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Generators of the intracranial P50 response in auditory sensory gating

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Abstract

Clarification of the cortical mechanisms underlying auditory sensory gating may advance our understanding of brain dysfunctions associated with schizophrenia. To this end, data from 9 epilepsy patients who participated in an auditory paired-click paradigm during pre-surgical evaluation and had grids of electrodes covering temporal and frontal lobe were analyzed. A distributed source localization approach was applied to intracranial P50 response and Gating Difference Wave obtained by subtracting the response to second stimuli from the response to first stimuli.

Source reconstruction of the P50 showed that the main generators of the response were localized at the temporal lobes. The analysis also suggested that the maximum neuronal activity contributing to the amplitude reduction at the P50 time range (phenomenon of auditory sensory gating) is localized at the frontal lobe.

Present findings suggest that while the temporal lobe is the main generator of the P50 component, the frontal lobe seems to be a substantial contributor to the process of sensory gating as observed from scalp recordings.

Keywords

Auditory EP; P50 response; gating; neuronal generators

Introduction

The P50 component of the auditory Evoked Potentials (EP) is elicited around 45-75 ms after the presentation of an auditory stimulus. This EP component is also known as the P1 component or the Pb complex (Yvert et al., 2001). In healthy subjects when paired click stimuli (interval

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about 500 ms) are presented, the second stimulus usually elicits a much smaller amplitude response for the P50 (Dolu et al., 2001;Waldo and Freedman, 1986). The current leading psychological interpretation of the P50 amplitude decrement in the normal population is that a continuous stream of incoming auditory information is gated or screened — that is, redundant or potentially irrelevant information is filtered out — in order to prevent overloading the limited capacities of higher-order stages of auditory information processing.

Specific interest in the P50 response was stimulated by a number of studies which demonstrated poor suppression of the P50 amplitude in a paired stimulus paradigm among schizophrenia patients. This finding has been proposed as a potential trait marker of brain dysfunctions associated with schizophrenia spectrum disorders (for review: Bramon et al., 2004). In this view, along with other possible brain dysfunctions, the gating mechanism in schizophrenia patients is impaired, leading to unfiltered transmission of auditory sensory information from primary auditory areas to hierarchically higher-order brain structures presumably located in prefrontal and frontal brain regions (for recent review on prefrontal and temporal lobe interactions see: Simons and Spiers, 2003).

The brain mechanisms subserving auditory sensory gating are not well understood. The P50 response is generated by the activity of neuronal populations, at which level there are several possible scenarios that may result in the phenomenon of gating:

Refractoriness of the P50 neural generators

(1) Neural generators of the P50 component may cease being active when physically identical information is retransmitted through the auditory sensory pathways and therefore activates the same neuronal populations. Although this interpretation of gating phenomena might appear plausible, based on well known refractoriness properties of individual neurons, mechanisms underlying EP refractoriness have not been determined at the level of neuronal populations (Javitt et al., 2000). The refractoriness of individual neurons may contribute to auditory sensory gating, however this factor can not by itself fully explain the decrement in activity of complex neuronal assembles in which neurons utilize sophisticated interneuronal relationships to open a gate for transmission of auditory information within the P50 time window. At the level of auditory cortex neurons, long-lasting suppression of neuronal firing after the first click (time intervals from 128 to 512 ms) was found only in 50% of recorded neurons. But even for these neurons suppression of the activity might be caused by a suppression of the synaptic inputs they receive from apparently intracortical synapses (Wehr and Zador, 2005). Moreover, there is no reliable evidence that faster or more efficient recovery after stimulation in schizophrenia patients compared with healthy subjects can be explained by membrane-based mechanisms of refractoriness at the level of individual neurons. If refractoriness were a significant factor in mediating sensory gating, it would be expected that the neural generators of the response to the initial stimulus will be the same as for the second identical stimulus, but with a much lower magnitude.

(2) Neuronal mechanisms of the phenomenon of gating (expressed in inhibition of P50 response) might be triggered by the neuronal activity originating beyond the location of primary temporal lobe generators of P50 and occurring at the time period between first and second click. During the response to the second click an inhibitory signals might suppress activity of primary generators of P50 resulting in the phenomenon of gating observable from the scalp recordings. In this hypothesis, an additional generator becomes (for some reason) less active in patients with schizophrenia brains compared to healthy subjects.

Finally, it is possible that a *combination of the above mechanisms contribute to the function of sensory gating*.

Clarification regarding which scenarios contribute to the mechanisms of normal and pathological auditory sensory gating will further advance our understanding of brain dysfunctions associated with schizophrenia (Edgar et al., 2003).

Brain generators of auditory P50

The neuronal sources of the scalp-recorded P50 are difficult to localize due to the low signal-to-noise ratio and also because the P50 brain response is preceded and followed in time (within 10-15 ms) by several EP components with brain localizations and biological significance that are distinct from the P50 neuronal sources.

Animal studies suggested that neuronal activity at the hippocampus might contribute to sensory gating (Freedman et al., 1996), however human hippocampus recordings did not found P50-like activity within the hippocampus (Grunwald et al., 2003).

Auditory EPs recorded intracerebrally in Heschl's gyrus have identified (within the limits dictated by the electrodes implantation locations) the following EP components: N30 (27-30 ms range latency), P50 (45-50 ms), N60 (55-65 ms), and N75 (at 70-80 ms: Godey et al., 2001;Liegeois-Chauvel et al., 1994). Scalp recorded EPs suggest that the P50 is preceded by a positive peak at 29 ms (Pa or P30) and negative peak (inverting polarity at temporal electrodes) around 40 ms (TP41 or Nb see: Cacace et al., 1990;Woods et al., 1995;Yvert et al., 2001). Two subsequent EP components - Pb1 (peaking about 52 ms) and Pb2 (peaking about 74 ms) comprise what might be described as the P50 or Pb complex (Yvert et al., 2001). Magnetoencephalographic (MEG) studies of the magnetic counterpart of P50 (M50 or P50m) support these findings by demonstrating peak responses at latencies 30, 40, 50 and 75 ms (Ackermann et al., 2001;Hertrich et al., 2000,2004;Makela et al., 1994;Onitsuka et al., 2003).

Edgar and colleagues (2003) noted that in some studies identification of the P50 peak among preceding and following EP components was difficult since filters that remove high frequency noise may mask latency differences between relatively weak components surrounding the P50, thereby falsely producing a single peak. If two approximately equal amplitude peaks were present in the data around the P50 latency, researchers may pick up either the earlier (Hertrich et al., 2000) or the later (Edgar et al., 2003;Hertrich et al., 2004;Onitsuka et al., 2000) of these peaks for the P50/M50 analyses. This multiplicity of peaks might reflect distinct neurobiological processes having distinct anatomical locations. For instance, it was shown that components characterized by peaks at 46 ms and 76 ms will behave differently with respect to the stimulated ear (Ackermann et al., 2001).

