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Language plasticity in aphasics after recovery: Evidence from slow evoked potentials

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With the present experiment we sought to investigate brain plasticity underlying language recovery in a group of seventeen patients with non-fluent aphasia mainly caused by stroke. Patients were screened along three domains of measures: analysis of linguistic components by the Aachener Aphasie Test, combined mapping of their lesion from CT/MRI scans, and functional measure of the reorganized linguistic processes by means of mapping of slow evoked potentials. The spatial dimension and temporal dynamics of word processing were measured in three tasks, Phonological, Semantic and Orthographic. Compared with the matched control group, patients showed relative inhibition (decreased negativity) of left central regions in perisylvian areas, which were damaged in most subjects. In addition, reorganization of linguistic functions occurred within the left hemisphere both at frontal and posterior sites corresponding to spared brain regions. Correlations between linguistic lateralization in the three tasks and AAT subtests point to functional reorganization of phonological processes over left frontal sites and dysfunctional reorganization of semantic processing over left posterior regions.

Keywords: Aphasia; Language; Brain plasticity; Lateralization; Evoked potentials; Contingent negative variation; Phonology; Semantics

Introduction

Both behavioral and brain imaging experiments have illustrated the plastic potential of the adult brain in both healthy subjects (Angrilli et al., 2001; Elbert et al., 1994, 1995; Flor et al., 1995; Raichle et al., 1994; van Turennout et al., 2000) and brain-damaged individuals (Angrilli et al., 2003; Belin et al., 1996; Breier et al., 2004; Cornelissen et al, 2003; Hagoort et al, 1996, 2003; Musso et al., 1999; Pulvermüller et al., 2004; Small et al., 1998). However, the exact cortical mechanisms underlying recovery and rehabilitation of higher-order neurocognitive disorders, such as aphasia, still remain poorly understood. In particular, the relationship between behavioral changes and co-occurring cortical reorganization of language in aphasics is largely unknown. Identifying mechanisms underlying this recovery is difficult, but determining the neural substrate of recovery and its relationship with specific aspects of word processing may provide important indications for language intervention. Strong evidence from clinical and neuroimaging brain plasticity studies on aphasic patients suggests that potential substitutes of functional recovery include either homologous right hemisphere areas (e.g., Belin et al., 1996; Thomas et al., 1997; Musso et al., 1999), undamaged portions of linguistic networks in the left hemisphere (e.g., Karbe et al., 1998; Warburton et al., 1999; Kessler et al., 2000) or both (e.g., Cappa, 2000; Cardebat et al., 2003; Jodzio et al., 2005; Price and Crinion, 2005; Saur et al., 2006). However, it is possible that past neuroimaging results depended on activation of the right and left hemispheres at different times of linguistic processing. It is still difficult to analyze the time-course of word processing with metabolic instruments such as fMRI and PET, yet this dimension is of special interest, as language plasticity involves the activation of neural networks, which succeed one after the other within tens of milliseconds.

From this view, several studies have been carried out using Event-Related Potentials (ERPs) to analyze the time-course and distribution of electrical activity over the scalp in functionally recovered aphasic patients (e.g., Altenmüller et al., 1993; Angrilli et al., 2003; Angrilli and Spironelli, 2005; Dobel et al., 2001, 2002; Friederici et al., 1999; Hagoort et al., 2003; ter Keurs et al., 1999; Thomas et al., 1997). However, only a few of these studies used an ERP paradigm devised to assess lateralization in specific linguistic tasks. For example, during a synonym generation task, Altenmüller et al. (1993) and Thomas et al. (1997) recorded slow negative potentials which were greater over the left than the right frontocentral cortical regions of aphasic patients. In their recent study with non-fluent aphasics, Angrilli et al. (2003) investigated cortical reorganization mechanisms by contrasting a rhyming and semantic judgment task. In aphasic patients, ERPs revealed clearcut reorganization of linguistic functions, which included both the cortical

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spatial dimension and the time-course of processing. In detail, during word reading, controls showed occipital activation in both linguistic tasks, whereas patients exhibited strong left-medial orbitofrontal involvement anteriorly to common damaged areas during the Phonological task, and bilateral orbitofrontal activation in the Semantic task. Analysis of the subsequent 2-s interval, associated with word encoding in working memory, revealed a pattern reversed between groups: significant left lateralization in controls and bilateral activation in patients, who showed greater inhibition over left frontal damaged regions, particularly during phonological processing. Very interestingly, patients revealed greater left posterior activation than controls in both tasks: this finding suggests that brain plasticity mechanisms are also involved in linguistic functions relatively spared by aphasic damage.

With respect to a prior experiment on ten aphasics (Angrilli et al., 2003), in the present study we collected a larger sample of non-fluent aphasics, added a control Orthographic task (Spironelli and Angrilli, 2006) and analyzed more intervals. In order to identify reorganization of aphasics' linguistic lateralization as functional or dysfunctional, we also correlated electrophysiological laterality indices with performance scores on the Aachener Aphasie Test (AAT), i.e., the linguistic test administered for assessing language recovery.

Materials and methods

Participants

Seventeen aphasic patients (nine women, mean age 49.35± 14.8 years, mean education 10.8 years) were recruited from the Padova section of A.IT.A (Associazione ITaliana Afasici, Italian Aphasic Association). All patients had been suffering from a single cerebrovascular accident of the perisylvian cortex in the left hemisphere; six patients had become aphasic after ischemic stroke, ten after hemorrhage, hemorrhagic stroke or arteriovenous malformation, and one patient as a consequence of head trauma. The average time since the vascular event was 44.5 months (range: 6–198 months). Patients had been diagnosed as non-fluent aphasics during the acute phase, on the basis of both CT/MRI documentation of the cortical lesion and neurological symptoms exhibited. Prior to the experimental session, all patients were also tested for language deficits by means of the Aachener Aphasie Test (AAT), validated for the Italian language (Luzzatti et al., 1987, 1994). On average, in AAT subtests, aphasics demonstrated a very mild deficit to Repetition and Written Language (59.8 and 61.9 transformed t scores, respectively), but reached the no-deficit level on the Token Test (63.5), Denomination (70.6) and Comprehension (64.2), thus showing substantial recovery of linguistic functioning.

Patients' lesion maps were made by the method of Damasio and Damasio (1989), starting from individual cortical CT or MRI scans of each patient. These scans were accurately mapped onto standard templates which ranged from A1 to A4 scan slopes, as suggested by Damasio and Damasio (1989). Template sets of all patients were then matched by means of an *ad hoc* Matlab program, in order to average individual templates in inclusive lesion mapping. In this way, the program drew a map in which each voxel representing a level of gray corresponded to lesion density (i.e., number of lesions falling within that specific voxel, a measure which spanned from 2 to 11 lesions in the final map). Fig. 1 shows the number of overlapping lesions, within patients' left hemisphere, projected in lateral and horizontal views. Different color intensity, ranging from pale gray to black, indicates the increasing number of patients with cortical/subcortical lesions in that voxel.

