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Signal quality of simultaneously recorded invasive and non-invasive EEG

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ABSTRACT

Both invasive and non-invasive electroencephalographic (EEG) recordings from the human brain have an increasingly important role in neuroscience research and are candidate modalities for medical brain–machine interfacing. It is often assumed that the major artifacts that compromise non-invasive EEG, such as caused by blinks and eye movement, are absent in invasive EEG recordings. Quantitative investigations on the signal quality of simultaneously recorded invasive and non-invasive EEG in terms of artifact contamination are, however, lacking. Here we compared blink related artifacts in non-invasive and invasive EEG, simultaneously recorded from prefrontal and motor cortical regions using an approach suitable for detection of small artifact contamination. As expected, we find blinks to cause pronounced artifacts in non-invasive EEG both above prefrontal and motor cortical regions. Unexpectedly, significant blink related artifacts were also found in the invasive recordings, in particular in the prefrontal region. Computing a ratio of artifact amplitude to the amplitude of ongoing brain activity, we find that the signal quality of invasive EEG is 20 to above 100 times better than that of simultaneously obtained non-invasive EEG. Thus, while our findings indicate that ocular artifacts do exist in invasive recordings, they also highlight the much better signal quality of invasive compared to non-invasive EEG data. Our findings suggest that blinks should be taken into account in the experimental design of ECoG studies, particularly when event related potentials in fronto-anterior brain regions are analyzed. Moreover, our results encourage the application of techniques for reducing ocular artifacts to further optimize the signal quality of invasive EEG.

Introduction

Electroencephalographic (EEG) recordings can be broadly divided in non-invasive EEG recordings obtained from electrodes attached to the scalp surface and invasive EEG recorded from intracranially implanted electrodes. Invasive EEG recordings can in turn be subdivided into two major kinds of recordings according to types of electrodes that are being used: (1) intraparenchymal recordings, also called stereo-EEG, obtained using depth electrodes that are stereotactically inserted, for instance in the hippocampus or in neocortical regions, and (2) the electrocorticogram (ECoG), obtained from electrodes implanted below the dura, directly on the surface of the brain. Invasive EEG recordings are frequently used for diagnostics in patients suffering from cases of epilepsy where pharmacological treatment is insufficient and the possibility of neurosurgical treatment is evaluated (Nair et al., 2008).

Because implanted electrodes are much closer to the brain than scalp electrodes, they allow for recordings of brain signals with considerably higher amplitudes and spatial resolution than scalp EEG (Engel et al., 2005). Next to their clinical importance, invasive recordings offer unique opportunities for electrophysiological investigations of human brain function with high spatial and temporal accuracy. An increasing number of studies have recently investigated motor (Ball et al., 2008; Brovelli et al., 2005; Crone et al., 1998; Rektor, 2000; Szurhaj et al., 2006), sensory (Crone et al., 2001a; Edwards et al., 2005; Steinschneider et al., 2005), and cognitive (Canolty et al., 2006; Crone et al., 2001b; Ray et al., 2008; Sederberg et al., 2007; Sinai et al., 2005) systems using invasive EEG data. Furthermore, ECoG recordings have been proposed as a technology for brain–machine interfaces (BMIs) for neuronal motor prostheses in paralyzed patients (Ball et al., 2009; Leuthardt et al., 2004; Mehring et al., 2004; Pistohl et al., 2008; Schalk et al., 2007).

Sources of artifact contamination in non-invasive EEG include blinks, eye movements such as saccades or also micro-saccades, head movements, and electromyographic (EMG) activity from muscles close to the recording sites (Crespo-Garcia et al., 2008; Croft and Barry, 2000; Fitzgibbon et al., 2007; Ghandeharion and Erfanian, 2006; Joynt, 1959; Li and Principe, 2006; ter Meulen et al., 2006; van de Velde et al., 1998; Yuval-Greenberg et al., 2008). A principal advantage of invasive EEG that has been repeatedly

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emphasized is that it is less susceptible to artifact contamination (Ball et al., 2004; Canolty et al., 2007; Engel et al., 2005; Lachaux et al., 2003; Leuthardt et al., 2004; Schalk et al., 2007). There are, however, only very few studies so far that investigated the possibility that similar types of artifacts as in non-invasive EEG might also be present in invasive recordings. For instance, Otsubo et al. (2008) recently reported a case of a single patient with intractable temporal lobe epilepsy, where muscle contractions during eating and seizures caused EMG artifacts in subdural recordings. This finding was interpreted as a reverse breach rhythm i.e. that EMG activity penetrated to the intracranial space through bone defects due to the craniotomy carried out for electrode implantation (see personal communication of J. Gotman cited in Otsubo et al., 2008). Another single patient case report of EMG contamination of invasive recordings was published by Liu et al. (2004). Together, these studies suggest that artifacts typically seen in scalp EEG such as due to eye blinks might also be measured intracranially.

Eye blinks are associated with characteristic potential changes for which four main mechanisms have been proposed: (1) eye movements occurring during the blink could generate potential changes through movements of the electrical field of the eye (Lins et al., 1993), (2) electrical resistance changes between the eye ball and the surrounding tissue due to lid closure and opening could cause potential changes, even without movement of the eye (Matsuo et al., 1975), (3) electromyographic (EMG) activity of the muscles moving the eye lid and eye ball may also be detectable (Bardouille et al., 2006) as well as (4) neuronal activity related to the motor control of blinking and to responses in the visual system that might be evoked by the blinks (Berg and Davies, 1988; Hari et al., 1994). Blink related brain responses in the frontal lobe – the anatomical region of interest of our study – have been addressed in a series of previous neuroimaging studies (Bodis-Wollner et al., 1999; Bristow et al., 2005; Kato and Miyauchi, 2003; Tsubota et al., 1999; van Eimeren et al., 2001). The regions that were most consistently reported to show blink related responses were the frontal eye field (FEF) (Bodis-Wollner et al., 1999; Bristow et al., 2005) and the supplementary eye field (SEF) (Bodis-Wollner et al., 1999; Bristow et al., 2005; Kato and Miyauchi, 2003). In contrast, Tsubota et al. (1999) found blink-related responses in the orbitofrontal cortex and proposed that this region might be the primary site of blink control, especially of the blink rate. Blink-related responses in the dorsolateral prefrontal cortex (DLPFC) were only found in one of the subjects investigated in Kato and Miyauchi (2003).