The relatively dense chronology of activations associated with sound processing in the time window around the P50 suggests that information about neuronal sources may be obtained only with high temporal resolution techniques. Due to its unsurpassed time resolution, the majority of attempts to localize P50/M50 generators have used MEG (Edgar et al., 2003;Hanlon et al., 2005;Onitsuka et al., 2000;Reite et al., 1988) and scalp recorded EP (Cardenas et al., 1993;Weisser et al., 2001).

From the methodological perspective scalp recorded EP is most commonly used way of recording P50 and phenomenon of gating. This approach allows the investigation of large clinical populations (Bramon et al., 2004;Heinrichs, 2004), effect of medications (Freedman et al., 1983;Light et al., 2000;Nagamoto et al., 1996) and genetic factors (Freedman et al., 2005;Myles-Worsley et al., 1996) associated with P50 gating. However, there are several limitations that reduce spatial resolution of P50 source localization methods using scalp EP data. One problem is that scalp recorded EP is a result of summation of all possible simultaneously active neuronal generators at the given time period. This makes separation and localization of individual P50 generators more difficult. Another problem is that currents that

determine the EEG potential differences are determined both by the topographies and electrical resistivities of the various kinds of tissue between the source and the head surface (Tepley, 2005). Some of these problems can be overcome with MEG approach. MEG studies of P50 gating provided valuable information about temporal lobe generators of P50 and a lateralized deficit in sensory gating for schizophrenia patients (Hanlon et al., 2005;Thoma et al., 2003). Since there is rapid attenuation of magnetic fields generated by neuronal sources, MEG offers a high spatial resolution for locating the position of reconstructed cortical sources. However MEG is less sensitive to brain generators that have radial orientation with respect to the magnetic sensors. Beginning with the first MEG attempts to localize P50/M50 sources (Huotilainen et al., 1998;Reite et al., 1988), it was suspected that, along with the conventionally observable pair of bilateral supratemporal sources, one or more additional generator(s) may contribute to the P50 response recorded by scalp EEG (Edgar et al., 2003). Indeed, studies suggest that the P50 is an overlapping potential (Onitsuka et al., 2000) that might receive contributions from another hypothesized source (presumably frontal; Weisser et al., 2001) that apparently is not detected reliably by MEG due to its orientation with respect to the MEG sensors. Simultaneous recording of P50 and M50 suggested activity of neuronal generators contributing to P50 which are not detectable by MEG (Huotilainen et al., 1998). According to the recent study (Huang et al., 2003) bilateral superior temporal gyrus generators of EP might account for 97% of scalp recorded variance of the signal at the latency between 30 and 100 ms in normal subjects and significantly less (86%) in schizophrenia patients. The authors hypothesized that putative non-temporal generators are highly synchronous with temporal sources and probably localized in hippocampus or thalamus (Huang et al., 2003).

The present study attempted to overcome the limitations of MEG (Halgren, 2004) in localizing P50 generators by recording P50 components intracranially over a relatively large cortical area covered by a dense electrode array. This was achieved during clinical diagnostics performed for the pre-surgical evaluation of epilepsy, on a select group of surgical candidates admitted for seizure recording via chronically implanted subdural strip and grid electrodes (Spencer et al., 1997). As any other methodological approach intracranial recordings from the human cortex have certain limitations. The recorded signal can characterize neuronal activity that mainly originated from the cortical areas that are covered by the electrode array. Variability of individual brain shapes and positions of electrodes makes it difficult to perform any type of group data analyses. A previous study from our group indicates that epileptogenic processes did not significantly affect P50 gating (Boutros et al., 2006). Similarly, Weate et al. (1995) found normal scalp-recorded P50 sensory gating in patients with frontal lobe epilepsy. Nevertheless, we applied in the present study strict patient inclusion criteria with respect to the “normality of EP morphology” in order to minimize possible effects of epilepsy. The main goals of the present study were to localize brain generators of the intracranial P50 response, and to evaluate the changes in activity of these generators during auditory sensory gating.

Methods

Subjects

Nine patients (aged 21-41 years, mean 33.8 ± 7.2 years; 2 males) who met the following inclusion criteria were chosen for the present study. All patients had drug-resistant focal epilepsies which were evaluated presurgically in the Department of Epilepsy, University of Bonn, Germany. None of these patients suffered from hearing deficits according to careful clinical examination and patient's history. Furthermore, there were no patients with severe cognitive deficits or low intelligence according to standardized neuropsychological examination, which is part of pre-surgical evaluation in epilepsy (Helmstaedter et al., 2003). Since preparation of the patients for the recording procedure required some time, patients who smoke cigarettes had to abstain from smoking at minimum one hour before the actual

recordings took place. Furthermore, patients have to abstain completely from smoking during the total clinical monitoring phase (1-3 weeks) which was always preceding the P50 recordings in our study. Due to the severity of their disease, 8 patients were on polytherapy and only 1 on monotherapy with anticonvulsant drugs at the time of the P50 recordings. Most patients suffered from complex partial seizures (see Table 1) which are characterized by an impairment of consciousness.

The study was approved by the Institutional Review Boards of Bonn and Yale Universities, and all patients gave informed consent to the procedure. Intracranial electrodes in these patients were placed on frontal and temporal lobe locations (Behrens et al., 1994). The electrode array consisted of strips and/or grids with stainless steel contacts (diameter of 2.2 mm) embedded in silastic (interelectrode spacing of 1 cm). Five patients had grids placed on the right hemisphere and four patients had grids placed on the left hemisphere.

In order to minimize the influence of epileptogenic processes on the results of the present study, and at the same time to obtain recordings from broad neocortical areas, the following subject inclusion criteria were applied to the candidates for the present study from the pool of available participants. A.) A subject's intracranial auditory EP components examined within an interval of interest (from 20 to 200 ms) must exhibit morphologies (amplitudes and latencies) that closely correspond to well-known normative parameters of auditory EP in normal population (Picton et al., 1974). These morphological parameters of EP denote a negativity (N1) that usually peaks at about 100 ms from stimulus onset and a positivity (larger or similar in amplitude) that peaks at around 180-200 ms. N1 is preceded by a small positivity, P50 or P1, which peaks at about 50 ms (Naatanen, 1992), B.) A subject should demonstrate normal sensory gating as indicated by at least 30% reduction of P50 amplitude (at least in one electrode) using the standard paired-click paradigm. C.) The grid of implanted electrodes should have more than 25 electrodes in order to sufficiently cover broad neocortical areas.

