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Left-hemispheric abnormal EEG activity in relation to impairment and recovery in aphasic patients

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Abstract

Focal electromagnetic slow-wave activity is generated in the vicinity of brain lesions. The present study confirmed this for the EEG delta band (1–4 Hz): Activity in the waking state was pronounced over the hemisphere of the lesion in 11 stroke patients suffering from aphasia, but not in 10 healthy controls. Changes of abnormal slow waves patterns were tracked from 1–3 months to 2 years poststroke by recording the EEG five times at 4-month intervals. Across the first year poststroke, mean left-hemispheric delta amplitude and equivalent current dipole strength decreased in parallel with the spontaneous recovery of language function, whereas the regional distribution of delta activity sources was stabile across time. No changes were observed during the second year poststroke. Results suggest that abnormal slow waves in the vicinity of brain lesions may be related to impairment in brain function, and that their measurement may assist in depicting the course of functional recovery.

Descriptors: Aphasia, Electroencephalography, Delta, Recovery, Brain lesion

Large amplitude and low-frequency activity in the delta (0.5–4 Hz) and theta (4–7 Hz) frequency ranges in electro- (EEG) and magnetoencephalogram (MEG) have been consistently found during the waking state in patients with brain lesions. Slow waves originating from focal brain regions often appear in the vicinity of a structural lesion like cerebral infarct, contusion, local infection, tumor, or subdural hematoma (De Jongh et al., 2001a; De Jongh, Bayen, de Munck, Puligheddu, & Stam, 2002; Möller et al., 2001; Tanaka, Kimura, Yoshinaga, Tomonaga, & Mizoguchi, 1998; Vieth, Kober, Ganslandt, Möller, & Kamada, 2001; Vieth, Kober, & Gummich, 1996; Vieth, Kober, Kamada, & Ganslandt, 1998). Generators of slow-wave activity in cortical and subcortical structures have been determined from intracranial recordings and, more recently, from the allocation of dipole density from the surface magnetoencephalogram (De Jongh et al., 2001b, 2002; Möller et al., 2001; Vieth et al., 2001) called magnetic source imaging (MSI; Elbert, 1998). Varying with changes in metabolism and blood flow consequent upon the insult (as verified by imaging procedures; Kamada et al., 2001; Nagata, Tagawa, Hiroi, Shishido, & Uemura, 1989; Strik, Klose, Kiefer, & Grodd, 2002; Tanaka et al., 1998; Vieth et al., 2001), abnormal slow-wave activity has been attributed to a dysfunctional state of the neuronal tissue (Elbert, 1998; Lewine & Orrison, 1995; Rockstroh, Fehr, Kissler, Wienbruch, & Elbert, 2001), "dysfunctional" characterizing a border zone between normal and seriously damaged brain tissue (de Weerd, Veldhuizen, Veering, Poortvliet, & Jonkman, 1988; Kamada et al., 2001), or a local deficit in cerebral blood flow and oxygen metabolism (Nagata et al., 1989), or other mechanisms that may lead to a deafferentation of neural networks from their major input source.

In the present study we examined to what extent focal slow activity can be determined from the surface EEG in aphasic stroke patients and to what extent a change in delta (1–4 Hz) activity over the structurally lesioned left hemisphere would parallel recovery of function in aphasia. We tested the hypothesis that slow-wave activity was abnormally pronounced (relative to healthy controls) during the acute state and changed in connection with language improvement as recovery progressed (see de Weerd et al., 1988). If so, measures of focal slow-wave activity like amplitude and dipole strength might assist in the identification of dysfunctional brain areas and the prognosis of recovery of brain functions in aphasia patients. For testing this hypothesis, left-hemispheric delta activity and neuropsychological measures of language function were examined over the course of a 2-year recovery period following a left-hemispheric stroke.

