, the deficit of central CNV was neither lateralized nor task-specific. Indeed, starting from a large literature, previous empirical studies have used the present paradigm to show lateralization and task-specific effects by means of quadrant analysis (Angrilli et al., 2000; Cohen et al., 2001).

In a previous work using the same paradigm in healthy subjects, rhyming elicited activation of the left hemisphere, with a negativity peak centered over left frontal areas (Angrilli et al., 2000). Lexical–semantic tasks, in evoked potential paradigms, were able to activate more widespread networks also involving the right hemisphere (Abdullaev and Posner, 1997; Angrilli et al., 2000). These results were replicated in the present study for the second epoch in controls. During rhyming, controls displayed a peak of activity over C3 (Figs. 3a and 5), and in general there was a strong lateralization due to greater negativity in left frontal compared with the right omologous electrodes. In addition, the cortical networks involved in the two tasks also differed across time, from the early stage of word reading (300- to 1000-ms epoch), characterized by reduced lateralization and occipital activation (Figs. 5 and 6), to the late epoch of word elaboration, showing a peak of activity over left frontal sites during rhyming (Fig. 4a and 5) and over right parietal sites during semantic performance (Fig. 6). Aphasics showed functional reorganization of cortical maps which varied across different tasks and different timing of word processing. During word reading in the rhyming task, controls showed greater activation of posterior areas, whereas aphasics had greater activation at the left-medial orbitofrontal cortex (Fig. 3b), anterior to their lesion sites centered on left frontotemporal regions (Fig. 1a). In the second epoch of the rhyming task, that is, during the interval between the two words, the pattern between the groups was reversed. The control group displayed greater frontal lateralization, with left negativity/activation and right positivity/inhibition. Instead, in the aphasics, early left orbitofrontal activation shifted toward left temporal sites (Figs. 1b and 4b), posterior to the damaged area common to most patients (Fig. 1a). Furthermore, aphasics revealed significant disinhibition (smaller positivity) of the right frontal cortex (Fig. 5). The significant inhibition (positivity) found on F7 (Fig. 5), corresponding to Broca's damaged area and observed during aphasics' rhyme encoding, suggests that the lesioned cortex was affected by functional impairment of phonological processing (Figs. 1a and b).

