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# The auditory P$_{50}$ component to onset and offset of sound

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## Abstract

*Objective:* The auditory Event-Related Potentials (ERP) of component P$_{50}$ to sound onset and offset have been reported to be similar, but their magnetic homologue has been reported absent to sound offset. We compared the spatio-temporal distribution of cortical activity during P$_{50}$ to sound onset and offset, without confounds of spectral change.

*Methods:* ERPs were recorded in response to onsets and offsets of silent intervals of 0.5 s (gaps) appearing randomly in otherwise continuous white noise and compared to ERPs to randomly distributed click pairs with half second separation presented in silence. Subjects were awake and distracted from the stimuli by reading a complicated text. Measures of P$_{50}$ included peak latency and amplitude, as well as source current density estimates to the clicks and sound onsets and offsets.

*Results:* P$_{50}$ occurred in response to noise onsets and to clicks, while to noise offset it was absent. Latency of P$_{50}$ was similar to noise onset (56 ms) and to clicks (53 ms). Sources of P$_{50}$ to noise onsets and clicks included bilateral superior parietal areas. In contrast, noise offsets activated left inferior temporal and occipital areas at the time of P$_{50}$. Source current density was significantly higher to noise onset than offset in the vicinity of the temporo-parietal junction.

*Conclusions:* P$_{50}$ to sound offset is absent compared to the distinct P$_{50}$ to sound onset and to clicks, at different intracranial sources. P$_{50}$ to stimulus onset and to clicks appears to reflect preattentive arousal by a new sound in the scene. Sound offset does not involve a new sound and hence the absent P$_{50}$.

*Significance:* Stimulus onset activates distinct early cortical processes that are absent to offset.

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*Keywords:* Event-Related Potentials; Gaps in noise; Change detection; Low-resolution electromagnetic tomography; Functional imaging

## 1. Introduction

The auditory P$_{50}$ component is the earliest (around 50 ms), the smallest in amplitude, the most variable and consequently the least studied of the auditory Event-Related Potentials (ERP). Early reports on long-latency evoked potentials typically reported its presence, as part of the obligatory exogenous "vertex potential" (e.g., Davis and Zerlin, 1966) or "P$_1$–N$_1$–P$_2$ complex" (e.g., Knight et al., 1980; Naatanen and Picton, 1987), but parametric effects were rarely elaborated.

The earliest report on human auditory evoked potentials (Davis, 1939) reported a response to onset as well as offset of a tone. A later study had better control of the acoustic properties of the onset and offset of the tone (Davis and Zerlin, 1966) and reported the on-response and the off-response to be "very similar", consisting of a P$_1$–N$_1$–P$_2$ vertex potential. In contrast, the auditory neuromagnetic P$_{50}$ field has been reported to be absent from offset responses but present and indistinguishable in its sources from N$_{100}$ in response to stimulus onset (Hari et al., 1987; Pantev et al., 1996). This neuromagnetic

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response, $P_{40m}$, peaking about 40 ms after stimulus onset, preceded a prominent field in the opposite direction at about 100 ms ($N_{100m}$). Both deflections could be explained by cortical activity within the Sylvian fissure (Hari et al., 1987). Striking similarities were found between the $N_{100m}$ of the on- and off-responses in their latency, estimated sources in the supratemporal plane and in their amplitude dependence on stimulus rate (Hari et al., 1987). However, only the on-response was preceded by $P_{40m}$ (Hari et al., 1987; Pantev et al., 1996), suggesting that $N_{100}$ is not dependent on a preceding $P_{50}$ (Hari et al., 1987). Moreover, while $N_{100}$ seems to reflect cortical activity related to any abrupt change in the auditory environment, e.g., sound onset as well as offset (Hari et al., 1987), $P_{50}$ was suggested to reflect a distinct process evoked only by stimulus onset. This contradiction between the early reports on the electric $P_{50}$ and the recent reports on the magnetic $P_{40m}$ has not been resolved.

A possible confound of studies on brain responses to sound onsets is the spectral change accompanying onset – from zero energy in silence to the spectral energy contained in the stimulus, resulting in spectral splatter introduced by sound envelope. Similarly, offsets of sounds are accompanied by spectral changes associated with the spectral splatter of the diminishing stimulus envelope. Brain responses to such spectral change could affect and override brain responses that are specific to onset and offset of sound, obscuring their differences. One way to overcome this limitation is to use interruptions in white noise: the wide spectral content of white noise remains flat even when abrupt gaps are introduced because both the abrupt envelope of gaps and white noise have the same spectrum. Comparisons of brain potentials to gap onset and offset, therefore, reveal the differences between the responses to offset and onset of sound without confounds of an associated spectral change.

The $N_{100}$ component to sound onset (gap offset) is single-peaked whereas to sound offsets (gap onsets) it is a double-peaked N-Complex. The first constituent of the N-Complex ($N_{1a}$) begins its downward slope at $\sim$50 ms and peaks at $\sim$100 ms, is frontal in distribution and similar to $N_{100}$ of clicks. The following peak ($N_{1b}$) occurs at $\sim$150 ms with a central/temporal scalp distribution, with distinct sources and time courses of their activity (Michalewski et al., 2005; Pratt et al., 2005). Whereas, $P_{50}$ to sound offset may be absent, the subsequent negativity ($N_{100}$) has a more complex configuration (consisting of $N_{1a}$ and $N_{1b}$) to sound offset compared to sound onset (consisting of a single-peaked $N_{100}$). An absence of $P_{50}$ to sound offset may thus be a result of the opposite polarity N-Complex to sound offset summating with $P_{50}$ to obscure it. This suggestion could be verified by comparing the sources of brain activity at the time of $P_{50}$ and $N_{100}$ to sound onset and offset.

The purpose of this study was to compare the auditory $P_{50}$ and its intracranial sources in response to stimulus offset and onset and to compare them to the P50 in response to two clicks with similar time separations as the onset and offset of sound.

## 2. Methods

The detailed description of procedures to study potentials to onsets and offsets of noise (offsets and onsets of gaps) and to compare them with their counterparts in response to brief transient sounds (clicks) is provided in an earlier report (Pratt et al., 2005).

