Published in final edited form as:

Psychiatry Res. 2007 July 15; 155(2): 121–133.

Towards a functional topography of sensory gating areas: invasive P50 recording and electrical stimulation mapping in epilepsy surgery candidates

Martin Kurthen^{*, **}, Peter Trautner^{*}, Timm Rosburg^{*}, Thomas Grunwald^{**}, Thomas Dietl^{**},
Kai-Uwe Kühn^{***}, Carlo Schaller⁺, Christian E. Elger^{*}, Horst Urbach⁺⁺, Kost Elisevitch⁺⁺⁺,
and Nash N. Boutros[§]

^{*}Dept. of Epileptology, University of Bonn, Germany ^{**}Swiss Epilepsy Center, Zurich, Switzerland ^{***}Dept. of Psychiatry, University of Bonn, Germany ⁺Dept. of Neurosurgery, University of Bonn, Germany ⁺⁺Dept. of Radiology, University of Bonn, Germany ⁺⁺⁺Department of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA [§]Dept. of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit Michigan, USA

Abstract

The filtering of sensory information, also referred to as “sensory gating”, is impaired in various neuropsychiatric diseases. In the auditory domain, sensory gating is investigated mainly as a response decrease of the auditory evoked potential component P50 from one click to the second in a double click paradigm. In order to relate deficient sensory gating to anatomy, it is essential to identify the cortical structures involved in the generation of P50. However, the exact cerebral topography of P50 gating has remained largely unknown as yet. In a group of 17 patients with drug-resistant focal epilepsy, P50 was recorded invasively via subdural electrodes, and the topography of functionally indispensable (“eloquent”) cortices was obtained by electrical stimulation mapping. These eloquent areas were involved in language, motor, and sensory functions. P50 could be identified in 13 patients in either temporal (n = 8) or midfrontal sites (n = 5). There were 6 occurrences (in 5 patients) of overlap of sites with maximal P50 responses and eloquent areas. Those were auditory (n = 1), supplementary sensorimotor (n = 3), primary motor (n = 1), and supplementary negative motor (n = 1). Results suggest that the early stage of sensory gating already involves a top-down modulation of sensory input by frontal areas.

Keywords

auditory evoked potentials; presurgical evaluation; electrocorticography

1. Introduction

Sensory gating, understood as the ability of the brain to suppress the processing of irrelevant, particularly repetitive sensory input, has gained increasing attention in biological psychiatry and cognitive neuroscience. It has long been speculated that gating deficits may lead to sensory overload and thus to broad cognitive-behavioral malfunction as apparent in psychotic

Corresponding author: Prof. Dr. Martin Kurthen, Swiss Epilepsy Centre, Bleulerstrasse 60, CH – 8008 Zurich, Switzerland, Email: martin.kurthen@swissep.ch, Telephone: 0041-44-3876111, Fax: 0041-44-387397

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

symptoms (McGhie & Chapman, 1961). Therefore, the process of sensory gating has raised much interest in schizophrenia research. Two electrophysiological paradigms have been developed to assess sensory gating: prepulse inhibition of the startle reflex and P50 suppression (Adler et al., 1982, Nagamoto et al., 1989, Freedman et al., 1983, Braff & Geyer, 1990). The latter paradigm was used in the present study. The P50 is a positive mid-latency acoustic evoked response (MLAER), recorded maximally over the vertex region and peaking between 40 and 90 ms after stimulation. As a MLAER, P50 mirrors early cortical processing of incoming auditory information. When two identical stimuli (i.e., S1 & S2) are presented with an interstimulus interval (ISI) of 500 ms, the second P50 response is suppressed. This “P50 suppression” is thought to indicate sensory gating, which is not an all-or-none phenomenon, but rather a graded response with some variation in different samples (Baker 1987, Oranje 1999, Adler 1982, Arnfred 2003). The suppression of the response to the second stimulus in gating experiments – usually expressed as the S2/S1 ratio of the two P50 responses – is diminished or absent in schizophrenics (Adler et al., 1982; Boutros et al., 1991), and also in their first-order relatives (Siegel et al., 1984), in patients suffering from mania (Franks et al., 1983) or Alzheimer's disease (Jessen et al., 2001), and in patients with Post-Traumatic Stress Disorder (Neylan et al., 1999).

The lesion study by Alho et al. (1994) pointed to a frontal modulation of P50: patients with frontal lesions exhibited a larger P50 in response to auditory stimuli, as compared to non-affected subjects. However, later studies located the P50 generator mainly bilaterally in temporal areas close to the auditory cortex (Godey et al., 2001; Weisser et al., 2001). In surface ERP studies, the P50 is usually maximal over the vertex, but this finding allows no straight conclusion concerning the cerebral sources of that response, since different cortical source configurations can produce a unique scalp voltage topography (Slotnick 2005). Weisser et al. (2001) revealed two sources of the P50 by source reconstruction on basis of scalp data. One was located bilaterally close to the primary auditory cortex, and another source in midfrontal regions. In a study with invasive P50 recordings from subdural strip and grid electrodes in epilepsy patients, Grunwald et al. (2003) also found two major areas of P50 gating, one temporoparietal and one pre- and midfrontal. The insensitivity of the magnetoencephalography (MEG) for the detection of a frontal component (Weisser et al., 2001; Thoma et al., 2003) indicates that this frontal source may originate from deeper structures or have a radial orientation, as MEG is known to be relatively insensitive for both kinds of sources.

The question of the cortical topography of P50 generators is crucial for a more thorough understanding of the role of sensory gating as part of more comprehensive cognitive functions. Therefore, it will be essential to map P50 distributions in gating experiments not just anatomically, but also functionally. At present, this is preliminarily achieved by interpreting more or less well-localizing P50 data against the background of neuroscientific knowledge about the areas that have been delineated. For example, the frontal generator may be interpreted against the background of the “cognitive control” approach to the midfrontal cortex (Miller 2000, Paus 2001). The most direct approach to a functional mapping of P50 generators, however, would apply the combination of neuroimaging, functional mapping techniques, and advanced P50 recording procedures to the same individuals. One area of clinical diagnostics where this combination of methods can be applied is in the presurgical evaluation of epilepsy, where a subgroup of surgical candidates undergoes seizure recording via chronically implanted subdural strip and grid electrodes (Spencer 1997). In these patients, electrical stimulation mapping (ESM) is often performed to delineate eloquent areas from regions to be resected for epilepsy treatment. “Eloquent” are those cortical areas that cannot be resected without irreversible impairment of functions relevant to everyday life, e.g. motor cortex, language cortex, primary sensory cortex. With the same array of chronically implanted electrodes, P50 sensory gating can be measured directly from the cortical surface (Grunwald et al., 2003).

