Sensory gating of auditory evoked and induced gamma band activity in intracranial recordings


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Oscillatory activity in the gamma band range (30–50 Hz) and its functional relation to auditory evoked potentials (AEPs) is yet poorly understood. In the current study, we capitalized on the advantage of intracranial recordings and studied gamma band activity (GBA) in an auditory sensory gating experiment. Recordings were obtained from the lateral surface of the temporal lobe in 34 epileptic patients undergoing presurgical evaluation. Two kinds of activity were differentiated: evoked (phase locked) and induced (not phase locked) GBA. In 18 patients, an intracranial P50 was observed. At electrodes with maximal P50, evoked GBA occurred with a similar peak latency as the P50. However, the intensities of P50 and evoked GBA were only modestly correlated, suggesting that the intracranial P50 does not represent a subset of evoked GBA. The peak frequency of the intracranial evoked GBA was on average relatively low (~25 Hz) and is, therefore, probably not equivalent to extracranially recorded GBA which has normally a peak frequency of ~40 Hz. Induced GBA was detected in 10 subjects, nearly exclusively in the region of the superior temporal lobe. The induced GBA was increased after stimulation for several hundred milliseconds and encompassed frequencies up to 200 Hz. Single-trial analysis revealed that induced GBA occurred in relatively short bursts (mostly ~100 ms), indicating that the duration of the induced GBA in the averages originates from summation effects. Both types of gamma band activity showed a clear attenuation with stimulus repetition.

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Introduction

Sensory gating refers to the basic ability of the brain to suppress the response to repeated (and possibly irrelevant) environmental stimuli (Venables, 1964). The typical experimental setup for electrophysiological studies of sensory gating in the auditory domain applies pairs of clicks, separated by a short interstimulus interval (ISI, 0.5 s) and a long interpair interval (8–12 s) (Adler et al., 1982). Healthy control subjects have on average reduced P50 amplitudes as response to the second stimulus, as compared to the P50 elicited by the first stimulus. This amplitude reduction or suppression is regarded as an indicator of sensory gating (Nagamoto et al., 1991).

Most studies on sensory gating are restricted to the analysis of the P50, although there were some studies investigating also the suppression of later auditory evoked potential (AEP) components (Boutros et al., 2004) and the suppression of the evoked gamma band activity (GBA) (Clementz et al., 1997). In neuromagnetic recordings, such an evoked (or phase-synchronized) GBA with a maximum at 40 Hz was reported to occur in a latency range of 30–100 ms (Pantev et al., 1991). GBA is of particular interest in neuroscience research as it has been linked to a variety of perceptual and cognitive functions such as feature binding, object representation or selective attention (Bertrand and Tallon-Baudry, 2000; Engel and Singer, 2001; Fell et al., 2003; Keil et al., 2001; Tiitinen et al., 1993; Varela et al., 2001). Alterations in GBA have also been related to pathological processes (Lee et al., 2003; Llinas et al., 1999).

The P50 and the evoked GBA are difficult to separate because they overlap in the time and frequency domain. It has even been proposed that P50 and evoked GBA represent the same phenomenon (Basar et al., 1987; Clementz et al., 1997). The AEP is typically filtered from 10 to 50 Hz for the study of the P50 and from 30 to 50 Hz for the study of the evoked GBA. Furthermore, the study of GBA and P50 in surface recordings is handicapped by...
small signal amplitudes and possible contamination with high-frequency muscle artefacts. Intracranial recordings avoid an attenuation of the EEG signal by intervening tissues between the cortical generators and surface electrodes particularly in the higher frequency range (Pfurtscheller and Cooper, 1975) and might, therefore, be regarded as ideally suited for the investigation of GBA. However, the opportunity for intracranial recordings in humans is rare and restricted to presurgical evaluation of epilepsy and tumor patients.