### 2.1. Subjects

Thirteen, right handed, normal hearing subjects, 18–25 years old, participated in the study. Subjects were paid for their participation and all procedures were approved by the institutional review board for experiments involving human subjects (Helsinki Committee).

### 2.2. Stimuli

Two types of binaural stimuli were presented separately through earphones (Sony MDR-CD770): (1) binaural continuous white noise with randomly distributed gaps of different durations; and (2) binaural click pairs presented in silence such that the first and second click of each pair corresponded in timing to gap onsets and offsets, respectively, in the noise condition (Fig. 1A). Thus, each offset and onset in the noise had a correspondingly timed click.

#### 2.2.1. Noise onsets and offsets

White noise was presented continuously throughout the noise condition, with randomly distributed short gaps of up to 20 ms durations ("short gaps") and longer gaps with a variable average duration of 500 ms ("long gaps"). Noise durations between gaps were 1500 ms. This report relates to the long gaps only. The variable duration of the long gaps provided sufficient temporal separation between the potentials evoked by gap onset (noise offset) and offset, as well as temporal jitter of gap offset (noise onset), precluding interference of noise offset and onset responses in the averaged waveform. One hundred random repetitions of the long gaps were presented. The spectral content of the noise was flat within 10 dB across the frequency range 100–10,000 Hz, and the gaps had abrupt (square) onsets and offsets resulting in a similarly flat spectrum. Noise intensity was 65 dBnHL. In this report the potentials to gap onset will be referred to as the noise offset potentials and those to gap offset as the noise onset evoked potentials (Fig. 1A).

#### 2.2.2. Click pairs

Clicks were generated by transducing 100 μs square electric pulses in the earphones. Spectral content of the clicks and white noise was the same: flat with a 10 dB increase in energy between 2 and 4 kHz. Click intensity was
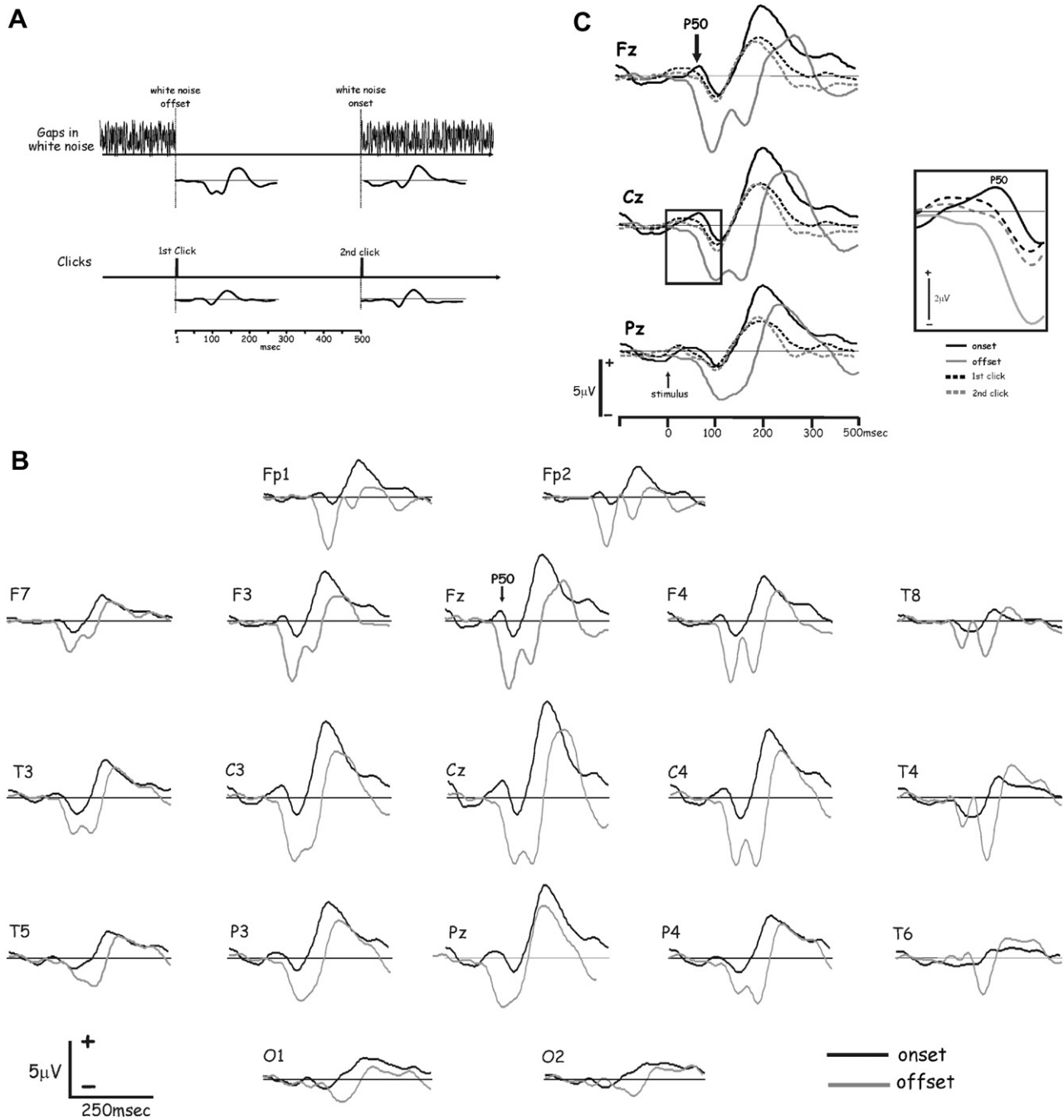
Fig. 1. (A) Binaural stimuli used in this study. Top: Binaural continuous white noise with randomly distributed gaps; Bottom: Click pairs presented with interstimulus intervals identical to the gap durations and intergap intervals. Potentials associated with noise offset, noise onset, first and second clicks in the pair were recorded. (B) Grand averaged waveforms (13 subjects) of potentials to noise offsets and noise onsets. In addition to the marked differences in $N_{100}$, note the clearly defined $P_{50}$ to noise onset, particularly at midline central and frontal electrodes, and its diminution to an earlier inflection from baseline in response to noise offset. (C) Potentials in response to noise onset, noise offset, first and second clicks of click pairs with the same 500 ms interclick intervals. Note the similar latencies and waveforms of potentials to noise onsets and to the first and second clicks in the pairs, comprising a $P_{50}$ followed by an $N_{100}$–$P_{160}$ sequence. In contrast, the potentials to noise offset, in addition to the bifid N-Complex, had no $P_{50}$ peak. The inset shows enlarged $P_{50}$ waveforms to the different stimuli. Note that waveforms evoked by clicks are intermediate between the waveforms to noise onset and offset. The definition of $P_{50}$ peak to clicks in this grand average is inferior to that of individual subjects, due to intersubject latency jitter.

