

Published in final edited form as:

*Neuroreport*. 2011 February 16; 22(3): 136–140. doi:10.1097/WNR.0b013e3283435c37.

## Time course of electromagnetic activity associated with detection of rare events

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### Abstract

The neural origins of the cortical response to rare, sensory events remain poorly understood. Using simultaneous event-related potentials and magnetic source imaging, we investigated the anatomical profile of regional activity at various processing stages during performance of auditory and visual variants of an oddball paradigm. The earliest rarity-detection response was found in sensory-specific cortices, rapidly spreading to tertiary association areas, mesial temporal and frontal cortices by 150–200 ms. P3m-related activity was not found in sensory-specific cortices. Based on the anatomic distribution of P3m-related activity, this component is likely to reflect more generalized cognitive abilities hosted by association cortical regions.

### Keywords

P300; oddball; association cortex; event-related potentials; magnetoencephalography

### Introduction

Despite its well known temporal characteristics, the neural event underlying the P300 (P3) component of event-related potentials (ERPs), typically elicited by the occurrence of a deviant (rare) stimulus in the context of an oddball task at ~ 300 ms, are not well-understood [1]. Indirect evidence from lesion studies reporting attenuated P3 effects have implicated frontal [2], temporo-parietal [3] and more variably, medial temporal regions [4,5] in the generation of this response. Furthermore, functional magnetic resonance imaging (fMRI) investigations have noted a distributed network of cortical regions thought to underlie target detection, including stimulus modality-specific regions, as well as prefrontal, anterior cingulate, sensorimotor and inferior parietal cortices [6,7,8].

Magnetoencephalography (MEG), which possesses millisecond temporal resolution and is not susceptible to the conductivity effects associated with ERPs, has provided further insight into neural basis of the P3 component and its magnetic counterpart (P3m) [9]. Several

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studies have shown that the P3m can be accounted for by activity sources in superior temporal, inferior parietal and medial temporal structures [10,11]. While electrical and magnetic responses to rare events are more pronounced during the P3 latency range, similar effects have been found during earlier processing stages (between approximately 150 and 250 ms) [3,12]. Little is known, however, on the potential inter-dependencies between the neural generators of the early and late responses to rare events.

The current study had two main goals. First, to determine whether the P3 component reflects primarily late neurophysiological activity in sensory-specific cortices or, primarily activity in association regions. Second, to examine whether frequent/rare effects on magnetic activity during the P3 latency window are similar, in anatomic distribution and modality specificity, to rarity responses that take place during earlier processing stages. Simultaneous ERP and whole-head MEG recordings were obtained during performance of two variants of an standard oddball task, and analyzed by application of the minimum norm estimate (MNE) technique.

## Materials and Methods

### Participants

Eleven right-handed, neurologically intact, volunteers (8 male; age range 22-43 years/mean  $31.4 \pm 7.3$ ) with normal to corrected-to-normal vision, and normal hearing, participated in the study. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board. All participants provided informed consent and were financially compensated for their time.

### Procedure

A standard oddball paradigm was used involving 500 stimuli. The probability of occurrence of rare auditory or visual stimuli was 20% (120 trials). For the auditory task, the stimuli were either a 1 kHz (frequent) or 2 kHz (rare) tone (100 ms duration/80 dB SPL), delivered binaurally. During the visual task, the stimuli were either a black-white (frequent) or yellow-black (rare) checkerboard (100 ms duration) on a back-projection screen positioned approximately 60 cm from the subject. The order of stimulus presentation in both tasks was randomized, with a variable inter-stimulus interval of 1 to 2 s, and the order of task presentation was counterbalanced across participants. Each participant was instructed to respond to the occurrence of a rare stimulus by raising the index finger of their right hand.

### MEG/EEG data acquisition and analysis

MEG recordings were conducted using a whole-head neuromagnetometer containing an array of 248 sensors (WH 3600, 4D Neuroimaging, San Diego, California, USA) housed in a sound-damped and magnetically shielded room. The magnetic flux measurements were digitized at 290 Hz, bandpass filtered from 0.1-20 Hz and subjected to a noise reduction algorithm that is part of the 4D-Neuroimaging software. Simultaneous ERP recordings were obtained at Cz (referenced to left ear lobe), using Ag/AgCl electrodes connected to a Neurofax EEG-1100 (Nihon Kohden). Impedances for all subjects were  $\leq 6\text{k}\Omega$ . The single-trial evoked fields (EFs) in response to 90-100 stimulus presentations for each condition, were epoched (-150 ms pre- to 750 ms post-stimulus onset) and averaged after excluding those containing eye movement or other myogenic or mechanical artifacts. Averaged ERP or EFs for the frequent condition were computed from the trials immediately preceding rare stimuli.

