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Evaluation of evoked potentials to dyadic tones after cochlear implantation

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Auditory evoked potentials are tools widely used to assess auditory cortex functions in clinical context. However, in cochlear implant users, electrophysiological measures are challenging due to implant-created artefacts in the EEG. Here, we used independent component analysis to reduce cochlear implant-related artefacts in event-related EEGs of cochlear implant users ($n = 12$), which allowed detailed spatio-temporal evaluation of auditory evoked potentials by means of dipole source analysis. The present study examined hemispheric asymmetries of auditory evoked potentials to musical sounds in cochlear implant users to evaluate the effect of this type of implantation on neuronal activity. In particular, implant users were presented with two dyadic tonal intervals in an active oddball design and in a passive listening condition. Principally, the results show that independent component analysis is an efficient approach that enables the study of neurophysiological mechanisms of restored auditory function in cochlear implant users. Moreover, our data indicate altered hemispheric asymmetries for dyadic tone processing in implant users compared with listeners with normal hearing ($n = 12$). We conclude that the evaluation of auditory evoked potentials are of major relevance to understanding auditory cortex function after cochlear implantation and could be of substantial clinical value by indicating the maturation/reorganization of the auditory system after implantation.

Keywords: cochlear implant; event-related potentials; hemispheric asymmetry; plasticity; independent component analysis

Introduction

Hearing can be restored in individuals suffering from severe and profound hearing loss using cochlear implants. These devices bypass the outer and middle ear and directly stimulate the fibres of the auditory nerve. Although, the implant-induced activation of auditory fibers is substantially different from the sound-induced activation in normal-hearing listeners, most cochlear implant recipients learn to interpret the artificial, electrical stimulation of the nerve as meaningful sounds. However, the outcome is different for speech and non-speech sounds. In contrast to gradual improvement in speech perception (Oh *et al.*, 2003; Peters *et al.*, 2007; Tyler *et al.*, 1997), implant users typically describe music as difficult to follow and unpleasant to listen to, even after several years of cochlear implant experience (Gfeller *et al.*, 2000; McDermott, 2004). However, qualitatively, good music perception has a positive impact for implantees, not only through the beneficial effects of music on cognitive and emotional functions

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(Baumgartner *et al.*, 2006; Jancke, 2008), but also by improving overall hearing (Drennan and Rubinstein, 2008). In combination with technical developments, research into the neurophysiological mechanisms of auditory perception in implantees, in particular regarding music and speech, is a necessary step towards further improving the rehabilitation of hearing function with a cochlear implant.

Rehabilitation would not be possible without the plastic capacity of the auditory cortex to adapt to the artificial, electrical input of an implant. Evidence of cortical plasticity in the auditory system has been observed in the adult human brain which shows structural and functional changes after intensive auditory training (Pantev *et al.*, 1998; Munte *et al.*, 2002; Schneider *et al.*, 2002; Fujioka *et al.*, 2004). Further evidence of reorganization in the human auditory system has been derived from cochlear implant users who have experienced congenital deafness/sensory deprivation and electrical afferentation after implantation of a cochlear prosthesis (Giraud *et al.*, 2000, 2001*a*; Sharma *et al.*, 2002; Green *et al.*, 2005; Kral and Tillein, 2006; Gilley *et al.*, 2008). Following implantation, users usually show increasing activity in the auditory cortex as they adapt to the signals after long-term auditory deprivation (Suarez *et al.*, 1999; Pantev *et al.*, 2006). At the same time, auditory association cortices show modified response properties, suggesting that deafness-induced loss of functional specialization in auditory association areas can be reversed by implantation, at least to some degree (for a review, see Giraud *et al.*, 2001*b*).

Auditory evoked potentials are important clinical tools that provide objective measures of auditory rehabilitation in cochlear implant users (Ponton *et al.*, 1996; Sharma *et al.*, 2002; Lonka *et al.*, 2004; Pantev *et al.*, 2006). Unfortunately, any acoustic stimulation in implantees generates an electrical artefact that inevitably corrupts the signal of the electro-/magnetoencephalogram (EEG/MEG) as it spatially and temporally overlaps with auditory brain activity. Thus, the utility of auditory evoked potentials for assessing auditory cortex function in individuals using a cochlear implant has been limited. Several approaches have been discussed to reduce or bypass these artefacts (Gilley *et al.*, 2006; Martin, 2007; Debener *et al.*, 2008) including sophisticated artefact reduction procedures (Pantev *et al.*, 2006) or the use of brief stimuli which temporally separates cochlear implant-related artefacts from auditory evoked potentials of interest (Ponton *et al.*, 1993, 2000). The latter procedure however prevents the study of speech and music stimuli, which usually overlap temporally with cortical auditory evoked potentials, and short stimuli such as clicks typically do not provide the necessary frequency resolution. Regarding the former, independent component analysis seems a promising approach, as it may separate auditory evoked potentials from electrical artefacts (Gilley *et al.*, 2006; Debener *et al.*, 2008). Source localization of auditory evoked potentials after independent component analysis correction has recently been reported, which seems important, since source analysis enables a more comprehensive study of auditory asymmetries than channel-based procedures (Debener *et al.*, 2008; Gilley *et al.*, 2008). The application of independent component analysis may provide a means to study auditory cortex function in response to natural sounds such as music and speech in cochlear implant users.

As for auditory processing in humans, a functional asymmetry has been proposed (Tervaniemi and Hugdahl, 2003). These hemispheric asymmetries in the auditory cortex have been investigated in both normal-hearing and hearing-impaired listeners, aimed at more precisely elucidating the functional neuroanatomy subserving auditory processing (Khosla *et al.*, 2003; Tervaniemi and Hugdahl, 2003; Firszt *et al.*, 2006; Hine and Debener, 2007; Hine *et al.*, 2008). In response to monaural sounds, activity in the auditory cortex is typically lateralized (Jancke *et al.*, 2002), with greater amplitude and shorter N1 latency at the hemisphere contralateral to the ear of stimulation (Wolpaw and Penry, 1977). This contralateral dominance effect appears to be stronger for left- than right-ear stimulation in normal-hearing listeners (Hine and Debener, 2007) as well as in unilaterally deaf listeners (Hine *et al.*, 2008). However, EEG/MEG studies have also reported modified hemispheric asymmetry for unilaterally deaf listeners, suggesting that experience-related changes in auditory cortex functions may be reflected by altered hemispheric preferences (Vasama and Makela, 1995; Fujiki *et al.*, 1998; Ponton *et al.*, 2001; Khosla *et al.*, 2003). It is thus reasonable to assume that the lack of experience due to sensory deprivation, and the restoration of sensory input after cochlear implantation, may cause altered hemispheric asymmetries in implant users. Despite being of utmost clinical relevance, not much is known about functional changes in the contra- and ipsilateral hemisphere after cochlear implantation (Roman *et al.*, 2005). In addition to the degree of hearing loss and the location of the speech-dominant hemisphere, knowledge of cortical reorganization following cochlear implantation could have implications for determining which side is implanted (Khosla *et al.*, 2003). Thus, the present study aimed to evaluate the side effects of implantation on auditory cortex activity contra- and ipsilateral to the cochlear implant device, thereby contributing to the understanding of hearing rehabilitation after cochlear implantation. Using dyadic tones with different pitch intervals, our study focused on left- and right-hemispheric recruitment during musical sound processing with cochlear implants, as efforts to understand and improve music perception in implantees seem of utmost importance. Given that musical sound processing can be challenging for implant users, we expected differences in auditory evoked potentials between implantees and normal-hearing listeners. Further, we hypothesized about different hemispheric asymmetries between cochlear implant users and normal-hearing listeners, presumably reflecting cortical reorganization in implant users as a function of profound deafness and restored auditory input.

