ERP correlates of word production before and after stroke in an aphasic patient

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Abstract

Changes in brain activity characterizing impaired speech production after brain damage have usually been investigated by comparing aphasic speakers with healthy subjects because prestroke data are normally not available. However, when interpreting the results of studies of stroke patients versus healthy controls, there is an inherent difficulty in disentangling the contribution of neuropathology from other sources of between-subject variability. In the present work, we had an unusual opportunity to study an aphasic patient with severe anomia who had incidentally performed a picture naming task in an ERP study as a control subject one year before suffering a left hemisphere stroke. The fortuitous recording of this patient's brain activity before his stroke allows direct comparison of his pre- and poststroke brain activity in the same language production task. The subject did not differ from other healthy subjects before his stroke, but presented major electrophysiological differences after stroke, both in comparison to himself before stroke and to the control group. ERP changes consistently appeared after stroke in a [...]
ERP correlates of word production before and after stroke in an aphasic patient

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Changes in brain activity characterising impaired speech production after brain damage have usually been investigated by comparing aphasic speakers with healthy subjects, since pre-stroke data is normally not available. However, when interpreting the results of studies of stroke patients versus healthy controls, there is an inherent difficulty in disentangling the contribution of neuropathology from other sources of between-subject variability.

Here we had the unlikely opportunity to assess this methodological point through the study of an aphasic patient with severe anomia who had incidentally performed a picture naming task in an event-related electrophysiological (ERP) study as a control subject one year before suffering a left-hemisphere stroke. The subject did not differ from other healthy subjects before his stroke, but presented major electrophysiological differences after stroke both in comparison to himself before stroke and to the control group. ERP changes consistently appeared after stroke in a specific time-window, starting about 250 ms after picture onset, and corresponded to a single divergent but stable topographic configuration of the scalp electric field with a cortical generator abnormally limited to left temporal posterior perilesional areas. The patient’s pattern of anomia revealed lexical-phonological impairment and the time-window of ERP changes in the post-stroke recording corresponded to that associated with lexical-phonological processes during picture naming in previous work. Thanks to the fortuitous recording of this patient's brain activity during a speech production task before his stroke, the changes observed after stroke can reliably be linked to impaired language production at the level of lexical-phonological processes.
Brain damage can drastically disrupt the fluent and automatic process of language production: word retrieval becomes effortful and words are substituted or distorted (paraphasias). Investigation on changes in brain activity during language processing after stroke usually compares aphasic patients to healthy controls, since pre-stroke data is normally not available. In electrocortical studies, aphasic patients and healthy control subjects have been recorded with magnetoencephalography (MEG) or electroencephalography (EEG) during a variety of language comprehension or language production tasks: word or sentence comprehension (Frederici et. al, 1999; Wassenaar and Hagoort, 2005; Hagoort et al., 1996; Breier et al, 2004), lexical decision tasks (Pulvermüller et al., 2004), semantic or syntactic judgment (Angrilli et al., 2003; Dobel et al., 2001; Hensel et al., 2004) or picture naming tasks (Cornelissen et al., 2003; Laganaro et al., 2009). While some studies have tracked changes in rhythmic activities in aphasic patients after brain lesion or during recovery (especially changes in slow waves: Hensel et al., 2004; Szelies et al., 2002; Meinzer et al, 2004), cognitive oriented investigations analysed event-related electrophysiological (ERP) differences between aphasic patients and a control group in the attempt to investigate the temporal course of changes accompanying reorganization of language production after stroke. These studies aimed to tease apart changes due to specific sub-processes underlying language production or perception. In the language comprehension domain, electrophysiological studies have compared aphasic patients to healthy controls using specific tasks, tapping into semantic or syntactic treatment during word or sentence comprehension (Friederici et al., 1999; Wassenaar and Hagoort 2005; Hagoort et al., 1996). When using single word receptive language tasks, modification of early ERP components in the aphasic patients, starting about 160–200 ms after stimulus presentation, have been reported with auditory presented (Breier et al., 2004) or visually presented single words (Pulvermüller et al., 2005).
Differences in later time-window, starting around 300 ms after stimulus presentation were reported in studies analysing the electrocortical reorganization after brain damage with speech production tasks. For instance, Dobel et al. (2001) and Angrilli et al., (2003) analysed mean amplitudes of electrodes from 4 regions at scalp with tasks demanding semantic or phonological encoding processes. They reported different activation patterns between healthy controls and aphasic patients starting around 300 ms after stimulus presentation. In a recent report comparing two subgroups of aphasic patients to healthy controls with a picture naming task, the time-windows of diverging ERPs varied, depending on the underlying anomic impairment (Laganaro et al. 2009). Early ERP divergences (100-250 ms after picture onset) appeared in aphasic patients with lexical-semantic anomia, whereas later ERP divergences (300-450 ms) were observed in aphasic patients with lexical-phonological impairment.