65 dBnHL. Click pairs with interclick intervals of up to 20 ms (short intervals) and 500 ms were presented with interpair intervals of 1500 ms. Click timing was adjusted such that first and second click positions along the train of clicks corresponded to offsets and onsets of noise,

respectively, in the noise condition (Fig. 1A). One hundred repetitions of the pairs with 500 ms intervals were randomly repeated. Only potentials evoked by onsets and offsets of half second gaps and click intervals of 500 ms were analyzed in this study.

## 2.3. Procedure

Twenty-two 9 mm silver disc electrodes were placed at: $F_{P1}$, $F_7$, $F_3$, $F_z$, $F_4$, $F_8$, $F_{P2}$, $T_3$, $C_3$, $C_z$, $C_4$, $T_4$, $T_5$, $P_3$, $P_z$, $P_4$, $T_6$, $O_1$, $O_2$, according to the 10–20 system, 1 cm above the left and right mastoids ($A_1$ and $A_2$), as well as the middle of the chin, which served as reference, and below the left eye, which was referenced to $F_z$, to control for eye movements (EOG). In total, EEG was recorded from 21 electrodes referenced to the center of the chin and EOG was recorded from one diagonal differential recording below the left eye referenced to $F_z$. An electrode on the left forearm served as ground. Impedance at each electrode was maintained below 5 k$\Omega$.

Subjects were then seated in a comfortable reclining armchair in a sound proof chamber and listened to the two types of stimuli in turn: gaps in noise and click pairs in silence. Subjects were instructed to read a complicated text on which they were to be examined, while stimuli were presented (not attending to sounds).

## 2.4. Data acquisition

Potentials from the EEG (X100,000) and EOG (X20,000) channels were amplified, digitized with a 12-bit A/D converter at a rate of 256 samples/s, filtered (0.1–100 Hz, 6 dB/octave slopes) and stored for offline analysis. EEG processing began with segmentation of the continuous EEG to epochs beginning 100 ms before until 1000 ms after noise offset, noise onset or click onsets. Eye movement correction (Attias et al., 1993) and artifact rejection ($\pm 150$ μV) followed segmentation. Average waveforms were then computed relative to noise offset, relative to noise onset, as well as relative to the first click in the pair and relative to the second click in the pair. These averages were computed for each subject, as well as across subjects to obtain grand mean waveforms. After averaging, the data were low-pass filtered (FIR rectangular filter with a low-pass cutoff at 24 Hz) and baseline (average amplitude across the 100 ms before stimulus onset) corrected.

## 2.5. ERP data analysis

ERP analysis included $P_{50}$ peak latency and amplitude comparisons among noise onsets, offsets and clicks, as well as comparisons of the respective source current densities and their distributions. Except for small amplitude differences, most probably due to marginal refractoriness from the 500 ms interclick interval, potentials to the first and second clicks in pairs were almost identical. Therefore, $P_{50}$ to noise onset and offset was statistically compared only to their counterpart in response to the first click of the click pairs.

### 2.5.1. Peak analysis

The amplitude and latency of $P_{50}$ to noise onset, first and second click and noise offset were measured for each subject in each channel. Because $P_{50}$ varied in its definition among the stimulus conditions, the following guidelines were used to define it: (1) when a peak was observed in the latency interval of 35–90 ms, this peak was defined as $P_{50}$ (such a peak was typically defined in response to clicks and to noise onset) and (2) when a peak could not be identified in this latency range (typically in response to noise offset), $P_{50}$ was defined at the point the waveform departed from baseline before $N_{100}$. Group grand averaged waveforms for each stimulus condition determined this latency range for peak identification.

ERP peak amplitudes and latencies were subjected to a repeated measures analysis of variance (ANOVA) with Geisser–Greenhouse correction for violation of sphericity and Bonferroni corrections for multiple comparisons. Factors were: stimulus type with three levels (noise offset, noise onset and first click in pair) and electrode group with three levels (Frontal – $F_{P1}$, $F_{P2}$, $F_z$; Central – $C_3$, $C_z$, $C_4$; Temporo-parietal – $T_3$, $T_4$, $P_z$). To determine the significance of $P_{50}$ amplitudes relative to baseline, amplitude was assessed across all electrodes for four stimulus conditions: $P_{50}$ to noise onset, $P_{50}$ to noise offset, baseline preceding noise onset and baseline preceding noise onset. Probabilities below 0.05, after Geisser–Greenhouse corrections, were considered significant.

### 2.5.2. Functional imaging

Standardized Low-Resolution Electromagnetic Tomographic Analysis (sLORETA, Pascual-Marqui et al., 1994; Pascual-Marqui, 2002) was applied on the 21-channel ERP records to image the estimated source current density throughout the duration of $P_{50}$ in response to noise onsets, offsets and clicks and to compare the current density distributions among stimuli.

sLORETA is a functional brain imaging method that estimates the distribution of current density in the brain given by the minimum norm solution. Localization inference is based on standardized values of the current density estimates. The solution space is restricted to cortical gray matter and hippocampus. A total of 6430 voxels at 5 mm spatial resolution are registered to the stereotaxic atlas of the human brain (Talairach and Tournoux, 1988). In this study, Statistical non-Parametric Mapping (SnPM) was used to assess differences in current density distributions to onset and offset of noise during $P_{50}$. The SnPM method estimates the probability distribution by using a randomization procedure, corrects for multiple comparisons and has the highest possible statistical power (Nichols and Holmes, 2002). SnPM, in the context of electrophysiological functional imaging, was validated in previous studies by comparing its results with more conventional ANOVA results (Laufer and Pratt, 2003; Sinai and Pratt, 2003).