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Methods

Participants

Eleven patients (1 female, mean age 54.1 years, range 33–66 years) suffering from aphasia after a left-hemispheric lesion (see Table 1 for clinical data) were recruited for a 2-year longitudinal study. At the beginning, the diagnosis was given with a probability > 95% in all patients according to the guidelines of the Aachen Aphasia Test (Huber, Poeck, Weniger, & Willmes, 1983). Aphasic syndromes were determined as Wernicke ($n = 4$), Broca ($n = 1$), amnestic ($n = 2$), and global aphasia ($n = 4$). The severity of aphasia ranged from severe ($n = 3$) to medium ($n = 6$) to slight ($n = 2$). Aphasia had resulted from left-hemispheric cortical plus subcortical ischemia ($n = 5$), subcortical ischemia only ($n = 1$), cortical ischemia only ($n = 2$), or subcortical and/or cortical hemorrhage ($n = 3$) during a maximum 3 months prior to the start of the investigation. Ten patients had been 100% right-handed and one was ambidextrous before the onset of the brain injury and aphasia (retrospectively evaluated using the Edinburgh Inventory; Oldfield, 1971). Patients were recruited from the local neurological rehabilitation centre (Kliniken Schmieder Allensbach). Speech therapy of the patients varied between no therapy and 1–2 h/week across the 2-year study.

Ten healthy volunteers (4 female, mean age 43.3 years, range 29–61 years; all right-handed as verified by a modified version of the Edinburgh Inventory, in which subjects were asked to demonstrate the movements asked for in the questionnaire) served as a control group. It was ascertained by interview that controls had not suffered from any neurological disorder.

Prior to the experimental session each participant was fully informed about purpose and protocol of the study, and about the guidelines of human right protection fulfilled by the experimenters. A written consent was obtained from every participant.

Design

Each patient participated in a total of five EEG recordings distributed across a 2-year period with an interval of 4 to 5 months between sessions. Aphasia was assessed with the Aachen Aphasia Test on the first, third, and fifth sessions. In each of the five sessions, the EEG was recorded during a semantic categorization task,[1] in which line drawings of concrete objects had to be classified according to whether they represented natural or artificial objects. Each stimulus was presented until the participant indicated his or her decision by pressing one of two adjacent buttons with the left index or middle finger. The stability of indices was examined in control volunteers who participated in two sessions separated by an average of 5.3 months.

Data Collection

The EEG was recorded with a DC-Amplifier (MES, Munich) from 30 locations according to the international 10–20 system including four locations at the forehead and the outer canthi of the eyes (for eye movement control). The vertex electrode (Cz) served as recording reference. The signals were amplified in the band from DC to 100 Hz (6 db/octave) and sampled at a rate of 500 Hz. Impedance levels of all electrodes were kept below 5 kΩ (which represents the upper limit specified by the amplifier system). The individual electrode positions were digitally recorded (Polhemus Inc., Colchester, VT, USA).

Data Reduction and Analysis

Changes in language function were evaluated by comparing the test profile (an estimation of general function, corresponding to the average performance in the subtests of the Aachen Aphasia Test) between the three assessments (first, third, and fifth sessions) and between syndromes (fluent, nonfluent) subgroups by means of repeated-measures analyses of variance (ANOVAs), effects being verified by post hoc Scheffé tests. The same statistical analyses were applied to measures of performance in the semantic categorization task, the median reaction time (RT in milliseconds from stimulus onset) and error rate (percent of the total 54 trials).

For EEG analysis, eye movement artifacts were corrected from the entire recording interval using the method of Berg and Scherg (1994, cf. also Ille, Berg, & Scherg, 1997). Epochs containing large artifacts remaining after correction were excluded from further analyses. Data were then converted to average reference and filtered from 1 to 8 Hz. During artifact-free epochs, the average Fast Fourier Transformation (FFT) was calculated using 1,024 points per 2.05-s interval and setting the amplitude threshold to 100 μV. The amplitude spectra and frequency bands were converted to determine the following indices for slow-wave/delta activity:

