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Attention effects on sensory gating - Intracranial and scalp recordings

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ABSTRACT

The function of sensory gating is usually studied in paired-click experiments and quantified by the decrease of the event-related potential (ERP) component P50 and other ERP components from the 1st to the 2nd stimuli. The impact of attention on these gating measures is still not fully resolved. In the current study, the impact of attention on sensory gating was studied by scalp and intracranial recordings. The study sample consisted of epilepsy and tumor patients undergoing presurgical evaluation by means of implanted electrodes. In the unattend condition, patients had no overt task. In the active condition, patients had to count simultaneously trials with paired clicks, as well as interspersed trials with single clicks. The ERPs in the active condition were characterized by an underlying negativity both for scalp and neocortical recordings, reaching their maximum at the N100 latency of the 2nd stimulus. A time–frequency analysis revealed that this attention effect comprised only low frequency signals (<3 Hz). In line with that, P50 amplitude and P50 gating were unaffected by attention when data were filtered from 10 to 50 Hz. In addition, attention effects were revealed for intrahippocampal ERP components and for induced high frequency neocortical gamma band activity. Findings indicate that N100 and P200 gating measures can potentially be affected by attention and have to be interpreted carefully when studying clinical populations.

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Introduction

Auditory sensory gating has been studied intensively in schizophrenia research, usually in paired-click experiments. In this experimental setup, sensory gating is quantified by the suppression ratio of the auditory evoked potential (AEP) component P50 or by its decrease from the 1st to the 2nd clicks in microvolts. Numerous studies found a reduced P50 gating in schizophrenia patients (for review: Bramon et al., 2004). Recently, the concept of sensory gating has been expanded and referred to other AEP components such as the N100 and P200 (Blumenfeld and Clementz, 1999; Boutros et al., 2004; Brockhaus-Dumke et al., 2008). This expansion of the concept to other event-related potential (ERP) components is justified by the idea that sensory gating reflects a multi-stage process (Boutros et al., 1999).

Experimentally, the expansion can be achieved without any problems, since clicks, like any tonal stimulation, elicit a cascade of ERP deflections (Picton et al., 1974) and most ERP deflections are suppressed by stimulus repetition. However, the AEP components P50, N100, and P200 are neither generated by the same brain structures nor necessarily closely associated in their function. As a consequence, sensory gating might be disrupted for one component, but not for

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others. For example, in the pioneering study of Freedman et al. (1983), a deficit was observed for P50 gating in schizophrenia patients, but not for N100 and P200 gating.

In addition, P50, N100 and P200 might differentially be affected by attention, as discussed already by Freedman et al. (1983). From dichotic listening experiments, there is ample evidence that selective attention can increase the N100 (Hillyard et al., 1973; Näätänen et al., 1981; Hackley et al., 1990; Woldorff and Hillyard, 1991). Furthermore, attention might possibly enhance early positive AEP components, including the P50 (Woldorff and Hillyard, 1991; Woldorff et al., 1993; but see Hackley et al., 1990). However, the effect of attention on sensory gating of the P50 is uncertain, with some studies reporting an attentional impact on P50 gating and others reporting no effect (Guterman et al., 1992; Guterman and Josiassen, 1994; Jerger et al., 1992; Kho et al., 2003; White and Yee , 1997; White et al., 2005).

The current study re-addressed the issue of attention effects on P50 and N100 gating in order to clarify to what extent attention effects might confound findings on clinical populations in paired-click experiments. Since longer intervals of no stimulation between the paired clicks are an inherent and essential part of these experiments, an active control of attention is rather difficult, not to say impossible to achieve. As consequence, subjects usually do not perform any kind of control task when tested in paired-click experiments. This in turn means that deficits in P50 and N100 gating in a clinical population could theoretically be due to deficits in attention (instead of being due to deficits in P50 and N100 gating





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could remain undiscovered because they are compensated by attentional resources.

In order to study the impact of attention on P50 and N100 gating, the current study capitalized the unique possibility of intracranial recordings in a sample of epilepsy patients. The amount of scalp P50 and N100 gating in epilepsy patients is usually in the range of healthy subjects (Boutros et al., 2006; Rosburg et al., 2008). In a recent dichotic listening study on epilepsy patients, the neocortical N100 was found to be increased by attention (thus, was similarly modulated by attention as the scalp N100 in healthy subjects), while attention had variable effects on the neocortical P200 (Neelon et al., 2006).

In addition to neocortical and scalp recordings, the current study encompassed recordings from the mesiotemporal lobe. Previous studies have shown that the hippocampus and the rhinal cortex become activated at latencies after the P200 (Grunwald et al., 2003; Boutros et al., 2005; Rosburg et al., 2007), but the functional role of this mesiotemporal activation in sensory gating is not yet understood. However, even patients with bilateral hippocampal sclerosis exhibit a relatively normal P50, N100, and P200 gating (Rosburg et al., 2008), suggesting that mesiotemporal regions are not crucially involved in sensory gating.