Specifically, in our study we used the pseudo-$t$ statistic which reduced noise in the data by averaging over adjacent voxels (Nichols and Holmes, 2002). In order to trace time segments of significant differences between responses, we compared them on a time-frame by time-frame, voxel-

by-voxel basis for the duration of $P_{50}$. A time segment was designated significant only if it contained at least five contiguous significant ($p < 0.01$) time frames. We employed this procedure to reduce the probability that time frames assigned with significance by chance alone due to alpha inflation would be included in the analysis. Average current density values were then obtained across the contiguous significant time frames to obtain a single sLORETA solution consisting of 6430 voxels representing the entire time segment that was found significant. The procedure outlined above was employed in order to trace significant time segments, utilizing the high temporal resolution of sLORETA, while extending (to the time domain) the method originally used by Nichols and Holmes (2002), of averaging significant *t*-values over space only.

## 3. Results

### 3.1. Waveforms to noise onset and offset

Clearly different evoked potentials were obtained in response to noise onsets and offsets, with the most obvious difference – a bifid N-Complex ($N_{1a}$ and $N_{1b}$) to noise offsets and a single-peaked $N_{100}$ to noise onsets (Fig. 1B). These differences have been detailed in previous reports (Michalewski et al., 2005; Pratt et al., 2005, 2007). In addition, $P_{50}$ was also clearly different to noise onset and offset: a clear positive component ($P_{50}$) was observed approximately 50 ms after noise onset (and clicks), with the largest amplitudes at the midline frontal and central electrodes. In contrast, $P_{50}$ was absent in response to noise offset and, at times, marked by a negative inflection from baseline (Fig. 1C).

### 3.2. Component comparisons across stimulus conditions

Potentials evoked by noise onset and noise offset were compared to each other as well as to potentials to the correspondingly timed first and second clicks of the click pairs. In general, the latencies of potentials to noise onsets and to the first and second clicks in the pairs were not significantly different, each comprising of a $P_{50}$, $N_{100}$–$P_{160}$ sequence. In contrast, the potentials to noise offset had no $P_{50}$ (Fig. 1C). Current density distributions associated with $P_{50}$ were significantly different among stimulus conditions (Fig. 2) and different than those of $N_{100}$ and the N-Complex.

### 3.2.1. Waveform comparisons

The latency of $P_{50}$ was not significantly affected by the stimulus type (noise onset, noise offset or clicks) that evoked it. When pairs of stimulus conditions were compared, $P_{50}$ latency to noise onset (56 ms) was significantly longer [$F(1, 12) = 4.81$, $p < 0.05$] than to noise offset (47 ms), but not significantly different than to clicks [53 ms; $p > 0.05$]. $P_{50}$ amplitude was significantly affected by stimulus type [$F(2, 22) = 9.01$, $p < 0.002$] with post hoc analysis indicating that in response to noise onset it was

larger (0.63 µV) than the inflection to noise offset (−0.25 µV), but not significantly different than to clicks (0.49 µV). Amplitude to noise offset was thus significantly different than to noise onset or to clicks.

To determine whether the amplitude to noise offset reflected a diminished peak (that was significantly larger than its baseline) or an absent peak (which was not significantly different than baseline), amplitudes during four types of events: $P_{50}$ to noise onset, the corresponding period to noise offset and their respective baselines, were assessed. Analysis of variance procedures revealed a significant effect of event type on amplitude [$F(3, 33) = 7.38$, $p < 0.001$]. Post hoc procedures indicated that only $P_{50}$ to noise onset was significantly larger than the baseline preceding it, larger than baseline preceding noise offset and larger than $P_{50}$ to noise offset. In contrast, the corresponding amplitude following noise offset was not significantly different than its baseline ($p > 0.05$).

### 3.2.2. Current density comparisons

Source current density estimates for the period of occurrence of the $P_{50}$ component to noise onset and offset revealed differences in current density distributions (Figs. 2 and 3A) and their time courses (Fig. 3B). Source current density distributions involved bilateral superior parietal and central regions (Brodmann areas 18, 19, 20, 23, 38, 7 and 31) in response to noise onset (Fig. 2 top) and left inferior temporal and occipital regions (Brodmann areas 18, 20, 28, 6 and 13) to noise offset (Fig. 2 middle). $P_{50}$ to clicks involved all these areas, but the most active areas (Brodmann areas 47, 31 and 20) were in left inferior frontal and temporal cortices (Fig. 2 bottom).

Statistical non-parametric *t*-value mapping of significant current density differences between $P_{50}$ to noise onset and offset confirmed differences in the distribution of brain activity between these conditions. During the peak of $P_{50}$, current density was significantly higher in response to noise onset than to offset in the vicinity of Brodmann area 40 (Fig. 3A) as well as the general location of Brodmann areas 39, 31 and 13. This significant difference extended over five time frames, beginning 12 ms before the peak of $P_{50}$ until 4 ms after it. Toward the very end of this period, activity in these areas was higher to noise offset than to onset, most probably because of activity associated with $N_{1a}$ of the subsequent N-Complex.