Methods

Participants

Twenty-four volunteers (20 females) participated in the present study. All participants (mean age 44 ± 13 years) were consistent right-handers according to the questionnaire developed by Annett (1970), and had no history of neurological or psychiatric illness. Twelve of the participants were cochlear implant users (Table 1). Six were implanted bilaterally, five of them were stimulated in the right ear. All of the implanted participants used a Nucleus cochlear implant system

Table 1 Subject demographics of the cochlear implant group

Subjects	Gender	Age	Stimulated ear	Cochlear implant processor	Aetiology	Age at onset of profound deafness (years)	Duration of deafness (years)	Cochlear implant use (months)	Second cochlear implant use (months)
1	Male	50	Left	Freedom	Sudden deafness	37	10	30	–
2	Male	21	Right	Esprit3G-22	Congenital	0	9	138	21
3	Female	48	Right	Freedom	Progressive	40	3	26	40
4	Female	54	Left	Freedom	Progressive	50	2	17	–
5	Female	28	Right	Esprit-3G	Congenital	0	21	80	34
6	Female	59	Left	Esprit-3G	Progressive	51	2	69	67
7	Female	47	Left	Freedom	Progressive	42	2	39	–
8	Female	54	Right	Esprit-3G	Progressive	41	1	143	28
9	Female	21	Left	Esprit-3G	Progressive	10	6	58	–
10	Female	47	Left	Esprit-3G	Progressive	36	5	69	–
11	Female	53	Right	Esprit-3G	Meningitis	46	1	62	4
12	Female	50	Left	Freedom	Progressive	45	4	16	–

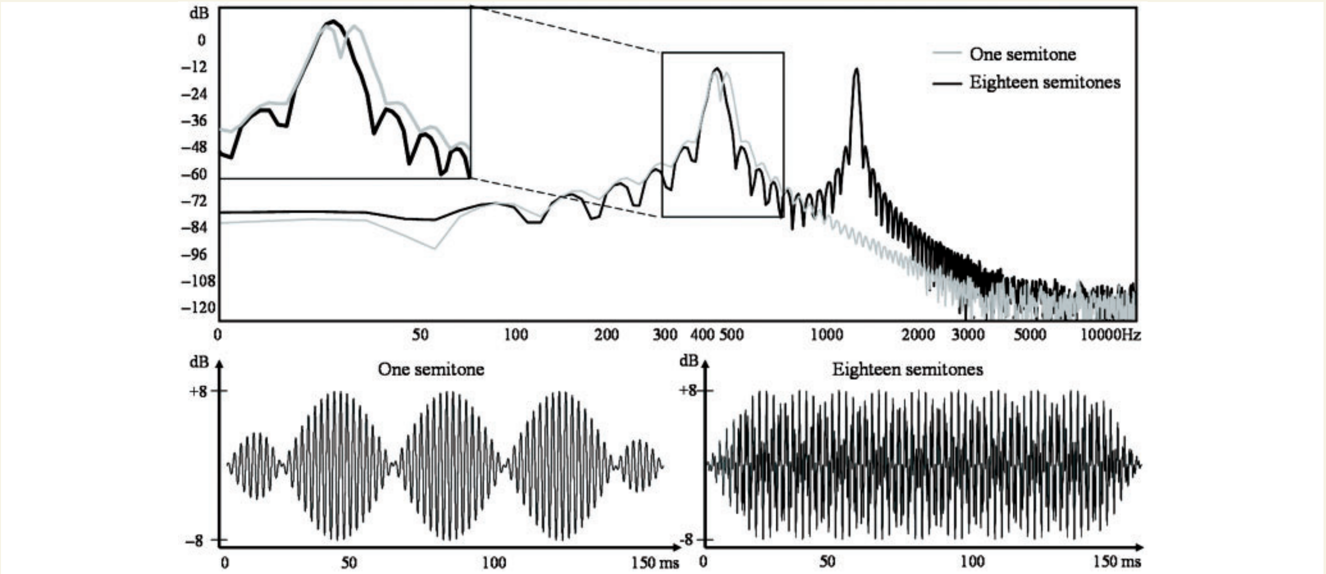

Figure 1 Spectrogram and sound waveforms of the stimuli used in the experiment. The spectrogram shows the frequencies of dyadic tones with pitch intervals of one semitone (grey) and eighteen semitones (black).

(Cochlear Ltd, http://www.cochlear.com), seven in combination with an Esprit-3G processor and five with a Freedom processor. All had been using their implants continuously for at least 16 months prior EEG recording. Each implanted individual was assigned to an age- and sex-matched control subject with normal hearing, as defined by hearing thresholds of 250–6000 Hz that were below 20 dB hearing level in the tested ear. Participants gave written informed consent prior to the experiment. All procedures were approved by the local ethics committee.

Stimuli

All participants listened to dyadic tonal intervals normalized to equal sound intensity. The stimuli were generated using the Adobe® Audition 1.5™ software. Stimulus duration was 150 ms (15 ms rise/fall). Dyadic tonal intervals consisted of two sinusoidal tones, sampled at 44.1 kHz and tuned to the equal-tempered chromatic scale in the range of A4 (440 Hz) and Eb6 (1245 Hz). These simple tones were paired at pitch intervals of 1 (minor second) and 18 (minor duodecim) semitones, resulting in two different dyadic tonal intervals (Fig. 1). These synthesized sounds consisted of two partials with the same on- and offsets, and of restricted spectral complexity, thus preventing uncontrollable degradation due to cochlear implant processing. Although pitch intervals are not perceived as identical to everyday music, dyadic tonal intervals, characterized by a frequency relation between two notes, represent fundamental elements of melodies, and generally, of music. For this reason, we refer here to dyadic tonal intervals as musical sounds, although cochlear implant users might perceive the stimuli less 'music-like' compared with normal-hearing listeners due to the poor spectral resolution of the implant.

The stimuli were presented monaurally via headphones (Sennheiser HD 25.1 II) in normal-hearing listeners or via an audio cable connected to the cochlear implant speech processor. Seven implant users were stimulated in the left ear and five in the right ear. The same number of matched normal-hearing listeners was stimulated in the left and right ear, respectively. For the controls, the intensity of the presented tones reached ~70 dB(A). Loudness scaling, a method usually used in clinical context (Allen *et al.*, 1990; Zeng, 1994; Muller-Deile, 1997), was applied to adjust loudness in implant users to a moderate level, which is equivalent to a level of 70–80 dB(A). Using a seven-point loudness-rating scale, the rating of implant users and normal-hearing individuals were similar, suggesting that dyadic tonal intervals were perceived with equal loudness in the two groups.

Procedure

Participants were seated comfortably in a recliner in front of a personal computer screen in an electromagnetically shielded and sound attenuated room. Stimuli were presented in a pseudo-random order with 1600–1900 ms stimulus onset asynchrony. The participants performed a passive listening task (control condition) in which they heard 80 repetitions of the stimuli presented in a randomized order. Participants further performed two blocks of an active listening task. In this auditory oddball task, 800 stimuli were presented in total. Target and standard probabilities were set at 20 and 80%, respectively. Participants were instructed to press a button whenever they heard the target stimulus. Dyadic tones were presented both as target and standard sounds which were changed between the two blocks of the auditory oddball task, i.e. the target from the first block became the standard of the second block, and the standard from the first block became the target of the second block.