Finally, the current study allowed the investigation of induced high frequency gamma band activity (GBA) (40–200 Hz) which is almost exclusively observed in neocortical recordings (Crone et al., 2001; Edwards et al., 2005; Trautner et al., 2006). In a recent intracranial study, we hypothesized that induced high frequency GBA might possibly reflect inhibitory ripple activity, also related to sensory gating functions (Rosburg et al., 2009). However, comparison of subjects with poor and good gating did not reveal any difference in induced high frequency GBA, thus did not corroborate our hypothesis (Rosburg et al., 2009). Another study proposed a close link between induced GBA and attention (Ray et al., 2008). Thus, we hoped that modulating attention might help to elucidate the yet unresolved functional role of high frequency GBA in auditory information processing in general and sensory gating in particular.

Sensory gating is commonly regarded as a filtering out of irrelevant information, since the second stimulus does not contain any new information, as compared to the first stimulus, and has no behavioral relevance. In the current study, we constructed an active condition in which the second click became behaviorally relevant. Subjects had to differentiate trials in which a second click occurred from single click trials. This experimental variation should lead to a gating-in instead of a gating-out of information (Boutros et al., 1999), and should consequently produce a large attention effect on sensory gating measures.

Taken together, the study aimed at clarifying in more detail the potential role of attention in sensory gating experiments by combination of scalp and intracranial recordings. The study investigated: (a) whether P50 and N100 gating can be affected by attention; and (b) the impact of attention on other kinds of activity (induced high frequency GBA and hippocampal ERPs) previously observed in paired-click experiments, but whose functional significance is still not fully understood.

Methods

Subjects

36 patients (21 male) with a mean age of 34.5 years (range 16 to 65 years) undergoing presurgical evaluation by means of implanted electrodes took part in the study. The sample consisted of 34 epilepsy patients and 2 tumor patients. The exact placement of intracranial electrodes depended on clinical considerations only. Patients were on stable anti-convulsive medication at the time of the recording. Eight patients had some psychiatric history, in most cases (n=6) one or more depressive episodes. One patient had both depressive episodes

and psychotic symptoms in the past. Another patient had a posttraumatic stress disorder.

The subject sample partially overlaps with the sample of two other studies of our group on sensory gating (Trautner et al., 2006; Rosburg et al., 2009), but the data of the attend condition has never been reported before. Patients gave written informed consent for participating in the study. The study was approved by the local ethics committee of the University of Bonn.

Data recording and stimulation

The EEG was recorded with the digital EPAS system (Schwarzer, Munich, Germany) and its implemented Harmonie EEG software (Stellate, Quebec, Canada). Recordings were simultaneously obtained from different intracranial electrodes and six electrodes on the scalp (Cz, C5, C6, T5, T6, Oz). Both scalp and intracranial EEG were measured against a reference of left and right mastoid electrodes with a sampling rate of 1000 Hz. Positions of implanted electrodes were determined by MRI recordings routinely acquired after implantation. Patients were seated on a comfortable chair in a quiet room illuminated by bright light. Stimulation consisted of short tone bursts of a single sine wave with 1500 Hz frequency and duration of 6.6 ms (including rise and fall times of 1.5 ms). Stimuli were administered binaurally by headphones at 60 dB above hearing level.

The experiments consisted of two runs with acoustic stimulation. In both runs, subjects were requested to sit relaxed and to watch a silent movie. In the unattend condition, stimulation consisted of 100 click pairs, administered with an interstimulus interval of 0.5 s and an interpair interval of 8 s. Subjects were told to focus on the movie. In the attend condition, stimulation consisted of 100 regular trials with click pairs and 10 interspersed single click trials. Subjects were requested to count silently both kinds of trials separately. At the end of this run, subjects were asked for their counts.

The order of the two conditions was balanced. In case subjects had their unattend condition after the attend condition, subjects were asked whether they had counted the stimuli (although they had not been requested).

Data analysis

The EEG was high-pass filtered with 0.1 Hz (24 dB) and segmented into single trials with a length of 2000 ms (Brain Vision Analyzer 1.05, Brain Products, Munich, Germany). Data were analyzed separately for scalp and intracranial recordings. All data were referenced to mastoids. The scalp EEG was quantified at Cz. The intracranial EEG was analyzed at a neocortical contact showing an N100 component, preceded by a P50 component. These contacts were located primarily over the temporal cortex. If several contacts exhibited an N100 component, the contact with the largest N100 amplitude (70–140 ms) was selected for further analysis.

In addition to the neocortical data, intracranial EEG was analyzed at a rhinal and hippocampal contact each. Here, ERPs exhibit later long-lasting components, but no P50 or N100 (Grunwald et al., 2003; Boutros et al., 2005; Rosburg et al., 2007). For the rhinal cortex the electrode with the most positive component and for the hippocampal cortex the electrode with the most negative component (250–450 ms) were selected. Only hippocampal data of the non-lesion side were analyzed.

An interval of 500 ms prior to the first stimulus was used for a baseline correction. Segments of scalp EEG with activity >75 μ V and segments of intracranial EEG with activity >300 μ V were rejected as artefacts. Data sets were excluded from the analysis if recordings contained artefacts in more than 40% of the segments in one or both conditions. This turned out to be the case only in scalp recordings. EEG segments were averaged for the unattend and attend condition, separately. Trials with single clicks were not included for the

calculation of the ERP of the attend condition. After averaging, ERPs were low-pass filtered at 20 Hz (24 dB). For the study of attention effects on P50, ERPs were filtered from 10 to 50 Hz (24 dB).