To clarify the question whether there are blink related artifacts in invasive EEG and how severe these potential artifact contaminations are compared to non-invasive EEG, it would be particularly desirable to compare simultaneously recorded invasive and non-invasive EEG, but to our knowledge, no such data is available yet. Therefore, in the present study we compare simultaneously recorded invasive and non-invasive EEG regarding their robustness against artifacts caused by eye blinks. We focused on two regions: the prefrontal cortex and the motor cortex. The prefrontal cortex was chosen because this region is close to the eyes and, therefore, eye related artifacts can be expected to be more pronounced in the prefrontal cortex than in other, more distant brain regions. The motor cortex was analyzed as a second region of interest because it has been the focus of a large number of previous ECoG studies and it has a high practical relevance because it has been proposed as a signal basis for BMI applications in paralyzed patients. Furthermore, we aimed to compare the effects found during blinking to potentials related to saccadic eye movements to different directions. There is a close similarity of the vertical EOG potentials related to eye blinks and upward saccades (Kennard and Smyth, 1963; Takemori, 1979). Therefore, we expected a similarity of blink related artifacts to those occurring during upward saccades.

Material and methods

Patients and data collection

For the analysis of simultaneously recorded blink-related non-invasive EEG and ECoG changes, data sets from four patients undergoing evaluation for epilepsy surgery were used. Sex, age and diagnosed anatomical pathologies of these patients were: Patient 1 (P1): female, 17 years, focal cortical dysplasia in the left fronto-polar cortex; patient 2 (P2): female, 16 years, focal cortical dysplasia in the right premotor–prefrontal cortex; patient 3 (P3): male, 17 years, focal cortical dysplasia in the left prefrontal cortex; and patient 4 (P4): male, 29 years, no structural pathology diagnosed. The seizure onset zones were in the medial parietal cortex (P1), in the medial fronto-parietal cortex and the inferior frontal cortex (P3), the latter region covered by the electrode grid, and in the anterior prefrontal region covered by the grid (P2 and P4). All patients gave written informed consent stating that the electrophysiological data obtained during the diagnostic process might be used for scientific purposes.

For the present study we aimed at obtaining a large number of trials for better statistical detection of possible small amplitude effects. Therefore we used blinks occurring during spontaneous behavior. The occurrence of spontaneous eye blinks was determined from digital video (25 Hz sampling rate). The exact onset of blinks was then determined using the vertical electrooculogram (VEOG) recorded simultaneously to the EEG and ECoG data. In particular, both digital video and EOG data were used to distinguish blinks from vertical saccades. Only eye blinks were analyzed that were not accompanied by any other overt movement such as arm, leg, mouth or head movements. Movements occurring simultaneous to the eye blinks were detected by EMG and in addition by digital video (25 Hz sampling rate). Those eye blinks related to other overt movements were not included in our analysis, to avoid movement related brain responses interacting with the eye blink artifacts. The numbers of trials obtained in this way were: P1 523 blinks, P2 598 blinks; P3 202 blinks; and P4 157 blinks. Thus, by using naturally occurring blinks, large numbers of trials could be achieved without additional burden on the patients.

In addition, spontaneous saccadic eye movements were determined in the same way as blinks in two patients (P1 and P2), resulting in 1121 saccades in P1 (199 upward, 88 downward, 395 to the left, 439 to the right) and in 612 saccades in P2 (165 upward, 121 downward, 192 to the left, 134 to the right).

Non-invasive EEG at standard scalp electrode positions according to the 10–20 system and ECoG from subdurally implanted grid electrodes were simultaneously recorded using the same clinical AC EEG-System (IT-Med, Germany). Sampling rates were 256 Hz (P1, P2, P3) and 1024 Hz (P4). Time constant was 5 s, corresponding to a high-pass filter with 0.032 Hz cutoff frequency. For mapping eye movements and other motor responses, electrical stimulation through the electrode grid was performed using an INOMED NS 60 stimulator (INOMED, Germany). Trains of 7 s duration consisted of 50 Hz pulses of alternating polarity square waves of 200 μs each. The intensity of stimulation was gradually

Table 1
Signal-to-noise ratios (SNRs) were computed as the ratio of ongoing brain activity to the amplitudes of blink related potentials (cf. Methods).

		P1	P2	P3	P4
Prefrontal	SNR EEG	0.08	0.04	0.08	0.11
	SNR ECoG	2.35	4.37	2.51	2.22
	Ratio	29	115	34	21
Motor	SNR EEG	0.57	0.15	0.15	0.52
	SNR ECoG	13.47	26.28	21.19	15.32
	Ratio	24	173	141	30

The SNR was computed for simultaneously recorded EEG and ECoG both from prefrontal and motor cortical regions. Results are shown for the 4 patients investigated (P1 to P4). Furthermore, the ratios between the SNR of the EEG and ECoG are given, showing 20 to above 100 times higher SNR of the ECoG as compared to the EEG data.