In the present study, the topography of eloquent (motor, language, and sensory) areas as determined by ESM is compared to the cortical distribution of invasively recorded P50 responses in a sensory gating setting. In particular, we investigated whether P50 generating areas might overlap with certain eloquent brain regions in individual patients. In addition, P50 topography was correlated to individual ictal onset areas to control for an overlap of functional and epileptogenic cortex. The hypothesis was that if the assumption of the presence of both midfrontal and lateral temporal P50 gating sites could be confirmed by direct measurements from these areas, it would be possible to obtain additional information about the functional characteristics of these P50-relevant cortices by means of ESM. In other words, this study on P50-ESM correlations is understood as an initial step towards a functional topography of P50 generators as contrasted with the mere determination of their anatomical distribution.

2. Material and Methods

2.1 Patient inclusion

Between November 2002 and February 2004, a total of thirty-seven patients with drug-resistant focal epilepsies were implanted for invasive seizure recordings as part of their presurgical evaluation at the University of Bonn Epilepsy Surgery Center (Behrens et al. 1994, Kral et al. 2002). In the course of diagnostic work-up, seventeen of these patients (9 males, mean age 34 [19 – 57] ys., see table 1 for clinical details) underwent ESM for the delineation of eloquent areas. None of these patients suffered from hearing deficits according to careful clinical examination and patients' history. Furthermore, there were no patients with severe cognitive deficits or low intelligence according to standardized neuropsychological examination, which is part of presurgical evaluation in epilepsy (Helmstaedter et al. 2003). Prior to ESM, the patients underwent a P50 recording from their subdural electrode arrays. There was no overlap between this patient group and the group reported in an earlier publication (Grunwald et al. 2003). All patients gave informed consent to the procedure. The study was approved by the Ethics Commission of Bonn University.

2.2 Patient characteristics and clinical methods

All patients were admitted to the University of Bonn Epilepsy Surgery Program for treatment of drug-resistant focal epilepsies. 15 patients were right-handed, two (patients no. 9 and 15) were ambidextrous according to the Edinburgh Handedness Inventory. Mean duration of epilepsy was 20.9 ys. (3 – 50). The standard diagnostic presurgical work-up was applied, which included epilepsy history and seizure semiology, neuropsychological testing, neurological examination, interictal and ictal video-electroencephalogram recordings with surface and subdural/depth electrodes for determination of seizure onset, and high-resolution MRI (Kral, 2003). Psychiatric status and history were assessed in a detailed psychiatric exploration and examination by an experienced psychiatrist (K.-U. K.). At the time of P50 recording, all patients were on standard therapy with anticonvulsant drugs, most of them (n = 15) receiving polytherapy due to the severity of their disease.

The ictal onset zone as the area of epileptic seizure origin was defined as the cortical area under those electrodes that showed an unequivocal ictal EEG pattern (low voltage fast activity or other rhythmic patterns with incremental characteristics) before or simultaneously with clinical seizure manifestation. Electrode placement was verified visually by an experienced neuroradiologist (H.U.) according to post-implantation MRI with axial and coronal T2-weighted and FLAIR-sequences (slice thickness 2 and 3 mm, respectively) as well as sagittal T1-weighted sequences.

2.3 P50 recording

In a paired-click paradigm, 75 pairs of identical clicks (S1 and S2; sinusoidal waves, frequency 1500 Hz, Gaussian envelope, duration 4 ms, onset and decay phase of 1.2 ms each) were presented via headphones with an interstimulus interval of 500 ms and an interpair interval of 8 s. Patients were asked to listen to the stimuli without any additional task. MLAERs were recorded from subdural strip and grid electrodes (sampling rate 1000 Hz per channel, epoch length 1200 ms, prestimulus baseline 200 ms), with reference to both mastoids (bandpass filter setting .03 - 85 Hz, 12 dB/octave). Subdural electrodes implanted at the Department of Neurosurgery at Bonn University Hospital consisted of strips or grids with stainless steel contacts with a diameter of 2.2 mm embedded in silastic with an interelectrode spacing of 1 cm (Behrens 1994). Electrode arrays were individually tailored according to the working hypothesis concerning the localization of the epileptogenic area (Kral et al. 2002). Grid electrodes were applied when broad coverage of a large cortical area was required, otherwise strip electrodes were used. In some patients, both grid and strip electrodes were implanted to cover multiple cortical areas. For individual electrode coverage see table 2 and the examples presented in the figures. Intrahippocampal depth electrodes, implanted in some patients, did not enter into the analyses, because no P50 responses were present at these electrodes (see also discussion below and Grunwald et al., 2003).

All contacts exhibiting P50 (S1) responses were identified by visual inspection. For the S1 response, the most prominent positive peak in the 40 – 100 ms time window preceding the regularly following, higher amplitude negative auditory evoked response around 100 ms (N100) response was selected as the P50 (S1) peak. For the S2 response, we selected the positive peak with a latency closest to that of the latency of S1. The responses were quantified by baseline-to-peak measures after prior additional filtering with 10-50 Hz bandpass. Sensory gating was quantified as the S2/S1 ratio. The values of individual ratios usually vary between 0 and 1, with higher ratios indicating less effective gating. In patients exhibiting a P50 at several leads, the electrode with the highest P50 amplitude (P50max-site) was chosen for the determination of the degree of sensory gating. In cases of two distant areas of positive responses (secondary area in the contralateral hemisphere or in a different cerebral lobe ipsilaterally), the “secondary P50max-site” was also documented as a separate correlate of sensory gating.