The described results are consistent with other experi-

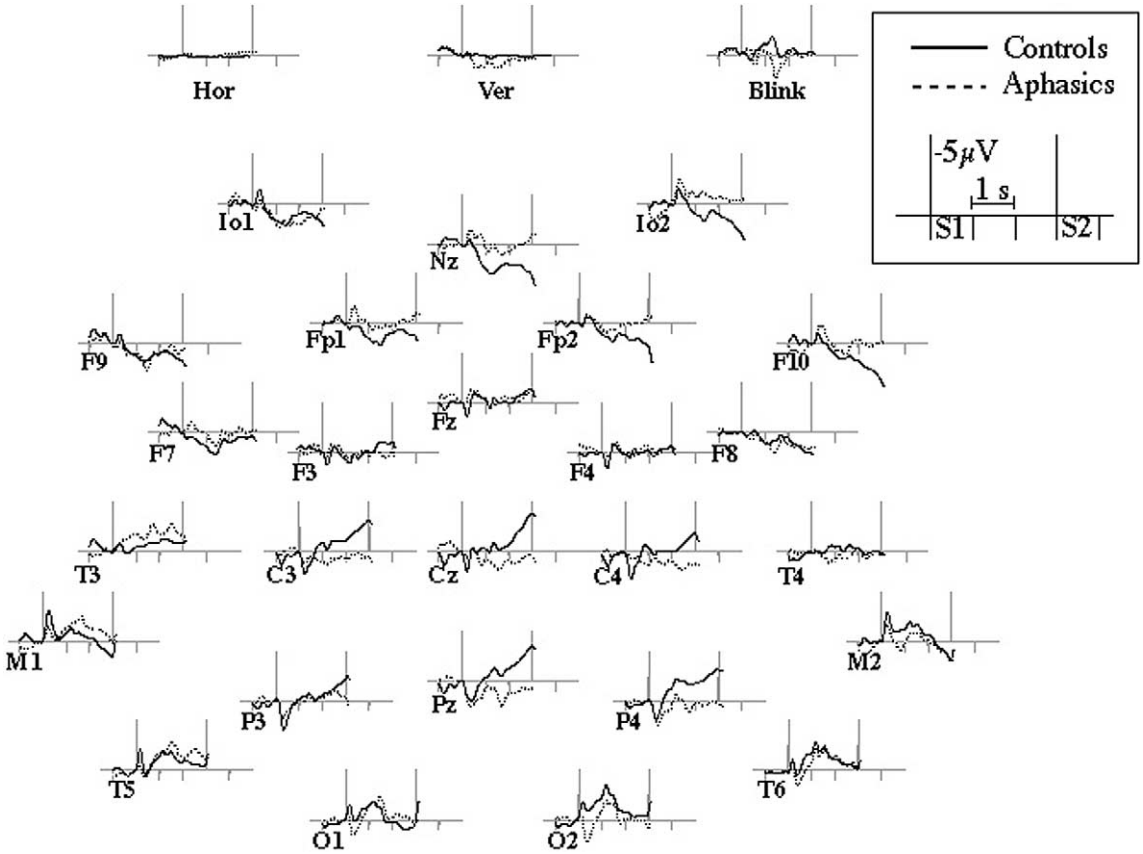



Fig. 6. Grandaverage waveforms of all electrodes for the semantic task in controls (solid line) and aphasics (dashed line). Displayed activity includes 1-s baseline, 1-s S1 presentation, and 2-s interstimulus interval. Large vertical bars indicate onset of S1 and S2 and represent $-5$ $\mu$V amplitude.

ments on cortical plasticity showing left frontal (Belin et al., 1996; Cohen et al., 2001; Karbe et al., 1998; Thomas et al., 1997; Warburton et al., 1999) and right frontal activation (Buckner et al., 1996; Calvert et al., 2000; Lazar et al., 2000; Müller et al., 1999a, 1999b) mainly in nonfluent Broca's aphasics. However, our experiment also showed that both left and right frontal regions are involved but in different functional–temporal stages of linguistic processes. The activation of left orbitofrontal cortex during the first epoch of rhyming judgment may be related to patients' attempts to anticipate phonological encoding of the first word, and this activity may be supported by intact areas near and anterior to the lesion (Fig. 1a). A candidate brain structure for this activation is the anterior portion of the cingulate gyrus. Both the anterior cingulate and the whole orbitofrontal cortex provide the highest number of connections with motor, premotor, and supplementary motor cortices. The cingulate itself is involved in motor functions and is a good candidate for replacing, in aphasics, the motor components required by word articulation on rhyming tasks. In line with our interpretation, some studies have demonstrated the activation of the anterior cingulate in a number of linguistic processes, some of which may have been enhanced by the substitutional strategies of our aphasics, such as word generation (Kircher et al., 2001), language translation (Price et al., 1999), and the use of generation nouns (Snyder et al., 1995).

Our last interesting result revealed that, during the second epoch of the semantic task, patients had greater activation on the left posterior sites whereas controls were more activated than aphasics over right posterior cortex (Figs. 3d, 3e and 6). Therefore, processing of the semantic features of the stimuli was also reorganized in our sample of aphasics. Similar left posterior activation on lexical semantic tasks was also found in another study with a Broca aphasic (Buckner et al., 1996). Although there is no direct evidence in this paradigm that left frontal cortex is involved in semantic processes, it is possible that this area exerts a facilitating influence far away in an enlarged linguistic network which includes the temporal lobes of both hemispheres. Indeed, it has been shown that the left inferior prefrontal cortex may play a role in some aspects of semantic elaboration, such as selection of semantic knowledge (Thompson-Schill et al., 1997).

It is worth noting that our sample of patients had a residual linguistic impairment which, according to the Aachen Aphasie Test battery, was overall classified as "slight deficit" (Table 1 for the Token and Comprehension tests). Most of patients were intact on the comprehension subtest and showed minimal impairment in the other

subtests, and we therefore assume that they had recovered most linguistic functions and that these functions were supported by the brain regions which we found activated in the present study.