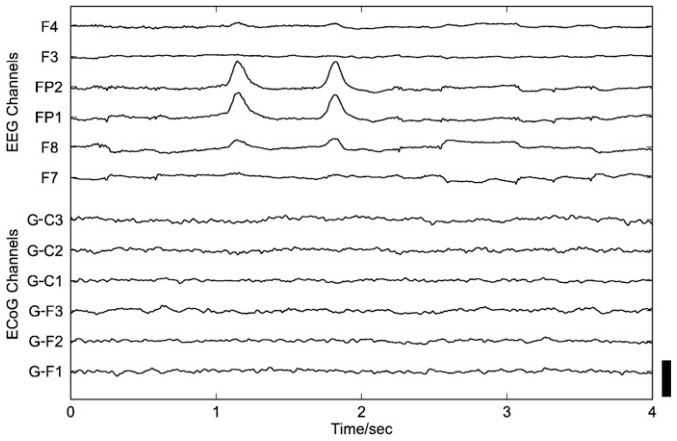

Fig. 1. Example of artifacts related to spontaneous eye blinks in simultaneous non-invasive, i.e. scalp recorded, EEG (upper 6 traces) and ECoG recorded using subdurally implanted electrodes (lower 6 traces). Scalp EEG is shown for anterior frontal (F7, F8) and fronto-polar (FP1, FP2) EEG channels, where ocular artifacts have a high amplitude, and also for more posterior channels (F3 and F4), where artifacts of lower amplitude can be observed. In the simultaneously recorded ECoG traces, no clear artifacts corresponding to those found in the scalp EEG are evident. The height of the black scale bar in the lower right corner of the plot corresponds to 100 μV.

increased up to 15 mA or to the induction of sensory and/or motor phenomena, whichever occurred first. The patients were unaware of the timing of stimulation, unless motor or sensory symptoms were evoked. The positions of the implanted electrodes were determined from a structural T1 weighed MRI scan of 1 mm isotropic resolution obtained during electrode implantation. This MRI data set was normalized to MNI space using SMP5 to obtain MNI coordinates of the implanted electrodes in order to enable inter-subject comparison of these electrode positions to those of other ECoG studies.

Data analysis

As a first step of data analysis, we re-referenced both the invasive and non-invasive EEG to a common average (CA) reference, as commonly used in ECoG studies (e.g. Ball et al., 2004, 2008; Canolty et al., 2006, 2007). To ensure that the results of our study are not restricted to the case of a CA reference, we also analyzed our data using a local average reference, where each non-invasive EEG and ECoG channel was referenced against its neighboring channels. The local average reference yielded similar results as the CA reference; fully supporting all conclusions of our study, therefore only the latter results are reported here.

Data epochs were generated from −3 s to +3 s around each blink onset and each trial was baseline corrected using the first second of the time window as baseline. We then determined the average blink related potential as the median across trials. The median was used for better robustness against outliers. The peak of the blink-related artifact in the VEOG was determined individually for each patient. In all cases, this peak occurred within 100 ms after blink onset. For this time point in each recording channel, we determined whether the median potential significantly differed from zero (sign test, $p<0.001$) and also computed the corresponding *Z*-scores. The topography of these *Z*-scores was then visualized for the entire implanted electrode grid.

Signal to noise ratios (SNRs) for both non-invasive EEG and ECoG were determined as follows. To compute the signal amplitude, data epochs without any eye blinks, saccadic or other eye movements, EMG-, movement-, or electrode-artifacts were identified and the typical amplitude of the ongoing brain activity in these epochs was determined as the standard deviation of the potential time series. The peak amplitude of the blink related potentials both in non-invasive EEG and ECoG was taken as 'noise', supposing that these potentials reflect artifact contamination and not brain signals (see Discussion). SNR was computed for non-invasive EEG and ECoG channels recording both from the prefrontal and motor cortex regions of interest (Table 1). Finally, ratios of these non-invasive EEG and ECoG SNR values were computed in order to quantify the signal quality of ECoG in comparison to non-invasive EEG.

Results

Examples of simultaneously recorded non-invasive EEG and ECoG recordings during blinking are shown in Fig. 1. These traces represent the non-invasive EEG and ECoG signals as typically used for clinical diagnosis, i.e. ongoing recordings obtained without any data averaging. Clear blink related artifacts stand out in the non-invasive EEG, in particular in the channels close to the eyes (FP1, FP2, F7, and F8). Similarly pronounced blink-related artifacts are not evident in the simultaneously recorded ECoG (Fig. 1, lower traces). Small blink related potentials might, however, still exist in the ECoG and might be concealed by the ongoing, large amplitude ECoG activity. We therefore determined blink-related potentials by averaging a large number of trials, thereby suppressing ongoing activity that is not phase locked to blink onset.

The resulting averaged non-invasive EEG and ECoG blink-related potential changes in P1 (based on 523 blinks) are shown in Fig. 2. The top row (Figs. 2a–c) shows blink related potentials in the non-invasive EEG of channels FP1 above left prefrontal cortex, F3 above left prefrontal/premotor cortex, and C3 above left motor cortex (for the assignment of these electrode positions to underlying brain areas see Okamoto et al., 2004). As expected, a pronounced blink-related potential of positive polarity is observed at FP1. A polarity reversal of the blink artifact can be seen at electrode position C3, above left motor cortex. This polarity reversal can be attributed to the common average reference that enforces an average potential of 0 μV across all channels at any point in time. In the ECoG, channels with significant blink-related potential changes of positive polarity were found at the anterior edge of the electrode grid, i.e. at the electrodes closest to the eyes (Figs. 2d, h). Next to the positive polarity, also the time course of these blink related ECoG potentials was very similar to the blink artifact seen in the simultaneously recorded non-invasive EEG (Fig. 2a; see also Fig. 5). Notably, the amplitude of the blink related potentials in the ECoG was relatively small compared to the amplitude of ongoing brain activity as indicated by the 25th and 75th percentiles of the data in the time period before the blink onset (the 25th and 75th percentiles are indicated by the upper and lower bounds of the grey bands in Figs. 2d–i), which explains why these potentials are