1. Delta *amplitude* was determined as integral of all amplitudes in the 1–4-Hz band across artifact-free epochs (grand average delta amplitude across all 27 electrodes). In addition, the distribution of delta amplitudes was examined by the laterality index (LI: all left- minus all right-hemispheric electrodes divided by their sum), and by regions of interest (ROI) that included anterior (Fp1, F9, F7, F3, C3) and posterior (T9, T7, P9, P3, P7) electrodes over the left hemisphere and their right-hemispheric homologs. These regions were chosen in an attempt to contrast frontocentral and parietotemporal speech areas.
2. Delta *dipole* location and strength was determined by source localization (BESA 2000, MEGIS GmbH) applied to 700-ms epochs starting 200 ms before and ending 500 ms after the onset of the delta wave. For each patient, a starting model was used consisting of two symmetrically located regional[2] sources, one in each hemisphere. Retaining this symmetry constraint, location was fitted to the EEG signals. Using the spatiotemporal model of BESA, this results in source waveforms that image the amplitude over time of the activity in each hemisphere. Using two symmetrical sources allows stronger conclusions than fitting a single source: It is possible to evaluate the simultaneous activity in each hemisphere. This fitting was possible in 7 of the 11 patients. (Figure 1 illustrates the result of fitting for the clearly visible delta activity in one patient.) Due to the absence of sufficiently large delta waves, source localization could not be accomplished in 4 patients

[1] From a series of experimental tasks designed to investigate changes in the event-related brain potentials across the 2-year recovery period, the semantic categorization task was chosen for the analysis of the spontaneous EEG as one that induced comparable levels of attention and activation in all subjects, as it required steady attention and included processing demands that were easily accomplished by every patient.

[2] Sometimes referred to as a "rotating" source: A regional source consists of three orthogonal dipoles at one location. These three components thus capture the activity of any generator at (or near) its location.

Table 1. *Demographic for Participants and Clinical Data for Aphasic Patients*

Patient ID	Age	Sex	Handedness	Aphasic syndrome (severity)	Nature of lesion	Location (left hemispheric)	Affected (speech relevant) areas	Clinical symptoms
1	50	M	right	Wernicke (medium)	Hemorrhage	subcortical	Wernicke	Right arm hemiparesis, right hand sensitivity deficit
2	33	M	right	amnestic (slight)	Ischemia	cortical	Wernicke, Gyrus Angularis	None
3	61	M	right	Broca (medium)	Ischemia	subcortical	Broca	Right arm hemiparesis, right facial paresis
4	60	M	right	Wernicke (medium)	Hemorrhage	cortical & subcortical	Wernicke	Reduced right hand fine motor control, ideomotor apraxia
5	35	M	right	global (severe)	Ischemia	cortical & subcortical	Broca	Right hemiparesis, right facial paresis
6	62	M	right	amnestic (slight)	Ischemia	cortical & subcortical	Wernicke	Reduced fine motor control of the right hand, slight coordination deficit
7	65	M	right	Wernicke (medium)	Ischemia	cortical	Gyrus Angularis, Gyrus Supramaginalis	Right hemiparesis, reduced fine motor control of the right hand
8	66	F	ambidextrous	Wernicke (medium)	Hemorrhage	cortical & subcortical	Wernicke, Gyrus Angularis, Gyrus Supramaginalis	Right arm hemiparesis, insecure gait
9	57	M	right	global (severe)	Ischemia	cortical & subcortical	all speech structures	Right hemiparesis
10	63	M	right	global (medium)	Ischemia	cortical & subcortical	all speech structures	Severe right hemiparesis
11	43	M	right	global (severe)	Ischemia	cortical & subcortical	all speech structures	Right hemiparesis
Control								
12	32	M	right					
13	33	M	right					
14	30	W	right					
15	61	M	right					
16	34	M	right					
17	42	W	right					
18	55	M	right					
19	29	M	right					
20	56	W	right					
21	61	W	right					

Brain lesions were verified by MRI in all participants.