Following the time course of activity in the differentially activated areas (Fig. 3B) revealed activity in BA 39 and 40 that peaked 16 ms before the peak of the surface-recorded $P_{50}$ in response to noise onset. Activity in BA 31 peaked 4 ms after $P_{50}$ peak, while in BA 13 activity peaked 16 ms before and 12 ms after the peak, with lower activity during the peak of $P_{50}$. In contrast, in response to noise offset, activity in these areas was unchanged and low throughout the duration, and only began increasing toward the end of this period, surpassing activity to sound onset at the very
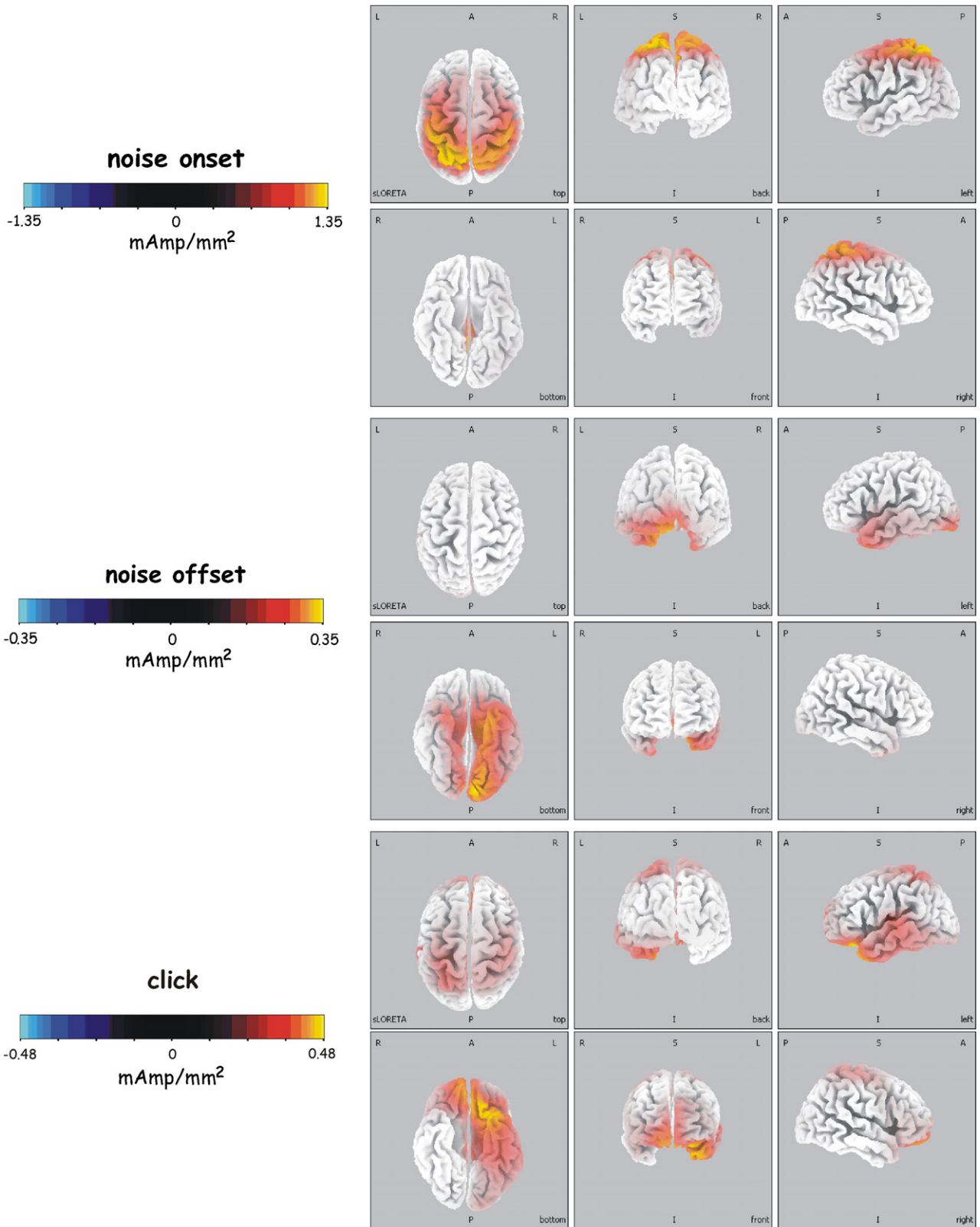
Fig. 2. Average source current density distributions in the time period of $P_{50}$ to noise onset, offset and to clicks. In response to noise onset (*top*) activity involved bilateral superior central regions (Brodmann areas 18, 19, 20, 23, 38, 7 and 31) while to noise offset (*middle*) left inferior temporal and occipital regions (Brodmann areas 18, 20, 28, 6 and 13) were activated. The $P_{50}$ to clicks (*bottom*) involved all the above areas, but the most active areas (Brodman areas 47, 31 and 20) were in the left inferior frontal and temporal cortices. Note the different calibrations of the current density color bars, underscoring the significantly lower activity to noise offset. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
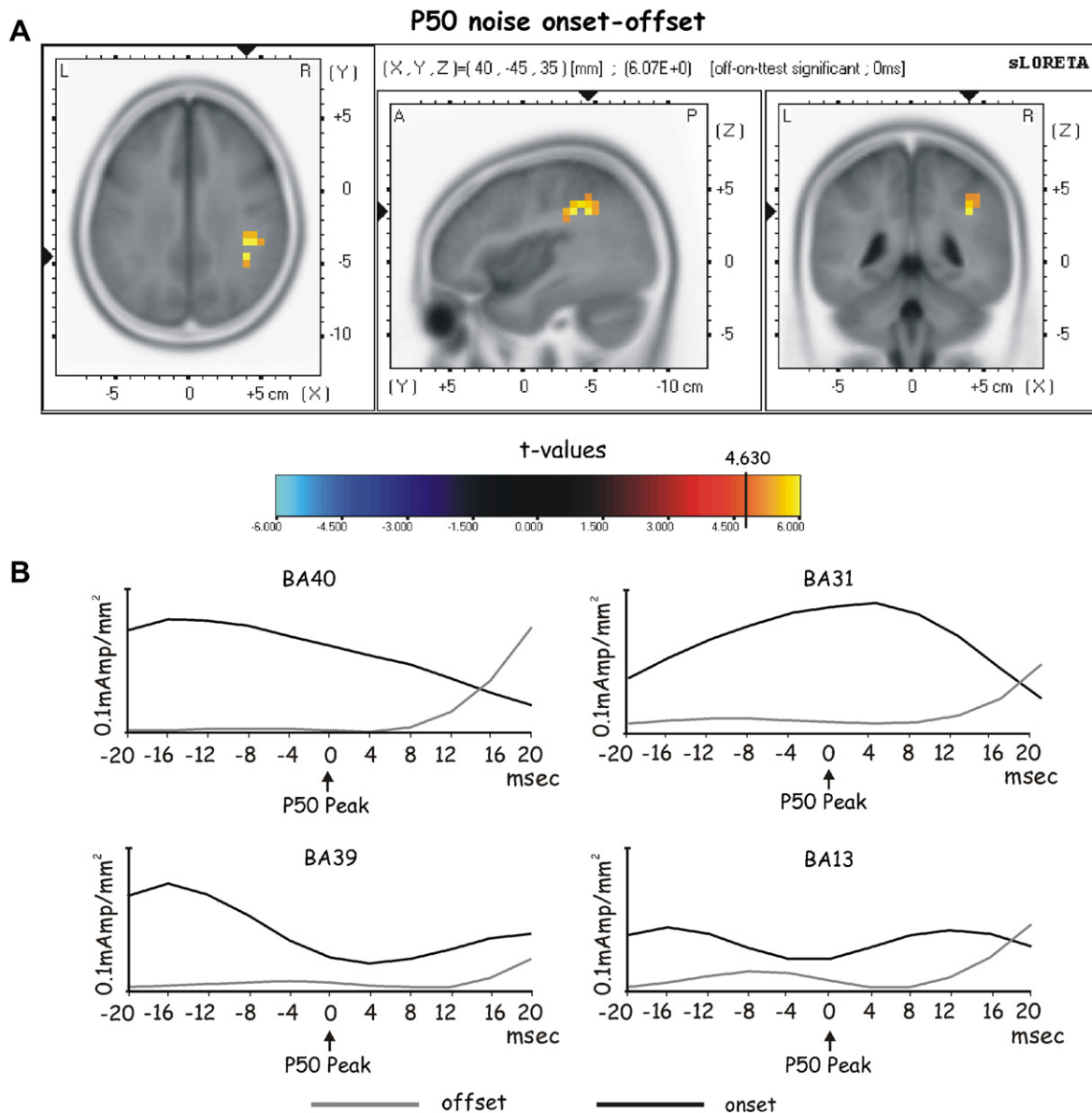
Fig. 3. (A) Statistical non-parametric *t*-value mapping of current density differences during $P_{50}$ between noise onset and offset. At the peak of $P_{50}$ current density was significantly higher in response to noise onset than to offset in the vicinity of Brodmann area 40 as well as the general location of Brodmann areas 39, 31 and 13. The *t*-value for statistical significance is indicated on the color bar. (B) The time courses of activity in the areas most differentially activated between noise onset and offset. In response to noise onset, activity in BA 39 and 40 peaked slightly before the scalp recorded peak of $P_{50}$, in BA 31 – slightly after the peak, while in BA 13 it peaked slightly before and slightly after $P_{50}$. In the plots to noise offset, 'peak' denotes the point of inflection from baseline. Note that in response to offset, activity in these areas was unchanged and low throughout the duration of $P_{50}$, increasing only toward the very end of this period.