Fig. 2. Simultaneously recorded blink-related potential changes in non-invasive EEG and ECoG in patient 1 (P1). In the top row (a–c), blink-related non-invasive EEG potentials are shown for three selected electrode positions: FP1 above the left prefrontal cortex (note the different scale used for visualizing the large amplitude potentials at this electrode position), F3 above the left premotor cortex, and C3 above the left motor cortex region, showing a typical blink artifact at FP1, that occurs with reversed polarity at C3. The black curves indicate the median potential; the grey bands extend from the 25th to the 75th percentile of the data. The vertical dashed line marks the peak of the blink artifact in FP1. In the lower part of the figure (d–f, h–j), blink-related ECoG potentials are shown for selected electrode positions. A map of the *Z*-scores of blink-related potentials is shown in (g). This map represents the time point of the peak of the blink related artifacts in FP1 as marked by the vertical dashed line in all subplots. The *Z*-score map is shown superimposed on the brain surface of the implanted patient at the anatomical position of the electrode grid as determined from a structural MRI scan (cf. Methods). Electrodes with significant changes ($p<0.001$) are marked by white asterisks. Electrodes marked 'A' and 'H' showed arm and hand motor responses upon direct cortical electrical stimulation. The electrode positions marked in black had poor contact with the cortical surface and were dropped from the analysis. An example of a significant blink-related potential recorded in the region with the highest *Z*-scores is shown in (d). Note that this potential has the same polarity as the blink artifact simultaneously recorded at FP1 and shows a very similar time course (see also Fig. 5). In this example, also negative potentials at two electrodes at more posterior positions were significant ($p<0.001$).

obscured in ongoing recordings. The maximal amplitudes of blink related artifacts near the anterior edge of the electrode grid in the four patients were 10.2 μV (P1), 11.0 μV (P2), 18.8 μV (P3), and 22.8 μV (P4) (see also Table 2). The same pattern was found in all four patients we investigated (Figs. 3, 4). In each case, the most significant blink-related ECoG potentials were found at the anterior edge of the electrode grid. Also, in each case, these potentials were of positive polarity, as were the corresponding blink artifacts in the simultaneously recorded prefrontal non-invasive EEG.

Potentials related to spontaneous saccades were investigated in two patients (results for P2 are shown in Fig. 4). Generally, saccade related ECoG amplitudes were smaller than those for blinks. Significant saccade related effects (sign test, $p<0.001$) were found at two electrode sites, both of them showed also significant blink

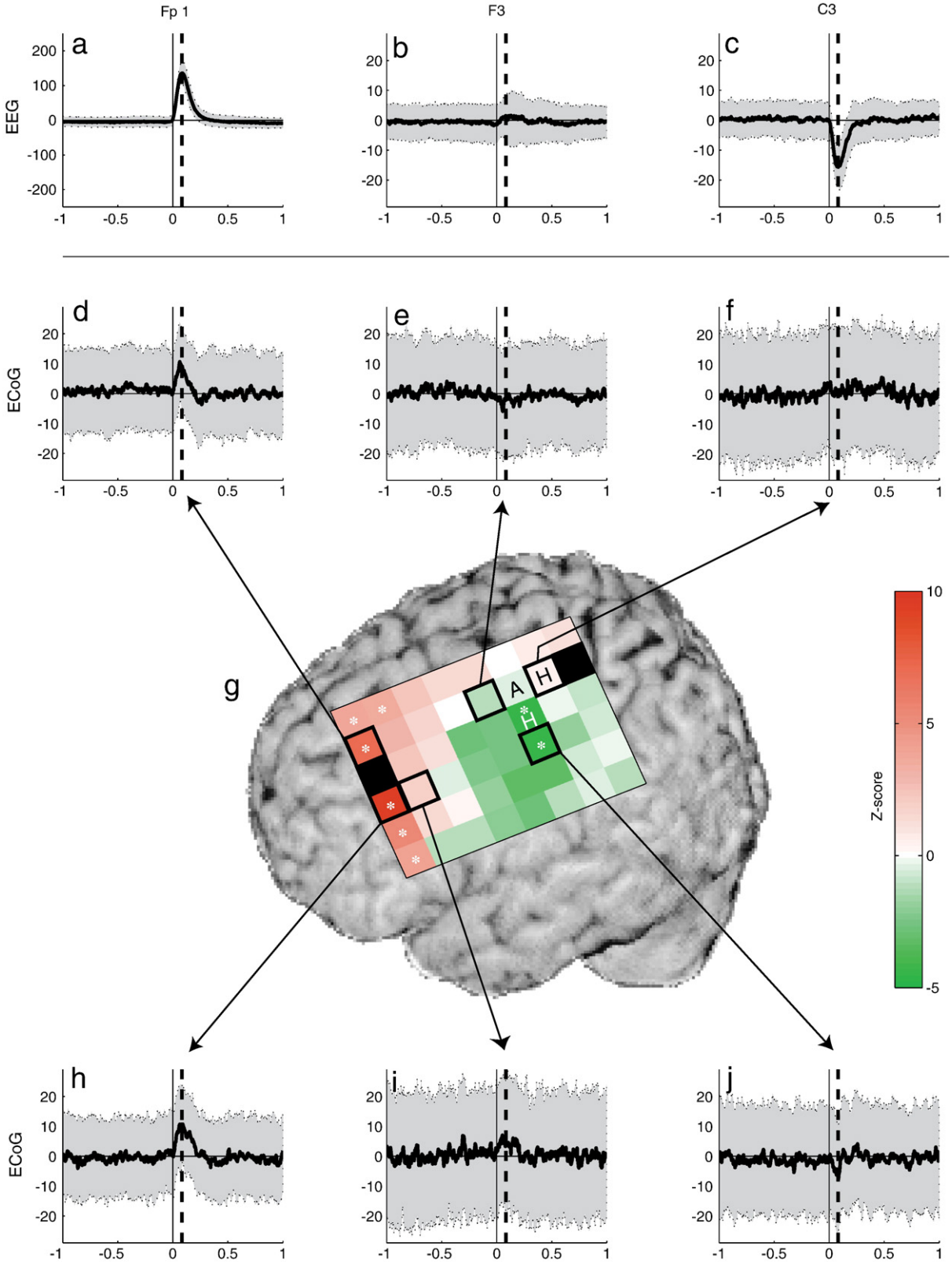

Table 2
MNI coordinates of all anterior prefrontal ECoG electrodes with significant blink related artifacts.