2.4 Electrical stimulation mapping (ESM)

ESM was used for delineating areas involved in motor, sensory (auditory, visual, and somatosensory), and language functions (Kral 2006). These areas would then have to be spared in the subsequent resection of the epileptogenic area. In the primary motor cortex, single electrical stimuli typically elicit single clonic unilateral movements according to the somatotopy of the motor homunculus in the precentral gyrus. High-frequency stimulus series produce slower, rather tonic contralateral movements. In the primary sensory cortices, high-frequency series of stimuli also elicit positive responses according to the respective modality, namely visual or auditory pseudohallucinations and somatosensory phenomena. On the other hand, by inducing temporary impairment of function in higher association cortices, mainly negative phenomena – that is, specific losses of some sorts of cognitive behavior - are observed based on the different organizations of these functional networks. Therefore, ESM in the present study included the application of single stimuli as well as a stimulus series dependent on the functions to be mapped. Electrical stimulation was performed and documented in a video-EEG setting and was performed with a Grass S88 stimulator and Grass constant current unit by way of a step-by-step stimulation of neighboring electrodes in a bipolar montage. On the second day of the examination, the whole procedure was repeated with a montage orthogonal to the preceding one in order to improve spatial resolution and to confirm the previous results. If the data were contradictory or inconclusive, the procedures were repeated. Stimulus intensity in the patient group reported here ranged between 2 mA and 5 mA,

depending on the individual threshold of afterdischarges, that is, unwanted repetitive spikes elicited by electrical stimulation. Biphasic rectangular stimuli with a total duration of 2.5 ms and a frequency of 30 Hz were used. The total duration of a single series ranged between 3 and 10 s depending on the test items applied (see below). When required, motor and sensory functions were mapped with single stimuli and stimulus series, respectively. For mapping of language and associated perisylvian functions (reading, calculation, writing, etc.), stimulus series just below the level of afterdischarges were given for the time of instruction and performance. After general prior instruction, specially selected short tasks were given repetitively with and without stimulation. For language testing, the following domains were evaluated: naming of visually presented objects, serial speech (counting), repetition of proverbs, body commands, and reading of short passages from a German novel. Additionally, simple tasks from the Token Test (de Renzi, 1962) were performed under stimulation. Repeated testing yields a reliable map of eloquent areas. Perisylvian cortical mapping also included writing (writing of single words or short sentences on verbal command), calculation (basic mental arithmetic: addition, subtraction, multiplication, division), and praxia (manual or facial movements on verbal command). Visual and auditory pseudohallucinations were documented and described by the patients in case of occurrence. The pattern of tasks applied was tailored according to individual clinical requirements (see table 2).

2.5 Timetable of clinical and experimental procedures

Due to the clinical requirements of presurgical evaluation, P50 experiments as part of the present explorative study had to be performed when the individual invasive diagnostic program was finished, and patients were waiting for their therapeutic surgical procedure and/or electrode explantation. In short, the sequence of procedures was as follows: one day after electrode implantation in the Dept. of Neurosurgery, patients were submitted to the Dept. of Epileptology, where seizures were recorded. In that period, MR imaging for control of electrode placement and ESM were performed. Due to the complexity of the ESM procedure, stimulation mapping usually had to be distributed over two or three days (see above). When all information required for a surgical decision had been obtained, P50 measurements were performed on a separate day before surgery.

3. Results

3.1 Clinical results

Psychiatric history was unremarkable in ten patients. Two patients had a history of postictal psychotic episodes (table 1). Three patients suffered from or had a history of depressive syndromes, and one patient had a history of one attempted suicide, presumably during a depressive episode, a few years prior to surgery. Furthermore, one patient had a history of temporary hallucinations without evidence of other psychotic symptoms.

On re-admission to the Epilepsy ward after implantation, there were no clinically relevant complications of implantation. As a result of ictal video-EEG, circumscribed ictal onset areas were detected in sixteen patients.

3.2 P50

All patients underwent the P50 experiment without any difficulties. In thirteen of the seventeen patients, cortical P50 could be recorded from subdural electrodes. Leads with P50 were identified with one exception in areas previously reported to show these responses in invasive recordings, namely the temporoparietal junction or posterior superior temporal gyrus, or (mid) frontal areas (Grunwald et al., 2003). Patient 9 with his P50-maximum in a motor cortex site is discussed in detail below. Three patients showed well-identified P50 deflections in two distinct areas of different hemispheres or in different lobes of one hemisphere. In most patients,

the electrode with the maximal P50-response was surrounded by contacts with decreasing P50 amplitudes. Mean amplitudes across all P50max-sites were: 18.6 μ V (SD 9.8 μ V) for S1 and 10.2 μ V (SD 6.9 μ V) for S2, resulting in an average gating ratio of 54.8 % when patients with completely absent S2 responses were excluded. Mean latencies were 51.4 ms (SD 11.1 ms) for S1 and 47.9 ms (SD 8.4 ms) for S2. P50-sensory gating as expressed by the S2/S1-ratio varied considerably among individuals (table 2). Only one patient showed no gating at all. In two patients, the absence of any response to S2 indicated “complete gating”, while in the remaining eleven patients, the S2/S1-ratio varied between 20.5 and 81.7, indicating a continuum of gradual gating in the total group. All patients with remarkable psychiatric histories showed more than 50% P50-gating (ratios below 50).

3.3 ESM

In two patients (table 2), ESM identified no eloquent cortices under the subdural grid and/or strip electrodes. In the other patients, there was a positive mapping of up to three of the functions in question (table 2). Motor and language functions as the clinically most significant target functions were identified in a high number of cases ($n = 10$ for motor, $n = 7$ for language functions). Details of the individual topographies of eloquent areas are presented in the figures of patients with cortical overlap of P50-generating and eloquent areas (figs. 1 and 2).

3.4 Overlap of P50max-site with eloquent areas according to ESM

There were six occurrences of overlap in five patients (table 2). Auditory cortex was involved in patient no. 9 (auditory sensations of unstructured sounds, fig. 1), while in the other patients, there was an overlap with supplementary sensorimotor or supplementary negative motor or primary motor cortex, respectively. In patient no. 8, a “pseudo-overlap” of motor cortex and P50-generation is assumed. In that patient, the P50max-site was located laterally in the precentral gyrus, right above the sylvian fissure. There were no further electrodes covering the superior temporal gyrus adjacent to that central lateral site. Hence P50-response, ostensibly generated close to the primary auditory cortex, was best recorded from the latter site. This interpretation is supported by a similar pattern in patient no. 13, who also showed such a “pseudo-overlap” of motor functions and one of the sites showing P50, while her maximal response was recorded from a superior temporal, infrasyllian site neighboring that frontal electrode.

In patient no. 10, ESM of the P50max-site elicited typical supplementary sensorimotor area (SSMA)-responses to serial stimulation of right-hemispheric medial frontal strip electrodes. Stimulus trains evoked complex bilateral tonic posturing of the arms without any evidence of primary motor responses to single stimuli. The same correlation was found for the contralateral medial frontal strip electrodes in this patient. Hence, this pattern of responses indicated the presence of sensory gating in both supplementary sensorimotor areas in this patient.