EEG recording

EEG was recorded using 61 electrodes placed according to the 10–10 system. Two additional channels were placed on the outer canthi of both eyes to record electro-oculograms. All channels were recorded against a nose reference. EEG and electro-oculograms were analogue filtered (0.1–100 Hz), recorded with a sampling rate of 1000 Hz and amplified using BrainAmp amplifiers (Brainproducts, http://www.brainproducts.de). Electrode impedances were kept below 5 kΩ.

Data processing

EEG data were analysed using EEGLAB 6.01 (Delorme and Makeig, 2004) running in the MATLAB environment (Mathworks, Natick, MA). Imported data were offline filtered with a 24 dB zero-phase butterworth filter from 1 to 30 Hz and down-sampled to 250 Hz. EEGs were re-referenced to a common average reference and segmented into epochs from −322 to 712 ms relative to stimulus onset. After baseline correction −322 to 0 ms), epochs were automatically screened for peak amplitudes exceeding ±150 μV. EEG data were further screened for unique and non-stereotyped artefacts using a probability function. In this procedure, epochs were removed containing signal values exceeding three standard deviations. Independent component analysis was then applied to remove ocular and other artefacts (Jung *et al.*, 2000*a*, *b*). This type of analysis is based on the assumption that EEG data recorded at multiple scalp sensors are linear sums of temporally independent components arising from spatially fixed, distinct or overlapping brain sources. The technique decomposes the data unmixed into a sum of temporally independent and spatially fixed components. Each independent component analysis component corresponds to a scalp topography which represents the relative projection strength of the component at each scalp sensor. In the present study, we used the infomax independent component analysis algorithm to reduce cochlear implant-created artefacts (Gilley *et al.*, 2006; Debener *et al.*, 2008). Independent component analysis topographies representing cochlear implant artefacts were identified by the centroid on the side of the implanted device, and by the cochlear implant pedestal in the time course of the respective component.

After independent component analysis-based artefact reduction, single trials from all electrodes were denoised using an algorithm based on the wavelet transform (Quian Quiroga and Garcia, 2003). Subsequent peak detection was performed on the global field power by visual inspection of global field power peaks in commonly used latency bands of P1, N1, P2 and P3 components (Naatanen and Picton, 1987; Micco *et al.*, 1995; Roman *et al.*, 2005). Latencies of cochlear implant-mediated auditory evoked potentials were corrected because the speech processor introduces a delay between the onset of the acoustic stimulus and the actual start of the electrical stimulation (1 ms Esprit-3G or 5 ms Freedom).

Differences and similarities between voltage distributions of cochlear implant users and normal-hearing listeners were evaluated using paired *t*-tests and correlation analyses. Individual coefficients of correlation for each implant user and the corresponding matched control were normalized and subjected to a one-sample *t*-test. The problem of multiple comparisons was controlled for by adjusting the *P*-values using the false discovery rate correction procedure (Benjamini and Hochberg, 1995).

Source modelling

Auditory evoked potential source modelling was used to assess the quality of artefact-corrected potentials in cochlear implant users over all conditions and to evaluate auditory cortex asymmetries in both implantees and controls. Single-subject 1–20 Hz band-pass filtered auditory evoked potentials, averaged over all trials, were submitted to dipole source analysis using BESA (Megis, Graefelfing, Germany). A standard four-shell ellipsoid head model was used with default radii and conductivity parameters. Using a symmetry constraint, the N100 global field power onset-to-peak interval was modelled and the resulting Talairach coordinates stored for each individual. To derive source waveforms, two symmetric equivalent current dipoles were seeded into superior temporal lobes [Talairach coordinates (x, y, z) = ±49.5, −17, 9; see also (Hine and Debener, 2007; Debener *et al.*, 2008; Hine *et al.*, 2008)]. The adequacy of this location for source waveform analysis was evaluated by determining the Euclidean distance between the free, symmetric source model and this reference location.

Source waveform analysis focused on the root mean square of regional source waveforms instead of current dipole moments for the following reason. In contrast to current dipole moments, which are sensitive to orientation, regional sources can be used to describe all activity in the vicinity of their location independent of spatial orientation. In our experience, reasonable, mirror-like tangential orientations cannot always reliably be obtained for the AEP N100 in response to monaural stimulation on a single subject level, and this was also the case in the present study. Therefore, the root mean square across all three orthogonal orientation moments was used, as it preserved moment information without a bias towards adequate orientation modelling.

Results

Behavioural data

In both groups of participants, accuracy collected for the oddball paradigm was high (normal-hearing mean: 99.84 ± 0.28%; cochlear implant mean: 99.01 ± 2.46%), and response times were rather fast (normal-hearing mean: 416 ± 40 ms; cochlear implant mean: 457 ± 100 ms). Statistical comparisons of accuracy or response times revealed no significant differences between the two groups (accuracy: $P = 0.23$; response time: $P = 0.21$). Comparing the response times for left- and right-ear stimulation separately, cochlear implant users with right-ear stimulation showed longer response times compared with matched normal-hearing controls ($P < 0.05$), while implant users with left-ear implantation were as fast as controls.

Independent component analysis based reduction of cochlear implant-related artefacts

Auditory evoked potentials of cochlear implant users were obscured by large implant-related artefacts, which were time-locked to the acoustic stimulation in all epochs (Fig. 2). The morphology of the artefact resembled a pedestal with an onset and offset ramp. Dependent on the type of cochlear implant processor, the slopes of the artefact occurred ~20 (Esprit-3G) and 24 ms (Freedom) after the onset, and ~46 (Freedom) and 58 ms (Esprit-3G) after the offset of the acoustic stimulation. Rejection of independent components representing cochlear implant-related artefacts (mean: 4 ± 3 components) resulted in auditory evoked potentials which were recovered from electrical artefacts.

Scalp-recorded auditory evoked potentials

After artefact reduction, both cochlear implant users and normal-hearing listeners revealed P1, N1 and P2 components (Fig. 3; Table 2). In addition, the two groups showed the deviance-related P3 component in the target condition. Repeated measures ANOVA with condition (standard, target, control) as within-subjects factor and group (cochlear implant, normal-hearing) and stimulation side (left, right) as between-subjects factors were conducted separately on amplitudes and latencies of P1, N1 and P2 components. ANOVAs revealed a significant main effect for group in N1 amplitude [$F(1,18) = 34.42$, $P < 0.001$], and a significant main effect for condition in P1 amplitude [$F(2,40) = 14.4$,