Patient	Area	X	Y	Z	Amplitude (μV)	Z-score
P1	Left middle frontal gyrus	−44	42	30	10.2	9.4
	Left superior frontal gyrus	−25	46	45	8.8	7.1
	Left middle frontal gyrus	−52	39	21	8.6	5.4
	Left inferior frontal gyrus	−57	36	10	6.4	4.1
	Left superior frontal gyrus	−15	48	51	5.9	3.8
	Left superior frontal gyrus	−16	36	56	4.1	3.5
P2	Right superior frontal gyrus	19	36	50	11.0	6.1
	Right middle frontal gyrus	38	30	40	7.2	4.6
	Right middle frontal gyrus	29	33	44	6.7	4.5
	Right inferior frontal gyrus	47	17	39	7.9	3.6
P3	Left superior frontal gyrus	−22	33	46	18.8	4.9
	Left superior frontal gyrus	−13	23	54	17.6	4.7
	Left middle frontal gyrus	−23	24	52	13.3	4.6
	Left superior frontal gyrus	−12	33	50	17.5	4.6
	Left middle frontal gyrus	−32	33	41	12.7	4.4
	Left middle frontal gyrus	−34	24	47	10.2	3.6
P4	Left middle frontal gyrus	−29	47	34	22.8	4.1
	Left middle frontal gyrus	−33	40	36	14.3	3.6

For each electrode position, the *Z*-score of the blink related artifact at the time point of the artifact peak (see Material and methods for further details) is given.

related changes. A similar topographic distribution of upward saccade related potentials and blink related potentials was also found in P1.

The very similar time course of non-invasive EEG and ECoG blink-related potentials is once more demonstrated in Fig. 5, showing both non-invasive EEG from prefrontal electrode positions with a pronounced ocular artifact and the simultaneously recorded ECoG traces from the same anatomical region directly superimposed for all four patients. Importantly, the region showing pronounced blink related ECoG potentials was, in all cases, clearly anterior to and distinct from the region of the frontal eye field (FEF, cf. Fig. 3), i.e. the region where based on previous functional imaging results (Bodis-Wollner et al., 1999; Bristow et al., 2005) blink-related brain response might have been expected (see Discussion).

Across subjects, electrode positions with significant blink-related ECoG potentials at the anterior edge of the electrode grids were above Brodmann areas 8, 9, 44, 45, and 46. MNI coordinates of these electrode positions are given in Table 2. More posterior ECoG channels in the central and parietal regions were, in all subjects, characterized by smaller positive or negative blink-related potentials (Figs. 2, 3). In two patients, negative potential changes at more posterior electrode positions were significant ($p<0.001$, 2 electrodes in P1, 2 electrodes in P2). These negative potentials had a similar shape as the sharp negative deflections recorded at more posterior EEG positions such as C3 (Figs. 2, 3) and might, therefore, be related to the common average re-referencing, similar to the negative potentials found in the same anatomical region (C3/C4).

To quantify signal quality, we computed the ratio of ongoing brain activity (constituting the 'signal') to the amplitudes of blink-related potentials (constituting unwanted 'noise', as these potentials are most likely ocular artifacts, rather than brain potentials, see Methods and Discussion). This was done both for non-invasive EEG and ECoG channels recording from the prefrontal region and from the motor cortex region. The resulting signal-to-noise ratios (SNRs) are summarized in Table 1. For prefrontal non-invasive EEG, SNR values ranged from 0.04 to 0.1, while the SNR of prefrontal ECoG channels (those ECoG channels with positive, significant blink-related potentials as shown in Figs. 2–5) ranged from 2.2 to 4.4. The SNR of the ECoG, thus, was 21 to 115 times that of the non-invasive EEG. This SNR ratio was similar for motor cortical channels (24 to 173 times higher SNR of ECoG than of non-invasive EEG). The higher SNR of the ECoG compared to the EEG was both due to smaller artifact amplitudes and larger amplitudes of ongoing brain activity in the ECoG (c.f. also Fig. 2).

Discussion

In the present study we investigated blink-related potential changes in simultaneous non-invasive EEG and in ECoG recordings. In non-invasive EEG, blinks are accompanied by stereotypical potentials, having their peak amplitudes in EEG channels closest to the eyes (c.f. Fig. 1). Source analysis from former studies (Lins et al., 1993) of these potentials demonstrated that they can be explained by two dipole sources that were found to be exactly localized in the eye bulbs. Residual variance (percentage of the recorded variance unexplained by the dipole model) was found to be very low (<1%), indicating that the typically observed, large amplitude blink-related potentials in the scalp EEG are an ocular artifact. In the present study we found, in anterior-frontal ECoG, blink-related potentials that coincided with the blink artifacts in the scalp EEG, simultaneously recorded from the same anatomical region (Fig. 5). As these ECoG potentials match the blink artifacts in the scalp EEG in terms of overall topography, polarity, and in respect to the time course of the recorded potentials, it appears extremely unlikely that these ECoG potentials represent brain activity related responses. We, therefore, conclude that these fronto-anterior ECoG potentials reflect ocular blink artifacts that extend to the intracranial space through mechanisms of electrical volume conduction. This conclusion is supported by the fact that previous neuroimaging studies on the neuronal basis of blinking lend little support for the assumption that the anterior prefrontal region is a major site of blink-related brain activation (Bodis-Wollner et al., 1999; Bristow et al., 2005; Kato and Miyauchi, 2003; Tsubota et al., 1999; van Eimeren et al., 2001). Exceptions like the dorsolateral prefrontal cortex responses reported by van Eimeren et al. (2001) may