and in the controls. For parametrization, fits were performed on delta waves that were averaged as follows: A channel that showed the largest delta activity was selected, and a time range was marked as a template. Using the pattern search in BESA (based on correlation between the template activity and test waveforms), artifact-free data segments containing comparable delta activity were averaged, each segment comprising 700 ms. Between 9 and 73 (mean = 27) segments contributed to each average. Talairach coordinates of the source location were saved in ASCII format and changes in the location of the dipoles between sessions were determined for the x- (medial-lateral), y- (anterior-posterior), and z- (inferior-superior) axes. Maximal dipole strength Q was determined for each hemisphere and each recording session in each subject. From the 7 patients for whom dipole localization was accomplished, individual digitized MRI recordings were available in 4 patients, so that dipole locations were coregistered with the MRI using BrainVoyager (Brain Innovation B.V.) in these four patients.

For these indices, differences between the groups in the first recording session were compared by ANOVA. Analyses of changes across time comprised the two recording sessions in the case of the control group. In the case of the aphasics, the first, third, and fifth sessions were compared as those sessions across the recovery period, in which neuropsychological and electrocortical data were collected on the same day. Because the large interindividual variability of delta *amplitude* in the aphasic group prevented parametric tests in this group, the Wilcoxon signed rank test served to analyze the amplitude measurement across sessions, in contrast to repeated-measures ANOVA used for the control group.

In aphasics only, the *dipole location and strength* (Q) were compared across time using repeated-measures ANOVAs. Bonferroni/Dunn tests were employed to verify interactions of recording session and dipole strength in the hemisphere. In controls, the dipole localization was unreliable because of an insufficient amount of large-amplitude delta waves.

In all analyses revealing interactions with degrees of freedom larger than 1, the degrees of freedom were corrected using the Greenhouse–Geisser procedure to account for possible violations of the sphericity assumption.

Results

Language functions of the patients, evaluated by the Aachen Aphasia Test, improved across time from the first to the last session. For the test profile, this resulted in a significant effect of session, $F(2,20) = 28.99$, $p < .001$. Post hoc Scheffé tests

