RESEARCH NOTE

Matthew S. Tata · Lawrence M. Ward

Early phase of spatial mismatch negativity is localized to a posterior "where" auditory pathway

Abstract The auditory mismatch negativity (MMN) is an event-related potential that reflects early processing of changes in acoustic stimulus features. Although the MMN has been well characterized by previous work, the number, roles, and anatomical locations of its cortical generators remain unresolved. Here, we report that the MMN elicited by occasional deviations in sound location is comprised of two temporally and anatomically distinct phases: an early phase with a generator posterior to auditory cortex and contralateral to the deviant stimulus, and a later phase with generators that are more frontal and bilaterally symmetric. The posterior location of the early-phase generator suggests the engagement of neurons within a putative "where" pathway for processing spatial auditory information.

Keywords Auditory cortex · Parietal cortex · Auditory perception · Spatial · Mismatch negativity

Introduction

The mismatch negativity (MMN) is an auditory event-related potential (ERP) component elicited when an unusual stimulus (a deviant) occurs among repetitive (standard) stimuli. The MMN was initially believed to be an automatic response to simple deviations in the physical characteristics of repetitive sounds (e.g., changes in pitch or loudness). It has since become clear that the MMN reflects a rapid and sophisticated processing of the complex spectrotemporal properties of acoustic

M. S. Tata (✉)
Department of Psychology and Neuroscience,
University of Lethbridge, 4401 University Drive,
Lethbridge, AB T1 K 3M4, Canada
E-mail: matthew.tata@uleth.ca
Tel.: +1-403-394-3994
Fax: +1-403-329-2775

L. M. Ward
Department of Psychology, University of British Columbia,
Vancouver, Canada

input at early stages of cortical processing. For example, an MMN (and its magnetic counterpart) can be elicited by abstract deviations in temporal pattern or rhythm, feature conjunction, or language-specific phonetic characteristics (see, Näätänen 1992; Näätänen et al. 2001; Näätänen and Winkler 1999; Picton et al. 2000; Schröger 1997a,b, for reviews).

The MMN is often manifested as a single focus over frontal midline scalp and is believed to be generated (at least in part) within or near the primary auditory cortex (A1) (Scherg et al. 1989). Two aspects of the MMN, the number and location of component sources and the degree of hemispheric lateralization, have recently come under scrutiny.

The MMN arises from multiple generators with independent time courses. The latency range over which the MMN emerges (about 100–200 ms post-stimulus) can be divided into early and late phases. Whereas the early-phase generator lies within or near the primary auditory cortex, the late-phase generator(s) could be in the frontal cortex (Deouell et al. 1998; Rinne et al. 2000), parietal cortex (Levänen et al. 1996), some combination of these two cortices (Kasai et al. 1999), or simply an additional supratemporal generator (Scherg et al. 1989). Yago et al. (2001), in contrast, have reported a frontal component that preceded a putative temporal cortex component, thereby emphasizing a need for further investigation of the sequence of these components.

The role of each hemisphere in generating the MMN is likewise unclear. Although both left and right auditory cortices receive input from both ears, cortical processing of acoustic features in general often appears to be somewhat lateralized to the hemisphere contralateral to the sound source (Kaiser and Lutzenberger 2001; Woldorff et al. 1999). Some MMN studies using lateralized stimuli have reported stronger (Deouell et al. 1998; Giard et al. 1990; Kaiser et al. 2000; Nager et al. 2003; Takegata et al. 2001) and/or earlier (Kaiser et al. 2000—for left lateralized stimuli only; Scherg et al. 1989) MMN responses in the hemisphere contralateral to the side of stimulation relative to that of the ipsilateral side.

Other studies have reported an asymmetric involvement of right-hemisphere generators (Deouell and Bentin 1998; Kasai et al. 1999; Levänen et al. 1996; Paavilainen et al. 1991). Speech sounds may be an exception because the MMN generator elicited by phoneme deviants is more prominent in the left hemisphere (Rinne et al. 1999). Other studies have reported a reduction of MMN elicited by stimuli contralateral to cortical lesions (Alain et al. 1998; Deouell et al. 2000).

Despite these studies, the evidence for a contralateral, biphasic MMN remains subtle, probably because of the temporal overlap of early and late generators and the non-spatial (i.e., frequency, duration, intensity, etc.) nature of the stimulus deviance often used in the MMN paradigm. Because deviation in spatial location of a sound source is known to generate an MMN response (Paavilainen et al. 1989), we examined the MMN elicited by changes in the free-field location of stimuli. Here, we report evidence of a clearly contralateral and biphasic MMN elicited by deviations in sound location. Furthermore, we present evidence that the cortical generators of the earlier phase of this spatial MMN are feature specific and located along a posterior auditory "where" pathway.

Methods

Participants

Fifteen students at the University of British Columbia were paid to participate after giving informed consent. Listeners reported normal hearing. Procedures were approved by the University's Human Subjects Ethics Review Committee and were in accordance with the 1964 Declaration of Helsinki.