Data collection and analyses

During a recording session, 100 pairs of two identical tones (S1 and S2; sinusoidal waves, frequency 1500 Hz, Gaussian envelope, duration 4 ms, onset and decay phase of 1.2 ms each) were presented (intensity 85dB) binaurally via headphones with an interstimulus interval of 500 ms and an interpair interval of 8 sec (Zouridakis and Boutros, 1992). Patients were asked to listen to the stimuli without any additional task. All recordings were performed in a sound-shielded room which utilized a digital EPAS system (Schwarzer, Munich, Germany) and Harmonie EEG software (Stellate, Quebec, Canada). EEG/EPs were recorded from subdural strip and grid electrodes (sampling rate 1000 Hz per channel; bandpass filter setting .03 - 85 Hz, 12 dB/octave) referenced to both mastoids. EEG epochs were created with a time interval of 300ms (100 ms pre-stimulus and 200 ms post-stimulus), and digitally filtered with a bandpass of 1-45 Hz. These epochs were averaged separately for S1 and S2 stimuli. Baseline correction (100 ms pre-stimulus interval) was applied to the averaged data. For source localization, the data were digitally reformatted to a common average reference.

The P50 responses were measured from responses to the S1 (first) stimulus of the pair, whereas the gating responses were measured from difference waves (Gating Difference Wave or GDW) obtained by subtracting the response to S2 (second) stimuli from the response to S1 stimuli. The GDW was computed by point-to-point subtraction of the S2 waveform from the S1 wave form. We used the GDW to isolate a portion of the EP activity that is elicited by the presentation of the second stimulus in the pair, and to establish whether the phenomenon of gating is spatially and temporally distinguishable from processes underlying the P50 generation. Although the logic behind this subtraction procedure is commonly used to isolate the brain activity associated with particular operations in a variety of EP studies (Johnson, 1995), as well as studies using

positron emission tomography and functional MRI, to our knowledge it has not been widely (Arnfred, 2006) used in auditory sensory gating studies.

Point-to-point computation of GDW was chosen based on the following assumptions and considerations: (1.) GDW will allow isolate in time and space maximal and minimal amounts of changes in EP that can be regarded as a manifestations of gating phenomenon at the P50 time range. (2.) If peak latency of GDW will closely match with P50 response to S1 it might indicate that gating related changes can be explained by the changes in P50 amplitude and probably suggest that neuronal generators that is activated during the first tone involved in phenomenon of gating. This result will be in line with studies that did not find difference between S1 and S2 in P50 latency (Clementz and Blumenfeld, 2001;Jerger et al., 1992); if peak latency of GDW will not match with P50 response to S1 it might indicate that phenomenon of gating can be accounted for latency shift of P50 response to the S2 that was observed in the recent study (Thoma et al., 2003). (3.) In either case phenomenon of gating at the P50 time range can be triggered by other neurobiological processes that do not exist during generation of P50 response to S1. A hypothetical candidate for these gating related processes might be hippocampal activation that has been reported at 250 ms after S1 (Grunwald et al., 2003). (4.) Establishing correspondence between brain localization of gating related changes (using GDW) and brain localization of P50 generators that are active during response to S1 might give a better understanding of these neurobiological processes. Ideally speaking in normal, healthy subjects P50 response to the S2 should be reduced in amplitude very significantly or totally absent. This would be an indication of “perfect gating”. In the reality it was reported that due to low signal to noise ratio localization of M50 dipoles was not possible in 30.8% of the patients and normal controls (Huang et al., 2003). In this situation implementation of GDW as a measure of gating-related changes is very convenient tool for brain localization of neuronal activity associated with gating, even in case of “perfect gating”.

To localize sources of our intracranial P50 data, we used the LORETA algorithm (Pascual-Marqui, 1999 as implemented by the CURRY software package, Neuroscan, Compumedics Ltd.) because it allows many distributed sources to be concurrently active in the current density reconstructions, without assuming a limited number of dipolar sources (for reviews on source reconstruction methods, see (Fuchs et al., 1999;Yao and Dewald, 2005).

Physical anatomy (Fig. 1a, 1c, and 1d.) along with positions of grid electrodes (Fig. 1a, 1b, and 1d.) were obtained from individual magnetic resonance (MR) images. Subject-specific source space models utilized high-resolution (approximately 5000 nodes) three-dimensional reconstructions of cortex. Thus, LORETA solutions were constrained to cortex (thickness approximately 2.5 mm; Figs. 1d, 1f, and 1g) based on the assumption that the recorded electrical activity was generated primarily by pyramidal cells in cerebral gray matter. However, to avoid over-sensitivity to cortical segmentation quality, we did not impose a cortex-normal orientation constraint, but employed a source model that permitted omni-directional current flows. Our volume conductor models likewise utilized individual MRs to segment head tissue compartments (brain, skull, scalp), within which conductivities were assumed to be homogeneous, isotropic and ohmic. The boundary element method (BEM) was used to solve the forward problem.

For obtaining brain geometry post-surgery MRIs, if possible, were used. In some cases, however, due to imaging artifacts caused by presence of large grid of electrodes, the MRI segmentation algorithm failed to adequately segment the cortical surface. In these cases pre-surgery MRIs were used for obtaining segmentations of the brain and cortex. Nevertheless, it should be noted that low-quality cortex segmentations (as can be seen for example in fig. 3 for subject 5) are not expected significantly affect source localization results as long as the spatial sampling of the source space is sufficiently dense. A significant effect is only to be expected

when cortical normals are used as a prior, which is not the case in this study (Fuchs et al., 1999). Forward calculated fields and potentials are much more sensitive to small changes in source orientation than source location. Consequently, in this study, a rotating source model was used in order to minimize the effects of suboptimal cortex segmentation.

LORETA algorithm solutions were calculated for each time point within the P50 and GDW time window. This was determined from each individual patient's EP and ranged usually from 40 to 75 ms. The time range for identification of P50 (also known as P1 or Pb and Pb1) was chosen based on the number intracranial (Godey et al., 2001;Liegeois-Chauvel et al., 1994), scalp (Woods et al., 1995) and MEG (Hertrich et al., 2000;Yvert et al., 2001) studies suggesting that this time range is appropriate for P50 data analyses. If in this time range 2 positive peaks were observable it was regarded as Pb complex (Yvert et al., 2001). Usually Pb complex consists of one EP component peaked around 50 ms and another around 60-70 ms. In this situation the peak that was close to the 50 ms time mark was identified as P50. Since we assume that GDW should reflect gating of P50 response the similar time window was used for GDW peak latency detection.

Using the method described by Fuchs et al. (1999), a current density regularization parameter lambda was optimized so that the residual deviation equaled 1/SNR (signal to noise ratio) for the latency yielding the highest SNR in the examined time range. Then a search for the minimum residual deviation was performed across the time window. If the found minimum was within 5-7 ms range from the EP peak latency of the electrode having the most prominent P50 (GDW) response, the corresponding solution was accepted as appropriate. Otherwise, the solution for the EP peak latency was chosen.

Results

Single-channel examples of prominent intracranial P50 (and corresponding GDW) recordings for each individual subject are illustrated in the Figure 2. In line with our selection criteria, these EP morphologies are close to normative, and evidently were not heavily affected by epilepsy.