In a study on epilepsy patients, GBA elicited by visual stimuli was recorded intracranially while patients performed a Kanizsa task (Lachaux et al., 2000). Interestingly, besides evoked GBA, induced (not phase-synchronized) GBA was observed, occurring in a time range from 200 to 500 ms. Similarly, both kinds of GBA were also recorded from the temporal lobe after auditory stimulation with tones and phonemes (Crone et al., 2001). In this study, power changes in GBA were analyzed in recordings from 4 subjects with tones and phonemes as stimuli. As a major finding, induced GBA was assumed to be confined not only to the well-known GBA at about 40 Hz but also comprised activity of considerably higher frequencies (80–100 Hz). The induced GBA started at about the same time as the invasively recorded N100 but outlasted this component. Topographically, it was found adjacent to electrode sites with a prominent N100 peak, but its topographical distribution was not identical to that of the N100. Induced GBA after acoustic stimulation was also observed in monkeys (Broesch et al., 2002).

The current investigation was conducted within the framework of a larger study on a functional neuroanatomical model of sensory gating. In general, this study targets to describe neuronal correlates of sensory gating by intracranial recordings in humans. Here, we investigated the occurrence of evoked and induced GBA in a typical sensory gating experiment with paired clicks. The first aim of the study was to examine whether evoked GBA can be observed at intracranial leads and compare such an evoked GBA to characteristics of P50. The second aim was to prove whether induced GBA is elicited also by the very short stimuli with a duration of a few milliseconds only, as usually applied in sensory gating experiments. Finally, the effect of stimulus repetition was assessed for evoked and induced GBA as well as for the AEP components P50 and N100. For these purposes, brain signals were analyzed in the time–frequency domain by wavelet transform.

**Experimental design and methods**

**Subjects**

Patients with medically refractory epilepsy who were implanted with electrodes for presurgical evaluation participated. The exact placement of electrodes always depended on clinical considerations and considerably varied between patients. Overall 47 patients took part in our recordings between January 2003 and June 2004, with 36 patients having electrodes placed in the region of interest (lateral surface of the temporal lobe). Two data sets had to be excluded from analysis owing to technical reasons, leaving a final study sample of 34 patients (17 male, mean age 36 years, range 19–57 years). Subjects gave written informed consent. The study was approved by the local ethics committee of the University of Bonn.

**Data recording**

The EEG was recorded with the digital EPAS system (Schwarzer, Munich, Germany) and its implemented Harmonic EEG software (Stellate, Quebec, Canada). The EEG was measured against a reference of left and right mastoid electrodes with a sampling rate of 1000 Hz. Electrode positions were determined by MRI recordings routinely acquired after implantation.

Patients were seated on a comfortable chair in a quiet room illuminated by bright light. During the experiment, the subjects were stimulated with repetitive acoustic stimuli by headphones. The stimuli used were short tone bursts of a single sine wave with 1500-Hz frequency and a duration of 6.6 ms (including rise and fall times of 1.5 ms). A set of 100 pairs of stimuli were administered with an ISI of 0.5 s and an interpair interval of 8 s.

**Data analysis**

The EEG was segmented into single trials with a total duration of 2000 ms. An interval of 500 ms prior to the first stimulus was included into each trial for baseline correction. Recordings were inspected thoroughly for epileptic activity, and contaminated segments were rejected (on average 10% of the trials). After averaging, all electrode contacts were explored for AEPs. For inspection of the AEPs, band-pass filters were applied (1–20 Hz, 12 dB/oct for the N100 and 10–50 Hz, 12 dB/oct for the P50). The N100 was expected to peak within a latency interval from 70–130 ms and the P50 from 35–75 ms. A possible P50 was only analyzed if an N100 was observed. Both components (P50, N100) were measured with respect to baseline. If a potential was found at more than one electrode, the electrode with maximal potentials was selected. These electrodes were tested for the occurrence of evoked GBA.