Stimuli and procedure

Listeners sat in a darkened sound-attenuating booth facing three horizontally arranged speakers, marked by LEDs. The center speaker was 105 cm distant and the peripheral speakers were located 35° laterally from center. Three types of stimuli, targets, standards, and deviants, were presented in a mixed stream separated by random interstimulus intervals of 400–800 ms. Targets consisted of two 30-ms 63-dBA SPL bursts of broad-band noise separated by either a 20- or a 50-ms gap of silence. The listener indicated the duration of the gap with a button press. Targets always occurred at the center and listeners were encouraged to ignore peripheral standards and deviants. Standards and deviants consisted of 20-ms tone pips (1,000 Hz, 70 dBA SPL, 5 ms rise/fall time) presented from the peripheral speakers. Within a block, standards were always presented from one side and deviants from the opposite side, randomized across blocks. This design allowed us to rule out differences in lateralization of

the N1 between left and right stimuli. For example, the ERP associated with 1,000-Hz deviants on the left could be compared to that of 1,000 Hz standards also on the left (from other blocks). Thus, only ERPs to physically identical stimuli were compared—any difference arising solely from the role (standard or deviant) played by the tone. Additional standards were presented in the interval between the target and the response. Thus, a block contained 20 deviants and 40 targets, but a variable number of standards (minimum 180) depending on the time taken to respond to targets. Blocks lasted approximately 2.5 min and were separated by brief rest breaks.

Electrophysiological recording

The electroencephalogram (EEG) was recorded at 63 sites with Ag/AgCl electrodes (standard 10–10 system plus A1, SI1, SIZ, SI2) (American Electroencephalographic Society 1994) referenced to the right mastoid and subsequently re-referenced to averaged mastoids. The electrooculogram was recorded with electrodes placed beside and below the left eye. Trials contaminated with eye-movement or blink artifact were automatically rejected, and data from one listener were rejected entirely because of excessive artifacts. ERPs elicited by left and right standards and deviants were computed separately. For topographic and dipole analysis, the MMN was computed by subtracting the ERP elicited by standards from the ERP elicited by deviants. Components of the MMN were taken to be foci at or near the peaks of the resulting difference wave during the latency window spanning 100–200 ms post-stimulus. ERPs to standards and deviants for each listener were entered into a 2 electrode (FC3, FC4) × 2 Field of Presentation (left, right) × 2 Condition (standard, deviant) repeated measures ANOVA.

Isopotential maps were computed for left-deviant and right-deviant MMNs as well as for the target-elicited N1 component between 100 and 200 ms. Dipoles were fitted separately within 8-ms windows spanning peaks of three identified components: the N1 and the early and late phases of the MMN (ANT Software BV, Enschede, The Netherlands). All dipole locations are reported in the coordinate system defined by the MNI/SPM99 Template Brain. Dipoles were fitted only to the grand average data. Thus, all statistical tests were carried out on measured voltage differences at individual leads rather than on computed dipole parameters.