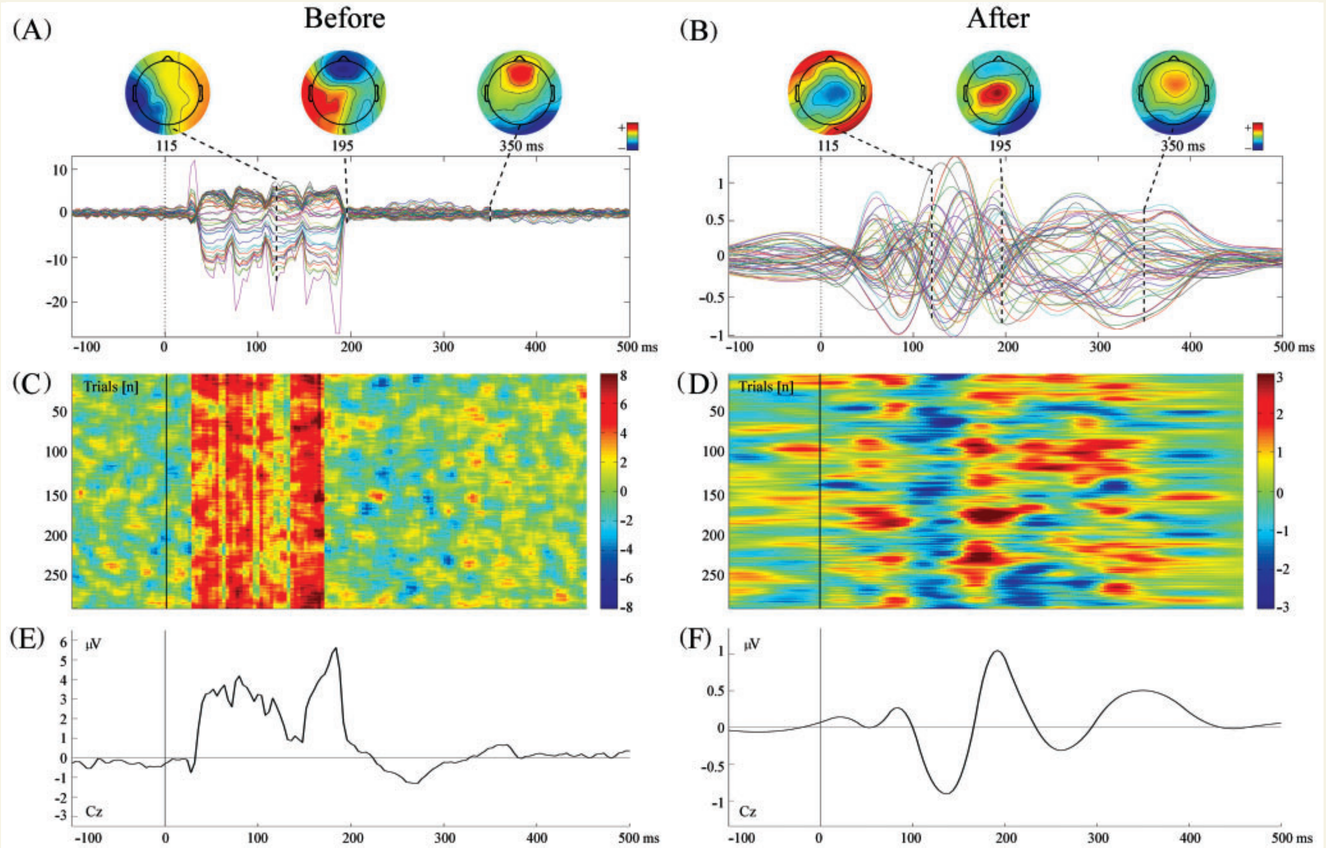

Figure 2 Butterfly plot of auditory evoked potentials and single-trial images showing EEG amplitudes of one representative implant user. Auditory evoked potentials to target stimuli are illustrated before (**A**) and after (**B**) independent component analysis-based artefact reduction together with the voltage maps at N1, P2 and P3 latencies. Voltage maps are scaled to the absolute maximum. Single trials and the corresponding grand average, recorded at a central scalp location (channel Cz), are illustrated before (**C** and **E**) and after (**D** and **F**) independent component analysis-based artefact reduction. Amplitude values (μV) of single trials are coded in colour. Note the different scaling of the auditory evoked potentials images.

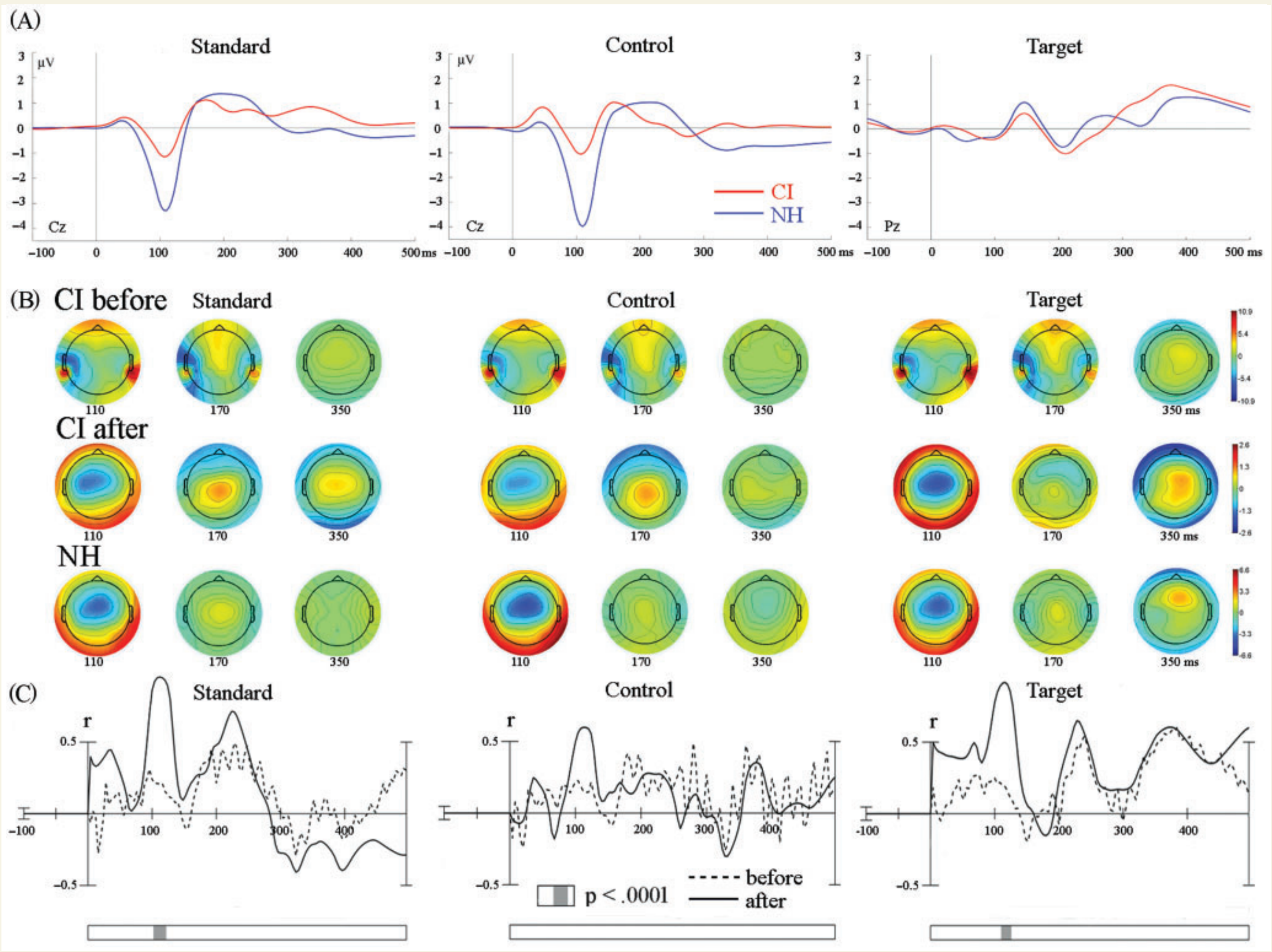

Figure 3 Averages of auditory evoked potentials and correlations between voltage maps of cochlear implant users and normal hearing listeners before and after reduction of cochlear implant-related artefacts. (**A**) Grand averages of auditory evoked potentials at a central (channel Cz) or parietal (channel Pz) scalp location for each group and experimental condition. (**B**) Voltage maps of normal hearing listeners and cochlear implant users before and after artefact reduction for each condition. Voltage maps are scaled to the absolute maximum. (**C**) Correlations between voltage maps of normal hearing listeners and cochlear implant users before (dotted line) and after (continuous line) artefact reduction. Coefficient of correlations (*r*) are illustrated as a function of time for the three conditions. Significant correlations between voltage maps are indicated by grey bars, referring to $P < 0.0001$.