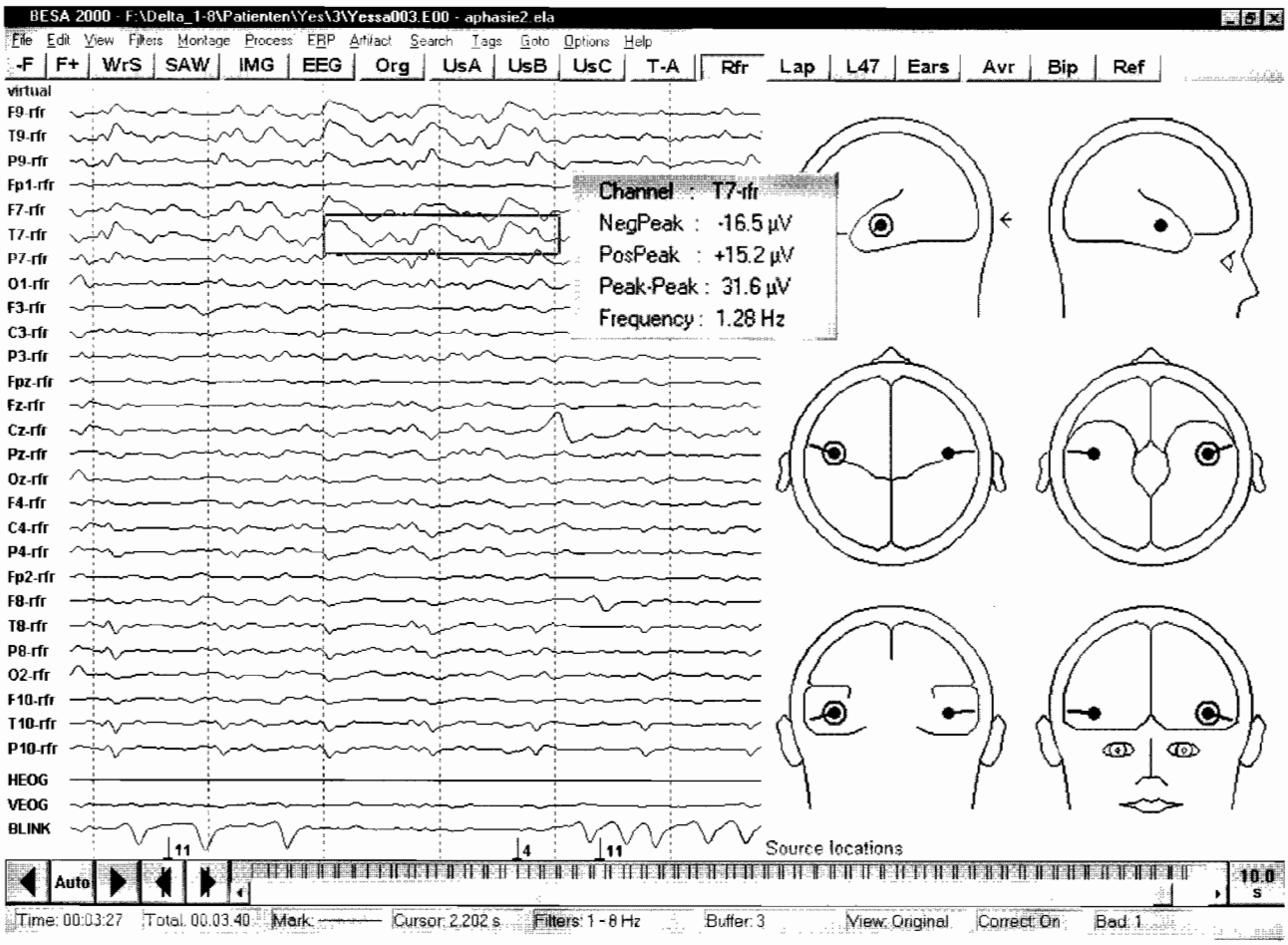

Figure 1. Display example of BESA 2000 used for dipole localization. The traces represent sections of EEG from an aphasic patient. Slow waves, visible upon inspection, are marked in the left part of the display for a left fronto-temporal channel (T7); these are examples of those slow waves, which would be averaged for equivalent dipole modeling. Right: A model consisting of two symmetrically located equivalent dipoles was fitted to the data. The strength of the regional source is indicated by the black circled dot symbols in the left-side schematic heads.

indicated the significant improvement ($p < .05$) from the first to the third session (i.e., within 11.1 months on average since lesion), whereas the change from the third to the fifth session was not significant. Fluent aphasics improved more than nonfluent [Syndrome × Session, $F(2,18) = 9.87$, $p < .01$]. Post hoc Scheffé tests confirmed that fluent aphasics tended to be better than nonfluent aphasics ($p < .08$), and that only fluent but not nonfluent aphasics improved significantly from the first to the third session ($p < .01$).

Performance in the semantic categorization task (reaction time and errors) did not change significantly across sessions [RT: $F(2,18) = 0.64$; errors: $F(2,18) = 3.33$[3]].

The grand average *delta amplitudes* in Session 1 were larger for patients (5.05 μV) than controls [3.60 μV; group, $F(1,19) = 7.00$, $p < .02$; see Table 2 for individual averages].

Because amplitudes measured during the first session were pronounced over the left hemisphere in patients and very small in controls, the laterality index (LI) differed significantly between groups [main effect for group, $F(1,19) = 15.8$, $p < .001$] being +.12 in patients and −.01 in controls. Analysis of delta amplitudes averaged for regions of interest (ROI) indicated that group and laterality differences were more pronounced over posterior than anterior regions [see Figure 2; Group × ROI × Hemisphere, $F(1,19) = 8.53$, $p < .01$; Group × Hemisphere, $F(1,19) = 10.93$, $p < .01$; ROI × Hemisphere, $F(1,19) = 8.10$, $p < .05$; group $F(1,19) = 8.33$, $p < .01$].