The striking overlap between the neuroanatomical data on lesion location and the spatial distribution of functional scalp electrical activity (Fig. 1) strongly supports our assumption (Rockstroh et al., 1989; Angrilli et al., 2000) that, in CNV paradigms like the present one, negativity must be interpreted as relative cortical activation and positivity as inhibition. Additional research has confirmed marked consistency between scalp electrical potentials evoked by linguistic stimuli and the activity of the underlying cortex as measured through PET regional blood flow (Snyder et al., 1995).

In conclusion, whereas controls showed greater left frontal lateralization in the second epoch, during phonological encoding of words in verbal working memory, aphasics were lateralized at earlier stages, during word reading, with a peak of activity located anterior to their lesions, that is, in medial orbitofrontal sites. Patients probably used a strategy aimed at anticipating the processing of the phonological aspects of words, a task relatively more difficult for them, especially after the offset of the first word. The observed effects can hardly be attributed to unspecific, language-independent, reorganization of activity as in this case, in aphasics, the same spatial and temporal distribution of activation would have characterized both tasks. Instead, the same sample of words used as S1 in semantic and rhyming tasks elicited different activation maps in the two samples of subjects in different epochs of language processing. Thus, in addition to spatial reorganization of the cortex, patients also had reorganization of the dynamic flow of networks recruited by language elaboration.

In the present study we used the term reorganization in the larger meaning, to indicate a redistribution of cortical linguistic activity following a brain lesion: from the present data we do not know the origin of the observed spatial and temporal redistribution of linguistic activity in the patients. Whether this change is an effective reorganization of cortical functions or a compensatory unmasking of previous silent regions is a matter for further investigation.

## Acknowledgments

Research was supported by the European Union (Grant TMR n.ERB4001GT962836 to A.A.). We thank Patrick Berg for useful advice on ERP analyses and Rita Minghetti for help in data collection.

## References

Abdullaev, Y.G., Posner, M.I., 1997. Time course of activating brain areas in generating verbal associations. Psychol. Sci. 8, 56–59.

Angrilli, A., Dobel, C., Rockstroh, B., Stegagno, L., Elbert, T., 2000. EEG brain mapping of phonological and semantic tasks in Italian and German languages. Clin. Neurophysiol. 111, 706–716.

Bavelier, D., Brozinsky, C., Tomann, A., Mitchell, T., Neville, H., Liu, G., 2001. Impact of early deafness and early exposure to sign language on the cerebral organization for motion processing. J. Neurosci. 21, 8931–8942.

Belin, P., Van Eeckhout, P., Zilbovicious, M., Remy, P., Francois, C., Guillaume, S., Chain, F., Rancurel, G., Samson, Y., 1996. Recovery from non-fluent aphasia after melodic intonation therapy. Neurology 47, 1504–1511.

Berg, P., Scherg, M., 1991. Dipole models of eye movements and blinks. Electroenceph. Clin. Neurophysiol. 79, 36–44.

Berg, P., Scherg, M.A., 1994. A multiple source approach to the correction of eye artifacts. Electroenceph. Clin. Neurophysiol. 90, 229–241.

Birbaumer, N., Elbert, T., Canavan, A., Rockstroh, B., 1990. Slow potentials of the cerebral cortex and behavior. Physiol. Rev. 70, 1–41.

Bortolini, V., Tagliavini, C., Zampolli, A., 1972. Lessico di frequenza della lingua italiana contemporanea. Aldo Garzanti Editore SpA, Milano.

Braun, C., Haug, M., Wiech, K., Birbaumer, N., Elbert, T., Roberts, L.E., 2002. Functional organization of primary somatosensory cortex depends on the focus of attention. NeuroImage 17, 1451–1458.

Braun, C., Schweizer, R., Elbert, T., Birbaumer, N., Taub, E., 2000. Differential activation in somatosensory cortex for different discrimination tasks. J. Neurosci. 20, 446–450.

Buckner, R.L., Corbetta, M., Schatz, J., Raichle, M.E., Petersen, S.E., 1996. Preserved speech abilities and compensation following prefrontal damage. Proc. Natl. Acad. Sci. USA 93, 1249–1253.

Cabeza, R., Nyberg, L., 1997. Imaging cognition: an empirical review of PET studies with normal subjects. J. Cogn. Neurosci. 9, 1–26.