Considerable heterogeneity of the voltage grid distribution (Fig. 3 and 5) and sources of P50 (Fig. 4 and 6) across all subjects can be accounted for uniqueness of the grid position and geometry of brain anatomy inherent to each studied patient.

Right Hemisphere

Despite considerable variability of grid locations and voltage distributions (Fig. 3) across individual subjects, all right hemisphere source reconstruction results localized P50 generators in the temporal lobe (Fig 4, left panel).

In all subjects results of source reconstruction indicated that primary global maximums of gating-related changes (reflected by the GDW) were not localized in the vicinity of temporal lobe generators of P50 (Fig. 4, right panel). While in Subjects 1 and 2 loci of global maximum of gating-related changes in P50 generators were not observable at the temporal lobe in Subjects 3, 4, and 5 some local maximums of gating-related changes of neuronal activity were localized beyond the temporal area that was active as a P50 response to the first stimuli (Fig.4, see sizeable changes in location of the LORETA solutions; subjects: 3-5; right panel).

Frontal lobe generators of P50 were observed in two cases (Fig.4, left panel, Sub.1 and Sub. 4) out of the four for which frontal lobe grid coverage was available (Subjects: 1-4). In each of these four subjects source reconstruction of gating-related changes (reflected by the GDW) localized global maximum in the right frontal lobe (Fig. 4, right panel, Subjects. 1-4). In the

two subjects who exhibited identifiable frontal lobe P50 generators (Subs. 1 and 4), localization of the gating activity reflected by the GDW was found near the P50 frontal lobe generators.

Although in some subjects the peak latency of the source localization solutions were not identifiable; based on the LORETA solutions across all subjects, the latency for the GDW (mean±SD: 60.4±8.5) had a tendency to be later than the P50 latency (mean±SD: 51.8±4.3).

Left Hemisphere

Signal to noise ratios for the left hemisphere recordings (mean±SD, for S1: 2.57±0.7; for GDW: 2±0.5) were lower than in right hemisphere (mean±SD, for S1: 3.6±0.59; for GDW: 2.52±0.43). This might explains the reduced consistency of our LORETA results in the left hemisphere relative to the right hemisphere.

Nevertheless, the main trends of brain activity in the left hemisphere were similar to those we found on the right. Source reconstruction of left hemisphere recordings showed temporal lobe loci of maximal generator activity that contributed to P50 generation (Fig.6 left panel Subjects. 6, 8, and 9). It can be noted that in two of four subjects (Fig 6, left panel, Subs. 6 and 8), temporal lobe generators were localized in the vicinity of the temporal-parietal junction. The localization of P50 generators in this area of the temporal lobe might explain the absence of temporal lobe generators in Sub. 7 since his/her temporal-parietal junction was not sufficiently covered by the electrode array (Fig 4 and 5, Sub.7). Similarly to right hemisphere data, left hemisphere source modeling of GDW showed that primary maximum of gating-related changes were not localized at the temporal areas of P50 generator activity in two subjects (Fig 6, right panel, Subs. 6 and 8). In two other subjects local maximum of gating-related changes in generator activity were observable beyond temporal-parietal junction that apparently was the locus of P50 generation (Fig 6, right panel, Subs. 7 and 9).

Left frontal lobe generators of the P50 response were observed in two subjects (Fig 5, left panel, Sub. 6 and 7). Each subject from the left hemisphere pool of patients exhibited gating-related changes of frontal lobe activity that is observable in GDW source reconstruction (Fig 5, right panel).

Discussion

A considerable body of research suggests that a large portion of the scalp-recorded P50 response may be explained by contributions from the temporal lobes (Huang et al., 2003). Our findings in the present study are consistent with these results. We demonstrated that a substantial part of the P50 generators found by the LORETA solutions are localized in temporal lobe areas. In addition to temporal lobe generators of P50, our results demonstrate frontal lobe activity during P50 generation in half of our subjects (on both left and right sides). This result is in line with EEG and animal studies demonstrating frontal lobe involvement in P50 generation (Grunwald et al., 2003;Mears et al., 2006;Weisser et al., 2001).

Since GDW is relatively new approach in P50 gating research for adequate interpretation of GDW results several aspects of these results should be taken in to consideration. First, GDW reflect changes that emerge in the brain activity before, during, and after S2 is presented. Therefore GDW at the P50 time range is reflecting changes of brain activity directly related to the process of gating. Second, brain localization of GDW does not explicitly show where response to the S1 or S2 is located but it provides direct information about the locations where changes of activity associated with gating occurring in the brain. Third, in the present GDW study we focused our interest to the maximum of gating related changes within P50 time range. While global maximums of GDW were found to be localized at the frontal lobe the local maximums apparently can be found at the temporal lobe areas.

Observation of the frontal lobe activity - especially frontal lobe activity changes during the process of gating - provide new empirical information about brain mechanisms of auditory gating. The difference between our findings in the frontal lobe and results from the previous attempts to model P50 generators might be explained in terms of differences between electric and magnetic signals recorded from the brain. While magnetic fields originating from neurons in Heschl's gyrus are usually oriented tangentially with respect to the head surface, and therefore may be readily detected, frontal lobe activity might have predominantly radial orientation, and thus may not be well evaluated with MEG sensors. In contrast to MEG studies (Edgar et al., 2003;Hanlon et al., 2005;Huang et al., 2003;Onitsuka et al., 2000;Reite et al., 1988;Thoma et al., 2003), the present study reflected electric signals sampled from relatively limited cortical areas using high density electrode arrays. These considerations may explain differences between our LORETA results and previous MEG-derived models of P50/M50 generators. It is possible that since the analog of frontal gating-related changes that was found in the present study was never reported in the MEG studies of gating it might mean that the frontal neuronal generators that underlie these gating related changes are less detectable by MEG due to their orientation with respect to MEG sensors.

Our finding that frontal lobe generators can contribute to auditory sensory gating (as assessed by GDW) is consistent with results demonstrating that patients with dorsolateral prefrontal damage have atypical sensory gating (Knight et al., 1999), and previous findings of our group indicating the participation of prefrontal cortex (Brodmann's areas 6 and 24) in P50 sensory gating (Grunwald et al., 2003). The most interesting aspect of our GDW modeling results is the finding that localization of frontal gating related changes were nearly identical with frontal P50 generators for the S1 stimulus (see Subjects 1, 4, 6, 7), which might suggests that gating related portion of the activity originated from frontal generators of P50 was absent as a response to the S1 stimulus. It is possible to suggest that this portion is reflection of inhibitory activity that might suppress or modulate activity of temporal generators of P50 resulting in the phenomenon of gating.