Eighteen healthy volunteers, matched for sex (eight women), age (mean: 55.55±10.2 years) and educational level (mean: 11.5 years) served as control group. Patients were on average 93% right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971), before the cerebral accident, a value very close to that of control subjects, who were on average 96% right-handed. Each participant also performed a digit span test in order to verify the extent of verbal working memory: compared with controls, aphasic patients showed significantly smaller digit span (6.00 vs. 4.56, respectively; $t(33)=4.20$, $p<0.001$). All subjects gave their informed consent to the study, according to the Declaration of Helsinki. Experimental procedures were approved by the local Ethics Committee.

Stimuli, tasks and procedure

Stimuli consisted of bi- or trisyllabic Italian content words selected from a frequency dictionary of 5000 written Italian words (Bortolini et al., 1972). Words were presented in pairs on a 17-in.

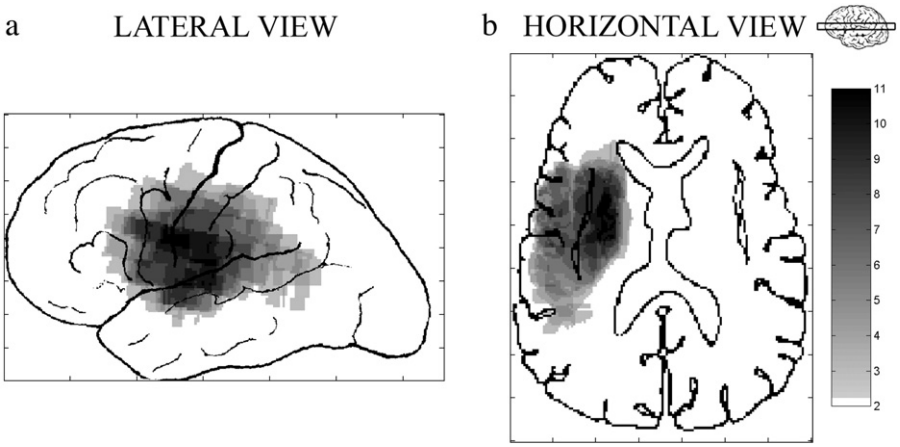

Fig. 1. Maps of lesions from 17 non-fluent aphasics projected: (a) on lateral view of left hemisphere, and (b) on horizontal view: colors from pale gray to black mark increasing number of patients with cortical/subcortical lesions.

computer monitor one at a time (see trial structure in Fig. 2a) with an inter-stimulus interval of 2 s: the first word (W1) remained on the screen for 1 s and the second word (W2 or target) until the subject responded by pressing a keyboard button, in any case no longer than 5 s. Word pairs were administered in three separate blocks, which corresponded to three linguistic tasks: thus, the same words were presented as W1, but in different randomized order across tasks. In the Phonological task, upon W2-target presentation, subjects had to decide whether word pairs rhymed (e.g., brodo-chiodo [broth-spike]) or not (e.g., neve-corda [snow-rope]); in the Semantic task, they had to judge whether target word W2 was of the same semantic category as W1 (e.g., brodo-minestra [broth-soup]) or not (e.g., neve-sveglia [snow-alarm]); in the Orthographic task (used as control) they had to decide whether word pairs were written in the same case (e.g., BRODO-FRUTTA [BROTH-FRUIT]) or not (lower vs. upper cases or vice versa, i.e., neve-PALESTRA [snow-GYMNASIUM]; Spironelli and Angrilli, 2006). For motor responses, subjects used their left index or middle finger to press the keyboard buttons corresponding to match–mismatch conditions. Each task included 80 trials/word-pairs. In all tasks, 50% matches were randomly interspersed with 50% mismatch trials. The task order was randomly varied across subjects.

Data recording and analysis

EEG cortical activity was recorded by 26 tin electrodes, 19 placed on an elastic cap (Electrocap) according to the International 10–20 system (Oostenveld and Praamstra, 2001); the other 7 electrodes were applied below each eye (Io1, Io2), on the two external canthi (F9, F10), nasion (Nz) and mastoids (M1, M2). All cortical sites were on-line referred to Cz. Data were stored using the acquire software NeuroScan 4.1 version. Amplitude resolution was 0.1 μV; bandwidth ranged from DC to 100 Hz (6 dB/octave). Sampling rate was set at 250 Hz, and impedance was kept below 5 KΩ.

Behavioral measures collected from each subject included error rates and response times to the second stimulus. EEG was continuously recorded in the DC mode and stored for following analysis. Data were off-line re-referenced to the average reference, and epoched into 13-s intervals, including 1 s before and 12 s after W1. To eliminate slow DC drifts, a linear detrend was performed on each epoch and channel. A 100-ms baseline preceding W1 was subtracted from the whole trial epoch. Single trials were corrected for eye movement artifacts, i.e., vertical and horizontal movements, and blinking. For this, BESA software (Brain Electrical Source Analysis, 5.1 version) was used to compute ocular correction coefficients, according to Berg and Scherg (1991, 1994). Each trial was then visually inspected for any residual artifacts: overall, 47% of trials were rejected (i.e., 48% from controls and 46% from aphasic patients). In addition, data were normalized in order to improve the signal-to-noise ratio, and to contrast groups regardless of individual levels of cortical activation. To contrast different time intervals corresponding to specific phases of word processing, three functional windows were chosen for data analysis (Fig. 2a): the last 0.5 s of W1 presentation, the first second of the Inter-Stimulus Interval (ISI) after W1 offset, the last second of the ISI. According to other studies which investigated slow ERPs using the W1–W2 paradigm (Angrilli et al., 2000; Birbaumer et al., 1990; Rockstroh et al., 1989; Rösler et al., 1997; Ruchkin et al., 1997; Spironelli and Angrilli, 2006), we separated the early Contingent Negative Variation (CNV) component, termed initial CNV (iCNV) and corresponding to the 1–2 s interval following W1 onset, from the late CNV component, termed terminal CNV (tCNV) and corresponding to the 2–3 s interval following W1 onset. Thus, we referred to the iCNV as an index of cognitive operations closely related to stimulus encoding (Ruchkin et al., 1988, 1997) in verbal working memory (Birbaumer et al., 1990; Rösler et al., 1997), and to the tCNV as an index of both W1 rehearsal and motor response preparation (Birbaumer et al., 1990; Rockstroh et al., 1989; Rösler et al., 1997). Maps were obtained by means of spline interpolation methods (Perrin et al., 1989).