Peak amplitudes

The P50 peak amplitude was determined as the most positive peak between 30 and 80 ms preceding the N100 and was measured relative to baseline, as all low frequency activity was removed by the filtering. The N100 amplitude was quantified as the most negative peak (70–140 ms) relative to its preceding trough (most positive peak 30–80 ms). The P200 is relatively difficult to detect in recordings of epilepsy patients (Boutros et al., 2006) and was, therefore, not analyzed as peak value.

Gating ratios

Gating was quantified as ratio of the S2 and S1 peak amplitudes (S2/S1 ratio), for post-hoc statistics only. Thus, smaller values indicate stronger suppression.

Mean amplitudes

In addition to the peak amplitudes, mean (non-rectified) amplitudes were obtained for non-overlapping time windows. For the ERP in response to the first click, the time windows covered the baseline period (-60-0 ms), the period before the N100 (0-60 ms), the N100 (70-140 ms), and the P200 (160-230 ms). For the ERP in response to the second click, the same time windows 500 ms later were analyzed. In order to compare single click and click-pair ERPs in the attend condition, the following later time windows were also analyzed: 750–850 ms, 850–950 ms, 950–1050 ms, 1050–1150 ms, 1150–1250 ms. The hippocampal ERPs were quantified for the 250–450 ms post-stimulus periods.

Event-related and induced activity

In order to show which frequencies contributed to the attention effects, neocortical data were also analyzed by a continuous wavelet transform with Morlet wavelets (6 cycles, 102 logarithmically spaced scales), using routines of Torrence and Compo (1998). For this analysis, EEG data were only high-pass filtered (0.1 Hz, 24 dB). A wavelet transform characterizes the event-related brain activity by its dispersion in the time and frequency domain. For each time point and each frequency scale the transform yields a complex wavelet coefficient, resulting in a total of 2000 × 102 coefficients per single trial.

Depending on how averages are calculated over the trials, phase locked activity (event-related activity, ERA) and non-phase locked activity (induced activity, IN) can be assessed. Because of its lack of phase locking, IN cancels out by averaging and is consequently not reflected in the ERP. For calculating ERA, the raw wavelet coefficients were averaged, allowing for cancellation of non-phase-synchronized activity, and power values were calculated after averaging. If power values are calculated for each trial before averaging, no cancellation of signal components occurs and the resulting values comprise the total signal power. In order to obtain the pure IN, ERA was subtracted from the total signal power (for more details see Rosburg et al., 2009).

As an estimator for non-task related activity, the inter-trial period (2000–8000 ms after S1 onset) was segmented in three segments of 2000 ms each and wavelet transforms were calculated. The median was calculated from all power values of all time points in all trials of a subject. This was done separately for each scale resulting in an estimator for the median inter-trial activity for that scale in a specific subject. These median power values per scale are referenced as the background activity.

Grand averages were calculated for IN, ERA and the background activity over all subjects. Variances over the subjects were also obtained for later *t*-tests. The comparison of ERA and IN between the attend and unattend condition was performed by paired *t*-tests. For a

sound interpretation of differences between the two conditions only larger aggregations of significant points should be interpreted. Therefore, all wavelet transforms were smoothed along both the wavelet scale axis and the time axis. Smoothing was done by an operator which has a similar footprint as the wavelet used. For the Morlet wavelet a suitable smoothing operator is given by Torrence and Webster (1999). This smoothing can be thought of as a kind of cluster approach to avoid false positives due to multiple testing. Of note, the smoothing operator lowers particularly isolated high *p*-values in the transform. For comparison, unsmoothed data are provided in Supplementary Fig. 1.

Wavelet transforms of ERA and IN show the signal with background activity subtracted. Thus, IN e.g. depicts the non-synchronized activity above the inter-trial background. To test if the depicted activity values (IN, ERA) were significantly above the background activity, *t*-tests were calculated. Areas with significance at the 95% level indicate signals being higher than the background activity and are outlined with a black line, whereas white lines indicate signals being lower than the background activity.

The calculations of the wavelet transforms and their statistical comparison were performed by scripts, written in the programming language Python (http://wiki.python.org/) by one of the authors (P.T.).

Statistics

The impact of attention on sensory gating on peak and mean amplitudes was analyzed by a repeated measure analysis of variance with REPETITION (1st vs. 2nd click) and ATTENTION (attend vs. unattend) as within-subject factors. A significant interaction between REPETITION and ATTENTION would indicate an impact of attention on gating, while an ATTENTION effect alone would indicate an effect of attention on ERP peak amplitudes in general. In case of significant interactions, post-hoc testing was performed by paired *t*-tests. The level of significance was set at $p \le 0.05$ (uncorrected) in order to maintain a high sensitivity for possible attention effects on sensory gating measures.