A slightly different response pattern was found in patient no. 12. She had only right-sided medial frontal strip electrodes, in which the P50-max site showed negative motor responses to ESM (supplementary negative motor area; fig. 2). Finally, in patient no. 3 electrical stimulation of the medial P50-max site resulted in somatosensory SSMA phenomena (paraesthesia of the upper contralateral extremity) at a frontal location anterior to the primary motor representation of the contralateral leg and posterior to a site with typical SSMA language responses.

3.5 Distribution of P50 positive sites in correlation with the primary epileptogenic area

In addition to eloquent areas according to ESM, lesional areas and ictal onset zones were controlled for overlap with P50 generating areas. There was no overlap of a lesion or ictal onset area with the P50max-site in any patient (table 1), although in some cases, the P50max-site was involved in ictal EEG activity very early in the course of the seizure (particularly in patients

no. 10 and 12). The P50max-site was located in the same lobe as the ictal onset area in eight patients, in a different lobe of the same hemisphere in three patients, and in the other hemisphere in two patients. In the non-lesional patient no. 9 with multifocal seizure onset the question of an overlap could not be addressed adequately. The lower number of P50max-sites in the contralateral hemisphere is biased by the far broader electrode coverage in the ipsilateral hemisphere, that is, the hemisphere suspected to harbor the epileptogenic area. Since none of the MRI-detectable lesions was directly located in those areas where maximal P50 sites could be expected to be recorded, the present study can not analyze the effects of a direct lesion of those areas with respect to sensory gating (table 1). Although patient 2 showed a focal cortical dysplasia in Heschl's gyrus of the right hemisphere this area was not directly accessible for evoked potentials recording with the electrode arrays used in the present study.

4. Discussion

The major findings of this study are that

1. in concordance with a previous study (Grunwald et al., 2003), invasively recorded P50-N100-complexes are preferentially recorded in two areas of either hemisphere, namely the superior posterior temporal cortex extending to the temporoparietal junction, and the frontal cortex. With the exception of one patient, P50 sensory gating is present to different degrees in all individual sites of maximal P50 responses.
2. there is an overlap of P50max-sites with eloquent areas according to ESM, namely with areas involved in auditory perception, and preparation of action, in a considerable proportion of cases (5/13; 38.5%),
3. there is no overlap of P50max-sites with lesions or ictal onset areas, and
4. there is a continuum of degrees of gating across patients rather than an all-or-none gating phenomenon.

What remains to be discussed are (a) methodological aspects of the generation of these data, and (b) the possible significance of the results for a general theory of P50-N100-generation and sensory gating phenomena.

4.1 Methodological considerations

An inevitable limitation of the present study is that the subdural electrode arrays vary among individuals and incompletely cover possible cortical regions of interest. The primary auditory cortex, the lateral aspects of which are assumed to harbor the P50 generator (Godey, 2001), is not directly accessible with the subdural and intrahippocampal depth electrodes used in the present study. Hence, the lateral temporal strip and grid electrodes may represent components originally generated in Heschl's gyrus. Unfortunately, there are as yet no invasive gating studies in patients with temporal depth electrodes inserted along a lateral-medial axis, although the P50 component as such has been investigated by such an approach (Godey, 2001).

However, there is some reason to assume that current recordings depict a realistic picture of the topography of P50 gating on the cortical surface. Although in the total group electrodes covered wide areas of all the cerebral lobes of both hemispheres, responses were almost exclusively found (bilaterally) in the two areas mentioned above. Basically the same topography was found in a previous study in a larger sample, not overlapping with the present one (Grunwald et al., 2003).

Another limitation derives from the fact that all these responses were obtained from brains of patients with epilepsy with ongoing anticonvulsive drug therapy, factors that in themselves might systematically alter the evoked potential (EP) components. This constraint, too, is

inevitable because invasive sensory gating studies have not been and – for ethical reasons - will never be performed in normal controls or in patients with exclusively psychiatric disorders. In the sample reported here, no systematic differences in P50- responses arose between patients with P50max-sites located distant from vs. close to the ictal onset area or lesion, while a literal overlap with lesional and ictal onset areas did not occur at all. Hence, it can be assumed that the P50-gating-topography reported here is not systematically altered by the topography of the epileptogenic areas. Nevertheless, it cannot be excluded that epilepsy as such influences some characteristics of the responses. Focal cortical dysfunction due to lesions and/or epilepsy in any part of an assumed frontotemporal gating network (see below) may indirectly influence P50 sensory gating. To demonstrate such effects, larger patient groups are required to statistically assess effects of the topography of the epileptogenic area and/or lesion. Earlier surface studies suggested a delay and reduction of P50 responses in temporal lobe epilepsy (Weate, 1995). However, in a recent surface study from our group comparing patients with focal lobe epilepsy to healthy controls (Boutros 2006), P50 auditory gating did not differ significantly between the groups.

As for effects of drug treatment, to the best of our knowledge, there is only one study examining the effects of anticonvulsant agents on P50 sensory gating (van Luijtelaa, 2003). In that study, application of a single dose of diazepam to healthy individuals did not alter P50 gating. In our laboratory, occasional recordings in patients under complete drug withdrawal did not show any difference in responses compared to recordings under anticonvulsive treatment (unpublished results). Although drug treatment may modify the response characteristics, the effects of rapid anticonvulsant withdrawal on P50 sensory gating are even less predictable. Therefore, in the particular clinical setting of invasive presurgical evaluation, it seemed advisable to record P50-responses under anticonvulsant drug treatment rather than complete withdrawal.

The major restrictions of ESM concern spatial resolution and the time windows for testing individual functions. By combinations of various montages, areas under single contacts can be determined as functionally relevant, but this allows for a spatial resolution of at best 5 mm, at worst about 10 mm. Furthermore, testing of individual functions is restricted to periods of 5-15 s, which are within the time window for application of low-amplitude serial electrical stimuli without unwanted sequelae. Item testing can, of course, be repeated as often as necessary. Despite these two restrictions, ESM has proved to be clinically valid and reliable, and it has remained the gold standard for surgical planning in epilepsy surgery centers worldwide. In the patients reported here, all results were reproducible and unequivocal after repeated testing.