In controls, a change in (the small) delta amplitudes across the two recording sessions was not significant, $F < 1$. In aphasics, changes in delta amplitudes varied considerably between subjects and therefore were not analyzed parametrically. Comparisons within the patient group indicated a tendency for decrease of left-posterior delta amplitudes from the first to the fifth session (for the Wilcoxon signed rank test, $Z = -1.96$, $p = .05$). In the third and in the fifth sessions, nonfluent aphasics showed higher delta amplitudes than fluent aphasics in the left and right anterior ROI (Mann–Whitney U tests, $p < .05$).

Source localization was applied to estimate the approximate individual generator locations of delta activity. The source of

[3]Patients displayed poorer performance when compared to controls in the first session. Analyses of variance confirmed main effects for group for RT, $F(1,18) = 19.58$, $p < .01$, and error rate, $F(1,18) = 4.71$, $p < .05$; as data were missing for 1 patient, analyses refer to 10 patients and 10 controls.

Table 2. *Integral Amplitudes (in Microvolts) in the 1–4 Hz Frequency Band*

	Patients				Controls			
	Anterior		Posterior		Anterior		Posterior	
Subject	Left	Right	Left	Right	Left	Right	Left	Right
1	4.36	3.96	6.96	4.52	3.50	3.46	3.78	3.72
2	2.56	3.14	3.20	2.88	3.56	3.28	3.14	3.20
3	6.48	4.46	5.64	4.42	3.14	3.28	3.30	3.12
4	4.74	4.82	4.74	3.72	3.10	2.86	3.12	2.96
5	5.68	4.52	5.28	3.76	3.20	3.56	3.30	3.56
6	2.24	2.68	2.20	2.08	3.18	3.20	2.52	3.14
7	6.22	6.26	7.82	4.28	4.00	4.22	4.28	4.62
8	4.82	4.34	4.66	4.50	4.10	4.00	3.54	3.36
9	9.10	6.46	11.28	5.40	2.92	2.90	3.26	3.02
10	4.06	3.36	5.22	3.32	2.98	3.38	3.50	3.68
11	6.94	5.04	10.18	5.10				
Means	5.20	4.46	6.11	4.00	3.37	3.41	3.37	3.44

delta activity was modeled as resulting from a single equivalent dipole per hemisphere and averaged separately for each subject. Its location in the vicinity of the structurally affected area is illustrated in Figure 3 for 2 subjects by overlaying it onto the individual MRI scans.

As described above, dipoles could be localized in this region in 7 of the 11 aphasics. In all 7 patients in which modeling was possible, dipole strength was significantly more pronounced in the left than in the right hemisphere (hemisphere, $F(1,6) = 32.37$, $p < .01$; see Table 3 for dipole amplitudes). Across sessions, dipole location remained rather stable ($F < 1$ for x-, y-, z-axes; see also Figure 3). In contrast, dipole strength in the left hemisphere decreased significantly, mainly from the first to the third recording [Session × Hemisphere, $F(2,8) = 12.37$, $p < .01$; session, $F(2,8) = 7.16$, $p < .05$; post hoc Bonferroni/Dunn for the comparison first–third $p < .05$, for first–fifth $p < .05$, for third–fifth n.s.].

Higher delta dipole strength in the first session correlated with poorer improvement of language functions, that is, less change in the Aachen Aphasia Test profile with $r = -.51$ (n.s., because of the small subgroup of $n = 7$, for which dipole modeling was possible; when one-tailed testing is accepted: $p > .1$). Those 3 patients with the highest dipole strength in Session 1 showed the smallest increases in the test profile, and those 3 patients with the smallest dipole strength in Session 1 displayed the most pronounced increase in test profile scores.