Results

Data of six subjects had to be excluded from the analysis because of their behavioral performance. Three subjects gave strongly inaccurate counts in the active condition, indicating that these patients did not comply with the instruction. The lack of compliance with the instruction was also evident in three other subjects: One subject could only report the number of paired clicks. One subject misunderstood the instruction and also counted the stimuli in the unattend condition. Another subject fell asleep several times in the unattend condition. The included patients counted 97.5 ± 9.7 (range 63-122) paired clicks and 10.7 ± 1.5 single clicks (range 8-19).

Scalp data

Data sets of 25 patients were included in the analysis of the scalp data. Five other data sets were excluded because the number of artefacts exceeded 40%. For the analysis of the P50, another two data sets had to be excluded because the P50 peak could not be identified unambiguously. The average amplitudes and latencies of both components are summarized in Table 1. The results of the statistical analyses can be found in Table 2.

Peak amplitudes

The peak amplitudes of the scalp P50 and N100 were significantly decreased by stimulus repetition, but attention did not affect peak amplitudes, neither alone nor in interaction with stimulus repetition. Stimulus repetition also led to decreased scalp N100 latencies, irres-

Table 1		
P50 and N100	peak amplitudes	and latencies.

. . .

	Unattend		Attend	
	S1	S2	S1	S2
Scalp				
P50 amplitude	2.2 ± 1.5	1.0 ± 0.7	2.4 ± 1.4	1.3 ± 1.0
N100 amplitude	-8.3 ± 3.3	-3.9 ± 1.9	-7.9 ± 3.5	-4.8 ± 2.1
P50 latency	55.3 ± 9.9	55.9 ± 11.9	54.1 ± 8.5	52.7 ± 9.9
N100 latency	98.4 ± 11.7	89.4 ± 12.8	102.7 ± 13.5	86.9 ± 12.8
Neocortical				
P50 amplitude	12.5 ± 7.0	5.6 ± 4.6	12.9 ± 7.5	3.7 ± 4.4
N100 amplitude	-48.2 ± 23.1	$-19.3\pm8.5^*$	-55.5 ± 29.5	$-14.4 \pm 13.4^{*}$
P50 latency	58.9 ± 14.7	55.4 ± 15.8	57.1 ± 13.3	57.7 ± 16.5
N100 latency	108.8 ± 13.7	$105.5 \pm 21.4^{*}$	108.9 ± 14.7	93.8±16.8*

The P50 and N100 peak amplitudes [in μ V] and latencies [in ms] in response to the 1st stimulus (S1) and 2nd stimulus (S2): data of scalp recordings are displayed at the top part, data of neocortical recordings at the bottom part. Significant differences between measures in the unattend condition (left columns) and attend condition (right columns) are marked by an asterisk (p<0.05). Note that N100 peak amplitudes were measured with regard to their preceding trough.

pective of the experimental condition. The latency of the scalp P50 was not influenced by any of the two experimental factors.

Mean amplitudes

In contrast to peak amplitudes, mean amplitudes (as measured to baseline) were affected by attention. Visual inspection showed a pronounced negativity underlying the ERP complex in the attend condition (Fig. 1). This negativity reached its maximum at about the latency of the N100 of S2. As a consequence of this increase, significant REPETITION*ATTENTION interactions for the mean amplitude of the scalp N100 ($F_{1,24}$ = 16.994, p<0.001) and scalp P200 ($F_{1,24}$ = 6.340, p = 0.019) were revealed, as well.

The effects of attention were subsequently analyzed in more detail by paired *t*-tests between ERP data of the attend and unattend condition. Descriptive data and results of the *t*-tests can be found in Table 3. The difference between the two conditions reached significance before the onset of S2 (440–500 ms). Attention effects declined after the N100 of S2. The highest level of significance was found before the N100 of S2.

Neocortical data

Peak amplitudes

An N100 could be identified at neocortical leads in 17 patients. Exemplary data are depicted in Fig. 2. The peak amplitudes of the neocortical P50 and N100 were significantly decreased by stimulus repetition (Tables 1 and 2). For the neocortical N100 amplitude, there was also a significant REPETITION*ATTENTION interaction. It tended to be larger in the attend condition in response to S1 ($t_{16} = 1.807$, p = 0.090), while it was significantly smaller in response S2 ($t_{16} = 2.173$, p = 0.045). As a consequence, the gating ratio S2/S1 of the neocortical N100 was significantly smaller in the attend condition (gating_{N100} = 0.28 ± 0.18) than in the unattend condition (gating_{N100} = 0.48 ± 0.27; $t_{16} = 3.415$, p = 0.004).

As in scalp recordings, neocortical P50 latency was unaffected by both experimental factors. In contrast, the neocortical N100 latency was influenced by attention and stimulus repetition: A reduced N100 latency by stimulus repetition was found in the attend condition (t_{16} =5.259, p<0.001), but not in the unattend condition (t_{16} =0.718, n.s.). As a result, the N100 in response to S2 peaked significantly earlier in the attend condition, as compared to the unattend condition (t_{16} =2.738, p=0.015).