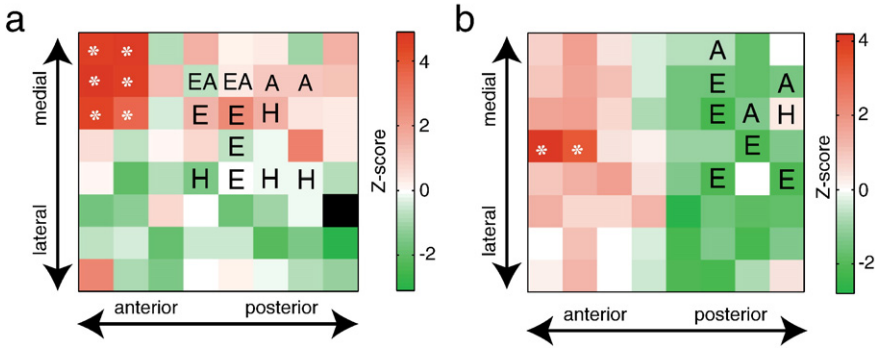

Fig. 3. Topography of blink-related ECoG effects in patient 3 (a) and patient 4 (b). All conventions for the maps of blink related ECoG effects are as in Fig. 2g. In addition, electrodes marked with 'E' showed oculomotor responses upon direct cortical electrical stimulation indicating the position of the frontal eye field (FEF). As in P1, the electrodes with the highest *Z*-scores were at the anterior edge of the grid. In both patients, the region of the FEF could be delineated by cortical electro-stimulation. Clearly, the significant, positive blink-related potentials at the anterior edge of the grid were outside the FEF region.

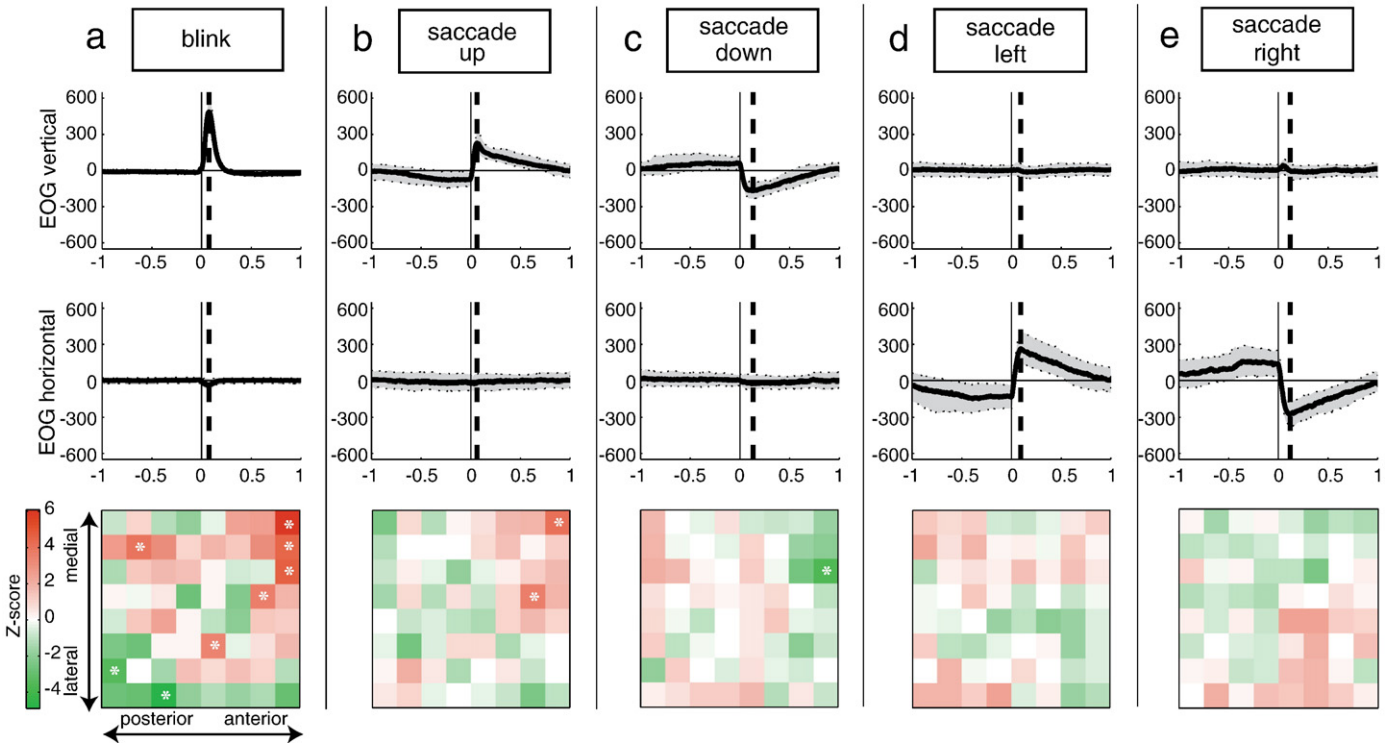

Fig. 4. Blink- and saccade-related EOG and ECoG potentials in patient 2. In the first column of the figure (a), blink related potentials in the vertical and horizontal EOG and a topographic map of blink related ECoG changes are shown, all conventions as in Figs. 2 and 3. In (b) to (e), the corresponding results for upward, downward, leftward, and rightward saccades are shown. Generally, saccade related ECoG amplitudes were smaller than those for blinks. Significant saccade related effects ($p<0.001$) were found at two electrode sites close to the anterior edge of the electrode grid. Both of these electrode sites showed also significant blink related changes as shown in (a). In this example, significant blink related potentials at some more posterior recording sites in (a) were not reproduced in respect to saccades.