Summarizing, the data presented here provide new insights in the behavior of P50 generators at the moment of gating. Although these data should be interpreted with caution, as more subjects are needed before any firm conclusions can be drawn, current results raise the possibility that (along with other possible contributing factors) the following neuronal mechanisms might underlie the reduction of amplitude of the P50 when a second identical auditory event is processed by the auditory system. First, since major maximums of gating-related changes (GDW results) were localized in the frontal lobe areas it is possible to suggest that a cortical network localized at the frontal lobe plays an important role in providing mechanisms of gating. Second, since in the present study the amount of gating-related activity at the frontal lobe was relatively larger than at the temporal and number of MEG studies (Thoma et al., 2003;Huang et al., 2003) showed significant gating-related changes in the temporal lobe it is reasonable to suggest that combination of neuronal activity in these two brain regions result in the phenomenon of gating observable from the scalp recordings. Taking into account differences between the present results and MEG studies, it is possible that there is a difference in brain mechanisms of gating inherent in the frontal and temporal lobes. It is possible that a combination of these two mechanisms ultimately results in a reduction of the P50 amplitude to the second tone measured at Cz.

Since the frontal lobe generator of the P50 is activated about 10 ms later in time than the temporal lobe generator (Weisser et al., 2001), it can be regarded as a higher level of auditory processing that collects and probably stores the outcome of S1 processing, such as information about the physical parameters of the first stimulus.

The above observations suggest a number of possible pathophysiological mechanisms to explain the gating deficit of P50 component in schizophrenia. First, it is possible that the deficit can be explained entirely based on aberrations of the temporal sources of the P50 (intracortical synaptic depression mechanisms; Wehr and Zador, 2005). Alternatively, the data raise the possibility that an aberration of fronto-temporal interaction might contribute to the gating deficit.

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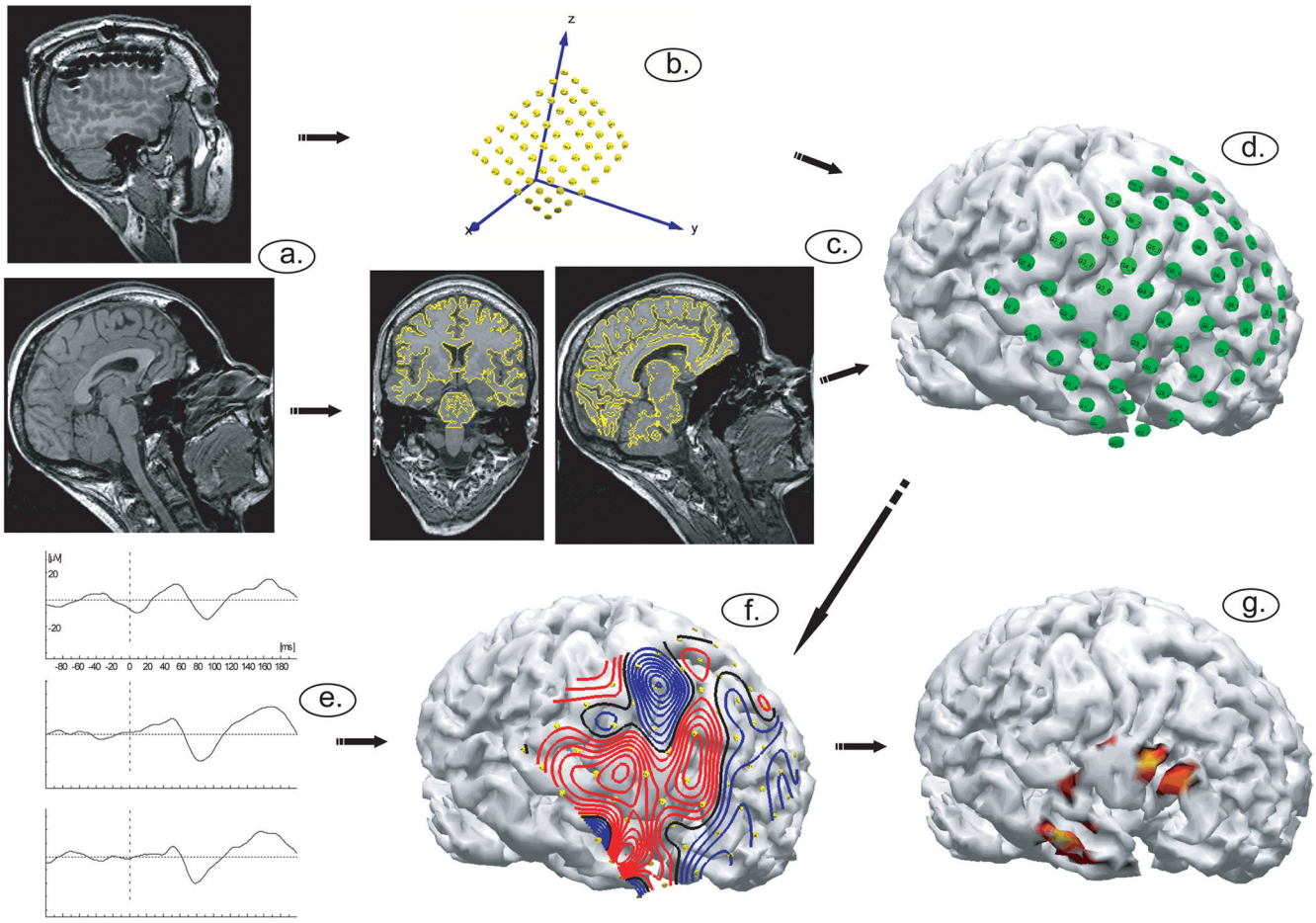

Figure1.

Schematic illustration of the LORETA source localization approach. a.) individual MRI image with intracranial electrodes; b.) position of intracranial electrodes derived from the MRI in 3-dimensional virtual space; c.) segmentation of the cortical surface derived from MRI; d.) grid electrodes superimposed on 3-dimentional reconstruction of individual cortex; e.) Evoked Potentials (EP) recorded from grid electrodes; f.) topographical map of recorded EP superimposed on reconstructed cortex; g) LORETA solutions superimposed on the anatomical cortical reconstruction for an individual brain.