Mean amplitudes

Visual inspection of the neocortical ERPs showed a pronounced negativity underlying the ERP complex in the attend condition (Fig. 3,

top). Compared to scalp recordings, REPETITION*ATTENTION interactions were weaker or even absent for the neocortical recordings (N100: $F_{1,16}$ = 3.856, p = 0.067; P200: $F_{1,16}$ = 0.318, n.s.), mainly due to the fact that attention effects became earlier apparent in neocortical recordings than in scalp recordings. The attention effect in neocortical recordings was already found for the N100 latency window of S1. Of note, the lack of an attention effect in scalp recordings was not the result of a different sample selection, as the analysis of scalp data of patients with a subdural N100 contact alone did not reveal a significant difference either. Attention effects in neocortical recordings declined after the 2nd N100, similar as in scalp recordings.

Event-related and induced activity

Attention effects in neocortical recordings were studied in more detail by wavelet transforms. Comparison of the attend and unattend condition showed that all attention effects in the event-related activity were comprised to low frequencies (Fig. 3, 2nd row). In addition, induced activity was affected by attention at high frequency bands (Fig. 3, 3rd row). In the attend condition, a larger amount of induced high frequency GBA was found shortly before and shortly after the onset of S2, as compared to the unattend condition. Of note, in the time–frequency range with the largest amount of induced high frequency GBA (40–120 Hz and 100–350 ms after S1 and S2), no attention effects were revealed.

Trials with single clicks

In an additional analysis of the attend condition, ERP differences between single click and paired-click trials were studied. These differences could only be investigated for the neocortical contact, as for scalp and hippocampal contacts the signal-to-noise ratio was not sufficient to obtain reliable ERP curves for single click trials.

Mean amplitudes

Trials of single clicks and paired clicks were on average virtually the same for the first 500 ms (Fig. 3, top row, middle). Somewhat surprisingly, paired *t*-tests revealed that differences were still absent at the time of the second N100 (570–640 ms, t_{16} =0.335, n.s.). Thus, although there was no 2nd click and, consequently, no 2nd N100 was elicited in single click trials, the mean amplitudes did not differ. At later time stages the ERP of single click trials was

Table 2	
Results of the ANOVA on P50 and N100 peak amplitudes and latence	cies.

	REPETITION	ATTENTION	REPETITION * ATTENTION
Scalp			
P50 amplitude	$F_{1, 22} = 31.786$ p < 0.001	$F_{1, 22} = 2.840$ n.s.	$F_{1, 22} = 0.161$ n.s.
N100 amplitude	$F_{1, 24} = 37.338$ p < 0.001	$F_{1, 24} = 0.499$	<i>F</i> _{1, 24} =3.205
P50 latency	$F_{1, 22} = 0.144$	$F_{1, 22} = 1.802$	$F_{1, 22} = 1.579$
N100 latency	$F_{1, 24} = 26.046$ p < 0.001	$F_{1, 24} = 0.126$ n.s.	$F_{1, 24} = 3.010$ n.s.
Neocortical			
P50 amplitude	$F_{1, 16} = 41.727$ p < 0.001	$F_{1, 16} = 1.112$ n.s.	<i>F</i> _{1,16} =2.408 n.s.
N100 amplitude	$F_{1, 16} = 50.330$ p < 0.001	$F_{1, 16} = 0.257$ n.s.	$F_{1, 16} = 7.604$ p < 0.001
P50 latency	$F_{1, 16} = 1.173$	$F_{1, 16} = 0.009$	$F_{1, 16} = 2.601$
N100 latency	$F_{1, 16} = 9.652$ p = 0.007	$F_{1, 16} = 5.212$ p = 0.036	$F_{1, 16} = 5.591$ p = 0.031

The results of the ANOVA on the P50 and N100 peak amplitudes and latencies; a significant REPETITION*ATTENTION interaction means that gating measures were affected by attention. The number in italics represents the level of significance.



Fig. 1. The grand average ERP, as recorded from the Cz electrode, for the unattend condition (left) and attend condition (middle) separately; for the attend condition only trials with paired clicks were included; the right graph depicts the difference between both conditions, reflecting the effect of attention; the onset of S1 and S2 is indicated by vertical dotted lines; ERPs were filtered from 0.1 to 20 Hz.

characterized by a stronger negativity, as compared to ERP of paired-click trials. These differences became significant after 660 ms (660–730 ms: t_{16} = 4.320, p = 0.001; 750–850 ms: t_{16} = 3.390, p = 0.004; 850–950 ms: t_{16} = 2.718, p = 0.015; 950–1050 ms: t_{16} = 2.922, p = 0.010; 1050–1150 ms: t_{16} = 3.237, p = 0.005; 1150–1250 ms: t_{16} = 2.255, p = 0.038).

Attention effects on hippocampal ERPs

Intrahippocampal ERPs were obtained in 11 patients but data of two patients had to be excluded (one patient had dislocated electrodes and one patients had a bilateral hippocampal sclerosis). The expected negative deflection in hippocampal recordings and the positive deflection in rhinal recordings between 250 and 450 ms were observed. Visual inspection of the ERPs revealed larger ERP deflections in the attend condition as compared to the unattend condition (Fig. 4). However, due to the variability of the data, only the attention effect for the hippocampal ERPs reached significance ($F_{1, 8} = 8.673$, p = 0.014). The effect of ATTENTION on the rhinal ERP failed to reach significance ($F_{1, 8} = 2.107$, n.s.). Further, no REPETITION *ATTENTION interactions were significant (hippocampal: $F_{1, 8} = 2.778$, n.s.; rhinal: $F_{1, 8} = 1.535$, n.s.).