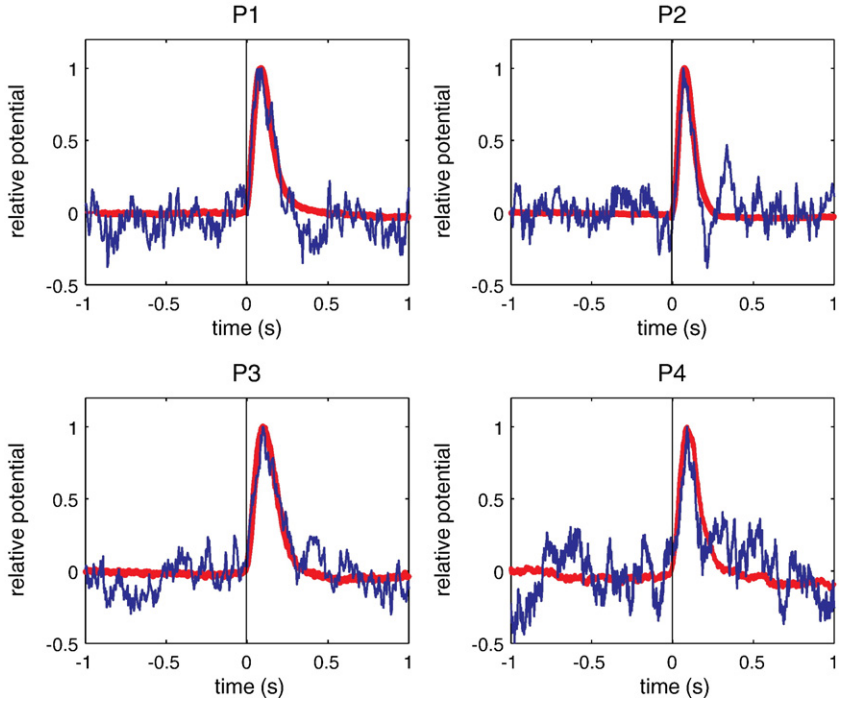

Fig. 5. Superimposed time course of simultaneously recorded blink-related non-invasive EEG and ECoG potentials. For each of the four patients (P1–P4), the time course of the EEG blink artifact in the prefrontal region is shown in red, normalized to its peak value. In blue, the time course of the simultaneously recorded ECoG from the same anatomical region is shown with its peak amplitude also normalized to 1 (the actual potential changes were much larger in the non-invasive EEG than in the ECoG, c.f. Figs. 2–4). ECoG is shown for channels near the anterior edge of the electrode grid with significant effects as indicated in Figs. 2–4. The transient potential detected in the ECoG after blink onset was very similar in shape to the blink artifact in the EEG, strongly suggesting that these ECoG potentials do not originate from brain activity but reflect the same type of ocular artifact as recorded in the scalp surface EEG. Vertical black line: blink onset.

be related to voluntary motor control of blinks and might therefore not be expected in spontaneous blinking as investigated in the present study. Other facts like the observation that positive potential changes at the anterior edge of the implanted grid electrode also occurred in respect to upward saccades, but less so in respect to saccades to other directions also support our conclusion, as there is a close similarity of the vertical EOG potentials related to eye blinks and upward saccades (Kennard and Smyth, 1963; Takemori, 1979).

Previous neuroimaging studies found blink-related neuronal activity in several frontal cortical regions including the SEF and FEF (Bodis-Wollner et al., 1999; Bristow et al., 2005; Kato and Miyauchi, 2003; Tsubota et al., 1999; van Eimeren et al., 2001). While the SEF was not covered by the electrode grids analyzed in the present study, the FEF region was covered in all patients investigated and eye motor responses upon cortical stimulation were found in two patients (P3, P4). In both of these latter patients, there were no significant potential changes at the electrode positions with eye motor responses. Therefore, our results do not lend support for the assumption that there is blink-related neuronal activity in the FEF that is detectable in ECoG recordings in the form of event related potentials. Whether, however, blink related neuronal activity in these exists in the form of gamma band activity – as recently found during voluntary saccades (Lachaux et al., 2006) – remains to be determined in future studies.

Two principal ways of extracranial-to-intracranial volume conduction may potentially contribute to ocular artifacts in intracranial data: (1) Ocular potentials may propagate through the different types of tissues surrounding the brain, including the bone of the skull and the meninges. This type of volume conduction would constitute the 'inverse' of the volume conduction from intracranial-to-extracranial, the latter underlying the measurable scalp EEG signals in healthy subjects (Fuchs et al., 2007; Holsheimer and Feenstra, 1977; van den Broek et al., 1998). (2) In the special case of epilepsy patients with subdurally implanted electrodes as investigated in the present study, volume conduction might also occur through the bone defects resulting from the craniotomy carried out for electrode implantation. Such volume conduction would constitute a reverse breach effect as was proposed by of J. Gotman, cited in Otsubo et al. (2008), as a mechanism for intracranially measurable EMG artifacts. The classical breach effect consists of focally increased amplitudes of alpha and beta activities in the scalp recorded EEG over or near bone defects (Cobb et al., 1979). Reverse breach effects can, therefore, also be expected to show up as rather focal changes in ECoG recordings. Both these different modes of volume conduction may be, to some extent, responsible for the variability of the topographies of blink-related potentials in the different subjects. Further investigations will, however, be required to clarify this issue, possibly using electrical source localization techniques similar to those that were developed for analyzing the opposite case, i.e. volume conduction from within the scull to the outside (Ball et al., 1999; Fuchs et al., 2007; Holsheimer and Feenstra, 1977; van den Broek et al., 1998), in particular using finite element method (FEM) volume conductor models (Zhang et al., 2006) for accurate modeling of the burr holes.