Table 2 Results from the global field power analysis obtained for normal hearing listeners and cochlear implant users: mean latency (ms) and amplitude (μV) ± 1 SEM

		Normal hearing			Cochlear implant		
Auditory evoked potential	Parameter	Control	Standard	Deviant	Control	Standard	Deviant
P1	Latency	50 ± 4	55 ± 2	58 ± 2	57 ± 4	58 ± 4	62 ± 3
N1	Latency	118 ± 8	119 ± 1	119 ± 1	117 ± 4	122 ± 4	124 ± 3
P2	Latency	215 ± 7	200 ± 7	216 ± 8	219 ± 8	190 ± 8	222 ± 10
P3	Latency			360 ± 9			371 ± 10
P1	Amplitude	0.9 ± 0.1	0.8 ± 0.1	1.3 ± 0.1	0.9 ± 0.1	0.6 ± 0.1	0.9 ± 0.1
N1	Amplitude	2.8 ± 0.2	2.2 ± 0.1	2.5 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	1.5 ± 0.2
P2	Amplitude	1.5 ± 0.2	1.4 ± 0.2	2.4 ± 0.3	1.0 ± 0.2	0.9 ± 0.1	2.1 ± 0.3
P3	Amplitude			2.6 ± 0.3			2.3 ± 0.4

$P < 0.001$], N1 amplitude [$F(2,40) = 7.6$, $P < 0.01$], N1 latency [$F(2,40) = 4.07$, $P < 0.05$] and P2 amplitude [$F(2,40) = 17.4$, $P < 0.001$]. *Post hoc* *t*-tests showed larger N1 amplitudes in normal-hearing listeners compared with cochlear implant users in all conditions ($P \leqslant 0.001$). Cochlear implant users showed longer N1 latencies in the target than control condition ($P < 0.05$), and smaller amplitudes in the standard than target condition for P1, N1 and P2 components ($P < 0.01$). With respect to P3 measures, *t*-tests revealed no group difference pertaining to P3 amplitudes or latencies. Similar findings were obtained for a follow-up analysis based on auditory evoked potentials measured at central and parietal scalp locations (not reported in detail here).

Topographic analyses

Paired *t*-tests between voltage distributions of cochlear implant users and normal hearing listeners revealed significant differences at frontocentral sites across all conditions in the time range between 86 and 122 ms after stimulus onset ($P < 0.05$) and were maximal at N1 latency (target: 106 ms; standard, control: 110 ms; $P < 0.05$). In addition, time-resolved spatial correlation analyses revealed strong relationships between voltage maps of normal hearing listeners and cochlear implant users specifically after independent component analysis-based artefact reduction (standard and target condition: $P < 0.001$). In contrast, voltage maps of normal hearing listeners showed no significant relationship with voltage maps of cochlear implant users before artefact reduction.

Auditory evoked potentials source localization

In both groups of participants, single subject dipole source localization revealed a good fit between the reference location in the auditory cortices bilaterally [Talairach coordinates: $(x, y, z) = \pm 49.5, -17, 9$] and the modelled location (Fig. 4). Source locations for implanted and normal hearing individuals revealed an overlap to a large extent. With the exception of one cochlear implant user (subject 11, see Table 1), source locations of implant users were within the range of controls, defined by the mean of the total group of normal hearing listeners ±2 SDs. For normal hearing listeners, the mean location was at $(x, y, z) = \pm 39.29, -19.91, 9.96$ and the mean euclidean distance to the reference location in Heschl gyrus was 15.8 mm (SD: 8.9 mm; range: 5.01–24.5 mm). With respect to cochlear implant users, the mean source location was at $(x, y, z) = \pm 30.32, -20.61, 12.51$ and the mean distance to the reference location was 23.7 mm (SD: 6.5 mm; range: 14.9–31.49 mm). Cochlear implant source locations had a mean euclidean distance of 7.8 mm to the matched control samples.

Source waveforms

Source waveform activity was statistically analysed by a non-parametric bootstrapping procedure which tested for significant differences between activity of the left and right Heschl's gyrus (Efron and Tibshirani, 1994). Confidence limits of 99.9% were obtained for difference waveforms based on 1000 iterations and using the bootstrap bias-corrected and adjusted method. Similar to previous studies of auditory evoked potentials, source waveforms were considered significantly different if the confidence interval of the difference source waveform did not include zero (e.g. Hine and Debener, 2007; Strobel *et al.*, 2008). Source waveforms of normal hearing listeners showed a clear contralateral dominance effect for left-ear stimulation, i.e. larger amplitudes at N1 latency in the right compared with the left hemisphere ($P < 0.05$) (Fig. 5). Further, normal hearing listeners revealed shorter latencies of root mean square peaks in the right than left hemisphere ($P < 0.05$). This is in contrast to the source waveforms of cochlear implant

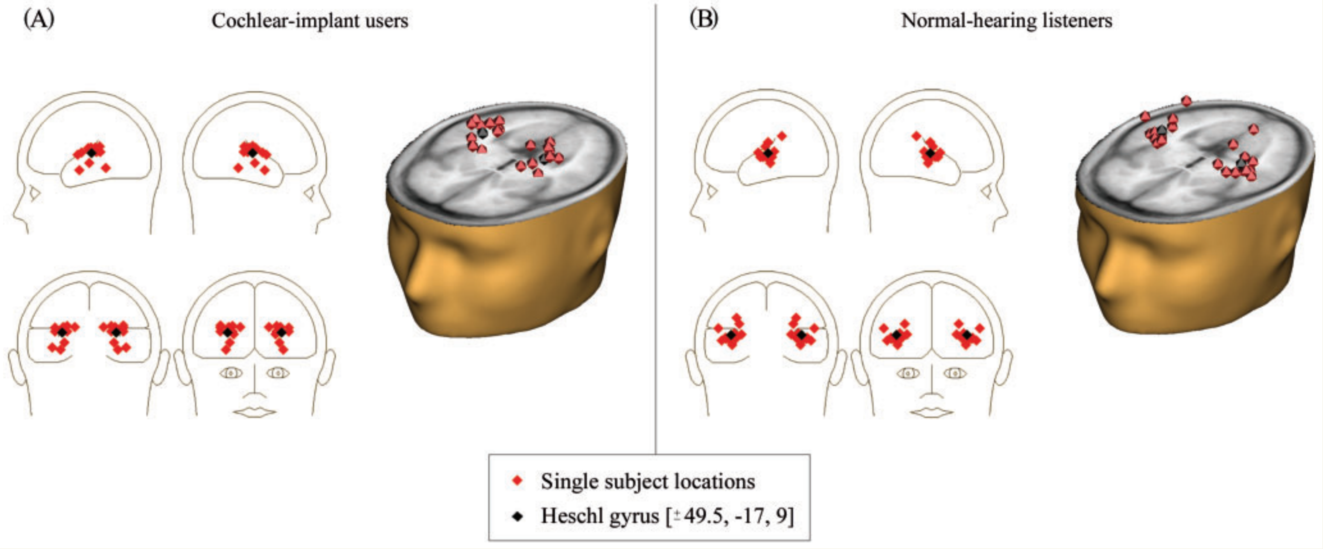

Figure 4 Single subject source localization of N1-auditory evoked potentials for cochlear implant users (A) and normal hearing listeners (B). The results are illustrated in two-dimensional and three-dimensional views, plotted on a standardized brain provided by the BESA software. Single-subject source localizations (red diamonds) are shown along with a reference coordinate in Heschl gyrus (black diamonds), given in Talairach coordinates.