Discussion

The main findings of the current study might be summarized as follows: as compared to the unattend condition, the ERPs in the attend condition were characterized by a large underlying negativity which had its maximum at about the N100 latency of S2 and declined shortly afterwards to baseline level, both in scalp and neocortical recordings. This attention effect in the ERP was constricted to low frequency signals (<3 Hz), as shown by the time–frequency analysis of the neocortical ERA. The time course of the attention effects slightly differed between scalp and neocortical recordings: in neocortical recordings, attention effects were apparent earlier than in scalp recordings. The amplitudes of the hippocampal ERP components were also increased by attention. In addition to increases of phase-

synchronized activity, attention led to increased levels of neocortically recorded induced high frequency GBA.

Effects on P50, N100 and P200 gating

Attention effects on the N100 amplitude were originally described more than 30 years ago (Hillyard et al., 1973). However, the setup of experiments studying attention effects on AEPs and the setup of sensory gating experiments are completely different. Attention effects on AEPs have usually been studied in dichotic listening tasks, with a preference for short ISIs in order to keep the load of information processing high (Hillyard et al., 1973; Näätänen et al., 1981; Hackley et al., 1990; Woldorff and Hillyard, 1991). In sensory gating experiments, the load of information processing is very low, as there are long intervals of no stimulation between the pairs of clicks.

It has been shown that effects of selective attention on early processes do not necessarily occur under conditions of low perceptual load (Lavie, 1995). Furthermore, attention effects in dichotic listening tasks might take time to emerge (Donald and Young, 1982). Thus, even though attention effects on the N100 have been described in dichotic listening experiments, it cannot be assumed that they occur per se in all kinds of experimental variations. However, we were able to show a strong attention effect on the ERP response (including the N100) by our experimental manipulation.

Since the long time intervals of no stimulation are an inherent part of the setup of sensory gating experiments, attention cannot be directed to other, task irrelevant auditory stimuli. Thus, in sensory gating experiments attention cannot be controlled in a similar way as in dichotic listening tasks and, therefore, attention has to be regarded as a potential confound in sensory gating experiments. In the unattend condition of our experiment, the ERP complex to S2 exhibited a slight negative shift, as compared to prestimulus activity. This negative shift might indicate that even in the unattend condition, ERPs were somewhat influenced by attention.

We interpret the negative shift of the ERP complex in the attend condition as a consequence of an underlying processing negativity (PN), as described in dichotic listening experiments. The impact of

Table 3	
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Mean	amp	litud	les.
mean	unp		

		-60-0 ms	0–60 ms	70–140 ms	160–230 ms	440-500 ms	500–560 ms	570–640 ms	660–730 ms
Scalp	Unattend	0.1 ± 0.8	0.5 ± 1.0	-5.1 ± 2.6	0.1 ± 3.2	-2.3 ± 2.9	-2.1 ± 2.5	-4.2 ± 2.8	-2.1 ± 2.8
	Attend	0.0 ± 1.3	0.2 ± 1.6	-5.2 ± 2.5	-0.7 ± 4.2	-5.0 ± 4.5	-5.7 ± 4.7	-8.1 ± 5.4	-4.6 ± 5.5
	t value	0.193	0.660	1.188	1.661	3.797	4.326	4.118	2.832
	p value	n.s.	n.s.	n.s.	n.s.	0.001	< 0.001	< 0.001	0.009
Neocortical	Unattend	0.5 ± 2.6	4.5 ± 4.3	-21.0 ± 19.1	7.1 ± 31.1	-7.4 ± 14.7	-7.3 ± 12.0	-15.9 ± 16.1	-7.8 ± 17.2
	Attend	0.8 ± 3.1	4.3 ± 5.1	-29.7 ± 19.4	0.1 ± 39.6	-22.1 ± 25.9	-26.9 ± 27.5	-34.6 ± 33.9	-16.7 ± 31.5
	t value	0.297	0.206	2.737	1.991	3.110	3.407	3.026	1.886
	p value	n.s.	n.s.	0.015	n.s.	0.007	0.004	0.008	n.s.

The mean amplitudes [in μ V] of the ERP for eight time windows: data of scalp recordings are displayed at the top part, data of neocortical recordings at the bottom part. Within each kind of recording, data for the unattend and attend condition are given, in addition to the statistical level of significance when both measures were compared to each other.



Fig. 2. Exemplary neocortical data, recorded in four subjects. Each row shows data of one subject, with the intracranial ERP recorded in the unattend condition in the left column, the corresponding ERP data of the attend condition in the middle column, and the location of the electrode selected for the analyses in the right column (marked as white dot).

attention is nicely shown by the comparison of single click vs. pairedclick trials: The PN continued longer in single click trials than in paired-click trials. In order to count trials as single or paired-click events, patients had to await S2. Once S2 was presented, the event could be counted as paired-click event and attention load presumably dropped considerably. In contrast, in single click trials subjects had to assure the non-occurrence of stimulation what requires a longer time, as this screening process is not terminated externally.