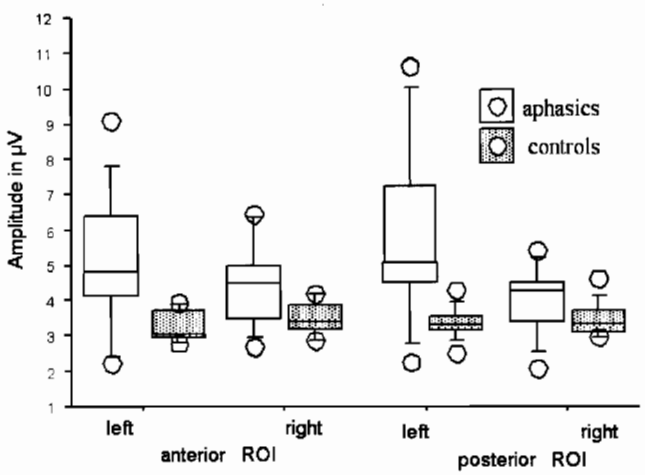

Figure 2. Box plots illustrating the triple interaction Group × ROI × Hemisphere, which resulted from the larger delta amplitudes (ordinate in microvolts) over the left posterior ROI in aphasics compared to controls. Open boxes represent the aphasic sample, shaded boxes the control sample.

Discussion

In line with previous studies (e.g., Nagata et al., 1989), the present study demonstrates that regional concentration of slow-wave activity can be determined from the surface EEG following cerebral lesions. In the present study, we verified this finding in *aphasic* patients using source localization procedures. The known evidence of pronounced delta activity in the surface EEG over the affected hemisphere in neurological patients is supported by the present results of (a) pronounced left- but little right-hemispheric delta amplitudes in patients who had suffered from left-hemispheric lesions, (b) little such activity in healthy subjects, and (c) a pronounced dipole moment of the dipoles located in the left hemisphere relative to minute strength in the right hemisphere for all of the patients. Moreover, projection of delta dipole location onto individual MRI (in 4 patients) confirmed the focus of slow-wave generators in the vicinity of the structural lesion. The source localization procedures in this study confirmed the stability of the dipole (and thus generator) location across a 2-year period, during which five recordings were obtained in all 7 patients.

Substantiated by imaging methods (e.g., Heiss, 2003; Kamada et al., 2001; Nagata et al., 1989), abnormal focal slow waves have been considered an indication for neuronal tissue affected by adjacent ischemic or hemorrhagic lesions, and, hence, a measure of disruption of normal brain functioning. The present results support this by the relationship of slow-wave activity to the degree of impairment and the change in delta amplitudes and delta dipole strength across the first year of recovery in aphasia.

Focally generated slow waves have been attributed to changes of metabolism and blood flow consequent upon ischemia or hemorrhage (de Weerd et al., 1988; Kamada et al., 2001; Tanaka et al., 1998; Vieth et al., 2001). Recovery from these metabolic changes, reduction in edema surrounding the site of lesion,