A major problem for the interpretation of results emanating from the comparison of stroke patients to healthy controls concerns inter-subject variability. Between-subject variability of EEG patterns has been observed not only among brain damaged subjects, but also among healthy control subjects (Campanella et al., 1999). By contrast, intra-individual EEG patterns have been reported to be quite stable, even over several months (Condacs and Szabó, 1999; Vuga et al., 2006). Between-subjects’ electrophysiological variability might preclude teasing out differences due to the pathological conditions from those due to other sources of between-subjects variability. Showing that a single subject does not differ from other subjects before the occurrence of brain damage, but presents electrophysiological changes after brain damage, would be direct evidence that any differences found between the brain-damaged subject and control subjects are indeed due to the stroke.
In the present study, we had the unlikely opportunity to compare the electrophysiological activation pattern of the same subject before and after a left-hemisphere stroke. The case presented here was recorded during a language production (picture naming) task as a control subject, one year before suffering a left hemorrhagic stroke which caused severe aphasia. The subject presented a severe anomaia after stroke, characterized by many phonological paraphasias and no responses. According to previous ERP studies on picture naming, impaired lexical-phonological processes should be associated with changes in a specific time window relative to picture onset. If differences observed after stroke appear both in the within-subject comparison of his activation pattern before and after stroke and in the comparison to a control group of healthy subjects, the observed changes in ERP patterns would reliably be attributable to stroke rather than to inter-individual variations.

Method

Participants
The patient is a 68 year-old man with university education (a retired psychologist) who suffered a left fronto-temporal parietal hemorrhagic stroke (Fig. 1). At the acute stage he was described as a Wernicke aphasic. Due to persistence of concomitant (non-neurological) health problems, the patient entered a rehabilitation program only 2.5 months post-stroke and a detailed neuropsychological evaluation was carried out 4 months post-stroke. At this time his language was fluent, but marked by frequent phonological paraphasias and neologisms (eg. ‘moto’ produced [mato]; ‘trompette’ (tRõpEt/ - trumpet) produced [pRõtEt]; cigarette produced [asës]); he experienced word finding difficulties. Naming was severely impaired in the French version of Boston Naming Test, (Thuillard-Colombo and Assal, 1992) with predominance of omission and
phonological errors. Repetition and reading aloud were also severely impaired with comparable performance on words and pseudo-words and a length effect in all production tasks.

Auditory comprehension was preserved for single words and simple sentences (Montreal-Toulouse 86 Aphasia Battery, Nespoulous, et al., 1992), but some errors were observed for complex sentences; written sentence and text comprehension were at ceiling on the subtest of the French version of the Boston Diagnostic Aphasia Examination (Mazaux and Orgogozo, 1981). Semantic assessment revealed normal performances on the Pyramid and Palm Trees Test (Howard and Patterson, 1992). He exhibited severe central agraphia with preserved automatic writing and letter formation. A mild oro-facial apraxia was observed with no signs of limb apraxia, visual, spatial agnosia or neglect. Performances were in the normal range on mental flexibility and auto-activation tasks (Frises de Luria and figural fluency, Regard, Strauss and Knapp, 1982) but performance on the Trail Making test was somewhat impaired (Reitan and Wolfson, 1985). Non-verbal intellectual processes were in normal range (short version of the progressive matrices, Raven, Court, & Raven, 1998).

In sum, 4 months post-stroke, the patient presented with severe expressive aphasia, characterized by anomia with phonological transformations in spontaneous and elicited speech as well as in repetition and reading aloud, relatively spared auditory and written comprehension and severe agraphia.

The patient was recorded three times, at 3, 4 and 5 months after the stroke, using the same picture naming task that he had already performed as a control subject one year before stroke.

[Figure 1 about here]
Fifteen other healthy subjects from the original group (Laganaro, Morand and Schnider, 2009), from which the patient’s data before the stroke was removed, made up the control group (mean age: 55, range: 34 to 72, 4 men). One of them (65 year-old woman, hereby “control subject S”) was recorded again 1 year later. The control subjects scored at ceiling on the picture naming task (97.4% correct, SD = 2.7%).