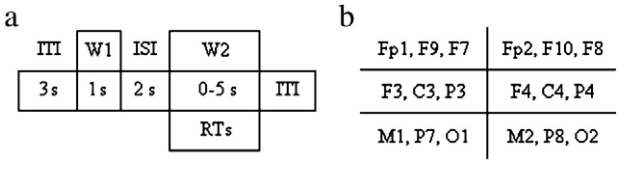

Fig. 2. Diagram showing (a) trial structure with first word presented (W1), Inter-Stimulus Interval (ISI), Inter-Trial Interval (ITI), and second word (W2); (b) the six clusters of electrodes entering statistical analysis.

According to past literature on slow evoked potentials and CNV, cortical negativity is considered as an index of relative brain activation and cortical positivity as indicative of relative brain inhibition (Angrilli et al., 2000, 2003; Birbaumer et al., 1990; Rockstroh et al., 1989; Spironelli and Angrilli, 2006).

CNV task-specific lateralization patterns were evaluated by means of analysis of variance (ANOVA) comparing, across time intervals, the average amplitude measured in six groups of electrodes, each representing a region of interest. On the basis of aphasics' lesion maps and after visual inspection of grand-average waveforms, six clusters with the average activity of three electrodes were selected (Fig. 2b): Anterior Left (AxLx: Fp1, F9, F7), Anterior Right (AxRx: Fp2, F10, F8), Central Left (CxLx: F3, C3, P3), Central Right (CxRx: F4, C4, P4), Posterior Left (PxLx: M1, P7, O1) and Posterior Right (PxRx: M2, P8, O2).

Four within-subjects factors entered the ANOVA: Interval (three levels: W1 vs. iCNV vs. tCNV), Task (three levels: Orthographic vs. Phonological vs. Semantic), Region (three levels: Anterior vs. Central vs. Posterior) and Laterality (two levels: Left vs. Right hemisphere). Post-hoc comparisons were computed using the Tukey HSD test ($p<0.05$), and the Greenhouse–Geisser correction was applied when necessary. With ERPs, the relative difference of activation across regions within the same group is more reliable than the absolute electrical difference between groups: for this reason, we focused our attention on patients' patterns of lateralization rather than on absolute ERP group effects.

In addition, for the patient group only, Pearson's correlation analysis was performed between AAT scores and laterality indices, obtained during task processing, in order to identify whether (and eventually which) AAT subtests could represent a behavioral correlate significantly linked to cortical reorganization. The laterality score was computed as the difference of the mean activity of right (electrodes: Fp2, F8, F10) minus left (electrodes: Fp1, F7, F9) anterior clusters; similar lateralization scores were also computed for both central [right (electrodes: F4, C4, P4) minus left (electrodes: F3, C3, P3) central quadrants] and posterior clusters [right (electrodes: M2, P8, O2) minus left (electrodes: M1, P7, O1) posterior quadrants]. Thus, the laterality score is a positive value when cortical activity is left-lateralized, and negative when it is right-lateralized. Therefore, positive correlations mark those patients with

higher scores on linguistic subtests, indexing recovery, and higher cortical lateralization scores, corresponding to greater left hemisphere activation for that specific task-dependent processing.

Results

Patients' lesion map

For most patients, the left lateral view of the lesion map (Fig. 1a) revealed core damage of the frontal operculum (BA 44), inferior agranular frontal gyrus (BA 6), lateral inferior portion of pre- and post-central gyri (BAs 4, 1) and central portion of the superior temporal gyrus (BAs 41–42). In a small number of aphasics, lesions also spread to the triangular area (BA 45), posterior granular frontal gyrus (BA 9), anterior supramarginal gyrus (BA 40) and posterior portion of the superior temporal gyrus (BAs 22–42). In addition, deep lesions affected the putamen, insula, internal capsulae and head of the caudate nucleus in the left hemisphere of most patients (Fig. 1b), and significant damage was found to both corona radiata fibers and superior longitudinal fasciculus, besides the inferior frontal gyrus.

Behavioral data

Performance analyses showed slower responses in aphasics (mean: 1547 ms) than controls (mean: 979 ms; Group: $F(1,32)=19.86$, $p<0.001$). Moreover, in both groups, response times were longer for both the Semantic (1493 ms) and Phonological (1364 ms) than for the Orthographic task (931 ms; Task: $F(2,64)=45.09$, $p<0.001$, GG $\varepsilon=0.90$).

The two-way Group by Task interaction (Fig. 3) revealed that aphasics were slower on the Semantic (1904 ms) and Phonological (1734 ms) tasks than on the Orthographic one (1002 ms), whereas healthy controls did not show any differentiation (1082 vs. 993 vs. 860 ms, respectively; Group by Task: $F(2,64)=16.94$, $p<0.001$, GG $\varepsilon=0.90$). Groups did not show any difference in error rates.

Electrophysiological data

Fig. 4 shows ERP spline interpolated maps of controls and aphasic patients during the three phases of word processing. Looking at the time-course of the Phonological task (Fig. 4, second row),

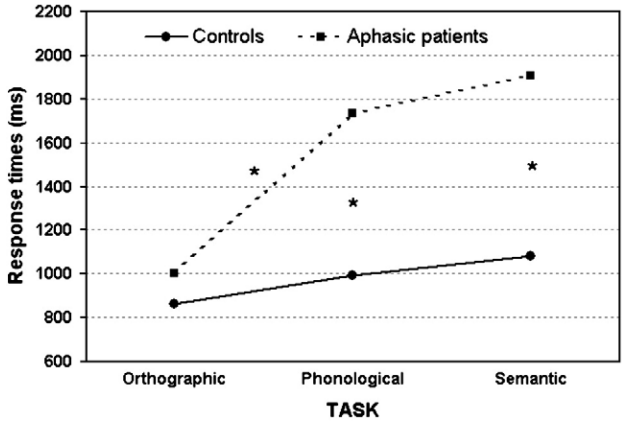

Fig. 3. Analysis of Response Times (RTs): significant two-way Group by Task interaction. Asterisks: significant post-hoc comparisons.

controls showed increasing negativity over the whole left hemisphere, which peaked during the tCNV interval. Instead, aphasic patients always exhibited larger left than right negativity on both anterior and posterior sites, showing clearcut greater positivity than controls, especially over left central locations.