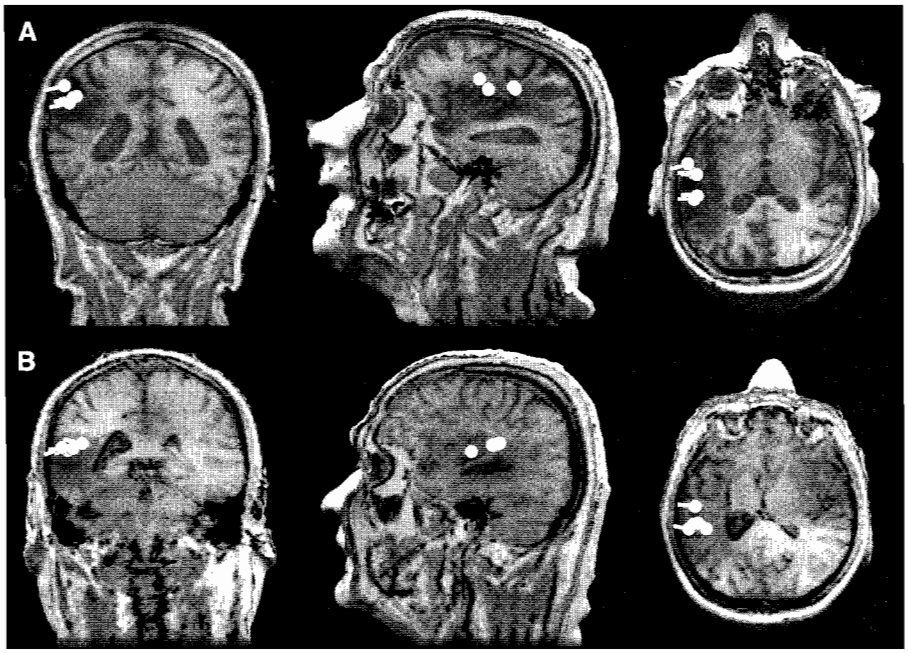

Figure 3. Examples of two patients in whom dipole locations are overlaid on their individual MRI (left = left hemisphere in the coronal, sagittal, and transversal plane). The five dipoles marked by white circles indicate the dipole fits for the five different measurements. The similarity of both locations and orientations of dipoles across sessions indicates stability of the neural generators over a 2-year poststroke period.

reversal of diaschisis (Cappa, 1998), or reperfusion in language areas have been observed in aphasic patients within the first year after the stroke (for review, see Goldenberg, 1997; Pizzamiglio, Galati, & Committeri, 2001) and parallel to improvement of language functions (e.g., Hillis & Heidler, 2002). The present results support this, in that significant reduction of delta amplitudes and delta dipole strength were found from the first (maximum 3 months after the stroke) to the third (average 11 months after the stroke) recording, but no more from the third to the fifth (2 years after the stroke) measurement.

Language functions, evaluated by means of a neuropsychological test, improved parallel to the changes in slow-wave activity. Although it is tempting to link the change in slow-wave activity and the improvement of language functions, and accordingly interpret the functional significance of slow-wave activity as an indication of dysfunction of language-related brain areas, such hypotheses remain to be validated and alternative explanations have to be considered. Because task performance did not change parallel to delta activity measures, the latter can hardly be explained as a consequence of improved nonspecific functions, for example, attention or practice. Still, validation of such a link requires assessment in a larger sample or more detailed correlation of functional gains and a finer time resolution of changes in delta activity. Analyses should also rule out parallel but not interrelated changes in language improvement. Finally, a further validation might include the manipulation of this relationship by, for instance, specific treatment intervention. If excessive focal slow-wave activity defines the dysfunctional state of areas involved in language functions, a training designed to activate those areas should induce a change of slow-wave activity. First support for such a functional relationship comes from investigations in which we observed systematic attenuation of abnormal slow wave after intensive aphasia therapy (Meinzer, Barthel, Djundja, & Rockstroh, 2003; Pulvermüller et al., 2001). Taken together, source imaging of abnormal brain waves may be a valuable tool in the investigation of recovery of function after brain lesion.

Table 3. *Mean Dipole Amplitudes in Nanoamperes between 50 and 300 ms*

	Session 1		Session 3		Session 5	
Patient	Left	Right	Left	Right	Left	Right
1	92.94	6.98	58.15	13.84	50.44	12.64
3	129.54	31.04	48.84	12.53	43.53	10.52
5	61.39	13.75	31.22	9.92	37.01	7.72
7	90.11	7.36	60.96	10.89	58.78	5.01
9	103.81	15.51	119.81	18.64	137.99	15.48
10	122.94	16.76	110.17	21.60	112.70	9.54
11	105.70	8.38	86.36	28.12	213.37	49.85
Means[a]	99.38	15.18	61.87	13.76	60.49	9.09

[a]The means exclude Subjects 9 and 11. Subject 9 had epileptic seizures between Sessions 1 and 3. Subject 11 had seizures between Sessions 3 and 5. For these subjects, delta amplitude increased after the seizures.

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