Task and material

High-resolution (128 channels) electroencephalogram (EEG) was recorded during a delayed picture naming task. The stimuli were 144 black-and-white line drawings selected from French databases (Alario et al., 1999; Bonin et al., 2003): they corresponded to mono-, di- and trisyllabic words (nouns) with name agreement above 65%. The pictures were presented at the center of a white computer screen as black outlines. Subjects sat 0.7m in front of the screen, viewing pictures of approximately 0.09m with a visual angle of 3.67 degrees.

Each picture was displayed for 2000 ms, followed by a response cue (question mark). The participants were asked to prepare the name matching the picture and to say it aloud when the question mark appeared on the screen. This procedure was adopted to avoid possible artefacts during motor preparation for overt naming.

EEG acquisition and pre-analyses

The electroencephalogram (EEG) was recorded continuously using the Active – Two Biosemi EEG system (Biosemi V.O.F Amsterdam, Netherlands) with 128 channels covering the entire scalp. EEG signals were sampled at 512Hz with bandpass filters set at 0.1-100 Hz.
Epochs from -100ms to 600ms relative to picture onset were averaged for each subject. Individual data were recalculated against the average reference and bandpass filtered to 1-30Hz. In addition to automated amplitude threshold detection, all trials were visually inspected, and epochs contaminated by eye blinks, movements or artefacts were rejected. Baseline correction was applied to the 100ms pre-stimulus period. A minimum of 78 epochs were averaged in each patient’s data.

**Waveform analyses**

The ERPs were first subjected to waveform analysis to determine the time periods in which amplitude differences over all electrodes were found between the patient and the control group, and between the patient’s pre- and post-stroke data.

T-tests were applied to compare voltages of the averaged ERP data (at each electrode and each time point over the whole period, from 0 to 600 ms in 2 ms steps) between the patient and the control group (Crawford t-tests, Crawford and Howell, 1998). For the comparison between the patient’s pre-stroke and post-stroke data, paired t-test (Bonferroni corrected) were computed on 50 randomly selected single epochs aligned to the stimulus onset. The same procedure was applied to compare the two recording sessions of a control subject (control subject S), who, as we recall, was recorded again one year later (but not suffering a stroke in between).

**Topographic analyses**

The differences observed on amplitudes can be a consequence of a modulation in the strength of the electric field, of a topographic change of the electric field (revealing distinguishable brain generators), or of latency shifts in brain processes. To differentiate these effects, topographic analyses were also performed. This approach allows one to summarize ERP data into a limited
number of electrocortical map configurations and to identify time periods during which different populations or different conditions evoke different electrocortical configurations.

Topographic (map) pattern analysis, based on a modified spatial k-means cluster analysis, was used to identify time periods with distinct electric field configurations (Michel et al., 2001; Pascual-Marqui et al., 1995) and to determine the optimal number of maps that best explained the averaged data sets ("temporal segmentation"). This method is independent of the reference electrode and insensitive to pure amplitude modulations across conditions (topographies of normalized maps are compared). Statistical smoothing was used to eliminate temporally isolated maps with low strength; a given topography had to be present for at least 15 time-frames (30 ms).

Spatio-temporal segmentation was performed on the averaged group control data, together with the patient’s pre and the three post-stroke data sets. The pattern of maps observed in this analysis was then statistically tested by comparing each map with moment-by-moment scalp topography of each individual control subjects’ ERPs (Murray et al., 2008). This “fitting” procedure allowed to establish how well maps explained patient’s and individual control’s patterns of activity. In order to take into account inter-individual variability among the control participants, the patient’s data was compared to individual subjects’ measures instead of the grand mean data. A map was considered divergent from the control group when its global explained variance (GEV) and its duration (number of time-frames) were beyond the maximum or the minimum values displayed by the control subjects and the topographic map was not observed in his own data before stroke.

Source localization

Estimation of the location of intracranial generators was carried out using a linear distributed inverse solution (LAURA, Grave de Peralta et al., 2001). This source imaging method is based on the physical law that the strength of a source regresses regularly with distance. Using a regular grid of solution points, the method incorporates this law in terms of a local autoregressive average with
coefficients depending on the distance between solution points (Michel et al., 2004). In the current analysis, solution points were distributed within the grey matter of a standard MRI for the control group and the patient’s pre-stroke data and on the patient’s post-stroke MRI. The latter was used for the source localization of the divergent microstates in the patient’s post-stroke data. A spherical head model with an anatomical constraint was used, applying the SMAC transformation method (Spinelli et al. 2000). In this head model, the solution space is restricted to grey matter subspace. The parameters used for the LAURA calculation were fixed at a neighbourhood size of 26 solution points and a regression with the inverse of the cubic distance (for vector fields). The regularization parameter was fixed to Alpha=1 for all maps (Pascual-Marqui et al., 2009).