During the Semantic task (Fig. 4, last row), the control group revealed bilateral activation at both central and posterior locations. Similar to the Phonological task, also in the Semantic task maximum negativity emerged over central sites during the last interval (tCNV). Unlike controls, aphasic patients showed greater left than right lateralization in all cortical regions and time windows, exhibiting greater positivity on right central-posterior regions, especially during W1 and iCNV intervals. Instead, during the Orthographic control task (Fig. 4, first row) both groups revealed a relatively similar pattern of activation, marked by left negativity in all cortical regions during the W1 interval, and narrowing over left anterior and central sites during CNV intervals.

ANOVA computed on normalized ERPs showed the significant main effects of all within-subjects factors. Thus, independent of group, greater negativity was found in either W1 or iCNV intervals compared with tCNV ($p<0.001$; Interval: $F(2,66)=9.15$, $p<0.01$, GG $\varepsilon=0.63$); either the Phonological or the Semantic task elicited greater negativity than the Orthographic one ($p<0.01$; Task: $F(2,66)=7.89$, $p<0.001$, GG $\varepsilon=0.93$), and either central or posterior regions showed more negativity than anterior areas ($p<0.01$; Region: $F(2,66)=6.42$, $p<0.01$, GG $\varepsilon=0.74$). Significant greater negativity in the left vs. right hemisphere emerged (Laterality: $F(1,33)=49.33$, $p<0.001$).

Concerning interactions, the five-way Group by Interval by Task by Region by Laterality interaction ($F(8,264)=2.51$, $p<0.05$, GG $\varepsilon=0.50$) revealed specific cortical activation by aphasics and controls in every task. During the Phonological task (Fig. 5a), controls showed significant greater left than right negativity in both anterior and central brain regions ($p<0.001$), at all time intervals. Posterior locations were also left-lateralized ($p<0.001$), but only during the W1 epoch.

Across intervals, controls' posterior regions were significantly more negative than central-anterior areas at the beginning of linguistic processing ($p<0.001$), and negativity then decreased in the following intervals. Instead, central sites exhibited increasing negativity across time, reaching the significantly greatest negative peak than either anterior or posterior sites during tCNV ($p<0.001$; see Fig. 4, left side, and Fig. 5a). To provide a better view of the time-course of linguistic processes, grand-average waveforms of both controls and patients were clustered in six regions of interest (Fig. 6). The mentioned greater negativity of controls, compared with aphasic patients, was particularly clearcut over central sites during the 1.5- to 3.5-s interval (Fig. 6a, dark gray lines).

A different pattern of activation emerged in controls' semantic processing (Fig. 5c): subjects revealed consistent, significantly left lateralization, sustained in all intervals, only at anterior locations ($p<0.01$), but stable bilateral negativity in both central and posterior sites (Fig. 6a, black lines). As in the earlier phases of word processing (W1 and iCNV conditions) of the Phonological task, during the Semantic task the greater negativity of posterior compared with both anterior and central regions ($p<0.001$) was also observed. Instead, during tCNV, the central areas were significantly more negative with respect to either posterior or anterior sites ($p<0.001$).

Independently of cortical region or time window, aphasic patients always showed greater left than right negativity during both Phonological ($p<0.001$; Fig. 5b) and Semantic tasks ($p<0.001$;

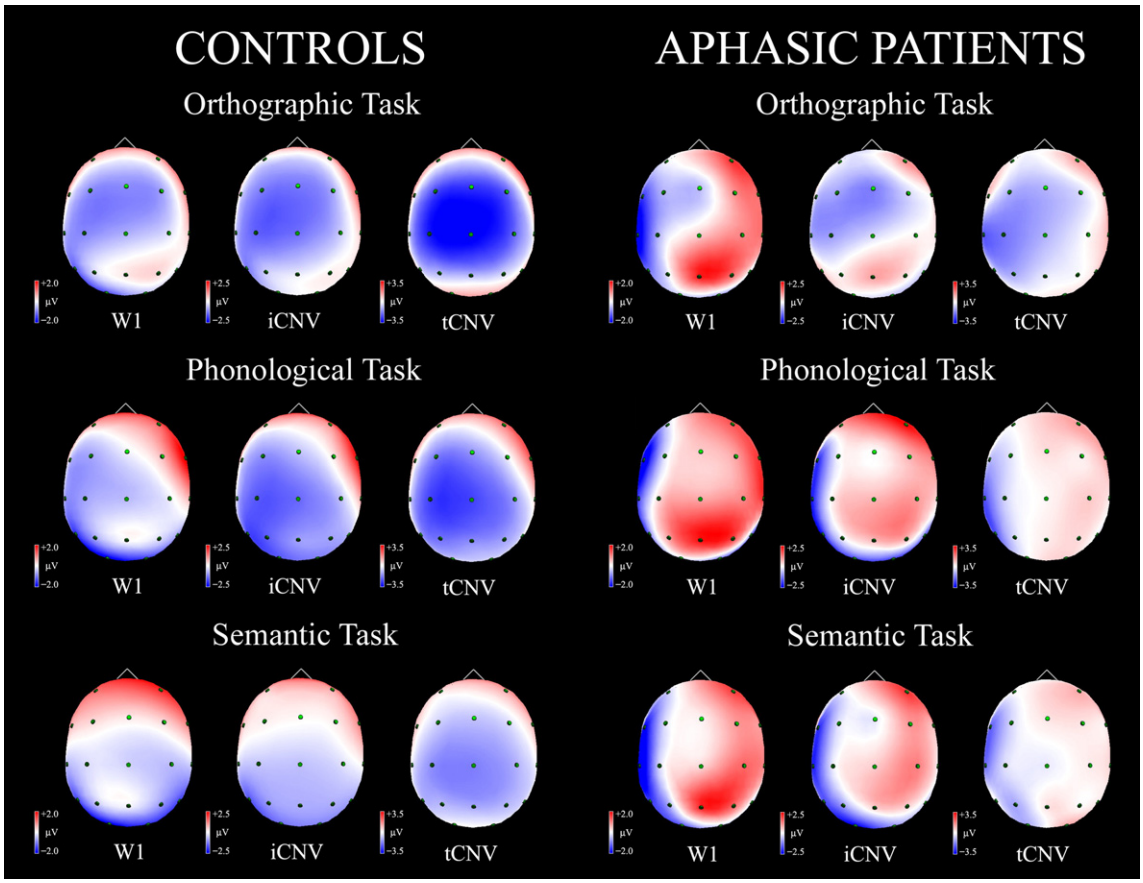

Fig. 4. Spline interpolated maps representing scalp top view of mean potential recorded in W1 (0.5- to 1-s epoch), iCNV (1- to 2-s epoch) and tCNV (2- to 3-s epoch) conditions for Controls (left) and Aphasic patients (right), during Orthographic (upper row), Phonological (middle row) and Semantic task (lower row).