The intracranial origin of EFs was analyzed using a minimum norm estimate (MNE) model to obtain estimates of the time-varying strength of intracranial currents (MNE Software, v.

2.5; <http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php>), and described in detail elsewhere [13]. Estimated current sources were anatomically constrained by a high-resolution T1-weighted MRI-derived surface model of each participant's brain. A fully-automated cortical surface reconstruction procedure was used to generate a single-compartment boundary element model with triangular tessellations. Each vertex of the brain surface was treated as a potential current dipole perpendicular to the cortical surface during the forward calculations. The inverse solution was subsequently reduced to obtaining an estimate of the scalar distribution of dipole strength across current sources within orientation-specific cortical patches of vertices.

### Statistical analyses

The latency window used to measure the peak amplitude and latency of the magnetic P3 response was determined from the distribution of individual peak ERP amplitude difference values between frequent and rare conditions. Minimum norm estimates of current amplitude waveforms were first obtained for each predetermined ROI, using automated gyral-based labeling system of Desikan and colleagues [14] implemented in the Freesurfer software [15] (see below). Next, peak degree of magnetic activity and peak latency (after stimulus onset) was determined for the frequent minus rare difference waveforms, separately for each modality and ROI. The data was then submitted to ANOVAs with Modality (auditory/visual) and Hemisphere (left/right) as the within-subjects factors, performed separately for each ROI. The following ROIs were examined in each hemisphere based on previous MEG and intracranial-recording studies: transverse temporal gyrus (TTG; primary auditory cortex), superior temporal gyrus (STG; excluding Heschl's gyri and the dorsal bank of the superior temporal sulcus), middle temporal gyrus (MTG; excluding the ventral bank of the superior temporal sulcus), cortex along the banks of the superior temporal sulcus (STS), inferior temporal gyrus (ITG), fusiform gyrus (FUS), supramarginal gyrus (SMG), angular gyrus (ANG), mesial temporal cortex (MTL; parahippocampal gyrus and entorhinal cortex), lateral occipitotemporal cortex (LOC); pericalcarine cortex (CALC); inferior frontal gyrus (IFG; pars opercularis and pars triangularis), middle frontal gyrus (MFG), the superior frontal gyrus (SFG); and the anterior (aCNG) and the posterior portions of the cingulate gyrus (pCNG). In addition, Time Bin\*Modality\*Hemisphere ANOVAs were performed for each ROI on the mean estimated difference current during the earliest 4 latency bins (100-300 ms) in order to determine the earliest latency at which reliable rarity response are first noted.

### Results

Mean accuracy rate for detection of the rare stimulus revealed near-perfect performance for all participants (Mean =  $99.6 \pm 0.9\%$  and  $97.6 \pm 3.4\%$  for visual and auditory stimuli, respectively).

During the *auditory* task, the earliest *peak* latency in the difference waveforms was observed in TTG ( $229 \pm 65$  ms) followed by peaks in STG ( $238 \pm 75$  ms), SMG ( $293 \pm 118$  ms), IFG ( $261 \pm 107$  ms) and MFG ( $279 \pm 142$  ms) in the left hemisphere, and MTG in the right hemisphere ( $288 \pm 67$  ms). During the *visual* task the shortest peak latency was noted in the left FUS ( $234 \pm 83$  ms), closely followed by ANG ( $263 \pm 73$  ms), MFG ( $268 \pm 120$  ms), and ITG ( $286 \pm 124$  ms), all in the left hemisphere.