end of $P_{50}$, most probably in association with the onset of $N_{1a}$.

### 3.3. Summary

Activity during $P_{50}$ to noise offset was no different than baseline before the stimulus. The $P_{50}$ component to noise onset was associated with distinct spatio-temporal patterns of activity. The response to the transient clicks combined features of both noise onset and offset but was more similar to noise onset, as indicated by their similar waveforms and scalp distributions.

### 4. Discussion

In this study the $P_{50}$ potentials to onset and offset of noise were compared to each other, as well as to the better studied potentials to short transient stimuli (clicks), while subjects were not attending to the stimuli. A clear $P_{50}$ was recorded in response to noise onsets and to clicks, but it was absent to noise offset. $P_{50}$ latencies and amplitudes to onset were not different than to clicks, but latencies were longer and amplitudes larger than to noise offset.

Refractoriness is highly unlikely to account for the amplitude differences between $P_{50}$ to noise onset and offset:

the practically identical $P_{50}$ amplitudes to the first and second clicks of the pairs, which corresponded in timing to noise offset and onset, indicate that there were no refractory effects on the amplitude or latency of P50 in the intervals used in this study. Moreover, because noise offset (at the beginning of gaps) always preceded noise onset (at the end of the gap), if there were refractoriness effects, they would have reduced $P_{50}$ to noise onset and not to offset.

The apparent discrepancy between the results of this study, showing very little adaptation effects on $P_{50}$, and earlier studies showing $P_{50}$ adaptation in pairs of clicks (e.g., Schall et al., 1997; Skinner et al., 1999; Rasco et al., 2000; Uc et al., 2003; Kisley et al., 2003a) may result from different degrees of adaptation at different stimulus intervals. Earlier studies on $P_{50}$ adaptation in pairs of stimuli used intervals that extended to shorter intervals than the 500 ms used in this study. One of them reported that in healthy subjects an interval of 100 ms, but not 500 ms, reduced $P_{50}$ amplitude to the second stimulus in the pair (Schall et al., 1997). Another study reported an age-related effect at the 250 ms interval, but not at the 500 ms interval (Rasco et al., 2000). Thus, our results of only a marginal effect of adaptation with a 500 ms interclick interval are actually compatible with earlier reports.

Sources of the scalp activity during $P_{50}$ to noise onset and during the corresponding time in response to noise offset were significantly different: noise offsets were associated with weak left inferior temporal and occipital activation whereas noise onsets and clicks, although different from each other, both activated mostly bilateral superior parietal areas. Source current density was significantly higher to noise onset in the vicinity of the temporo-parietal junction. These findings suggest that early brain responses to onset and to offset of sound are distinct.

### 4.1. Earlier studies on $P_{50}$

Although $P_{50}$ is the least studied of the auditory ERPs, some early reports detailed $P_{50}$ latency and amplitude values stating that they were not affected by factors such as age (Barnet et al., 1975) or attention (Picton and Hillyard, 1974). More recently, reports described extensive changes in $P_{50}$ with maturation, beginning with its domination of the $P_{50}$–$N_{100}$–$P_{160}$ complex in young children (Sharma et al., 1997; Ceponiene et al., 2002) to its small amplitude in adults (Sharma et al., 1997). The normal maturation of $P_{50}$ (Sharma et al., 1997) has been used to determine a period of about 3.5 years during which the human central auditory system remains maximally plastic and therefore optimal for cochlear implantation (Sharma et al., 2002). The latency of $P_{50}$ was used as the indicator of auditory system maturation and the effects of deprivation due to deafness on auditory function (Eggermont et al., 1997). $P_{50}$ was found to increase in amplitude in normal aging and increase more with cognitive decline (Golob et al., 2007). Maturation of $P_{50}$ evoked by pairs of clicks has also been studied to define sensory adaptation or gating in schizophrenia (Erwin et al.,

1994; Schall et al., 1997; Kisley et al., 2003a), autism (Buchwald et al., 1992), Parkinson's disease (Teo et al., 1998) and major depression (Franks et al., 1983). Adults with sensory hypersensitivity without additional health or mental problems have been reported to have less robust $P_{50}$ suppression (Kisley et al., 2004) alongside "over-inclusion" of irrelevant sounds into their focus of attention.