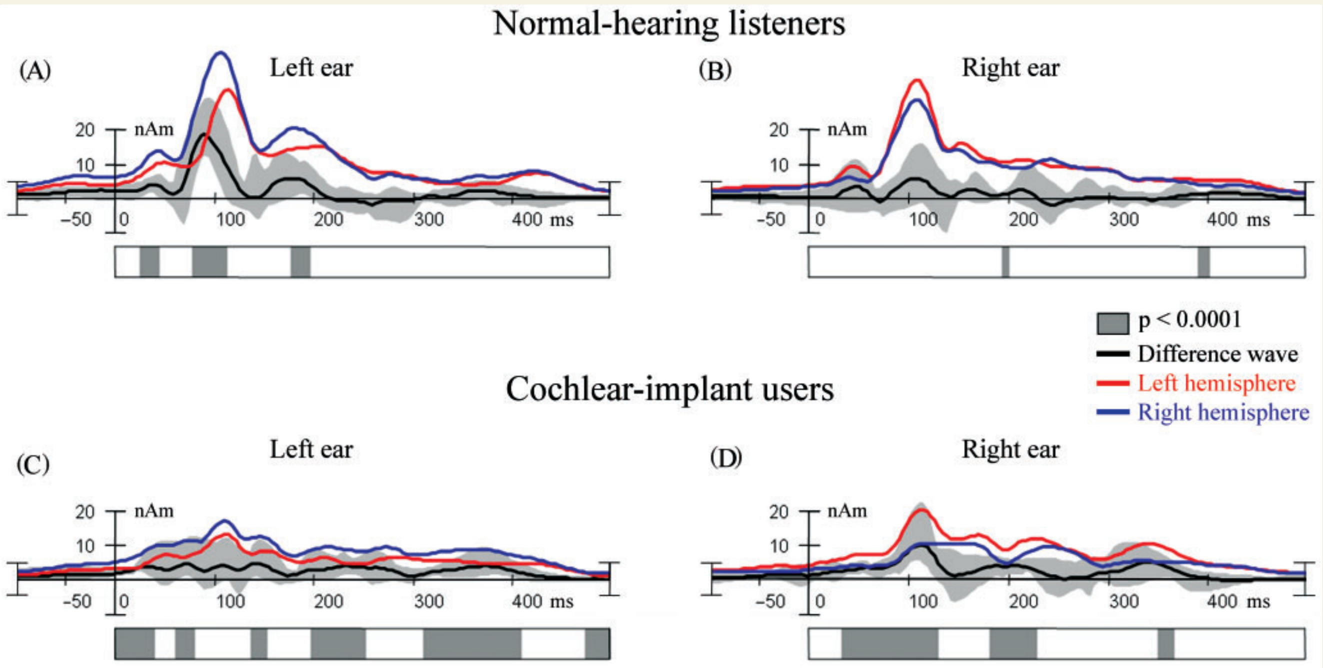

Figure 5 Grand average regional source waveforms obtained for the reference location in the auditory cortex [Talairach coordinates (x, y, z) = ±49.5, −17, 9] to stimulation of the left (**A** and **C**) and right ear (**B** and **D**). Source activity is shown for the sources of the left (red) and right hemisphere (blue) separately for normal hearing listeners and cochlear implant users. In addition, difference waves (black) are plotted together with the bootstrapping-derived confidence interval (grey). Significant differences between source waveforms are indicated by grey bars, referring to $P < 0.0001$.

users obtained for left-ear stimulation. Root mean square amplitudes and latencies of these source waveforms were more symmetric compared with matched controls, i.e. source waveforms of cochlear implant users were not significantly different between the left and right hemisphere for left-ear stimulation. Conversely, for right-ear stimulation, a contralateral dominance pattern was found in cochlear implant users but not in normal hearing individuals. That is, cochlear implant users but not normal hearing listeners showed larger root mean square amplitudes in the left compared with the right hemisphere ($P < 0.05$). Root mean square latency for right-ear stimulation was not different, neither for cochlear implant users nor for matched normal hearing controls. Comparing root mean square amplitudes of cochlear implant users between left-ear and right-ear stimulation for each hemisphere, the results revealed significantly reduced amplitudes in the right hemisphere for right-ear stimulation compared with left-ear stimulation ($P < 0.05$).

Relationship between auditory regional source activity, duration of cochlear implant use, and behavioural performance

Spearman non-parametric correlation analyses revealed a negative relationship between duration of cochlear implant use and root mean square latency in the left and right hemisphere for left-ear stimulation (left hemisphere: $r = -0.74$, $P = 0.05$; right hemisphere: $r = -0.81$, $P < 0.05$) but not for right-ear stimulation (left hemisphere: $r = -0.11$, $P = 0.86$; right hemisphere: $r = -0.67$, $P = 0.22$) (Fig. 6). In contrast, a positive relationship was found between duration of cochlear implant use and root mean square amplitude in the left hemisphere for right-ear stimulation (left hemisphere: $r = 0.90$, $P < 0.05$; right hemisphere: $r = -0.1$, $P = 0.87$) but not for left-ear stimulation (left hemisphere: $r = 0.54$, $P = 0.21$; right hemisphere: $r = 0.41$, $p = 0.36$). Cochlear implant users stimulated in the right ear further revealed a positive correlation between auditory evoked potential asymmetry [computed as (contralateral activity - ipsilateral activity)/(contralateral activity + ipsilateral activity)] and performance in speech intelligibility, measured by means of a vowel and monosyllabic word test (vowels: $r = 0.90$, $P < 0.05$; monosyllabic words: $r = 0.82$, $P < 0.1$). Generally, duration of implant use was more systematically related to auditory evoked potential source waveforms compared with topographic EEG data. There was no significant relationship between duration of cochlear implant use and auditory evoked potentials at central scalp locations (channel Cz) or global field power peaks, except from a negative correlation between duration of cochlear implant use and N1 latency at Cz for left-ear stimulation ($r = -0.90$, $P < 0.01$), and a negative correlation between duration of cochlear implant use and latency of P3 global field power peaks for right-ear stimulation ($r = -0.90$, $p < 0.05$).

Discussion

The present study examined auditory evoked potentials in cochlear implant users and matched normal hearing controls to evaluate