Fig. 5d). However, the most clearcut and important differences between controls and aphasics were found during the first two intervals of phonological processing, in which relative reduced negativity was found in left central locations (corresponding to the areas of maximum lesion, Fig. 1b) compared with posterior ($p<0.001$) and (only at W1 interval) anterior clusters ($p<0.001$; Fig. 6b, black lines). Late phases of word processing (tCNV condition) revealed greater negativity in left anterior and central clusters compared with posterior sites only during the Semantic task ($p<0.001$; Fig. 5d).

In the Orthographic task, both samples showed significantly left lateralization of all cortical regions during W1 condition ($p<0.05$ for controls, $p<0.001$ for patients), and greater left negativity only over anterior and central sites during the following CNV intervals (all $p<0.01$). Instead, the posterior clusters revealed bilateral activation, which did not differ between groups (Fig. 4, upper row; Fig. 6, light lines). Very interestingly, only during the tCNV condition of this task did aphasic patients show significantly increased negativity over central regions, in comparison with both anterior and posterior areas ($p<0.001$) — a result comparable with that of controls (Fig. 4, upper row).

Pearson's correlations

This analysis, made only on patients' data, provided essential information for interpreting aphasics' language hemispheric reorganization. Pearson's correlations were computed between transformed t-points, from patients' AAT, and laterality scores, obtained from slow evoked potentials in the three intervals of task processing. As mentioned above, positive correlations indicate that activities in the left hemisphere are correlated with greater linguistic performance to an AAT subtest (Token Test, Repetition, Written Language, Denomination or Comprehension). In other words, we expected EEG activity in the Phonological task to be correlated with the Repetition subtest, and EEG activity during semantic processing to be correlated with the other subtests (Token Test, Written Language, Denomination), particularly Comprehension, all requiring activation of semantic networks at some level. Thus, a positive correlation provides strong evidence in favor of the functional reorganization of linguistic function because of its link with the unidirectional hypothesis and correlation between different domains of left hemisphere functions. Instead, negative correlations do not provide a comparable clearcut functional interpretation, as there is no unidirectional hypothesis on the right hemisphere and linguistic functions within it. Therefore, negative correlations may be interpreted either as markers of dysfunctional plasticity (i.e., greater left activity is associated with lower linguistic subtest performance) or as marker of functional reorganization/substitution in the right hemisphere (i.e., greater right activation is associated with greater linguistic subtest performance). Due to this essential ambiguity and the hypothesis underlying the present experiment, negative correlations are less important and clearcut than positive ones. To avoid inflation of significant results due to multiple comparisons, we only considered a result as important if two or more

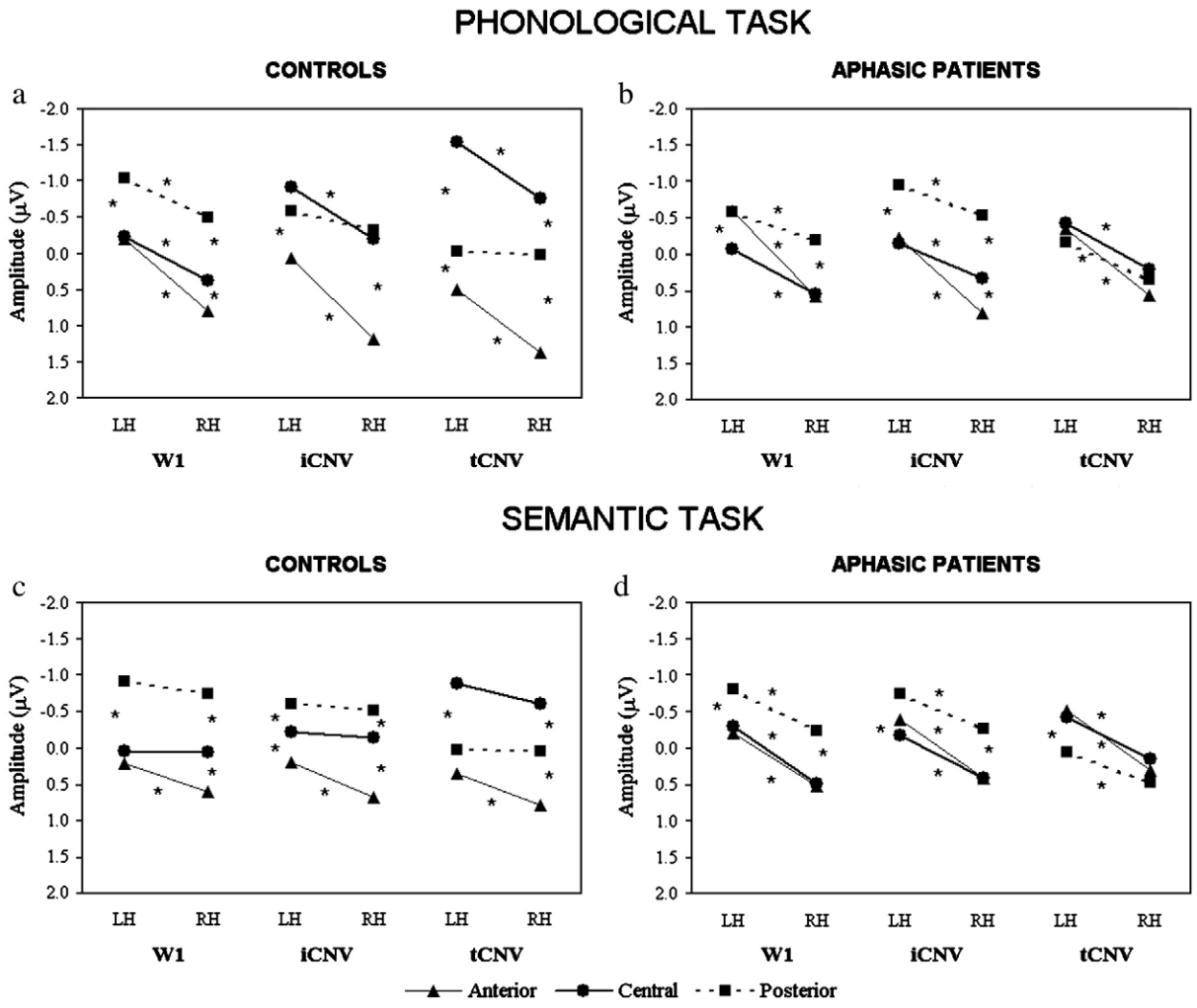

Fig. 5. Evoked Potential analysis: significant five-way Group by Interval by Task by Region by Laterality interaction. Phonological (a, b) and Semantic (c, d) tasks are depicted for Controls (a, c) and Aphasic patients (b, d). Asterisks: significant post-hoc comparisons.

correlations were significant in adjacent cortical regions (i.e., anterior, central, posterior) or adjacent time intervals (i.e., W1, iCNV, tCNV).