The generators of $P_{50}$ have been attributed to the primary auditory cortex at Heschl's gyrus (Wood and Wolpaw, 1982; Reite et al., 1988; Pool et al., 1989; Liegeois-Chauvel et al., 1994; Huotilainen et al., 1998; Ponton et al., 2002), with the earlier work describing $P_{50}$ as part of the middle-latency potentials $P_b$. However, more recent work suggests that these are distinct components, with $P_{50}$ involving generators that also include the hippocampus, planum temporale and the lateral temporal cortex (Howard et al., 2000; Liegeois-Chauvel et al., 1999) and neocortical areas (Grunwald et al., 2003; Kisley et al., 2003b).

The variety of conditions affecting $P_{50}$ could be indicative of the brain processes reflected by this component. A number of studies reported $P_{50}$ sensitivity to reticular formation non-specific cholinergic activation (Buchwald et al., 1991) and consequently to levels of arousal (Erwin and Buchwald, 1986; de Lugt et al., 1996), sensory activation and a variety of disorders. Sensory gating (Skinner et al., 1999) and habituation (Gillette et al., 1997; Pitman et al., 1999) of $P_{50}$ was found impaired in subjects with Post-Traumatic Stress Disorder (PTSD) compared to controls, indicating dysregulation of sensory processing in PTSD. Such decreased gating was also observed in normal adolescents compared to normal older subjects (Rasco et al., 2000). The amplitude of $P_{50}$ was found to be attenuated in autism (Buchwald et al., 1988, 1992), Alzheimer's disease (Buchwald et al., 1989; Green et al., 1992; Fein et al., 1994; O'Mahony et al., 1994), Huntington's disease (Uc et al., 2003), Attention Deficit Hyperactivity Disorder (ADHD) (Kemner et al., 1996) and narcolepsy (Boop et al., 1994), suggesting decreased reticular arousal by sound. $P_{50}$ was reported to be diminished and prolonged or absent in Parkinson's disease, improving following posterior ansapallidotomy, except in one patient who showed mild worsening attributed to post-operative sleepiness (Mohamed et al., 1996). Increased $P_{50}$ amplitudes in mild cognitive impairment identified individuals who will subsequently convert to dementia (Irimajiri et al., 2005; Golob et al., 2007). Similar relationships have been identified in HIV-1 infection, correlating with indices of disease progression (Schroeder et al., 1994). The amplitude of $P_{50}$ in an auditory task was reported to be significantly increased in Irritable Bowel Syndrome (IBS) patients compared to controls, compatible with a generalized preattentive increase in central nervous system reactivity in this disorder (Berman et al., 2002).

A common denominator of all these earlier reports is cortical arousal which is: (1) sensitive to sleep; (2) involves ascending activation by reticular formation; and (3) can be predictive of subsequent processing of sound, independent

of attention. These findings therefore suggest $P_{50}$ to be associated with multiple generators involved in preattentive arousal by sound and gating its subsequent processing.

### 4.2. Comparison of early brain responses to noise offset, onset and to clicks

The ERPs to sound onset and offset, particularly in the context of gaps in noise, are different. The potentials to noise onset (gap offset) are similar to the potentials to transients, consisting of a clear $P_{50}$–$N_{100}$–$P_{160}$ sequence with a single-peaked $N_{100}$ (Michalewski et al., 2005; Pratt et al., 2005). In contrast, the potentials to noise offset (gap onset) include a double-peaked N-Complex ($N_{1a}$ and $N_{1b}$) followed by $P_{160}$ (Michalewski et al., 2005; Pratt et al., 2005), which, as shown in this study, are not preceded by a $P_{50}$.

Neuromagnetic studies have shown a $P_{50}$ field to stimulus onset which was indistinguishable in its sources from $N_{100}$, whereas to stimulus offset $P_{50}$ was absent (Hari et al., 1987; Pantev et al., 1996). These findings were interpreted to suggest that while $N_{100}$ seems to reflect cortical activity related to any abrupt change in the auditory environment (Hari et al., 1987), $P_{50}$ reflects a distinct process which is unique to stimulus onset. This would imply a unique source activity during stimulus onset $P_{50}$ that is absent in response to stimulus offset and is distinct from that of $N_{100}$.

The absence of $P_{50}$ in response to sound offset compared to its presence to sound onset may have an alternative explanation. In contrast to $P_{50}$, s absence in response to sound offset, the subsequent negativity ($N_{100}$) is more complex and double-peaked to sound offset than to onset. The absence of $P_{50}$ may therefore be explained by the $N_{100}$ activity to sound offset that extends earlier than to sound onset. This explanation would imply that $P_{50}$ to onset and offsets share the same generators, but the offset response is overwhelmed by temporally overlapping activity from N-Complex generators. These alternative explanations can be validated by comparing the sources of $P_{50}$ to noise onset and offset to each other and to the sources of $N_{100}$.

The results of this study showed distinct sources for $P_{50}$ to noise onset and offset, which were different than those of $N_{100}$ and the N-Complex (Pratt et al., 2005). In response to noise onset, the time course of activity in BA 39 and 40 peaked slightly before $P_{50}$, activity peaked slightly after in BA 31, while in BA 13 it peaked slightly before and slightly after $P_{50}$ and decreased during the peak of $P_{50}$. In contrast, in response to noise offset, activity in these areas was unchanged and low throughout this time. Thus, the distinct sources and time courses of activity suggest that $P_{50}$ reflects brain processes that are present to noise onset and absent to offset and are also distinct from those underlying $N_{100}$.