As there was no presumption about the exact location of induced GBA, all electrodes were screened by the ‘frequency extraction’ procedure of the Brain Vision Analyzer software (Brain Products, Munich, Germany). This tool is easy applicable and allows to assess possible contributions of frequency bands in the time domain. For the current purpose, power values were extracted for the frequency band from 60–160 Hz and subsequently averaged over trials. If visual inspection supported the assumption of systematic high frequency activity at an electrode, data were more thoroughly analyzed by means of continuous wavelet transform (Torrence and Compo, 1998). This transform characterizes the brain activity by its dispersion in the time and frequency domain. Within this transform, data were also tested statistically for significance. Morlet wavelets (6 cycles, 102 scales) were used for data transformation. In such a procedure, the frequency content is obtained for each time point, stored in a complex number with real part \( R(t,f) \), cosine components and imaginary part \( I(t,f) \), sine components. From the transformed single trials, two different representations of the data can be obtained by averaging over the trials using either the unchanged wavelet coefficients with preserved phase information or the power values \( |I(t,f)|^2 + |R(t,f)|^2 \) at each time point without any phase information. If phase information is preserved, signals will increase with their phase locking, while signals which are not phase locked will cancel out each other. Such a transform
results in a representation of the event-related potential in the time–frequency domain (ERP(t, f)).

$$ERP(t, f) = \frac{1}{n} \left( \sum_{i=1}^{n} I_i(t, f)^2 + \sum_{i=1}^{n} R_i(t, f)^2 \right)$$

If phase information is neglected, the average power is obtained. The difference of the background activity (see below) and the event-related activity from these averaged power values is referred as the induced signal IN.

$$IN(t, f) = \frac{1}{n} \left( \sum_{i=1}^{n} I_i(t, f)^2 + \sum_{i=1}^{n} R_i(t, f)^2 \right) - \text{background}(t, f)$$

To determine significance levels for the wavelet transforms, we decided to use the experimentally measured EEG data from the 8 s interpair interval as representative for the background activity. From each of the 100 interpair intervals, a period of 6 s was segmented into three trials, yielding a total of 300 background trials with the same length as for the event-related trials. These trials were wavelet transformed and the obtained power values were sorted into a histogram, separately for each frequency scale. This histogram represents the probability distribution function from which the cumulative density function is retrieved and significance levels can be obtained. Power values with a cumulative density greater than 0.95 indicate decreased power against the background. The power value at 0.5 is used as the median background level for a particular scale. This estimation of background activity is also used as reference value for calculating the induced signal IN.

With this procedure, significance levels for the wavelet transforms of single trials were retrieved. To obtain significance levels for an average of trials, the same procedure was used, but prior to sorting the power values into the histogram, background trials were averaged using the same number of trials as in the average for which the significance level was to be determined. Grand averages over data sets from different patients were calculated by merging all available single trials into one dataset and calculating the average and the significance levels as described above.

The obtained significance values are threshold values. They indicate that the probability of a found intensity (e.g., in an event-related single trial) to belong to the distribution of intensities found in the background trials is $P < 0.05$. Plotting this threshold as a contour line might be interpreted as multiple testing with a 5% probability of error. To reduce the likelihood to mark signals erroneously as significant as result of multiple testing, data points were finally marked as significant only if they belonged to a cluster of 51 consecutive significant data points. Extracted GBA activity values and amplitudes of AEP components were tested for a possible decrease from S1 to S2 by paired $t$ tests.

**Results**

**Auditory evoked potentials and evoked GBA**

P50 and N100 potentials could be observed in 18 of the 34 patients. In all but one patient, the maximum N100 and maximum P50 were located at the same electrode. The N100 was observed on average at 104.4 ms (–46.0 $\mu$V) for S1 and at 102.3 ms (–23.2 $\mu$V) for S2. The P50 had a latency of 48.8 ms (19.5 $\mu$V) for S1 and 46.3 ms (9.1 $\mu$V) for S2. As expected, the amplitudes of both components decreased significantly from S1 to S2 (P50: $t_{17} = 5.307, P < 0.001$; N100: $t_{17} = 3.834, P < 0.005$).

In order to elucidate the relation between P50 and evoked GBA, the evoked GBA was quantified at all electrode positions with the maximal P50 amplitude. Data from these electrodes were wavelet transformed, and the ERPs in the time and frequency domain were calculated. These wavelet spectra showed that both S1 and S2 were followed by a short lasting evoked GBA (Fig. 1a). For estimation of the response decrease from S1 to S2, GBA was quantified by calculation of the sum of intensities in the frequency range from 30 to 50 Hz (Fig. 1b). Due to high data variance, the GBA decreased from S1 to S2 only on a trend level ($t_{17} = 1.831, P < 0.1$). High correlations were found between the P50 amplitudes at S1 and S2 ($r = 0.715, P < 0.001$) and between the evoked GBA at S1 and S2 ($r = 0.823, P < 0.001$) but only marginal correlations between P50 amplitudes and evoked GBA at S1 ($r = 0.422, P < 0.1$) and at S2 ($r = 0.461, P < 0.1$). The maxima of the evoked GBA were observed at 47.7 ms for S1 and 44.1 ms for S2 and were thus in close proximity to the peak maximum of the P50 (Figs. 1b and c).