4.2 Clues to an understanding of sensory gating

Previous invasive electrophysiological and MEG studies have suggested that the P50 response is generated in the primary auditory cortex (Liegeois-Chauvel, 1994; Godey, 2001; Scherg, 1989). Furthermore, there is now accumulating evidence from invasive EEG (Grunwald et al., 2003), EP source analyses (Weisser, 2001) and MEG (Thoma, 2003) studies that P50 sensory gating in a double-click paradigm is also topographically related to that sensory area. This is in accordance with the repeated finding of a cluster of superior posterior temporal P50max-sites in the present study and with the occurrence of a co-location of the sites with ESM-associated auditory pseudohallucinations and P50-gating in our patient no. 9.

All these findings suggest that the temporal P50 gating phenomenon is best interpreted as the correlate of a local preattentive mechanism for the suppression of auditory stimuli of low significance. The midfrontal and lateral prefrontal gating-relevant areas that were found in the present study and in the EEG- and source-analysis-experiments mentioned above qualify as candidate regions for an early cross- or supra-modal aspect of gating, because these areas are known to be generally involved in attention, sensory inhibition, and the preparation of

externally triggered action (Miller, 2000). Aside from its general physiological plausibility, the idea of a central supra-modal gating mechanism has been derived from early findings of gating processes and modality-independent habituation in various sensory modalities (Ishikawa 1968, Shagass 1978, Bolino 1993). There is some converging evidence from different areas of neuroscientific research that primary sensory and frontal areas are functionally coupled:

First, the source-analysis-studies mentioned above as well as the earlier (Grunwald et al., 2003) and the present EP-study suggest the existence of brain regions that are topographically and functionally distinct from the P50 generators in the auditory cortex, although they respond surprisingly early in the same time window and also “gate” their responses to second stimuli in paired clicks. Weisser (2001) reported that apart from their distinct topography, mid-frontal responses differed from temporal ones in amplitude and – slightly – in latency. According to visual analysis of 3D-MRI surface renderings, Grunwald et al. (2003) located their midfrontal sensory gating area in the SSMA. In the present sample, ESM demonstrated SSMA (or supplementary negative motor area)-type responses in most of the frontal P50max-sites. None of these areas is strictly “sensory” in nature, but there is evidence from animals and humans that there are significant connections between auditory and lateral and medial frontal cortices that may become active within 100 ms after an auditory stimulus (Romanski, 1999; Barbas, 1999; Picton, 1999). As for the SSMA proper, this area is known for its mixed somatosensory and motor representations despite its frontal location (Lim, 1994). Functionally, it would make sense that the SSMA receives very early sensory information in the auditory mode, since auditory stimuli supplement tactile stimuli as they convey action-relevant information from mid-distant objects with a very short delay. With respect to volition, the SSMA, as a premotor region, is known to be involved in self-initiated and externally cued movement (Cunnington, 2002; Toma, 2003). Its activity precedes that of the primary motor cortex in intentional movement (Weilke, 2001). In most of these studies that demonstrate the involvement of the SSMA in volition, *auditory* cues are chosen for external triggering of movements (e.g., Cunnington, 2002; Toma, 2003; Kurata, 2000).

Second, the prefrontal cortex may contribute to sensory gating as part of its general role in attention and inhibitory control of sensory flow. This is suggested by the observation that P50 amplitudes are *increased* in patients with frontal lesion (Alho et al., 1994). A similar finding was obtained in the somatosensory domain (Chao and Knight, 1995). In the complex network for the integration of sensory inputs, motivational states, memory, and intentional action, one of the functions of the prefrontal cortex (PFC) is that of top-down control of sensory information (Miller, 2000). The medial PFC, and particularly the anterior cingulate cortex (ACC), seems to be more specifically involved in error detection and conflict monitoring (Paus, 2001) rather than direct top-down control of sensory input. The ACC is located anterior to the SSMA on the medial surface of the frontal lobe. Interestingly, P50 responses have neither been found in the previous invasive study (Grunwald et al., 2003) nor in the present study in anterior frontal interhemispheric strip electrodes, although in both series there was a considerable coverage of the medial surface anterior to the SSMA.

4.3 Sensory gating and epilepsy

The higher amplitudes of the invasively recorded responses allow degrees of gating to become more apparent. In the non-invasive P50 literature, many researchers used group comparisons of mean gating ratios to compare normal controls with patients (e.g. Adler, 1982; Knight et al., 1999). S2/S1-ratios for healthy controls varied between 18.6 % (Baker, 1987) and 77.8 % (Oranje, 1999) with a majority of mean ratios below 50 % in studies screened for this discussion. Ratios in schizophrenics were between 95 % (Adler, 1982; Nagamoto, 1989) and 32 % (Arnfred, 2003) with a majority of mean ratios above 50 %. The lack of a control group

notwithstanding, the mean S2/S1-ratio in our epilepsy patients was found to lie in the range of the various „pathological“ groups rather than that of the normal control groups reported in noninvasive studies.

Amplitudes, latencies, and gating ratios varied considerably among individuals in the present study. This may mirror a genuine physiological phenomenon, or it may be due to individual differences in electrode coverage or clinical variables like the location of the primary epileptogenic area or anticonvulsive drug load which was generally high in the total group. Future analyses with larger samples will have to address this question more comprehensively. The present sample was too small for statistical comparisons between gating ratios in different regions, different hemispheres, or in clinically different subgroups. Patients with a history of postictal psychosis gated better than average on a descriptive level. There were no patients with a history of chronic interictal psychosis in this sample. Hence, the question of whether actual psychiatric disorders alter invasively recorded P50 gating remains unanswered for the time being.

Although the present data were obtained in a sample of epileptic patients, the findings may bear some relevance for the issue of sensory gating in psychiatry. If an impairment in sensory gating in schizophrenic patients, at least in part, underlies sensory overload and attention dysfunctions in these patients, then the assumption of a “frontotemporal network” (Thoma, 2003) for gating is theoretically much more plausible than that of a modal bitemporal gating network. Attention, cognitive control, and top-down modulation of sensory input are mainly frontal functions that may be applied to an input which has already, in part, been “gated” modally in the respective sensory areas. The recent gating studies with advanced techniques like MEG, source analysis, and invasive EP measurement provide the opportunity to assess both the temporal and the frontal correlates of gating. It may thus be advisable to further investigate P50 gating in schizophrenic patients and other diseases not only with the traditional surface EP techniques, but preferentially with MEG and source analysis in order to assess the significance of the P50 gating phenomenon as a neuropsychiatric marker. As for the temporal components of the putative P50 network, mesial temporal structures seem not to be involved in sensory gating in that time window. A recent study on recordings from intrahippocampal depth electrodes in epilepsy patients (Boutros 2005) showed that while no mesial temporal P50 is detectable, there are later (starting around 200 ms) rhinal and hippocampal responses. Although responses in that time window may still be interpreted as elements of the “multistage operation” (Boutros 2004) of sensory gating, it is now obvious that the mesial temporal structures are not specifically involved in early (< 100 ms) auditory sensory gating in humans.