Results

The naming scores of the patient were at ceiling before stroke and were severely impaired at 3, 4 and 5 months post stroke (see Fig. 2), with a slight but significant improvement from 3 to 4 months (McNemar Change Test : ChiSquare = 6.231, p = 0.012) and stable performance between 3 and 4 months (ChiSquare = 1.6, p= 0.2). His error distribution reveals a preponderance of omission and phonological errors; some semantic errors were also observed, especially at the first (3 months post stroke) recording session. Error distribution also differed between the first and second assessment sessions (Pearson $\chi^2 (3) = 8.2, p < .04$), but not between the last two sessions ($\chi^2 (3) < 1$).

[Figure 2 about here]
The patient’s post-stroke ERPs were compared to the control group of 15 healthy subjects and to his own data before stroke.

[Figure 3 about here]

The analyses indicated similarly distributed differences in amplitudes after stroke when comparison was carried out with the control group (Fig. 3A) and with himself (Fig. 3B). In all comparisons, amplitudes consistently differed after stroke from about 250-270 to 400-450 ms after stimuli presentation, especially in the posterior right and left regions and on the left anterior and central electrodes. A second period of diverging amplitudes appeared in the 4 and 5 months post-stroke recordings from 450 ms to the end of the recording period on the anterior (right and left) electrodes. By contrast, the patient did not differ from the rest of the control group before stroke (Fig. 3C, top); also, the control subject S did not display any significant changes in amplitudes at one year interval.

A strong divergent electrocortical response with a unique map topography appeared after stroke relative to his pre-stroke data and to the control group in the 250-400 ms time-window (Fig. 4). The same divergent topography was observed in the 3 post-stroke recordings in the same time window.

[Figure 4 about here]

This topographic map was not observed, either in his own data before stroke or in the grand average of the control group. Abnormality was further confirmed by a spatial fitting procedure that showed
higher global explained variance (GEV) and longer duration of this map in the patient as compared to the individual control subjects (GEV: patient after stroke: 86 – 94%, maximum controls: 48%; duration: patient after stroke: 162-168ms, maximum duration in control subjects: 138ms).

By contrast, the map template observed in this time-window in the control averaged data, was not displayed in the patient post-stroke data. It had however been apparent in his pre-stoke date around 250 ms and in 13 out of the 15 control subject starting, on average, around 300 ms.

Source localization computed with the patient’s own post-stroke head model indicated a left inferior and middle temporal activation after stroke during the 250-400 ms time-window (Fig. 4, inferior right corner), whereas the left middle temporal and anterior and superior temporal lobe was activated in the control subjects and in the patient’s data before stroke (source localization for map template in Fig. 4).

**Discussion**

Similar results were observed when comparing ERPs recorded during picture naming in an aphasic patient to his own ERPs recorded with the same task one year before stroke and to a control group. Different amplitudes and topographic maps after stroke appeared across all comparison around 250 ms after picture presentation and remained very stable at 3, 4 and 5 months post-stroke. These results, together with the observation that the patient did not differ from the control group before stroke and that no changes appeared in a healthy subject at one year interval, indicate that the observed ERP divergences in the aphasic patient are linked to the stroke and cannot be attributed to inter-individual or intra-individual variability.

We will discuss the main implications that can be drawn from these reliable findings for the cognitive changes in language processing in aphasia.
First, changes in ERP patterns after stroke during a picture naming task consistently appeared around 250 ms after stimuli presentation. These results confirm that divergent ERP patterns observed during a language production task after stroke appear in a specific time-window, which we can relate to impairment in specific cognitive processes. Behavioral and ERP studies with healthy subjects estimated that lexical-semantic processes (conceptually driven lexical selection) occur between 150 and 250 ms after stimuli presentation in picture naming tasks (Indefrey and Levelt; 2004, Vihla et al., 2006; Maess et al., 2002). Word-form (lexical-phonological) encoding has been estimated to start later, around 250-275ms (around 300 ms in Vihla et al., 2006) after stimulus presentation. According to these estimations the unchanged ERP correlates from 0 to about 250 ms and the time-window of electrophysiological changes observed in this patient after stroke, suggest unimpaired visual and semantic processes. This fits with the patient’s anomic pattern: he did not display any semantic impairment and his pattern of errors revealed impaired word-form retrieval and encoding (lexical-phonological impairment). The time-window of his divergent ERP pattern is also in line with results from a previous group study on patients with lexical-semantic or lexical phonological anomia (Laganaro et al., 2009, see the Introduction). Taken together, the results indicate that divergent ERPs starting around 250-300 ms after picture presentation characterise impaired single word production in aphasic patients with impaired lexical-phonological encoding.