For further analysis, frequency spectra were calculated at the peak latency of the evoked GBA. These spectra revealed that the evoked GBA exhibited on average no distinct maximum around 40 Hz but rather in the range of the higher beta band (25 Hz for S1 and 18 Hz for S2, Fig. 1d). A possible down sloping of the induced GBA by stimulus repetition could statistically not been verified owing to problems to quantify this value in all individuals, as frequency spectra of some individuals showed a continuous decline of intensity from low to high frequencies.

**Induced GBA**

Induced GBA was revealed by the frequency extraction procedure in 11 patients at a total number of 25 electrodes. Data from these electrodes were wavelet transformed, and time–frequency spectra were calculated. The induced GBA was found to be significant in 10 of the 11 patients. Topographically, nearly all contacts with a significant induced GBA were found in the perisylvian region. The exact locations of electrodes with significant induced GBA are depicted in Fig. 2. In 7 patients, induced GBA was found at more than one electrode, but only in one subject at more than two electrodes.

Fig. 3 shows the time–frequency maps of the induced signal (IN(t, f), Fig. 3a) and of the evoked signal at the same electrode (ERP(t, f), Fig. 3b), averaged for all patients with induced GBA. The induced GBA covers a frequency range up to 200 Hz. It had an onset of approximately 100 ms and lasted for more than 300 ms. Comparison with the evoked signal shows that phase-locked GBA did not contribute to the induced GBA as there was nearly no overlap between the induced and evoked GBA in the time–frequency range. In 9 of the 10 patients, an AEP was observed at the same electrode as the induced GBA. In 6 of 10 patients, the induced GBA occurred at electrodes also exhibiting a typical P50 and N100 component. In the three other patients, there was also evoked activity at these electrodes but at longer latencies (130–200 ms).

The induced GBA was further studied in single trial analysis. Contrary to our expectation to find GBA with the same characteristics as in the average, albeit with a much poorer
signal to noise ratio, the analysis of the single trials revealed that GBA occurred in bursts with a variable duration and frequency content. Three exemplary trials are depicted in Figs. 4c to e. In these time–frequency plots, bursts with significant higher intensity as the background activity are marked with a black contour line and can be compared to the characteristics of the averaged signal which is indicated by the transparent area and in Figs. 4a to b. Several bursts distributed in time and frequency could be observed within a single trail and these bursts did not show the characteristics of the averaged signal. While the induced gamma band responses in the averaged signal lasted over several hundred milliseconds, the gamma bursts in the single trials typically showed a rather short duration ($\approx$100 ms).

In order to analyze the response suppression of the induced GBA by stimulus repetition, activity was quantified by the number of significant bursts in the frequency range 30–160 Hz. For this purpose, maximal intensities and latencies of the bursts were extracted for all single trials of an individual, with the additional assumption of a minimum distance of 50 ms between two bursts (exemplary individual data are shown in Fig. 4f). The number of bursts was compared between the baseline interval ($-500$ to $0$ ms) and the two post-stimulus intervals (S1: $0$–$500$ ms; S2: $500$–$1000$ ms). This analysis revealed that the number of bursts significantly decreased from S1 to S2 ($t_9 = 5.871$, $P < 0.001$). In both S1 and S2 intervals, the number of bursts surmounted the number of bursts in the baseline interval ($t_9 = 5.225$, $P < 0.001$ and $t_9 = 2.619$, $P < 0.05$). The number of bursts in S1 and S2 intervals was highly correlated ($r = 0.804$, $P < 0.005$).