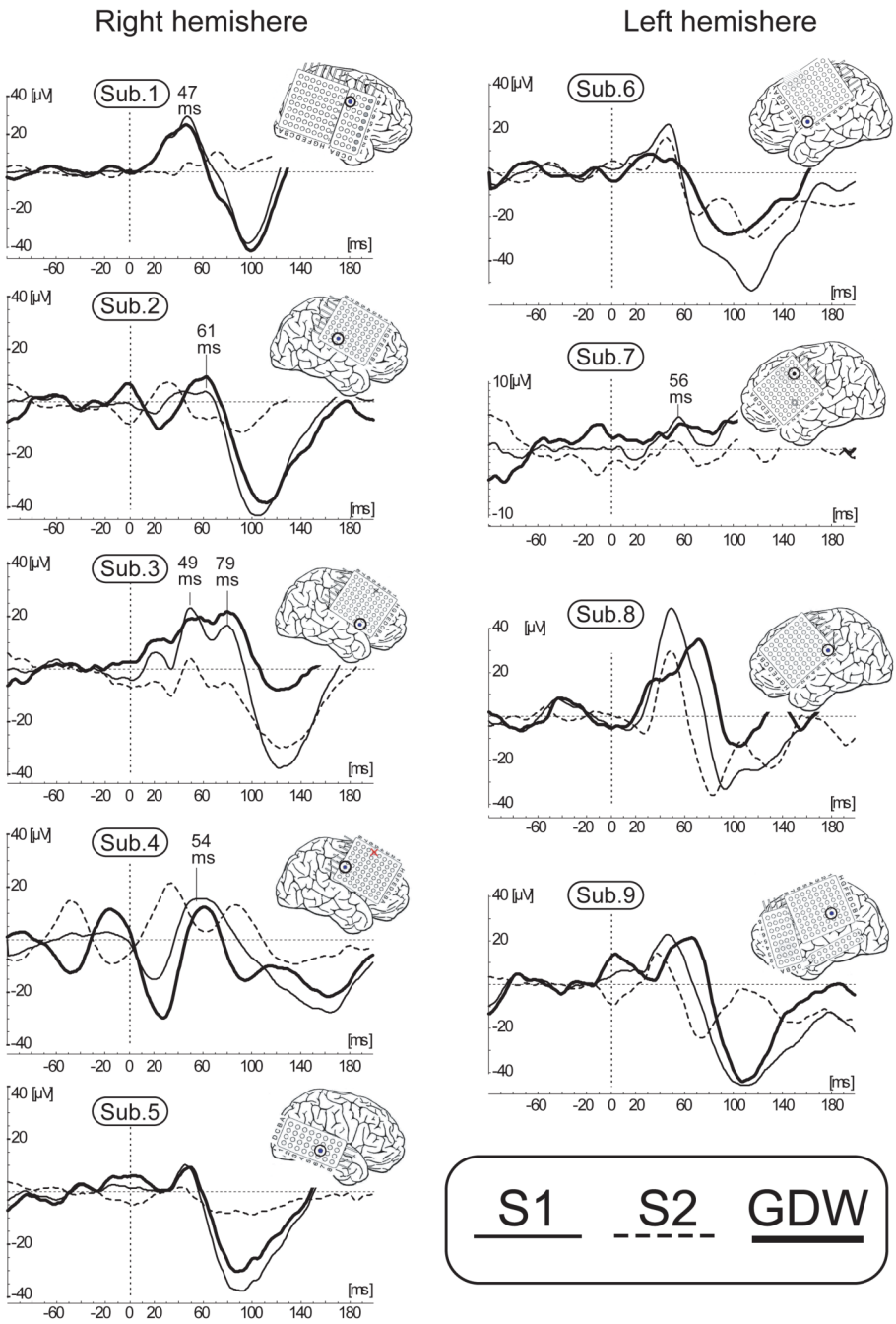

Figure2.
Illustration of EP morphology and GDW waveforms for each individual patient recorded at one of the most prominent electrode.

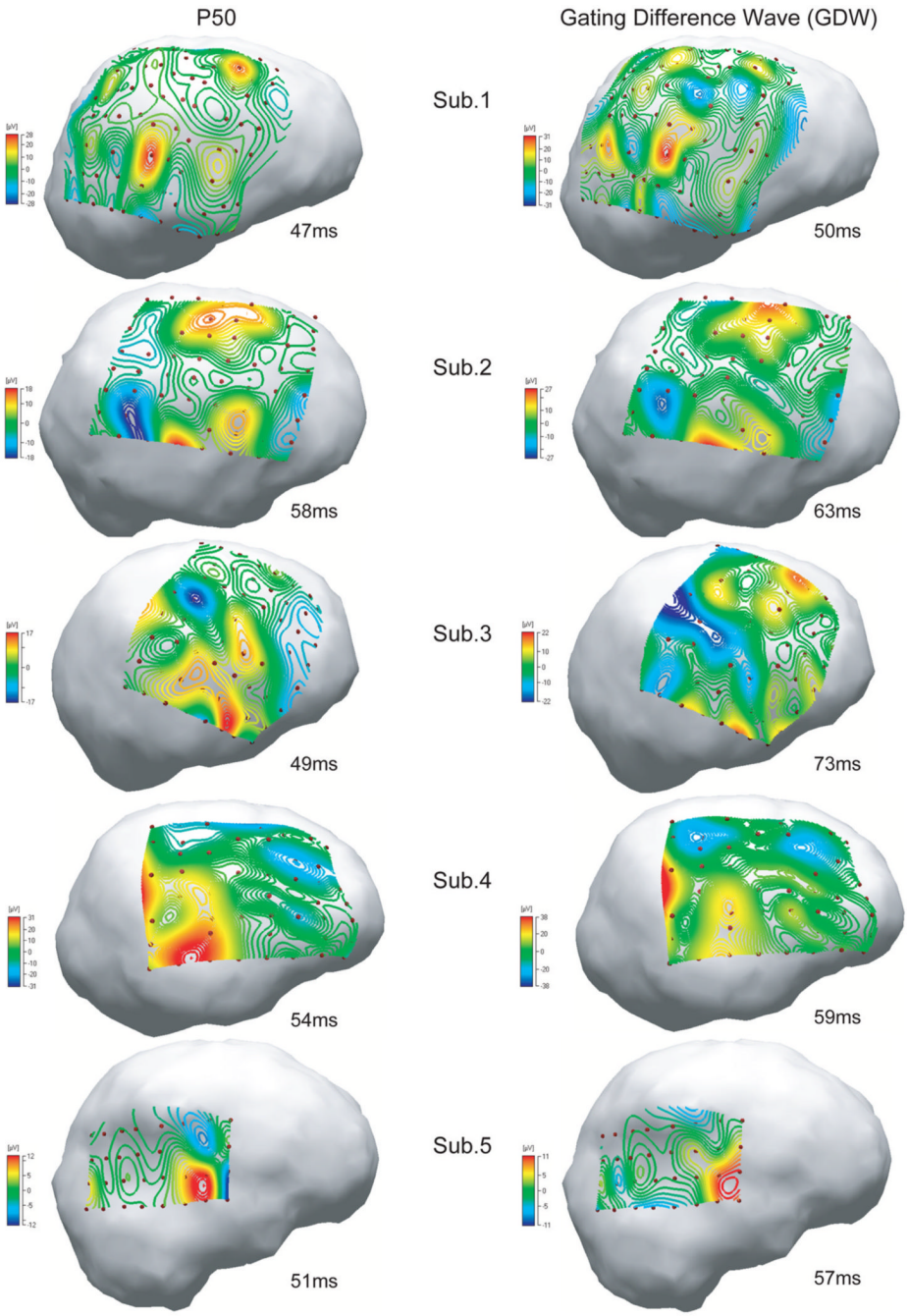

Figure3.
Results of data analyses for five patients who had grid of electrodes placed over the RIGHT hemisphere. Left panel: voltage grid distribution at the latency of P50 response to the first stimulus. Right panel: corresponding voltage grid distribution at the peak latency of Gating Difference Wave.