While blink-related artifacts were observed in ECoG data, their amplitudes were relatively small compared to the amplitude of ongoing brain activity as indicated in Figs. 2 and 3. This might explain why these potentials are typically obscured in ongoing recordings — in contrast to the scalp EEG, where blink artifacts clearly stand out against the ongoing activity (c.f. Fig. 1). Nevertheless, the blink related ECoG artifacts that we described in the present study may be of practical importance for ECoG research. While event related ECoG responses in many cortical areas including the prefrontal cortex can have amplitudes of 50 μV and above (e.g. (Chen et al., 2007; Crone et al., 2001a; Edwards et al., 2005; Matsumoto et al., 2004), in numerous examples in the literature the amplitudes of the reported ECoG responses were much smaller. In the prefrontal cortex – the region where we found significant blink related artifacts – cognitive event related ECoG changes in the range of +/−15 μV were for instance described by Rosburg et al. (2005) during a mismatch negativity paradigm. Similarly, ECoG potentials related to cognitive motor control from lateral prefrontal cortex in the range of approx. +/−20 μV are depicted in Ikeda et al. (1999). There are also many examples from other cortical areas and different experimental paradigms showing that reported ECoG responses may be of amplitudes of +/−20 μV and below (Fig. 2e in Edwards et al., 2005; Fig. 5 in Crone et al., 2001a; see also Satow et al., 2003 and Table 3 in Ohara et al., 2004). Also movement related ECoG potentials can be of 50 μV to above 100 μV amplitudes (Ikeda et al., 1992; Kunieda et al., 2000; Satow et al., 2003; Yazawa et al., 2000), but there are also examples of movement related ECoG potentials of smaller amplitudes, often below 10 μV and sometimes even below 5 μV (e.g. Table 2 in Kunieda et al., 2000 and Table 1 in Yazawa et al., 2000). Thus, in summary, there are many published examples of event related ECoG potentials both from prefrontal and other cortical regions with peak amplitudes well within the range of the amplitudes of the blink related artifacts that we describe in the present study, i.e. approx. 10 to 20 μV. Therefore, these artifacts are of amplitudes that may be relevant for ECoG studies.

This is especially the case if eye blinks occur synchronized to the events of an experiment as may for instance be the case in experiments involving visual stimulation where the blink reflex may be evoked by light stimulation; this effect is observed constantly in all healthy subjects (Manning and Evinger, 1986; Rushworth, 1962; Yates and Brown, 1981). The blink reflex can also be triggered by auditory and somatosensory including painful stimulation (Manning and Evinger, 1986). Importantly, eye blinks have also been found to synchronize to cognitive processing (Fogarty and Stern, 1989; Fukuda, 1994) which may especially be relevant for studies of prefrontal cortex, i.e. the region where we found blink related artifacts. In situations where blinks are synchronized to the experimental task, the amplitude of blink artifacts would less or not at all be reduced by trial averaging, depending on the degree of synchronization. Moreover, there are increasing numbers of studies using ECoG as a control signal for prototypes of real-time biomedical applications such as brain–machine interfaces (BMIs) (Ball et al., 2009; Leuthardt et al., 2004; Mehring et al., 2004; Pistohl et al., 2008; Schalk et al., 2007). In those cases, ECoG is analyzed on a single trial basis and there is no artifact reduction through trial averaging, which may be of relevance if a BMI approach uses a frequency range of the ECoG signal that is affected by ocular effects. However, it can be argued that it is of minor importance whether patients are actually capable of controlling BMI devices with their brain signals or by means of eye movements, therefore controlling for ocular artifacts might be especially important for experimental BMI studies which want to simulate the situation of completely paralyzed patients incapable of ocular movement.

To quantify the relation between the desired signal (i.e. brain activity) and unwanted "noise" – here blink artifacts –, we calculated a signal-to-noise ratio (SNR) as the ratio of the amplitude of ongoing brain activity (taken from artifact free epochs) and the amplitude of the blink-related potential changes, both for non-invasive EEG and ECoG. In this way, the SNR of the ECoG was found to be 20 to above 100 times higher than that of scalp EEG, highlighting the much better signal quality of invasive as compared to non-invasive EEG.

Regarding scalp-recorded EEG, there is an extensive literature on artifacts and their removal. Some of these studies aim at a careful characterization of the major types of artifacts (Lins et al., 1993), while other studies report rare sources of artifacts such as palatal myoclonus (Joynt, 1959), lightning (Jacome and Risko, 1986), and fluidized beds (Brunel et al., 1989). Furthermore, there is a growing field of research dedicated to the development of methods for reduction of artifact contamination in non-invasive EEG data (Croft and Barry, 2000; Erfanian and Mahmoudi, 2005; Ford et al., 2004). By contrast, potential sources of artifacts in intracranial data have until now only

received very little attention. Together with two recent case studies (Liu et al., 2004; Otsubo et al., 2008), the present investigation provides first steps to systematically characterize artifacts in intracranial data and might inspire further research into this direction.

Our findings indicate that blinks and eye movements can be of relevance to invasive EEG studies, in particular regarding ECoG recordings from prefrontal cortex. To estimate whether ocular artifacts may be of importance for a particular study, the following factors may be considered: (1) *Degree of synchronization of blinks to the experimental task*. As summarized above, blinks may be evoked by different kinds of sensory stimulation and may also synchronize to cognitive tasks in a tightly time locked manner. If, however, the degree of synchronization is low, the residual blink artifacts may be negligible. (2) *Position of the intracranial electrodes*. In the present study, blink artefact amplitudes in the prefrontal region reached, on average, 15 μV. Artifacts of smaller amplitudes can be expected in other brain regions with a larger distance to the orbitae. (3) *Amplitude of recorded ECoG potentials*. As discussed above, these amplitudes vary considerably in previous ECoG studies. Thus, for example, if blinks occur tightly synchronized to a stimulus in a third of the trials, residual mean blink artifacts of approx. 5 μV may be on average expected in prefrontal ECoG. The limit of tolerable artifact contamination, however, crucially depends on the way a data set is analyzed and interpreted. Therefore it may be helpful to instruct patients participating in ECoG experiments to avoid blinks and ocular movement, if the experimental design allows such an instruction. Furthermore, it may be advantageous to routinely record EOG to reliably detect blinks and eye movement in ECoG experiments and to reject trails with ocular artifacts from analysis. Comparing results with and without artefact rejection is then a suitable way to determine the precise impact of ocular artifacts in ECoG investigations.

Furthermore, the findings of the present study may encourage adaptations of artifact reduction procedures that were originally developed for scalp surface EEG to reduce blink-related artifact contamination (Croft and Barry, 2000; Erfanian and Mahmoudi, 2005; Ford et al., 2004) also for application to the ECoG. An interesting study would be to compare signal quality of non-invasive EEG and of ECoG after application of artifact reduction to both signals. Progress achieved in these directions would be potentially helpful for experimental studies using intracranial signals and also for neuroprosthetic applications based on intracranial recordings from the human brain.

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