**Discussion**

Evoked and induced GBA were recorded from subdural electrodes at the lateral surface of the superior temporal gyrus in a paired click paradigm. The temporal characteristics of the evoked GBA resembled recordings of evoked GBA by means of magnetoencephalography (MEG) and surface EEG recording (Jokeit and Makeig, 1994), but the mean frequency of the maximum evoked GBA in our recordings was clearly lower than expected from the literature on extracranial recordings (see especially Figs. 1b and d).
Furthermore, the evoked GBA in our intracranial data was not very well pronounced despite the high sensitivity of the recording method. The signal to noise of the intracranial P50 is far superior to extracranial recordings of this component. Therefore, we had expected also a much more pronounced signal of the intracranial evoked GBA. Besides that also the mean frequency of the evoked GBA was lower than expected from the literature on extracranial recordings. It seems therefore reasonable to assume that the intracranially recorded evoked GBA at the lateral surface of the temporal lobe reflects a somewhat different subset of cortical activity as compared to extracranial recorded GBA.

Source reconstruction of MEG data led to the assumption that evoked GBA originates from the supratemporal auditory cortex at the floor of the Sylvian fissure (Pantev et al., 1991). Because MEG is nearly insensitive to sources radially oriented to head surface, the neuromagnetic GBA necessarily stems from mainly tangentially oriented sources, but also EEG data would be in line with such an assumption of a tangential source in this region, as the electric evoked GBA is usually recorded maximally over the frontal vertex. In contrast to evoked GBA, the P50 and N100 recorded from the lateral surface of the superior temporal gyrus (STG) display a high similarity to extracranial P50 and N100.
However, recently we could show that the N100, recorded from the posterolateral STG, and the N100, recorded at Cz, are differentially affected by stimulus repetition (Rosburg et al., 2006). This finding proposed that the N100 recorded from the posterolateral STG is only partly reflected in extracranial recordings, while it seems reasonable to assume that the N100 at Cz is mainly generated by tangential sources in or around the Heschl’s gyrus (HG) (see also Picton et al., 1999; Scherg and von Cramon, 1985). Furthermore, other researchers were able to show that ERPs recorded from posterolateral STG and HG exhibit a differential recovery function, proposing that the posterolateral STG represents an auditory area functionally distinct from the HG (Howard et al., 2000).

Evoked GBA as recorded in the current study might originate from radial sources in the posterolateral STG, thus explaining the lower frequency of the maximum evoked GBA as compared to extracranial ERPs (Pantev et al., 1991). Unfortunately, the coverage of electrodes over the temporal lobe and the number of electrodes containing a signal did not allow any attempts to reconstruct the sources of GBA. However, also other factors as the anti-convulsive medication of the patients and the disease itself have been taken into account as possible confounding factors for a lower frequency of GBA. Unfortunately, studies of drug effects on evoked GBA are relatively rare and mostly restricted to effects on its amplitudes rather than on frequency shifts. Temazepam as benzodiazepine, e.g., was reported to reduce the amplitude of the evoked GBA (Jaaskelainen et al., 1999). To our knowledge, a study on possible alterations of GBA in epileptic patients has so far not been conducted.

Evoked GBA with significant frequency contents up to 70 Hz was observable at electrodes where the maximal intracranial P50 was recorded. Nevertheless, the current finding suggests that P50 and evoked GBA, recorded at the posterolateral STG, represent two different kinds of cortical activity as the amplitudes values were only marginally correlated. It can also be derived from Fig. 1 that the P50 at the posterolateral STG mainly consists of signals of lower frequencies (<30 Hz), thus does not overlap with typical range of GBA. As the recordings of the current study were limited to the lateral surface of the temporal lobe and did not target the HG, this conclusion cannot be drawn for P50 and evoked GBA in HG. It should be stated once again that the implantation of electrodes was guided solely by clinical considerations.

Besides the observation of evoked GBA, the current study replicates the finding of high frequency non phase-synchronized GBA induced by auditory stimulation (Crone et al., 2001), which was also observed in invasive recordings in monkeys (Brosch et al., 2002). While Crone and co-workers observed induced GBA in response to stimuli of 300–400 ms duration, this activity was elicited in the current study by events of a few milliseconds duration. The duration of the induced GBA in the two studies was quite comparable, strongly suggesting that the stimulus duration has no major impact on it, although the impact of stimulus duration was not directly tested. If stimulus duration has no effect on induced GBA, it is probably not or at best in a minor extent be associated to further ongoing stimulation.