In order to determine the earliest latency bins at which reliable rare-frequent amplitude differences emerged in each ROI, single-sample t-tests were performed on the difference current waveforms during the early latency window (100-300 ms comprising 4 50-ms latency bins; evaluated at  $\alpha = .001$  to correct for multiple comparisons). The earliest differential response to rare *auditory* events occurred in TTG and in nearby STG and SMG

between 100-150 ms (see Table 1). Rarity responses in MTG, MTL, and IFG were first noted in the subsequent latency bin (150-200 ms). Next, reliable differences between rare and frequent auditory events were found in frontal regions (MFG, SFG, aCNG, and pCNG, starting at 200 ms). The earliest rarity-detection response latencies were noticeably longer in the *visual* modality, occurring between 200 and 250 ms in FUS and MFG, followed by the response in SFG and pCNG (between 250 and 300 ms). Rarity responses in the remaining ROIs were first noted during the P3 latency window.

### Peak amplitude measures

According to the distribution of individual-subject peaks in the electrical response to rare stimuli (Fig. 1), the latency range of the magnetic P3 response was set between 300 and 450 ms ( $\pm 1$  SD around the group-mean across modalities). Significant ROI\*Modality interactions were found for both the early (100-300 ms),  $F(15,150) = 4.57$ ,  $p < .0001$ , and late latency windows (300-450 ms),  $F(15,150) = 4.24$ ,  $p < .001$ . For the early responses, follow up one-way ANOVAs (evaluated at  $\alpha = .05/16 = .003$ ) revealed significantly greater difference amplitudes for the auditory as compared to the visual task in TTG,  $F(1,10) = 12.50$ ,  $p < .003$ ; MTG,  $F(1,10) = 13.55$ ,  $p < .002$ ; STG,  $F(1,10) = 12.65$ ,  $p < .003$ ; and SMG,  $F(1,10) = 14.23$ ,  $p < .002$ . P3m difference amplitudes were larger for the auditory as compared to the visual task in STS,  $F(1,10) = 16.67$ ,  $p < .002$ ; STG,  $F(1,10) = 16.93$ ,  $p < .002$ ; SMG,  $F(1,10) = 21.48$ ,  $p < .001$ ; and pCNG,  $F(1,10) = 23.16$ ,  $p < .001$ .

Individual subject data generally corroborated group-level results. In this approach we first determined the minimum peak P3m current value that reliably exceeded the peristimulus amplitude in each ROI (defined as the higher 95% confidence interval limit for the mean amplitude between 0-50 ms in the same ROI). The difference amplitude of P3m significantly exceeded the peristimulus current for both tasks in the following ROIs: SFG, aCNG and pCNG bilaterally, right MTL and MFG. Using this criterion, P3m-related activity to *auditory* rare events was also found in TTG, MTG, and IFG, bilaterally, in the left STS and the right SMG. Visual rare stimuli evoked significantly greater-than-peristimulus amplitudes in ANG bilaterally, in the left SMG and in the right STS, MTG, ITG, and FUS (see Figure, Supplemental Digital Content 1 and 2, which shows the mean spatiotemporal activation profiles during the P3 latency range, in regions common to both auditory and visual modalities).

### Discussion

Application of a Minimum Norm Estimate model to magnetic activity oddball tasks we found the earliest rarity-detection responses in primary and surrounding modality-specific association cortices in response to auditory stimuli. Corresponding regions displaying early activity in response to visual rare events included sensory-specific association areas (ventral occipito-temporal cortex). Next such activity was noted in tertiary association cortices in the temporal (MTG, STS) and parietal lobes (SMG for auditory and ANG for visual stimuli) and also in mesial temporal cortices (auditory stimuli). Rarity-detection responses were first noted in certain frontal regions (IFG) as early as 150-200 ms after stimulus onset, although the majority of prefrontal (MFG, SFG) and mesial frontal regions (cingulate gyrus) first displayed such responses somewhat later (between 200 and 300 ms). Magnetic activity that takes place during the range of the electric P3 was accounted for by neurophysiological activity in corresponding sensory-specific association cortices (STG for auditory and FUS for visual stimuli) and by concurrent activity in tertiary association cortices (inferior parietal and mesial temporal) as well as in lateral prefrontal regions and the cingulate gyrus.

Consistent with findings from earlier MEG studies [9,10,11] and comparable studies employing fMRI [6,7,8], increased activity in association cortices at the peak of the P3

response to rare stimuli reported here suggest that this component reflects the engagement of higher order cognitive mechanisms, as opposed to isolated changes in primary sensory processing. It has been proposed that enhanced activity in temporal lobe structures in response to a rare stimulus may underlie processes such as categorization and target detection [8], with elevated levels of activity in parietal and posterior cingulate cortices reflecting bottom-up, and subsequent working memory, processes [16]. In contrast, the effects observed in frontal and anterior cingulate brain regions may be indicative of top-down attentional processes involved in the discrimination of novel stimuli [8,17]. Furthermore, despite the active response mode of the present study, the observation of P3 effects in studies under passive conditions further attest to the automaticity of these cognitive processes underlying rarity detection [18].