For the Phonological task, an interesting and clearcut correlation result concerned the last interval tCNV: two significant positive correlations between the laterality scores of the anterior and central clusters and the Repetition subtest were found ($r=0.51$, $p<0.05$ and $r=0.54$, $p<0.05$, respectively). The more left-lateralized the anterior and central regions, the higher the score reached during the Repetition subtest (Figs. 7a and b, respectively).

In the Semantic task, only negative correlations in posterior sites emerged: with Comprehension subtest in the W1 and iCNV intervals ($r=-0.58$, $p<0.01$ and $r=-0.54$, $p<0.05$ respectively), and with Token Test in the iCNV and tCNV intervals ($r=-0.49$, $p<0.05$, and $r=-0.52$, $p<0.05$ respectively).

Discussion

The present study aimed at measuring the spatial and temporal dimensions of functional cortical reorganization after language recovery in seventeen non-fluent aphasic patients. To this end, we contrasted three tasks which have been successfully demonstrated to activate specific functional and neuroanatomical linguistic networks (Angrilli et al., 2000, 2003; Elbert et al., 1999; Penolazzi et al., 2006; Spironelli and Angrilli, 2006): the rhyming task was used to enhance phonological processing and activate cortical circuits close to Broca's area (Paulesu et al., 1993; Zatorre et al., 1992). Because of their brain damage, it was expected that non-fluent aphasics would be relatively impaired on this task. More generally, in agreement with previous studies (Angrilli et al., 2003; Angrilli and Spironelli, 2005), the functional redistribution of the whole linguistic network was foreseen in relatively spared areas within the left hemisphere. With respect to early evoked potentials, for which interpretation of negativity–positivity as activation is more ambiguous, slow negative potentials are less ambiguous indices of superficial cortical layer activity (Angrilli et al., 2000, 2003; Birbaumer et al., 1990; Rockstroh et al., 1989; Spironelli and Angrilli, 2006). In line with past literature (Angrilli et al., 2000; Spironelli and Angrilli, 2006), statistical analysis revealed that controls recruited task-specific cortical networks which were differentiated across intervals: thus, phonological processing showed increasing activation across time of left anterior and central regions (Fig. 5a), whereas semantic categorization involved bilateral activation, spreading to both central and posterior locations (Fig. 5c).

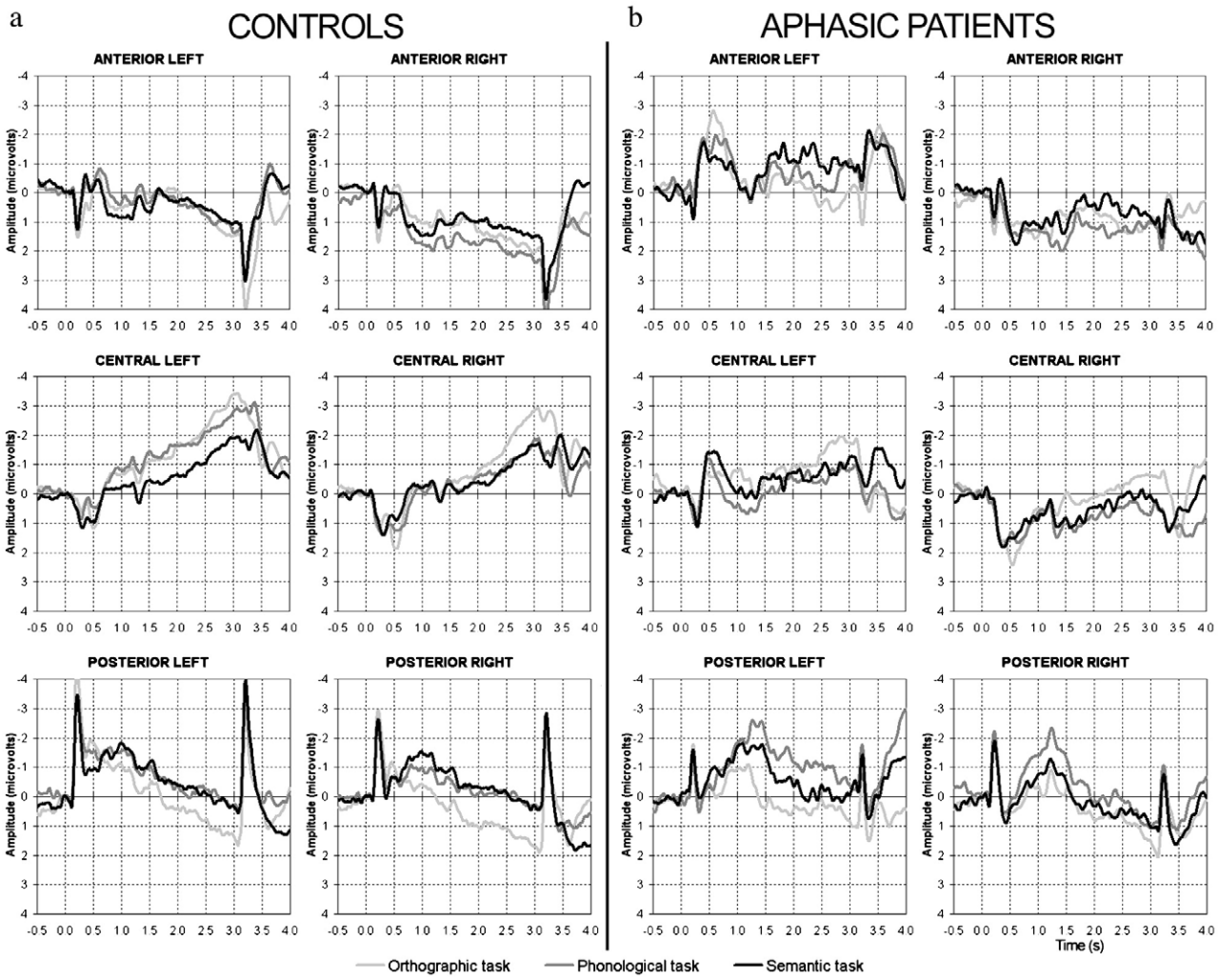

Fig. 6. Grand-average waveforms of all regions of interest showing time-course of linguistic processing in (a) Controls and (b) Aphasic patients during Orthographic (pale gray line), Phonological (dark gray line) and Semantic (black line) task. Negativity is displayed toward top.