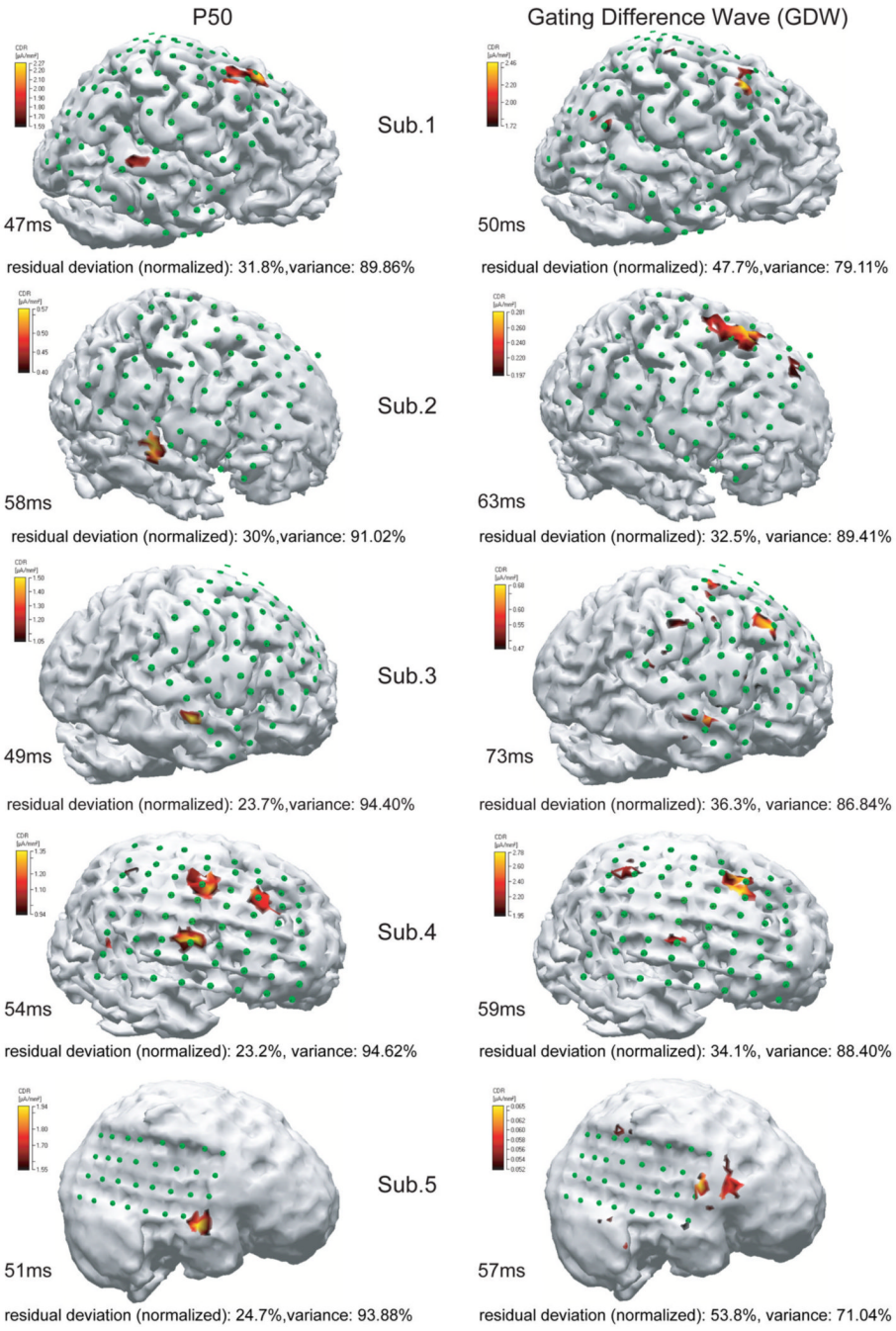

Figure4.

Left panel: LORETA results for the P50 source localization. Right panel: Localization results for the Gating Difference Wave source, also calculated with LORETA.