Summary

Based on the current findings, it can be hypothesized that early sensory gating is represented not only in sensory areas, but also in those frontal areas that are involved in the initiation of movement (i.e., SSMA) and top-down control of sensory input (i.e., lateral PFC), but not in those frontal areas that have a major role in more complex, evaluative functions (the ACC and other medial, ventral, and anterior parts of the PFC) for the preparation and modulation of subsequent behavior. Further experiments can be designed to test this hypothesis. First, additional MEG- and invasive EP-studies of the type discussed here can further improve our knowledge of the topography of sensory gating with respect to functionally different components of the premotor and prefrontal cortices. Second, cross- and/or multi-modal gating studies could help to separate modal from cross- and/or supra-modal gating processes outside the respective primary sensory areas, particularly in the frontal lobes. Third, EP- and MEG-responses outside the conventional P50-sensory-gating time window, namely in the range of 100 to 300 ms after stimulus onset, would have to be analyzed under the same topographical perspective to assess later components of the presumably multi-stage process of sensory gating

(Boutros, 1999). Analyses of that latter sort would have to include the memory-relevant medial temporal areas, where specific late responses in a double-click experiments have already been demonstrated (Grunwald et al., 2003). These further experiments might mark the next steps to embed the concept of sensory gating into a more general neuroscientific theory of integrative behavior.

Acknowledgements

This study was supported by the NIH, Bethesda (grant no. R01 MH063476)

Reference List

- Adler LE, Pachtman E, Franks RD, Pecevic M, Waldo MC, Freedman R. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biological Psychiatry* 1982;17:639–654. [PubMed: 7104417]
- Alho K, Woods DL, Algazi A, Knight RT, Näätänen R. Lesions of frontal cortex diminish the auditory mismatch negativity. *Electroencephalography and Clinical Neurophysiology* 1994;91:353–362. [PubMed: 7525232]
- Arnfred SM, Chen AC, Glenthøj BY, Hemmingsen RP. Normal P50 gating in unmedicated schizophrenia outpatients. *The American Journal of Psychiatry* 2003;160:2236–2238. [PubMed: 14638598]
- Baker N, Adler LE, Franks RD, Waldo M, Berry S, Nagamoto H, Muckle A, Freedman R. Neurophysiological assessment of sensory gating in psychiatric inpatients: comparison between schizophrenia and other diagnoses. *Biological Psychiatry* 1987;22:603–617. [PubMed: 3580435]
- Barbas H, Ghashghaei H, Dombrowski SM, Rempel-Clower NL. Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *The Journal of Comparative Neurology* 1999;410:343–367. [PubMed: 10404405]
- Behrens E, Zentner J, van Roost D, Hufnagel A, Elger CE, Schramm J. Subdural and depth electrodes in the presurgical evaluation of epilepsy. *Acta Neurochirurgica (Wien)* 1994;128:84–87.
- Bolino F, Di Michele V, Manna V, Di Cicco L, Isidori MV, Casacchia M. Acoustic and electrically elicited startle reaction: similar patterns of habituation and reflex modifications in humans. *International Journal of Neuroscience* 1993;73:13–21. [PubMed: 8132414]
- Boutros NN, Belger A. Midlatency evoked potentials attenuation and augmentation reflect different aspects of sensory gating. *Biological Psychiatry* 1999;45:917–922. [PubMed: 10202580]
- Boutros NN, Korzyukov O, Jansen B, Feingold A, Bell M. Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. *Psychiatry Research* 2004;126:203–215. [PubMed: 15157747]
- Boutros NN, Trautner P, Rosburg T, Korzyukov O, Grunwald T, Schaller C, Elger CE, Kurthen M. Sensory gating in the human hippocampal and rhinal regions. *Clinical Neurophysiology* 2005;116:1967–1974. [PubMed: 16000257]
- Boutros NN, Trautner P, Rosburg T, Korzyukov O, Grunwald T, Schaller C, Elger CE, Kurthen M. Mid-latency auditory evoked potentials and sensory gating in focal epilepsy. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2006in press
- Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. *Archives of General Psychiatry* 1990;47:181–188. [PubMed: 2405807]
- Chao LL, Knight RT. Human prefrontal lesions increase distractibility to irrelevant sensory inputs. *Neuroreport* 1995;6:1605–1610. [PubMed: 8527724]
- Cunnington R, Windischberger C, Deecke L, Moser E. The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. *Neuroimage* 2002;15:373–385. [PubMed: 11798272]
- De Renzi E, Vignolo LA. The token test: A sensitive test to detect receptive disturbances in aphasics. *Brain* 1962;85:665–678. [PubMed: 14026018]
- Franks RD, Adler LE, Waldo MC, Alpert J, Freedman R. Neurophysiological studies of sensory gating in mania: comparison with schizophrenia. *Biological Psychiatry* 1983;18:989–1005. [PubMed: 6416309]