Instead, aphasics exhibited a very similar pattern of cortical activation on the Phonological and Semantic tasks, showing greater left lateralization of anterior and posterior areas than controls (Figs. 5b, d). At the same time, during W1 processing, patients exhibited marked inhibition of left central compared with posterior and frontal sites, which extended to the following iCNV interval. In these two intervals, patients' left posterior sites also showed the greatest negativity/activation. This antero-posterior asymmetry was inverted with respect to controls: indeed, during the Phonological task, they showed increasing left central negativity/activation across intervals with respect to left posterior and anterior sites, which peaked in the last interval. It is important to note that the location of aphasics' maximum lesion was consistently associated, at functional level, with relative inhibition of left central region compared with left anterior and posterior areas, and this occurred in the precise task which was most specifically impaired in non-fluent aphasics, i.e., the Phonological task.

These findings highlight not only the importance of patients' damage in clarifying relationships between brain and behavior (Clark et al., 2005; Damasio et al., 1996; Nestor et al., 2003), but also the mechanisms which are specifically involved in brain plasticity (Bates et al., 2003). With regard to their lesions, most aphasics revealed greater damage of several deep structures within the left hemisphere, such as insula, putamen and internal capsule (Fig. 1b). In addition, the disruption of fiber bundles from cerebral white matter, such as corona radiata and the superior longitudinal fasciculus, a tract which connects the frontal cortex with parieto-occipital and temporal regions, may have substantially interfered with patients' functional recovery. In this case, the redistribution of linguistic functions to unimpaired superficial cortical areas may be the most parsimonious explanation of the observed results. As Fig. 1 shows, the posterior portion of Broca's area was only partially damaged: whereas the opercular area (BA 44) was severely damaged, most patients showed relative sparing of the triangular area (BA 45). This anterior part of Broca's area may be the strategic center for developing a new, functionally reorganized, linguistic network able to control most aspects of language. Unlike the control group, aphasics exhibited clearcut left lateralization even when they processed and categorized semantic stimuli (Fig. 5d) through the activation of both anterior and posterior left regions. This finding is in agreement with recent fMRI literature aimed at studying the semantic system organization in the adult brain (Bookheimer, 2002): in particular, semantic processes, elicited in most experiments, clustered around the *pars orbitalis* (BAs 47/45) in the an-

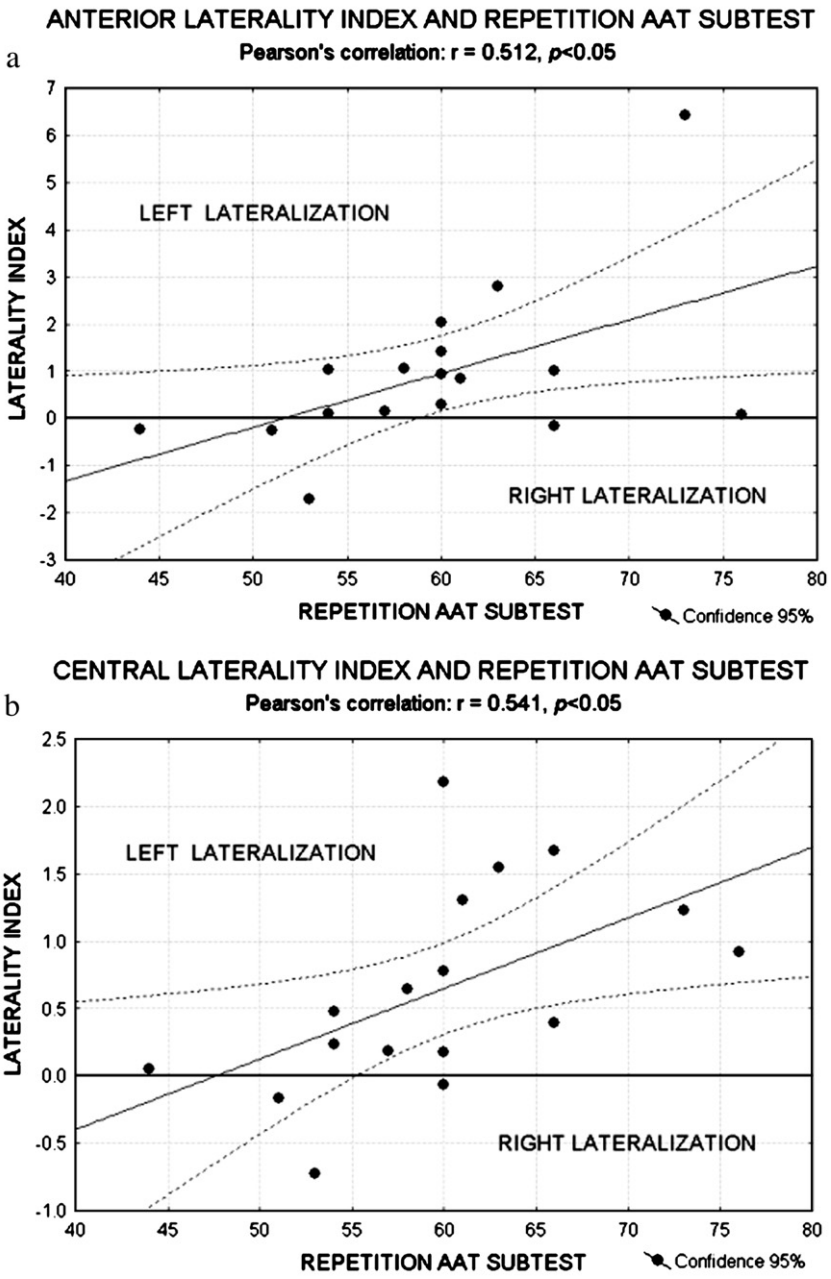

Fig. 7. Positive Pearson's correlation between laterality scores of anterior sites, referred to (a) anterior and (b) central Phonological tCNV activation and Repetition AAT subtest.

terior region of the inferior frontal gyrus (IFG). The present data are also in line with past neuroimaging literature, in which language recovery was suggested to occur in a pre-existing temporo-frontal network by upregulation of the remaining, undamaged tissue within the left hemisphere (e.g. Karbe et al., 1998; Kessler et al., 2000; Müller et al., 1999; Warburton et al., 1999). Moreover, there is growing recent evidence which supports the idea that Broca's area and, more generally, the left IFG, plays an important role in unification processes (Hagoort, 2005), able to organize not only linguistic functions but also hierarchically structured behaviors (Koechlin and Jubault, 2006). The activation pattern shown by aphasic patients may represent effective linguistic reorganization in the intact anterior portion of Broca's area (i.e. the *pars triangularis*, BA 45), as the same cortical regions were not activated by the control task, which required only visuo-perceptual word matching. In both groups, the Orthographic task elicited very similar patterns of cortical activation, with more distributed and bilateral negativity – compared with the other two tasks – also in aphasics (Fig. 4). This argument is strengthened by results on behavioral performance: on average, patients revealed a general slowing of response times during both the Phonological and Semantic tasks, but they were comparable to controls in the Orthographic one (Fig. 3).