Second, the modified neurophysiological pattern observed after stroke remained quite stable over several months. The same sequence of topographic maps and similar modification of amplitudes appeared across the three post-stroke recordings. These results contrast with those reported in previous studies with patients who underwent successive EEG recordings during picture naming tasks after stroke and displayed modification of topographic maps, amplitudes, or both across the recording sessions (Cornelissen et al.,2003; Laganaro et al., 2008). However, these modifications
were accompanied by behavioral changes, since all patients in those studies displayed some degree of recovery across the study periods. By contrast, the stable ERP pattern after stroke in the present study was observed together with an unchanged behavioral response (severe anomia), especially during the 4 to 5 months post-stroke period. However, an increase in divergent amplitudes from 450 to 600 ms characterized the two last recording sessions relative to the 3 months post-stroke data. A minor, but significant behavioral change was also observed between the first and the following post-stroke recordings (10% improved naming accuracy and a slight different distribution of errors); this pattern might be associated with the ERP differences observed between the first and the two following recording sessions.

The cortical generator of the divergent topographic map was localized with the patient's own post-stroke head model using a procedure of source localisation. This procedure has been validated in a recent investigation on patients with focal epilepsy (Brodbeck et al. 2009). This study showed that localisation was no less accurate in patients with large brain damage than in patients without brain damage; this finding therefore increases our confidence in the accuracy of source localisation in stroke patients as well.

Source localization applied to the 250-400 ms time-window of divergent ERPs indicated a fixation on a posterior perilesional area, while the superior temporal lobe was activated before stroke during this time-window. Although perilesional activation has been shown to accompany recovery from aphasia (Belin et al., 1996; Leger et al., 2002), in this case, it seems to remain circumscribed to posterior areas of the middle and inferior temporal lobe with a lack of activation of the superior temporal lobe; this latter activation was observed in the pre-stroke recording and it is the very locus which is thought to be implied in the encoding of word form (Indefrey and Levelt, 2004; Levelt et al., 1998). This finding suggests that the lesion disconnects the superior temporal lobe from the
inferior and posterior temporal regions, severely disabling word-form encoding. The stability of the divergent electrocortical response over several months also suggests a lack of cortical reorganization in brain-damaged subjects, with limited behavioral changes during the same period.

In conclusion, the same ERP modifications were observed during word production in an aphasic patient in comparison to pre-stroke data from the same subject and to a group of healthy control subjects. These findings increase our confidence that the observed time-window of the electrophysiological modification characterise impaired word production after stroke at the level of lexical-phonological encoding.

**References**


FIGURES

Figure 1. The lesion. A T2-weighted MRI (TE 122 ms; TR 8690 ms) at 4 months shows a left temporal-parietal hematoma in resorption with extended destruction of the posterior superior temporal lobe (area 22, including Wernicke's area) and the white matter underlying areas 22 and 40, including the arcuate fasciculus in the temporal stem.

Figure 2. Performance on the naming task (accuracy) before and after stroke and error distribution at 3, 4 and 5 months post-stroke.

Figure 3. Significant differences (p values, at p<.01 and p<.001) on electrode amplitude on each electrode (Y axes) and time point (X axes): A. between the patient and the control group at 3, 4 and 5 months post stroke; B. in the intra-individual comparison (before and after stroke); C. between the patient before stroke and the control group and between the two recording sessions of control subject S. Bottom: evoked potential curves in the control group and patient’s data at 8 specific electrode positions and the arrangement of all 128 electrodes with positions on the scalp for the displayed electrodes (black dots).

Figure 4. Grand average ERPs (128 electrodes) of the control group and patient before stroke (top) and of the 3, 4 and 5 months post-stroke data (bottom) and sequences of stable topographic maps in each data (positive values in red and negative values in blue). Topographic maps for the 250-400 ms time period in which the analysis revealed different map template between the post-stroke data and the pre-stroke data are highlighted. On the right side: top: source localization for the map in the data
of the control group (within a standard MRI); bottom: source localization for the divergent micro-
state in the patient after stroke (calculated on the patient’s post-stroke MRI).
FIGURES

Figure 1

Figure 2
Figure 3

A. Patient vs. control group

B. Patient before vs after stroke

C. Patient before stroke vs. control group

Control subject S session 1 vs. session 2

Electrodes C3, C4, Pz, Fz, P7, P8, Oz, Cz