- Freedman R, Adler LE, Waldo MC, Pachtman E, Franks RD. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. *Biological Psychiatry* 1983;18:537–551. [PubMed: 6134559]
- Godey B, Schwartz D, de Graaf JB, Chauvel P, Liegeois-Chauvel C. Neuromagnetic source localization of auditory evoked fields and intracerebral evoked potentials: a comparison of data in the same patients. *Clinical Neurophysiology* 2001;112:1850–1859. [PubMed: 11595143]
- Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernandez G, Schaller C, Elger CE. Neuronal substrates of sensory gating within the human brain. *Biological Psychiatry* 2003;53:511–519. [PubMed: 12644356]
- Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Annals of Neurology* 2003;54:425–432. [PubMed: 14520652]
- Ishikawa K. Studies on the visual evoked responses to paired light flashes in schizophrenics. *Kurume Medical Journal* 1968;15:153–167. [PubMed: 5191760]
- Jessen F, Kucharski C, Fries T, Papassotiropoulos A, Hoenig K, Maier W, Heun R. Sensory gating deficit expressed by a disturbed suppression of the P50 event-related potential in patients with Alzheimer's disease. *The American Journal of Psychiatry* 2001;158:1319–1321. [PubMed: 11481170]
- Kral T, Clusmann H, Urbach J, Schramm J, Elger CE, Kurthen M, Grunwald T. Preoperative evaluation for epilepsy surgery (Bonn Algorithm). *Zentralblatt für Neurochirurgie* 2002;63:106–110.
- Kral T, Kurthen M, Schramm J, Urbach H, Meyer B. Stimulation mapping via implanted grid electrodes prior to surgery for gliomas in highly eloquent cortex. *Neurosurgery* 2006;58:S36–S43.
- Kurata K, Tsuji T, Naraki S, Seino M, Abe Y. Activation of the dorsal premotor cortex and pre-supplementary motor area of humans during an auditory conditional motor task. *Journal of Neurophysiology* 2000;84:1667–1672. [PubMed: 10980036]
- Liegeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P. Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroencephalography and Clinical Neurophysiology* 1994;92:204–214. [PubMed: 7514990]
- Lim SH, Dinner DS, Pillay PK, Luders H, Morris HH, Klem G, Wyllie E, Awad IA. Functional anatomy of the human supplementary sensorimotor area: results of extraoperative electrical stimulation. *Electroencephalography and Clinical Neurophysiology* 1994;91:179–193. [PubMed: 7522147]
- McGhie A, Chapman J. Disorders of attention and perception in early schizophrenia. *The British Journal of Medical Psychology* 1961;34:103–116. [PubMed: 13773940]
- Miller EK. The prefrontal cortex and cognitive control. *Nature Reviews. Neuroscience* 2000;1:59–65.
- Nagamoto HT, Adler LE, Waldo MC, Freedman R. Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. *Biological Psychiatry* 1989;25:549–561. [PubMed: 2920190]
- Neylan TC, Fletcher DJ, Lenoci M, McCallin K, Weiss DS, Schoenfeld FB, Marmar CR, Fein G. Sensory gating in chronic posttraumatic stress disorder: reduced auditory P50 suppression in combat veterans. *Biological Psychiatry* 1999;15:1656–1664. [PubMed: 10624547]
- Oranje B, van Berckel BN, Kemner C, van Ree JM, Kahn RS, Verbaten MN. P50 suppression and prepulse inhibition of the startle reflex in humans: a correlational study. *Biological Psychiatry* 1999;45:883–890. [PubMed: 10202576]
- Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nature Reviews. Neuroscience* 2001;2:417–424.
- Picton TW, Alain C, Woods DL, John MS, Scherg M, Valdes-Sosa P, Bosch-Bayard J, Trujillo NJ. Intracerebral sources of human auditory-evoked potentials. *Audiology & Neuro-otology* 1999;4:64–79. [PubMed: 9892757]
- Romanski LM, Tian B, Fritz J, Mishkin M, Goldman-Rakic PS, Rauschecker JP. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nature Neuroscience* 1999;2:1131–1136.
- Scherg M, Hari R, Hämäläinen M. Frequency-specific sources of the auditory N19-P30-P50 response detected by a multiple source analysis of evoked magnetic fields and potentials. In: Williamson, SJ., editor. *Advances in biomagnetism*. New York: Plenum; 1989. p. 97–100.
- Shagass C, Straumanis JJ, Roemer RA, Amadeo M. Evoked potentials of schizophrenics in several sensory modalities. *Biological Psychiatry* 1978;12:211–235.

- Siegel C, Waldo M, Mizner G, Adler LE, Freedman R. Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. *Archives of General Psychiatry* 1984;41:607–612. [PubMed: 6732421]
- Slotnick, SS. Source localisation of ERP generators. In: Handy, TC., editor. *Event-Related Potentials A Methods Handbook*. Cambridge (Mass.): MIT Press; 2005. p. 149-166.
- Spencer, SS.; Sperling, MR.; Shewmon, DA. Intracranial electrodes. In: Engel, J.; Pedley, TA., editors. *Epilepsy: a comprehensive textbook*. New York: Lippincott-Raven; 1997. p. 607-612.
- Thoma RJ, Hanlon FM, Moses SN, Edgar JC, Huang M, Weisend MP, Irwin J, Sherwood A, Paulson K, Bustillo J, Adler LE, Miller GA, Canive JM. Lateralization of auditory sensory gating and neuropsychological dysfunction in schizophrenia. *The American Journal of Psychiatry* 2003;160:1595–1605. [PubMed: 12944333]
- Toma K, Ozawa M, Matsuo K, Nakai T, Fukuyama H, Sato S. The role of the human supplementary motor area in reactive motor operation. *Neuroscience Letters* 2003;344:177–180. [PubMed: 12812834]
- Van Luijckelaar G. The effects of diazepam on sensory gating in healthy volunteers. *Neuroscience Letters* 2003;341:65–68. [PubMed: 12676345]
- Weilke F, Spiegel S, Boecker H, von Einsiedel HG, Conrad B, Schwaiger M, Erhard P. Time-resolved fMRI of activation patterns in M1 and SMA during complex voluntary movement. *Journal of Neurophysiology* 2001;85:1858–1863. [PubMed: 11353002]
- Weisser R, Weisbrod M, Roehrig M, Rupp A, Schroeder J, Scherg M. Is frontal lobe involved in the generation of auditory evoked P50? *Neuroreport* 2001;12:3303–3307. [PubMed: 11711875]

Fig 1. Patient no. 9: overlap of auditory area (contact A8) and P50max-site
Patients with overlap of eloquent areas and P50max-sites.

- a. MR images of electrode sites; P50max-sites are marked with the color of the respective eloquent area.
- b. Schematic drawing of ESM results in electrodes around the P50max-site. Red: primary motor cortex, yellow: language-relevant cortex, blue: SSMA, green: cortex with auditory phenomena in ESM
- c. P50/N100-responses from the P50max-electrode in the respective patients.

Fig 2. Patient no. 12: overlap of P50max-site with SSMA
 Patients with overlap of eloquent areas and P50max-sites.

- a. MR images of electrode sites; P50max-sites are marked with the color of the respective eloquent area.
- b. Schematic drawing of ESM results in electrodes around the P50max-site. Red: primary motor cortex, yellow: language-relevant cortex, blue: SSMA, green: cortex with auditory phenomena in ESM
- c. P50/N100-responses from the P50max-electrode in the respective patients.