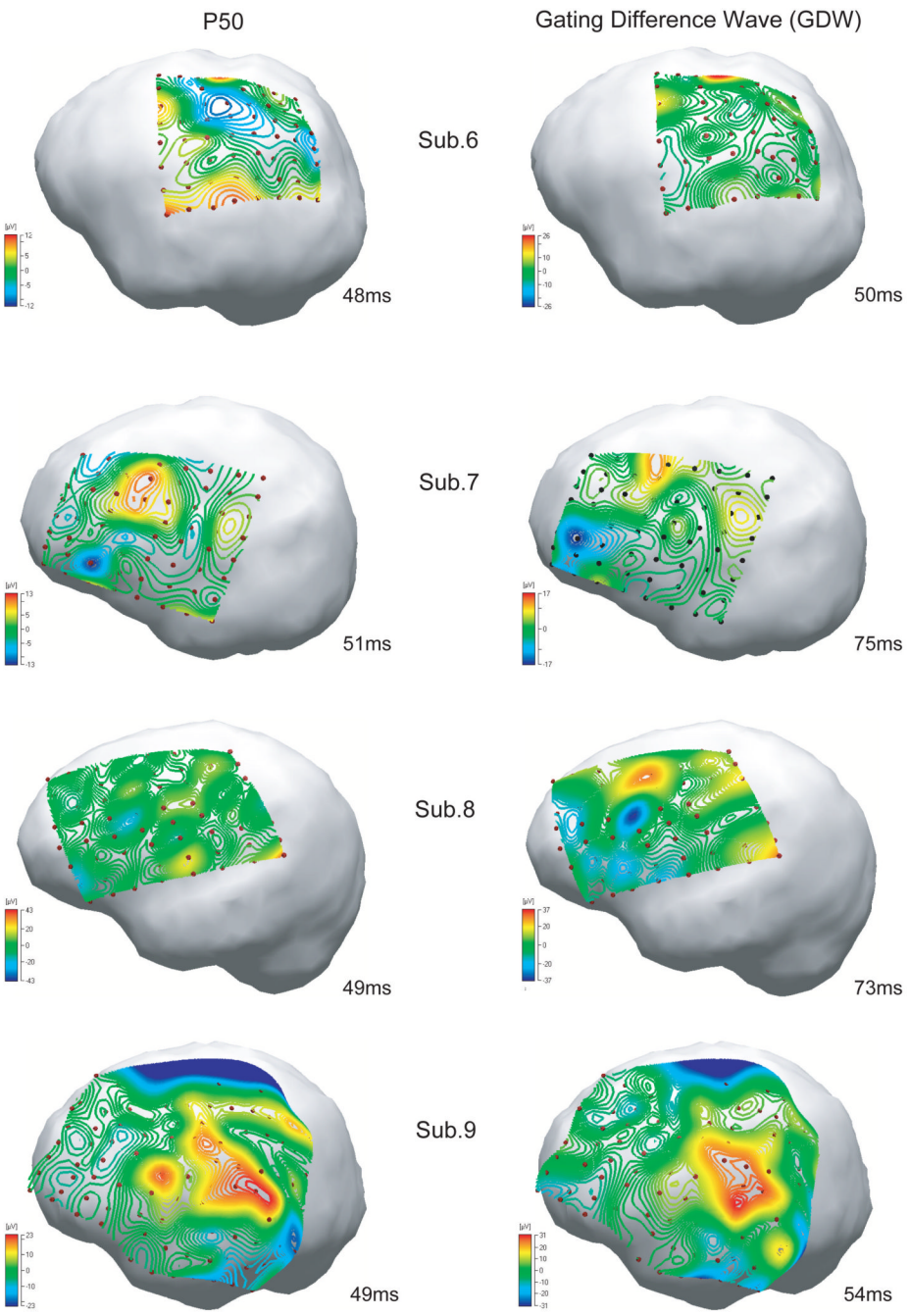

Figure5.
Results of data analyses for five patients who had grid of electrodes placed over the LEFT hemisphere. Left panel: voltage grid distribution at the latency of P50 response to the first stimulus. Right panel: corresponding voltage grid distribution at the peak latency of Gating Difference Wave.

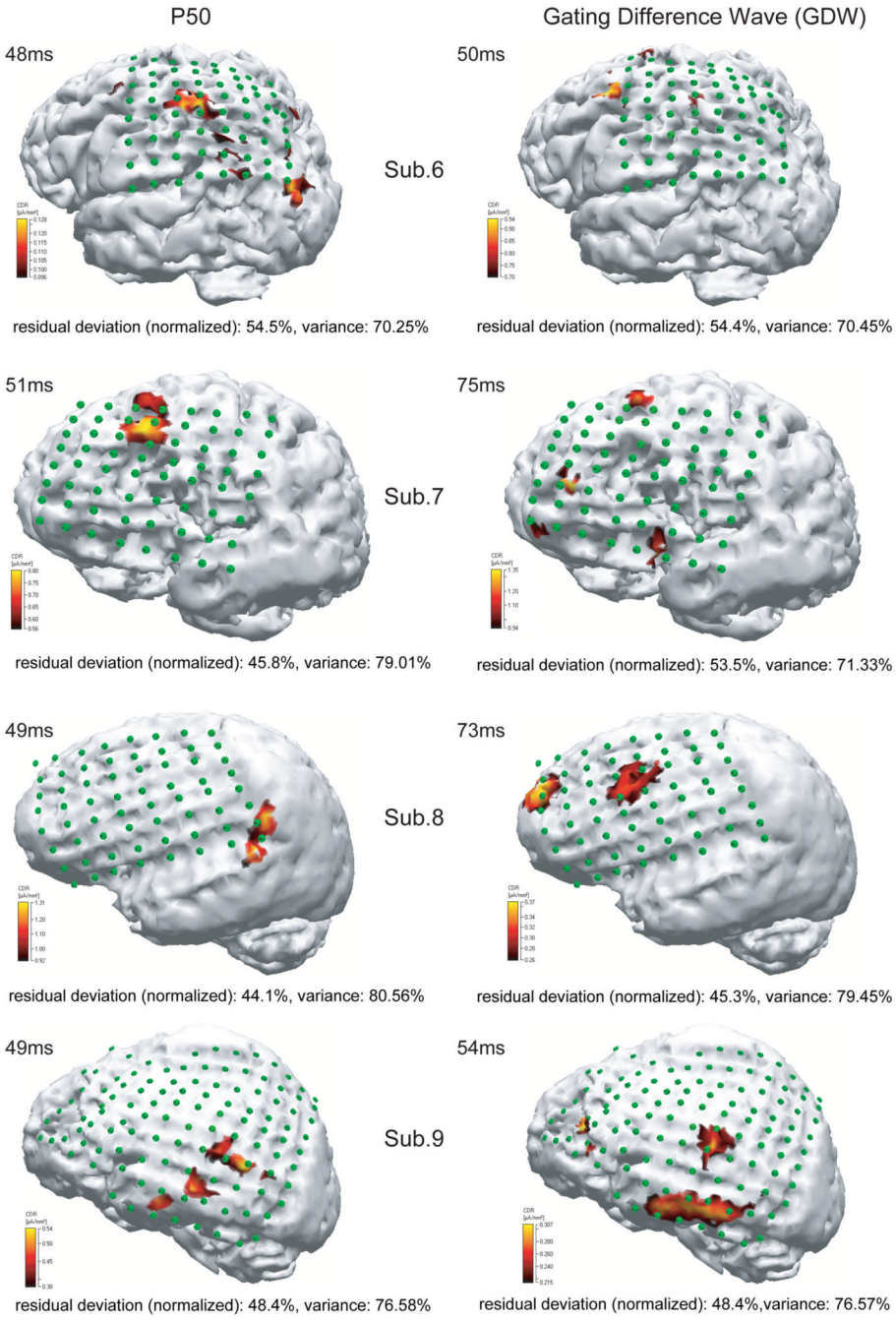

Figure6.
Left panel: LORETA results for the P50 source localization. Right panel: Localization results for the Gating Difference Wave source, also calculated with LORETA

Table. 1

Patients information.

patient	Age (ys)	age at onset (ys)	type(s) of seizures	MRI lesion	ictal onset	Gating (%)
Sub.1	24	11	sps/cps	HS (r), bilateral occipital	hippocampus (r)	26.5
Sub.2	21	4	cps/gtc	FCD (r) frontal	frontal (r)	30.3
Sub.3	34	12	cps/gtc	FCD (r) frontal	frontal (r)	61.2
Sub.4	31	3	sps	FCD (r) frontal	frontal (r)	32.9
Sub.5	39	28	sps/cps	HS (r), temporal (r)	temporal (r)	66.1
Sub.6	41	36	sps/cps	FCD (l) central	Central (l)	70.9
Sub.7	40	8	cps/gtc	defect (l) frontal	frontal (l)	32.3
Sub.8	35	3	cps/gtc	FCD (l) frontal	frontal (l)	68.2
Sub.9	40	6	sps/cps	no MRI lesion	frontal (l)	71.1

Seizure types: sps = simple partial seizures; cps = complex partial seizures; gtc = generalized tonic-clonic seizures. MRI lesions: HS = hippocampal sclerosis; FCD = focal cortical dysplasia Side: l = left; r = right. Gating: Gating ratio calculated as S2 amplitude divided by S1 amplitude multiplied by 100.