At first glance, the two linguistic tasks – Semantic and Phonological – elicited similar lateralization patterns in patients, a result which could lead to the conclusion of a non-specific reorganization

of language due to stroke. However, as shown in Fig. 5b, in the Phonological task aphasics had relatively greater left lateralization in anterior than in central sites at both W1 (see post-hoc comparison of anterior vs. central clusters within the left hemisphere) and iCNV (see post-hoc comparison of anterior vs. central clusters within the right hemisphere). Controls exhibited greater lateralization, very similar to that shown by patients, in anterior and central locations (Fig. 5a), but central clusters also showed an overall increasing negativity across intervals (i.e., the typical CNV develop). Conversely, during the Semantic task, aphasics showed overlapped cortical activity in anterior and central sites and comparable left lateralization, which extended to all intervals (Fig. 5d). Thus, only during the Phonological task were patients' left frontal sites more left-lateralized than central sites. This effect, related to the core damage of the left perisylvian regions, and to the positive correlation with Repetition subtest (see below), can be interpreted as a functional shift of activity over left intact anterior sites, in agreement with our previous experiment on another sample of aphasics characterized by more anterior lesions including the whole of Broca's area (Angrilli et al., 2003).

Other interesting suggestions arise from correlations between the EEG laterality indices of each task and AAT subtest scores. Detecting the common linguistic features between our tasks and each AAT subtest is very important, as it allows us to draw general conclusions about the functional meaning of the mechanisms involved. In this view, in our tasks the same word sample was used, and therefore different associations between our experimental manipulations and AAT subtests pinpoint specific connections of linguistic functioning across the same verbal material.

Correlational analyses may be interpreted and summarised in two main findings. The first most important result was the positive correlation between anterior/central left lateralization during the tCNV of phonological processing, and the score on the Repetition subtest (Figs. 7a, b): this finding highlights the main role of left anterior areas in the recovery of phonological encoding, which is necessarily associated with an efficient articulatory process and with repetition. For this sample, indeed, repetition was the most impaired linguistic function found in the AAT test (Repetition subtest: mild impairment), thus suggesting that, among all subtests, this was probably the component most affected in the acute phase following brain damage. This is also consistent with the observation in most patients of deep fiber lesions which included both corona radiata and superior longitudinal fasciculus. This specific type of lesion disconnects posterior and anterior linguistic centers and especially affects repetition processing: the significant correlation between left frontal lateralization and Repetition AAT performance suggests that part of the damaged subcortical linguistic pathway was probably substituted by the most superficial intact cortical areas within the left hemisphere (see lesion map in Fig. 1).

A second, less strong and clearcut (as already mentioned a negative correlation does not allow a clear functional interpretation as a positive one) result was the negative correlation found between left posterior lateralization in the Semantic task and Token Test/Comprehension subtests. All correlations involving semantic processing indicate that patients with greater left posterior activation performed worse in these two subtests related to language comprehension, a linguistic function known to be located mainly in left temporo-parietal cortex. Indeed, semantic activation involves typically the integrated bilateral activation of left and right temporo-occipital sites in control subjects (see Fig. 4, left column of last row; for semantic-related bilateral posterior activation, see also Angrilli et al., 2000; Spironelli and Angrilli, 2006). One simple interpretation that puts together all available information, suggests that semantic processing requires a cortical network distributed in bilateral posterior regions, since patients who reorganized their activity and activated mainly left hemisphere clusters performed less well on Comprehension and Token tests, whereas patients with more bilateral EEG activation (similar to controls) performed better. It may seem strange that non-fluent aphasics are impaired in semantic processing, as this function should be spared in these patients: first, it may be that a linguistic process is reorganized without being apparently affected — this holds especially for processes spread over large cortical regions such as the semantic one. Second, a focal lesion, like that of our aphasics, mainly affects the corresponding specialized function (phonological activity and Repetition test), but it also induces a substantial physical reorganization of the whole linguistic circuitry. In this way linguistic functions less affected by the focal lesion are also reorganized. Indeed, the core damage of our sample included the center of the linguistic network of the left hemisphere (i.e., perisylvian cortical and subcortical structures): a lesion at this level is expected to impair high-level linguistic processes deriving from integration and connectivity of distant areas (e.g., by limiting transmission of information in the contralateral right homologous areas involved in semantic processing). Consistent with this view, semantic processes and comprehension performance were not completely intact in our sample: if ceiling performance had been found in Comprehension and Token subtests, the variance of these variables would have been close to zero and no significant correlations would have been found. Finally, classification of an aphasic as fluent/non-fluent does not imply that the patient is free of deficit in secondary domains, in our case in semantic processes. In the present study, patients were comparable to healthy subjects when they performed the Orthographic control task (in both EEG laterality and RTs), whereas, in addition to the target Phonological task, they were significantly slower than controls also in the Semantic task.

In sum, lesions in the left central linguistic perisylvian centers may have affected the balance of the whole intact posterior linguistic network, subserving both semantic access and language comprehension. The left posterior activation of patients, already observed in our past experiment (Angrilli et al., 2003), may therefore be dysfunctional, as it was inversely correlated with the above-mentioned AAT comprehension subtests.

Conclusions

Analysis of late phases of word processing in aphasic patients revealed similar patterns of cortical activation for Phonological and Semantic tasks, thereby showing greater left lateralization of both anterior and posterior areas than controls. At the same time, patients exhibited marked inhibition of left central sites, which corresponded to the damaged cortical–subcortical areas, especially during the first interval (W1) of word reading. Aphasics' lesion maps suggest that the residual anterior part of Broca's area is the starting center for developing reorganization of most linguistic functions in unimpaired cortical areas of the left hemisphere: unlike the control group, patients exhibited clearcut left lateralization even when they processed and categorized semantic stimuli, although semantic processing is relatively spared in non-fluent aphasics. As expected, patients did not differ from healthy subjects in the Orthographic control task, which required only visuo-perceptual word matching. The significantly positive correlation found in patients

between left anterior/central activation of the Phonological task and the Repetition AAT subtest further supports our interpretation of functional language redistribution on intact left frontal cortices. In conclusion, patients reorganized activity in the cortical space by shifting activation to their intact cortical areas beside the damaged sub-cortical regions of the left hemisphere, yet the reorganization processes also involved the temporal domain, as the spatial patterns of aphasics' activity evolved differently from those of controls across all word encoding phases.

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