Calvert, G.A., Brammer, M.J., Morris, R.G., Williams, S.C.R., King, N., Matthews, P.M., 2000. Using fMRI to study recovery from acquired dysphasia. Brain Lang. 71, 391–399.

Cappa, S., Perani, D., Grassi, F., Bressi, S., Alberoni, M., Franceschi, M., Bettinardi, V., Todde, S., Fazio, F., 1997. A PET follow-up study of recovery after stroke in acute aphasics. Brain Lang. 56, 55–67.

Cohen, R., Dobel, C., Berg, P., Koebbel, P., Schönle, P.W., Rockstroh, B., 2001. Event-related correlates of verbal and pictorial feature comparison in aphasics and controls. Neuropsychologia 39, 489–501.

Damasio, H., Damasio, A., 1989. Lesion Analysis in Neuropsychology. Oxford University Press, New York.

Dobel, C., Cohen, R., Berg, P., Nagl, W., Zobel, E., Köbbel, P., Schönle, P.W., Rockstroh, B., 2002. Slow event-related brain activity of aphasic patients and controls in word comprehension and rhyming tasks. Psychophysiology 39, 747–758.

Elbert, T., Candia, V., Altenmüller, E., Rau, H., Sterr, A., Rockstroh, B., Pantev, C., Taub, E., 1998. Alteration of digital representations in somatosensory cortex in focal hand dystonia. Neuroreport 9, 3571–3575.

Elbert, T., Dobel, C., Angrilli, A., Stegagno, L., Rockstroh, B., 1999. Word vs. task representation in neural networks. Behav. Brain Sci. 22, 286–287.

Elbert, T., Flor, H., Birbaumer, N., Knecht, S., Hampson, S., Larbig, W., Taub, E., 1994. Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. Neuroreport 5, 2593–2597.

Elbert, T., Keil, A., 2000. Imaging in the fourth dimension. Nature 404, 29–30.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., Taub, E., 1995. Increased cortical representation of the fingers of the left hand in string players. Science 270, 305–307.

Fiez, J.A., Petersen, S.E., 1998. Neuroimaging studies of word reading. Proc. Natl. Acad. Sci. USA 95, 914–921.

Flor, H., Elbert, E., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., Larbig, W., Taub, E., 1995. Phantom limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 375, 482–484.

Friederici, A.D., Yves von Cramon, D., Kotz, S.A., 1999. Language related brain potentials in patients with cortical and subcortical left hemisphere lesions. Brain 122, 1033–1047.

Gold, B.T., Kertesz, A., 2000. Right hemisphere semantic processing of visual words in an aphasic patient: an fMRI study. Brain Lang. 73, 456–465.

Hagoort, P., Brown, C.M., Swaab, T., 1996. Lexical–semantic event-related potential effects in patients with left hemisphere lesions and aphasia, and patients with right hemisphere lesion without aphasia. Brain 119, 627–649.

Jasper, H.H., 1958. The ten–twenty electrode system of the International Federation. Electroenceph. Clin. Neurophysiol. 10, 371–375.

Karbe, H., Thiel, A., Weber-Luxenburger, G., Herholz, K., Kessler, J., Heiss, W.D., 1998. Brain plasticity, in post-stroke aphasia: what is the contribution of the right hemisphere? Brain Lang. 64, 215–230.

Kircher, T.T.J., Brammer, M., Andreu, N.T., Williams, S.C.R., McGuire, P.K., 2001. Engagement of right temporal cortex during processing of linguistic context. Neuropsychologia 39, 798–809.

Lazar, R.M., Marshall, R.S., Pile-Spellman, J., Duong, H.C., Mohr, J.P., Young, W.L., Solomon, R.L., Perera, G.M., DeLaPaz, R.L., 2000. Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation. Neuropsychologia 38, 1325–1332.

Luzzatti, C., Willmes, K., Bisiacchi, P., De Bleser, R., Faglia, L., Mazzocchi, A., Posteraro, L., Tarocco, M., 1987. L'Aachener Aphasie test (AAT-II): proprietà psicometriche della versione italiana. Arch. Psicol. Neurol. Psichiatria 48, 480–519.