The sources of $P_{50}$ to clicks, although more similar to those of noise onset, were a composite involving the generators activated by both onset and offset. This is congruent

with the onset and offset of sound associated with short transient clicks. Thus, $P_{50}$ to clicks is a composite of onset and offset responses, with overlapping activity evoked by both. This is reflected in the waveforms of $P_{50}$ to clicks, which are intermediate between the waveforms to stimulus onset and offset (Fig. 1C, inset). Accordingly, the latency of $P_{50}$ to clicks was slightly shorter than to sound onset, being biased by the shorter latency of the offset evoked contributions.

### 4.3. Processes associated with $P_{50}$ to noise onset and offset

The differences in morphology and sources of $P_{50}$ to noise onset and offset appear to reflect distinct brain processes to onset and offset that are different from those associated with the N-Complex and $N_{100}$. The auditory $P_{50}$ has been most often studied in response to transient stimuli such as tone pips or clicks. It has been typically associated with auditory cortex activation (Wood and Wolpaw, 1982; Huotilainen et al., 1998; Reite et al., 1988; Pool et al., 1989; Liegeois-Chauvel et al., 1994; Ponton et al., 2002), but in addition more complex generators have been indicated, including the hippocampus, planum temporale and the lateral temporal cortex (Liegeois-Chauvel et al., 1994; Howard et al., 2000; Liegeois-Chauvel et al., 1999) and neocortical areas (Grunwald et al., 2003; Kisley et al., 2003b). Moreover, $P_{50}$ habituates at intervals as long as 500 ms, in contrast to the auditory middle-latency potentials that are optimally recorded with much shorter intervals of 100 ms. This difference in habituation suggests that $P_{50}$ is not part of primary auditory cortical processing, and its sources would therefore not be expected to be confined to the temporal lobe.

$P_{50}$ was found to be sensitive to reticular formation nonspecific cholinergic activation (Buchwald et al., 1991) and hence to levels of arousal (Erwin and Buchwald, 1986; de Lugt et al., 1996) and sensory activation (Kisley et al., 2004). More specifically, $P_{50}$ was reported to be present during waking and REM sleep but not slow wave sleep (Erwin and Buchwald, 1986), i.e., present during states driven by ascending reticular projections with no attentional involvement. The blocking of $P_{50}$ by a muscarinic cholinergic antagonist (Buchwald et al., 1991) suggests it is generated by ascending reticular cholinergic projections.

$P_{50}$ was attenuated in conditions involving decreased arousal by and processing of sound, such as autism (Buchwald et al., 1988, 1992), Alzheimer's disease (Buchwald et al., 1989; Green et al., 1992; Fein et al., 1994; O'Mahony et al., 1994), Huntington's disease (Uc et al., 2003), ADHD (Kemner et al., 1996) and narcolepsy (Boop et al., 1994). Increased $P_{50}$ amplitudes have been reported in mild cognitive impairment involving memory and language functions (Irimajiri et al., 2005; Golob et al., 2007), in HIV-1 infection (Schroeder et al., 1994), but also in normal elderly subjects (Smith et al., 1980). The increased amplitude of $P_{50}$ in mild cognitive impairment (MCI) patients with memory and language difficulties (Golob et al., 2007) is of particular

interest. $P_{50}$ has been reported to be sensitive to reticular formation non-specific cholinergic activation (Buchwald et al., 1991). Dementia is known to involve decreased cholinergic function, yet the MCI patients paradoxically presented with enhanced, rather than diminished, $P_{50}$ amplitudes as would be expected with impaired cholinergic activation. Notably, this increased amplitude was only observed in a subset of these patients with language difficulties. Thus, the alterations in $P_{50}$ amplitude appear to be related to aspects of auditory processing in addition to the non-specific ascending activation. Earlier reports on factors affecting $P_{50}$ suggested that the differences between $P_{50}$ to stimulus onset and offset may be related to specific aspects of auditory processing. This specificity is supported by reports of diminished $P_{50}$ habituation in disorders that involve auditory hallucinations such as schizophrenia (Erwin et al., 1994; Schall et al., 1997; Kisley et al., 2003a) or altered sensory perception such as autism (Buchwald et al., 1992) and less robust suppression of $P_{50}$ in sensory hypersensitivity (Kisley et al., 2004). The common aspect of the abnormalities that affect $P_{50}$, in addition to general arousal, is altered control of brain activation by auditory stimuli.

The brain areas that were differentially activated by noise onset and offset during $P_{50}$ include mostly the vicinity of the supramarginal and angular gyri (BA 39 and 40), at the temporo-parietal junction, as well as the general location of the dorsal posterior cingulate (BA 31). These areas have been associated with aspects of spatial orienting, including motion sensitivity (Luks and Simpson, 2004), action planning (Ruby et al., 2002) and multisensory integration (Matsuhashi et al., 2004; Lenggenhager et al., 2006). These areas have also been implicated in stimulus-driven reorienting of attention in processing of competing stimuli (Corbetta et al., 2002; Thiel et al., 2004; Meister et al., 2006), temporal and spatial orienting and exploration (Coull et al., 2001; Himmelbach et al., 2006), directing attention to salient events (Marois et al., 2000; Astafiev et al., 2006; Gomot et al., 2006) across all modalities, even when they are behaviorally neutral (Downar et al., 2002). Our findings show these areas to be active in response to noise onset but not to noise offset, even when subjects were not attending to the sounds. All this suggests that $P_{50}$ to noise onset reflects preattentive arousal by the new sound and its integration into the multisensory scene in which the subject is immersed. Noise offset does not induce these processes and hence the absence of $P_{50}$. The brain response to termination of an ongoing stimulus occurs about 100 ms later and manifests in the N-Complex as $N_{1b}$ (Pratt et al., 2005). In response to clicks these processes begin but are abruptly terminated because of the short duration of this transient stimulus resulting in a clear $P_{50}$ and a single-peaked $N_{100}$.

### 4.4. Summary

The results of this study show that $P_{50}$ to stimulus onset involves cortical processes with spatio-temporal distributions that are absent to sound offset. The aspects of auditory processing associated with $P_{50}$ that are absent to noise offset appear to be preattentive arousal by a new sound in the scene.

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