Table 1

Clinical characteristics of the seventeen patients with ESM and P50 recordings.

Patient no.	sex	age (ys)	age at onset (ys)	type(s) of seizures	MRI lesion	histopathology	Language dominance (method)	Psychiatric history	ECoG ictal onset
1	f	24	11	sps/cps	HS (r), bioccipital lesions	HS	BR (fMRI)	two post-ictal psychotic episodes	hippocampus (r)
2	f	31	11	sps/cps/gtc	FCD (r) STG	FCD with balloon cells	LD (fMRI, IAT)	suicide attempt	STG (r)
3	f	41	36	sps/cps	FCD (l) central	No resection	unknown	unremarkable	central (l)
4	f	31	23	cps	HS (l) and lesion MTG	HS	LD (IAT)	unremarkable	hippocampus (l), temporal lateral
5	f	22	19	sps/cps/gtc	tumor MTG (r)	ganglioglioma	LD (IAT)	anxiety disorder, depressive episode	temporal lateral (l)
6	m	54	20	cps/gtc	HS (l)	HS and ganglioglioma	LD (fMRI and IAT)	unremarkable	temporal (l)
7	m	39	27	cps	Cavernoma (l) temporal	cavernoma	LD (fMRI)	unremarkable	temporal lateral (l)
8	m	27	6	cps/gtc	Post-resection frontal (l)	Astrocytoma WHO I	BR (IAT)	history of pddgmc with hallucinations	frontal (l)
9	m	27	18	cps	non-lesional	No resection	LD (IAT)	depressive disorder	multifocal
10	f	32	4	cps/gtc	non-lesional	no resection	unknown	one post-ictal psychotic episode	medio-frontal (l, r)
11	f	35	3	cps/gtc	FCD (l) frontal	FCD with balloon cells	LD (fMRI) RD (IAT)	unremarkable	frontal (l)
12	f	34	12	cps/gtc	FCD (r) frontal	FCD with balloon cells	unknown	unremarkable	frontal (r)
13	m	57	7	cps	FCD right frontal, HS right	FCD with balloon cells	LD (fMRI)	history of depression	frontal (r)
14	m	40	8	cps/gtc	defect (l) frontal	post-haemorrhage	LD (fMRI)	unremarkable	frontal (l)
15	m	38	4	eps/cps	FCD (r) parietal	missing	RD (IAT and fMRI)	unremarkable	frontal (r)
16	m	19	4	eps/cps/gtc	FCD right frontal	FCD with balloon cells	BR (IAT and fMRI)	unremarkable	frontal (r)
17	m	27	9	cps/gtc	HS (l)	no resection	RD (fMRI) BR or RD (IAT)	unremarkable	temporo-parietal (l)

Sex: f = female; m = male.

Side: l = left; r = right.

Seizure types: sps = simple partial seizures; cps = complex partial seizures; gtc = generalized tonic-clonic seizures.

MRI lesions: HS = hippocampal sclerosis; FCD = focal cortical dysplasia; STG = superior temporal gyrus; MTG = middle temporal gyrus.

Language dominance: LD = left hemisphere dominance; BR = bilateral representation; RD = right hemisphere dominance; fMRI = functional magnetic resonance imaging; IAT = intracarotid amobarbital procedure

Table 2

ESM- and P50-results.

patient no.	P50max-site	P50 latency (ms)	P50 amplitude (µV)	P50 S2/ S1 ratio (%)	Overlap P50/ ESM	ESM: type of response	electrode coverage
1	GRF3	43	22.9	0	-	visual	MTL (r), occipital, temporal, parietal (r), occipital (l)
2	TLL 11 temporal posterior	57	16.8	59.5	-	auditory Jamais experience	lateral and ventral temporal (l), parietal (l)
3	GL H1	47	21.0	70.1	-	Motor, Somatosensory, SSMA	fronto-central, frontal medial (l)
4	IHL a1	58	19.1	20.5	+	(SSMA)	MTL (r, l), lateral and ventral temporal (l)
5	GL C8 (temporal posterior superior)	54	43.6	50.2	-	Motor	MTL (r, l), lateral and ventral temporal (l)
6	GL A6	42	21.1	45.3	-	-	lateral and ventral temporal (l)
7	TLR 3	50	15.7	46.8	-	Motor, Language	MTL and lateral and ventral temporal (l, r), frontal (l)
8	GL A8 (temporal posterior superior)	37	6.7	101.6	-	Language	lateral temporal (l)
9	GL D8	46	8.3	77.9	+	(motor)	left fronto-central, interhemispheric (l)
10	GR A8 (temporal superior posterior)	41	27.4	46.3	+	(auditory)	MTL, frontal, lateral and ventral temporal (r, l)
11	IHR b1	72	14.4	32.7	+	(SSMA)	lateral and medial frontal (r, l)
12	ILB2	77	9.6	0	+	(SSMA)	frontal, central, temporo-parietal (marginal) (l)
13	GL H8 (temporo-parietal)	50	33.0	81.7	-	Motor, Language	medial and lateral
14	GR A3	48	15.7	62	-	Motor, SNMA	frontal, central (r)
15	IHR b3	58	13.4	34.6	+	(SNMA)	right fronto-central and MTL
16	GR A6	42	8.7	37.5	-	-	frontal (l)
17	-	-	-	-	-	Language, SMA	frontal, parietal (r)
18	-	-	-	-	-	Motor, Visual	Interhemispheric (l, r)
19	-	-	-	-	-	Motor, SMA	frontal (r, l) Interhemispheric (r, l)
20	-	-	-	-	-	Language, Auditory	MTL, lateral and ventral temporal (r, l (grid))

Side: 1 = left; r = right.

Regions: SSMA = supplementary sensorimotor area; SNMA = supplementary negative motor area; MTL = medial temporal lobe.

Terminology for subdural electrodes: GL = grid left hemisphere; GR = grid right hemisphere; TLL/TLR = left/right temporal lateral strip electrode; IHL a, b, c = anterior, middle, and posterior left interhemispheric strip electrode; IHR a, b, c = anterior, middle, and posterior right interhemispheric strip electrode. – Electrode contacts are numbered sequentially from the most distal (1) to the most proximal (4, or 8, or 16) contact, respectively. In grids, single contacts are identified by a number (1-8, or 1-4) and a letter (A-H, or A-D) in a two-dimensional notation pattern (see figures).