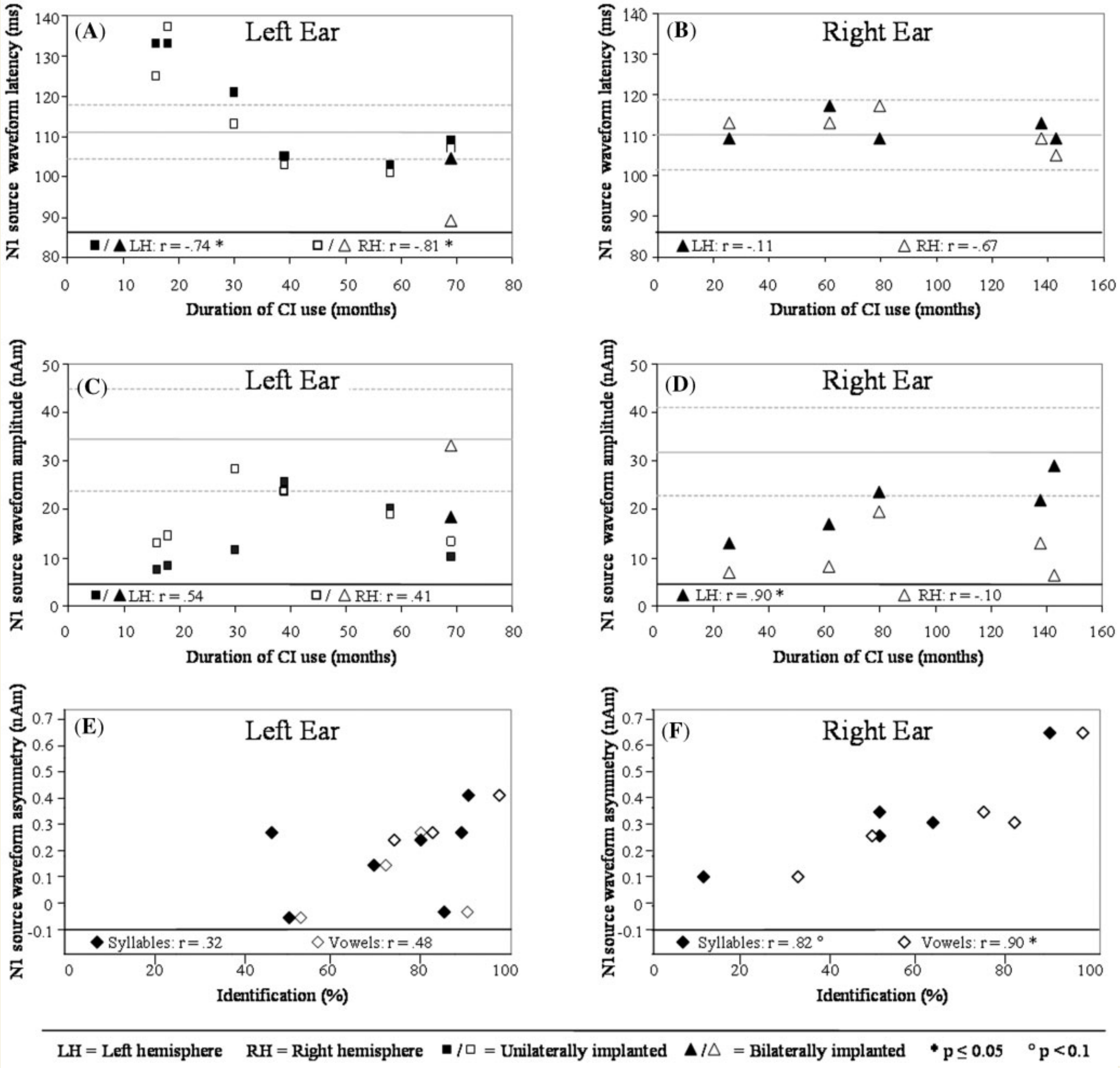

Figure 6 Relationship between auditory regional source activity, duration of cochlear implant use and speech perception ability in cochlear implant users. (**A** and **B**) Correlations between duration of cochlear implant use and peak latencies in the left and right hemisphere for left-ear (**A**) and right-ear stimulation (**B**). (**C** and **D**) Correlations between duration of cochlear implant use and source waveform amplitudes in the left and right hemisphere for left-ear (**C**) and right-ear stimulation (**D**). Filled symbols (squares/triangles) indicate unilaterally implanted cochlear implant users, while empty symbols indicate bilaterally implanted cochlear implant users. Note the horizontal lines in each of the four subplots which illustrate the mean of source waveforms across the two hemispheres (continuous horizontal line) ± 1 SD (dotted horizontal lines) for normal hearing listeners. (**E** and **F**) Correlations between N1 source waveform asymmetry and speech perception ability of cochlear implant users stimulated in the left (**E**) and right ear (**F**). Asymmetry of N1 source waveforms was calculated as (contralateral activity − ipsilateral activity)/(contralateral activity + ipsilateral activity). Speech intelligibility was measured by means of a vowel and monosyllabic word test.

left- and right-hemispheric recruitment during dyadic tone processing with cochlear implant. In good agreement with previous work, normal hearing listeners showed a contralateral dominance effect specifically for left-ear stimulation (Hine and Debener, 2007). Implant users on the other hand showed a contralateral dominance effect specifically for right-ear stimulation. Moreover, we found that auditory regional source activity correlated with duration of cochlear implant use and performance in speech perception ability indicating that auditory evoked potential measures in the left and right hemisphere are sensitive to cochlear implant experience and are related to behavioral performance.

Reduction of cochlear implant-related artefacts

The present study revealed similar N1 source locations for cochlear implant users and normal hearing listeners, and strongly correlated voltage maps between the two groups specifically after independent component analysis-based artefact reduction. Consistent with recent work, our findings demonstrate that cochlear implant-related artefacts can successfully be reduced by means of independent component analysis (Debener *et al.*, 2008; Gilley *et al.*, 2008). One potential drawback of this approach is that artefact reduction by means of independent component analysis may artificially affect the amplitudes and topographies of reconstructed auditory evoked potential components. However, supplementary analyses of the present study render this interpretation unlikely (Supplementary Fig. 1).

Artefact reduction in the EEG signal of cochlear implant users is of particular significance since in previous research, technical drawback had considerably restricted the detailed study of auditory cortex functions in cochlear implant users. Functional imaging techniques such as PET and functional MRI have been of limited utility to study neurofunctional changes in cochlear implant users because of the invasive characteristic and safety concerns, respectively (for a review, see Giraud *et al.*, 2001*b*). Thus, the EEG/MEG seems a more suitable tool to study the dynamics of auditory plasticity after cochlear implantation, in spite of cochlear implant artefacts in EEG/MEG recordings of cochlear implant users (Sharma *et al.*, 2002; Pantev *et al.*, 2006; Debener *et al.*, 2008; Gilley *et al.*, 2008). Because of these large electrical artefacts, spatial evaluation auditory evoked potentials in cochlear implant users typically limited to non-overlapping latencies. Therefore, previous work about spatial aspects of late cortical auditory evoked potentials in cochlear implant users was restricted to evoked potentials to short-duration stimuli, i.e. brief clicks (Ponton *et al.*, 1993, 2000) or late components (Henkin *et al.*, 2004). However, the present results show that the problem of cochlear implant artefacts can be overcome by independent component analysis and this enables a detailed investigation of auditory cortex activity elicited by complex, natural sounds, in particular music and speech. It may be of great clinical relevance to use auditory evoked potentials as objective markers for auditory cortex functions after cochlear implantation, particularly in young children (for a review, see Sharma and Dorman, 2006).

Successful independent component analysis-based artefact reduction enabled a spatial evaluation of auditory evoked potentials provided by means of dipole source analysis. The validity of this procedure is underscored by the observation that correlations between duration of cochlear implant use and source waveforms were more systematic than between duration of cochlear implant use and scalp-based auditory evoked potential data. We therefore conclude that independent component analysis in combination with dipole source analysis allows for a sensitive investigation of cortical changes in the central auditory system of cochlear implant users.