Single click trials might also have elicited other kinds of responses, such as the so-called "omitted stimulus response" (OSR, Simson et al., 1976; Busse and Woldorff, 2003) or such as the mismatch negativity (MMN) in response to tone omissions (Tervaniemi et al., 1994; Yabe et al., 1997). However, the elicitation of an MMN in response to tone omissions usually requires rather short ISIs (Yabe et al., 1997). The OSR is characterized in scalp recordings by a small posterior negativity (180-280 ms), followed by a larger anterior positive wave. A late positivity in response to tone omissions has also been observed in previous invasive recordings from the lateral temporal lobe (Alain et al., 1989). Taken together, the temporal characteristics of the neocortical ERP in response to single clicks do not resemble these characteristics of the OSR, as observed in previous scalp and intracranial studies. Thus, we regard both the MMN and the OSR as more unlikely candidates for the additional ERP effect, observed in neocortical ERPs to single click trials as compared to paired-click trials.

The time-frequency analysis revealed that in neocortical recordings the attention effect (paired-click trials in the attend

condition vs. paired-click trials in the unattend condition) was constricted to phase-synchronized activity <3 Hz. In line with that, P50 activity which was investigated by using a filter from 10 to 50 Hz was virtually unaffected by attention. This is in line with the majority of studies on attention effects in sensory gating experiments (Guterman and Josiassen, 1994; Jerger et al., 1992; Kho et al., 2003; White and Yee, 1997).

Some studies reported *reduced* P50 amplitudes in attend conditions (White and Yee, 1997; White et al., 2005). However, in the active condition of these experiments subjects had to do mental arithmetic aloud. In such a case, the subject's utterance has to be regarded as equivalent to other, external stimulation of the auditory system and might therefore result in a reduction of ERP amplitudes (Hari and Makela, 1988). Alternatively, this amplitude reduction might be regarded as consequence of corollary discharge in the sensory cortex (Ford et al., 2007). Whether findings are interpreted the one way or the other, experimental conditions using verbal or other acoustic utterances should be avoided for the study of attention effects on sensory gating measures.

There is, however, another study showing *increased* P50 amplitudes to S2 in active conditions (Guterman et al., 1992). In this study, S2 stimuli were high or low pitch tones which had to be differentiated (silent counting or motor response). Thus, selective attention to tone pitch might have an impact on P50 amplitude even under conditions of low perceptual load and not only under conditions of high perceptual load (Woldorff and Hillyard, 1991; Woldorff et al., 1993).



Fig. 3. Data from neocortical contacts exhibiting the largest N100 response (n = 17); in the top row the grand average ERP, in the second row the event-related activity (ERA), and in the third row the induced activity (IN) as time-frequency plots. In the left columns the data of the unattend condition and in the middle row the data of the attend condition are depicted. The dotted line in the middle graph of the top row depicts the ERP in response to single clicks. The amplitudes of ERA and IN in the time-frequency plots are color coded. A black line indicates activity which is significantly above the level of background activity, while a white line indicates activity which significantly below the level of background activity. In the right column, the difference between the unattend and attend condition is shown (ERP, right top) or the *t* values of the pairwise comparison (ERA and IN). For the difference ERP, significant differences between the two conditions are surrounded by a black line. All depicted wavelet transforms were smoothed along both the wavelet scale axis and the time axis (see Methods). The impact of smoothing can be assessed by comparison with Supplementary Fig. 1, showing the data without smoothing.

However, the standard sensory gating experiment uses pairs of identical stimuli. In the current experiment, we could not show attention effects on P50 amplitude, neither in scalp nor in neocortical recordings, when using identical S1 and S2 stimuli. The finding of Guterman et al. (1992) cannot be explained by the existence of a PN in the attend condition, as the P50 was measured as peak-to-peak amplitude in that experiment.

For the N100, we observed some dissociation between scalp and neocortical data: an attention effect was observable for neocortical N100 amplitude to S1, but not for scalp N100 amplitude. In addition, a shortening of the S2 N100 latency by attention was observed for neocortical recordings only. For practical issues of clinical recordings, these findings are of minor relevance, as sensory gating is commonly investigated only by scalp recordings. However, these discrepancies might help to get a better understanding of cortical sources underlying N100 generation.

We have already recently reported on a dissociation between scalp and neocortical N100 data (Rosburg et al., 2006). In that study, we found a shortening of the N100 latency by stimulus repetition in scalp, but not in neocortical recordings, and we assumed that the neocortical recordings measure activity only of a subset of generators underlying the scalp N100. The activity of this subset might be influenced by attention in a different way as the summed up N100 activity reflected in the scalp N100.



Fig. 4. Corresponding to Fig. 1, the ERPs as recorded from the rhinal cortex (top row) and hippocampus (bottom row).