It has been speculated that induced GBA reflects an object representation as proposed for the visual domain (Bertrand and Tallon-Baudry, 2000; Lachaux et al., 2000). Also the variation of induced GBA with stimulus material would be in line with this interpretation of the induced GBA. Induced GBA was greater and observed at more electrodes after stimulation with phonemes as compared to tones (Crone et al., 2001). However, the current study in comparison to the findings of Crone et al. (2001) suggests that the induced GBA is more likely to be associated to stimulus onset and/or to representation of object features (as frequency and loudness), and not a complete object representation (as “gestalt”), as in auditory domain a complete object representation cannot be accomplished before stimulus offset. In that case, one would expect that the duration of the induced GBA depends on stimulus duration. However, further studies are warranted to elucidate the functional role of the induced GBA, systematically varying experimental conditions, as, e.g., attention load and perceptual complexity. It is worth mentioning that time–frequency spectra obtained by intracranial recordings in a visual task had a striking similarity to current data (compare to Fig. 1 in Lachaux et al., 2005).
Fig. 4. (c–e) Wavelet spectra (clustering 21) of three exemplary single trials from patient A (Fig. 2). Significant induced GBA bursts are marked with a black contour line. The shaded area shows the induced GBA signal from the grand average of this individual. The lower parts in panels (c–e) show the sum of significant intensities in the frequency range from 30160Hz from which latencies and intensities of induced GBA burst were retrieved in each trial. In panel (f), latencies and intensities of significant gamma bursts in this patient are shown on a scatterplot. The number of significant bursts decreased from S1 to S2. (a–b) Analogue data as depicted in Figs. 3(a–b) for patient A. All color scales are logarithmic.
Data analysis on single trial basis revealed that the induced GBA consisted of high amplitude bursts of high frequencies, neither time nor phase locked. These gamma bursts typically have a short duration (mostly \( \approx 100 \) ms). Thus, the rather long duration of the averaged induced gamma band responses appears to originate from the averaging process and is not a characteristic of single trial activity. Although such an effect has been described for simulated data (Tallon-Baudry and Bertrand, 1999), to our knowledge, this phenomenon has been practically demonstrated for the first time in the present study. The probability of an occurrence of a gamma burst was largest approximately 100–200 ms after stimulation, but single bursts were also observed in a minor extent before stimulation. The probabilistic behavior of GBA resembles recordings of single cells, but owing to the lack of variation of stimulus material (or experimental task), it is nearly impossible to interpret it more in detail. Crone et al. (2001) speculated that the broadband nature of induced GBA could be due to the spatial summation of multiple neuronal populations oscillating at different, perhaps broadly tuned, frequencies, allowing parallel computation of information within the same cortical region.

One characteristic of induced GBA is its suppression by stimulus repetition. The exact mechanism of response suppression by stimulus repetition is not fully understood. As shown for the induced GBA, it can be clearly seen that the total number of bursts is reduced by stimulus repetition. In contrast, the reduction of ERP components might also be explained by the loss of phase synchronization (Jansen et al., 2003). The suppression of GBA (and other ERP components) elicited by the second stimulus might simply be regarded as the result of refractoriness, because the large interpair interval (8000 ms) but not the short ISI within the pair (500 ms) allows for full response recovery of event-related activity. However, in addition to this mechanism, the first stimulus might also elicit an active inhibition process, suppressing the cortical activity evoked by the second stimulus, as proposed by the study of Sable and co-workers (Sable et al., 2004). The authors proposed an additional inhibition process taking place which becomes fully active after 300–400 ms after stimulation. This inhibition phase might also be involved in the formation of sensory memory trace (Nätäinen and Rinne, 2002).

In this context, it is noteworthy that in hippocampal recordings of sensory gating experiments no P50 was observed, but a later and long lasting activity (Grunwald et al., 2003). Whether the observed induced GBA possibly contributes to gating or memory functions has to be targeted in future studies.

References


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