Electrophysiological correlates of musical sound perception with a cochlear implant

The present study revealed electrophysiological correlates of musical sound perception in implanted and normal hearing individuals. Consistent with previous cochlear implant-related literature on speech sounds and sinusoidal tones, cochlear implant users showed substantially smaller N1 amplitudes compared with normal hearing listeners (Micco *et al.*, 1995; Groenen *et al.*, 2001; Beynon *et al.*, 2005; Kelly *et al.*, 2005). Multiple reasons may account for smaller amplitudes in cochlear implant users compared to normal hearing listeners, including reduced synchronization of neuronal activity, or reduced number of activated cortical neurons involved in generating auditory evoked potentials (Pantev *et al.*, 1998; Groenen *et al.*, 2001). In spite of group differences in N1 amplitude, cochlear implant users and normal hearing listeners showed bilateral activation during processing of dyadic tones. This finding suggests bilateral recruitment during perception of musical sounds with cochlear implant, and corroborates the view of bilateral involvement of auditory cortex in processing musical tones (Meyer *et al.*, 2006), and more generally, in processing music (for a review, see Peretz and Zatorre, 2005). In particular, the current results support the finding that both the left and right auditory cortex is critical for pitch interval processing (Liegeois-Chauvel *et al.*, 1998), even though the right temporal lobe seems to be particularly important in computing pitch relations (e.g. Johnsrude *et al.*, 2000; Patterson *et al.*, 2002). However, future research needs to use larger sets of stimuli from different classes which allows for a more systematic examination of left- and right-hemispheric recruitment during musical sound processing with a cochlear implant.

Knowing the neurophysiological basis of music perception with cochlear implant is of particular interest at present, because listening to music is not satisfying with current-day implants but could substantially improve quality of life in cochlear implant users. Cochlear implants are primarily designed to enable speech discrimination, but qualitatively good music perception has been recognized as an important goal, because of the beneficial impact of music on cognitive and emotional functions in healthy and brain-injured individuals (Baumgartner *et al.*, 2006; Drennan *et al.*, 2008; Jancke, 2008; Sarkamo *et al.*, 2008). This is the reason for increasing efforts to improve quality of music perception with a cochlear implant, including the development of technical improvements and behavioural training protocols (Gfeller *et al.*, 2002*b*). A comprehensive investigation of the neurophysiological mechanisms of music perception in normal hearing listeners and hearing-impaired individuals would help achieve the long-term goal of a more complete restoration of hearing with a cochlear implant.

Hemispheric asymmetry for dyadic tone processing

Auditory regional source waveforms revealed a contralateral dominance effect on different ears for cochlear implant users and normal hearing individuals, i.e. different hemispheric asymmetries for dyadic tone processing between the two groups of participants. Consistent with the present results, normal hearing listeners were previously shown to have a greater degree of lateralization for left-ear compared to right-ear stimulation (Hine and Debener, 2007), thereby supporting the view of functional specialization of the auditory cortex in the two hemispheres (Tervaniemi and Hugdahl, 2003). While the left auditory cortex seems to be specialized for processing of rapidly changing acoustic cues, the right auditory cortex has been suggested to be more sensitive to spectral information (for a recent review, see Zatorre and Gandour, 2008). Thus, the finding that normal hearing listeners show a dominance effect specifically for left-ear stimulation might originate from the right-hemisphere specialization for processing spectral aspects of sounds, although alternative accounts exist for hemispheric asymmetries in auditory functioning (Poeppel, 2003; Boemio *et al.*, 2005).

The current results revealed a contralateral dominance in cochlear implant users specifically for right-ear stimulation. This is in contrast to normal hearing listeners, who typically show a contralateral dominance for left-ear stimulation. The reasons for finding different hemispheric asymmetries between the two groups of participants could be: first, different hemispheric asymmetries could be caused by different stimulus properties as a consequence of acoustic (normal hearing listeners) versus electric (cochlear implant users) stimulation; or second, in cochlear implant users hemispheric asymmetries might have changed due to cortical reorganization following profound deafness and cochlear implantation. To address the former concern, we performed a follow-up measurement of normal hearing listeners that revealed similar patterns of hemispheric asymmetry for original stimuli and noise-vocoded stimuli (i.e. cochlear implant simulation by processing the stimuli with a noise vocoder) (Supplementary Fig. 2). In addition, possible differences caused by acoustic versus electric stimulation were minimized in the current study by using a simple, synthesized stimulus contrast, which prevented uncontrollable degradation of the stimuli by cochlear implant processing.

Rather than stimulation differences, hemispheric differences between the two groups might be caused by differences in auditory experience, i.e. plastic changes in cochlear implant users as a function of auditory deprivation and subsequent restored, artificial input. In fact, our observations in cochlear implant users, showing changes in the normal pattern of cortical response asymmetries, support the finding of changed hemispheric asymmetry in individuals with profound hearing loss (Fujiki *et al.*, 1998; Ponton *et al.*, 2001). In addition, our results agree with previous observations of cortical reorganization following cochlear implantation (Suarez *et al.*, 1999; Giraud *et al.*, 2001*a*; Sharma *et al.*, 2002; Green *et al.*, 2005; Pantev *et al.*, 2006), in the auditory cortex ipsilateral and contralateral to the cochlear implant device (Kral *et al.*, 2002), as indicated by the current correlations between cochlear implant experience and source waveform activity in the left and right auditory cortex.

Changes in hemispheric asymmetry for dyadic tone processing in cochlear implant users compared to normal hearing listeners suggest functional differences between these groups. Because electrical stimulation does not deliver detailed spectral information and temporal fine-structure (Drennan *et al*., 2008), processing of complex sounds, in particular music and speech, can be challenging with cochlear implants, and implant users have to develop a perceptual strategy which allows them to use the reduced cues of sound properties constrained optimally. Due to poor spectral resolution, cochlear implant users are typically not able to discriminate between multiple harmonic components of complex sounds (Drennan *et al*., 2008), while they can discriminate between fundamental frequencies of complex sounds, despite the rather poor and variable discrimination performance across cochlear implant users (Gfeller *et al.*, 2002*a*). In contrast to cochlear implant users who are constrained due to technical reasons, normal hearing listeners can discriminate pitch of complex sounds either based on the fundamental frequency (fundamental pitch) or based on spectrum frequency (spectrum pitch) (Platt and Racine, 1990; Terhardt, 1974). Consistent with the view of top-down modulated input processing in the cortical auditory system (Tervaniemi and Hugdahl, 2003; Kral and Eggermont, 2007), the two modes of pitch perception seem to be strongly associated with different hemispheric asymmetry, i.e. with stronger left-hemisphere activation for fundamental pitch, and stronger right-hemisphere activation for spectral pitch (Schneider *et al.*, 2005). Since cochlear implant users are hardly capable of processing spectral pitch, fundamental pitch together with the temporal envelopes should be considered the most principal acoustic information cochlear implant users rely on during complex sound processing. Thus, the current finding of contralateral dominance in cochlear implant users specifically for right-ear stimulation might be explained by increased left hemisphere activation, presumably associated with the perceptual strategy of focusing on the fundamental pitch of musical sounds, i.e. by top-down modulated information processing in the auditory cortex.

Summary and conclusion

The present study examined hemispheric asymmetry for dyadic tone processing in cochlear implant users to evaluate the effect of cochlear implantation on neuronal acitivity. The results revealed bilateral hemispheric recruitment during perception of musical sounds with a cochlear implant. Implant users further showed altered hemispheric asymmetries of auditory regional source waveform activity. Compared with normal hearing listeners, suggesting experience-related changes in the normal pattern of cortical response asymmetries. In particular, our results indicate that auditory experience with an implant induces cortical reorganization in the hemisphere ipsilateral and contralateral to the cochlear implant device. Eventually, the results imply that independent component analysis is an efficient approach to overcome the problem of cochlear implant artefacts. Successful reduction of cochlear implant-related artefacts by independent component analysis may be of clinical relevance as enables the routine usage of auditory evoked potentials in cochlear implant users.

Supplementary material

Supplementary material is available at *Brain* online.

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