Therefore, similar to the P3, this distributed early activity does not appear to be secondary to activity in the primary auditory cortex, resulting from spatially intercorrelated regional activity estimates (i.e., an artifact reflecting the summation of volume currents in modality-specific brain regions). Furthermore, this early activity, combined with concurrent activation in nearby SMG and MTG, is likely to underlie rarity-detection processes that precede the late onset of the P3. This inference regarding the anatomical distribution of early activity in the auditory domain concurs with findings from an earlier study [3].

The role of frontal and cingulate regions during the early phases of stimulus discrimination have been alluded to by Baudena et al. [12] who, employing depth-electrodes, reported peak activation in dorsolateral prefrontal and cingulate regions at approximately 210 ms in response to distractor and omitted stimuli, in both the auditory and visual modalities. Importantly, this network appears to be modality-independent as suggested by several lines of evidence, including the present study, and the fact that a similar pattern of responses has been found by MEG in the context of a somatosensory oddball task [19].

## Conclusion

Attention orienting and contextual updating processes may occur earlier than expected as supported by distributed cortical activity preceding the P3 latency. Concurring with contemporary theories, the spatiotemporal profile of rarity-detection cortical responses implicates a frontal and temporo-parietal network, hypothesized to underlie distinct components of attention-orienting and working memory.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

This study was supported by grant P01-HD35946 awarded to JMF from the National Institute of Child Health and Human Development (NICHD).

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**Fig. 1.**

Traces from a representative participant exhibiting the time-locked P3 ERP component (red trace) and its magnetic counterpart (EF) in response to a deviant stimulus during the auditory and visual variants of the oddball task (dashed vertical line denotes time of stimulus onset,  $t=0$ ).

**Table 1**

Time-dependent differential responses to rare events by modality.

Latency Window			
	ANOVA results <sup>†</sup>	Auditory <sup>#</sup>	Visual <sup>#</sup>
STS	M*T, F=4.24, p<.0001	250-300 ms	--
MTG	M*T, F=3.14, p<.001	150-400 ms	350-500 ms
STG	M*H*T, F=2.90, p<.001	100-350 ms (LH) 250-450 ms (RH)	350-450 ms
TTG	M*T, F=2.99, p<.001	100-200 ms	--
SMG	M*T, F=2.95, p<.001	100-500 ms	450-500 ms (LH)
ANG	T, F=2.98, p<.001	350-450 ms <sup>‡</sup>	400-500 ms <sup>‡</sup> (LH)
ITG	T, F=7.32, p<.0001	250-400 ms <sup>‡</sup>	350-450 ms <sup>‡</sup>
FUS	T, F=4.40, p<.0001	300-350 ms <sup>‡</sup> (RH)	200-500 ms <sup>‡</sup>
MTL	T, F=3.56, p<.0001	350-450 ms <sup>‡</sup> (RH)	350-400 ms <sup>‡</sup>
MFG	T, F=4.98, p<.0001	200-250 ms 650-700 ms <sup>‡</sup>	200-300 ms 400-450 ms <sup>‡</sup>
IFG	M*H*T, F=3.14, p<.001	150-650 ms (LH)	400-450 ms (LH)
SFG	T, F=6.06, p<.0001	200-450 ms <sup>‡</sup>	250-350, 650-750 ms <sup>‡</sup>
aCNG	M*T, F=2.78, p<.001	200-350 ms	350-400 ms (RH)
pCNG	T, F=3.60, p<.0001	200-650 ms	250-450 ms

<sup>†</sup> Modality (M)\*Hemisphere (H)\*Time (T) with 12 and 120 degrees of freedom and evaluated at  $\alpha = .05/16 = .003$ .

<sup>#</sup> Follow-up single-sample t-tests assessing the deviation of difference current waveforms from zero performed separately for each stimulus modality.

<sup>‡</sup> Single-sample t-tests were conducted as planned tests in the absence of a Modality\*Time interaction. All t-tests were evaluated at  $\alpha = .001$ .