Luzzatti, C., Willmes, K., De Bleser, R., Bianchi, A., Chiesa, G., De Tanti, A., Gonella, M.L., Lorenzi, L., Bozzoli, C., 1994. Nuovi dati normativi per la versione italiana dell'Aachener Aphasie test (AAT). Arch. Psicol. Neurol. Psichiatria 55, 1086–1131.

Moore, W.H., 1986. Hemispheric alpha asymmetries and behavioral responses of aphasic and normal subjects for the recall and recognition of active, passive, and negative sentences. Brain Lang. 29, 286–300.

Müller, R.A., Behen, M.E., Rothermel, R.D., Muzik, O., Chakraborty, P.K., Chugani, H.T., 1999a. Brain organization for language in children, adolescents, and adults with left hemisphere lesion: a PET study. Prog. Neuro-Psychopharm. Biol. Psych. 23, 657–668.

Müller, R.A., Rothermel, R.D., Behen, M.E., Muzik, O., Chakraborty, P.K., Chugani, H.T., 1999b. Language organization in patients with early and late left-hemisphere lesion: a PET study. Neuropsychologia 37, 545–557.

Musso, M., Weiller, C., Kiebel, S., Müller, S.P., Bülau, P., Rijntjes, M., 1999. Training-induced brain plasticity in aphasia. Brain 122, 1781–1790.

Ohyama, M., Senda, M., Kitamura, S., Ishii, K., Mishina, M., Terashi, A., 1996. Role of nondominant hemisphere and undamaged area during word repetition in post-stroke aphasics. Stroke 27, 897–903.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9, 97–113.

Paulesu, E., Frith, C.D., Frackowiak, R.S.J., 1993. The neural correlates of the verbal component of working memory. Nature 362, 342–345.

Price, C.J., Green, D.W., von Studnitz, R., 1999. A functional imaging study of translation and language switching. Brain 122, 2221–2235.

Pulvermüller, F., 1999. Words in the brain's language. Behav. Brain Sci. 22, 253–336.

Rockstroh, B., Elbert, T., Canavan, A., Lutzenberger, W., Birbaumer, N., 1989. Slow Cortical Potentials and Behavior. Urban and Schwarzenberg, Munich.

Selinger, M., Prescott, T.E., Suchard, D.W., 1989. Auditory event-related potential probes and behavioral measures of aphasia. Brain Lang. 36, 377–390.

Snyder, A.Z., Abdullaev, Y.G., Posner, M.I., Raichle, M.E., 1995. Scalp electrical potentials reflect regional cerebral blood flow responses during processing of written words. Proc. Natl. Acad. Sci. 92, 1689–1693.

Stefan, K., Kunesch, E., Cohen, L.G., Benecke, R., Classen, J., 2000. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123, 572–584.

Sterr, A., Müller, M.M., Elbert, T., Rockstroh, B., Pantev, C., Taub, E., 1998. Changed perceptions in Braille readers. Nature 391, 134–135.

Stevens, J., 1990. Intermediate Statistics: A Modern Approach. Erlbaum, Hillsdale.

Swaab, T., Brown, C., Hagoort, P., 1997. Spoken sentence comprehension in aphasia: event-related potential evidence for a lexical integration deficit. J. Cogn. Neurosci. 9, 39–66.

Thomas, C., Altenmüller, E., Marckmann, G., Kahres, J., Dichgans, J., 1997. Language processing in aphasia: changes in lateralization patterns during recovery reflect cerebral plasticity in adults. Electroenceph. Clin. Neurophysiol. 102, 86–97.

Thompson-Schill, S.L., D'Esposito, M., Aguirre, G.K., Farah, M.J., 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a re-evaluation. Proc. Natl. Acad. Sci. USA. 94, 14792–14797.

Warburton, E., Price, C.J., Swinburn, K., Wise, R.J.S., 1999. Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. J. Neurol. Neurosurg. Psychiatry 66, 155–161.

Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Müller, S., Bier, D., Dutschke, K., Woods, R., Noth, J., Diener, H.C., 1995. Recovery from Wemicke's aphasia: a positron emission tomographic study. Arch. Neurol. 37, 723–732.

Zatorre, R.J., Evans, A.C., Meyer, E., Gjedde, A., 1992. Lateralization of phonetic and pitch discrimination in speech processing. Science 256, 846–849.