However, if neocortical recordings measure activity of a subset of N100 generators underlying the scalp N100 and attention increases the activity of this subset in response to S1, how can it be possible that the scalp N100 to S1 is not affected by attention? Intracranial studies provided evidence for two distinct sub-regions of N100 generation, one located in the superior temporal gyrus and located in the Heschl's gyrus (Howard et al., 2000). One potential explanation is that the N100 recorded from the lateral surface of the posterior superior temporal gyrus reflects activity of a radial source at the peak latency of the scalp N100 (previously proposed by Rosburg et al., 2006), while the scalp N100 at Cz is generated primarily by tangential sources (Näätänen and Picton, 1987). The contribution of the radial source to the scalp N100 might be much smaller than that of the tangential source(s) and, thus, the impact of attention seen in neocortical recordings might not be detected by scalp recordings.

Effects on hippocampal activity

Hippocampal activity can only be measured by intracranial recordings, because the hippocampus is arranged cylindrically, forming a closed field (Klee and Rall, 1977). In the current study, the morphologies of the hippocampal and rhinal ERPs were similar to those observed previously (Grunwald et al., 2003; Boutros et al., 2005; Rosburg et al., 2007). For the hippocampal ERPs, attention resulted in significantly increased amplitudes.

As the hippocampus is assumed to act as comparator and novelty detection system (Sokolov, 1960; Vinogradova, 2001) and is involved in the P300 generation (Halgren et al., 1980), the observation of attention effects on hippocampal processing of auditory events is not unexpected. However, the current study provides the first empirical evidence that attention increases the late hippocampal ERP deflection (250–450 ms) elicited by auditory stimulation at long ISIs (Grunwald et al., 2003; Boutros et al., 2005; Rosburg et al., 2007).

The functional significance of these late hippocampal ERP deflections in response to auditory stimuli is currently unclear. In previous studies, stimuli were delivered without any active task, and the elicited hippocampal activity was found to be strongly suppressed by stimulus repetition (Grunwald et al., 2003; Boutros

et al., 2005, 2008; Rosburg et al., 2007). It was, however, also elicited by salient stimuli at short ISIs (Rosburg et al., 2007). Both its sensitivity to salience and its increase with attention might indicate that it reflects P300 activity. The currently measured amplitude of this component in the attend condition is still smaller than the mesiotemporal lobe P300 amplitude in active oddball paradigms (Grunwald et al., 1999; Ludowig et al., in press), but this might be referred to differences in the experimental set-ups: The amplitude of the scalp P300 is known to be reduced by counting both targets and standards, instead of targets only (Spencer and Polich, 1999). In line with that, a scalp P300 was hardly observed in previous sensory gating experiments using attend conditions (Guterman et al., 1992; Kho et al., 2003) and in the current study. Like ours, these previous studies reported data from Cz and not data from Pz, minimizing the chance to observe P300 activity.

Effects on induced high frequency GBA

Induced high frequency GBA has been studied nearly exclusively by intracranial recordings (e.g. Crone et al., 2001; Edwards et al., 2005; Lachaux et al., 2005; Trautner et al., 2006). Many aspects of its nature and its functional significance still need to be elucidated. Recent studies in the visual domain have suggested that induced GBA is modulated by attention but in a relatively complex manner (Tallon-Baudry et al., 2005). To our knowledge, there is only one study of attention effects on high frequency GBA in the auditory domain (Ray et al., 2008). In that very recent study on three epilepsy patients, an attentional modulation of gamma power was observed at ~400 ms after stimulus onset.

The current study confirms and extends these previous findings. Here, we can show that for the first 300 ms after stimulus onset the induced GBA in the attend and unattend condition is virtually the same. In addition, we clearly see dissociations in the temporal course of attention effects on ERP activity and induced GBA activity: Attention effects on ERP amplitude were most pronounced after S2 onset, while largest effects on GBA were observed before S2 onset. Most importantly, attention effects on GBA were absent at the latency of the N100 both to S1 and S2 when the GBA is maximal in the unattend condition. The maximum of the attention effect on induced GBA activity before S2 is not in line with the proposal of Ray et al. (2008) that induced GBA is strongly linked to attention. Such a linkage appears to be unlikely because in our study the first 300 ms of GBA (100–400 ms and 600–900 ms) were not affected by attention. Instead, we think that expectancy is one factor modulating induced GBA. An association between expectancy and induced GBA was recently shown in motor behavior experiments (Gonzales Andino et al., 2005). We think that the data of Ray et al. (2008) do not argue against an expectancy effect because in their study the critical difference between simple and complex stimuli (which served as targets) started 400 ms after stimulus onset. In addition, it might be noted that expectancy and attention are not exclusive functions.

Conclusion

The current study shows a number of attention effects on ERP components, induced activity and sensory gating, but not on P50 activity. While some of the attention effects are more of general academic interest, other findings have implications on sensory gating research in clinical populations. As outlined, sensory gating experiments are usually conducted without active control of attention. Thus, some participants in these studies might pay attention to the stimuli, even if they were instructed to ignore the auditory stimulation and were engaged in a task like watching a silent movie. One practical way to test potential attention effects on N100 (and P200) gating could be the application of a 3 Hz high-pass filter. Genuine group differences in sensory gating should not be affected by this filtering, while systematic group difference in attention should be eliminated.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.06.063.

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