Results

Figure 1 displays a robust MMN contralateral to the deviant between 100 and 200 ms post-stimulus [electrode (FC3, FC4) × stimulus side (left, right) × condition (standard, deviant) interaction: $F_{1,13} = 14.5$; $P = 0.002$]. The MMN was biphasic with a lateralized early phase
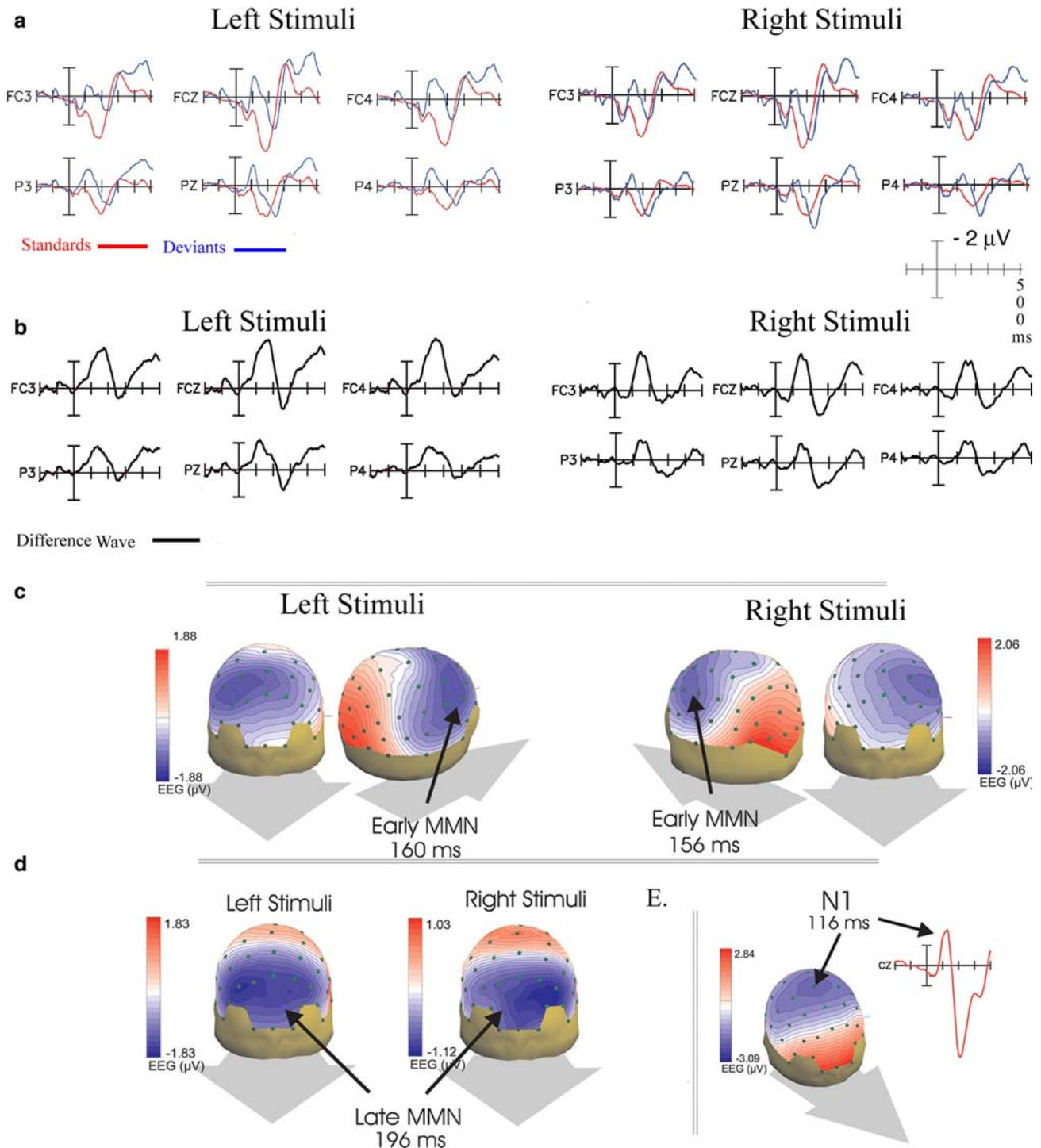
Fig. 1 Mismatch negativities (*MMN*) for left and right deviants. **a** Event-related potential (*ERP*) waveforms elicited by left and right standards (*red*) and spatial deviants (*blue*) at selected sites. **b** Deviant minus standard difference waves for these sites. **c** Isopotential maps indicating the contralateral distribution of the early MMN for left and right stimuli. Heads face in the direction of the arrows. **d** Isopotential maps of the late MMN. **e** Target stimulus ERP at Cz and the corresponding isopotential map of the N1 component

peaking at 160 ms for left deviants and 156 ms for right deviants followed by a later fronto-central phase focused nearer to the midline and peaking at 196 ms for deviants from either side.

Behavioral data suggest that listeners maintained their attention at the center and did not orient to the location of the deviants. Listeners were not significantly slower or less accurate in responding to targets preceded

by deviants (840 ms mean response time (RT) and 86% mean accuracy) than to targets preceded by standards (832 ms mean RT and 88% mean accuracy) [difference in RT: $t(13) = -0.773$, $P = 0.46$; difference in accuracy: $t(13) = 1.4$, $P = 0.18$].

Since the early-phase MMN was focused over the hemisphere contralateral to the stimuli, we first seeded the dipole analysis procedure with a single dipole in contralateral Heschl's gyrus (Rademacher et al. 2001). For left and right deviants, we found dipoles medial and posterior to Heschl's gyrus accounting for 94.7 and 96.4% of the variability in the scalp distribution, respectively (standard coordinates for left deviants: 26, −48, 15; right deviants: −36, −43, 5) (Fig. 2). We also considered the possibility that bilaterally symmetric generators could better account for the early phase of the MMN. For left-field deviants, bilateral dipoles seeded in Heschl's gyri and constrained to be mirror symmetric accounted for 96.8% of the scalp distribution (±27, −28, 19). The strength of the contralateral (right) generator was −34 nA m, whereas the ipsilateral generator was –21 nA m. For right-field deviants, this approach similarly accounted for 97.2% of the scalp distribution and the contralateral dipole (−34 nA m) was stronger than the ipsilateral one (−8 nA m).

The near-midline focus of the late-phase MMN suggested bilateral generators and required a more complex model. To obtain anatomically plausible solutions (i.e., sources off of the midline) it was necessary to fix seeded dipoles at ±42 in the x dimension (commensurate with Heschl's gyrus, Rademacher et al. 2001) and constrain them to be mirror symmetric in the y and z dimensions. Dipoles of similar magnitude (for left deviants: left hemisphere, −16 nA; right hemisphere, −13 nA; for right deviants: left hemisphere, −10 nA; right hemisphere, −5 nA) located anterior to Heschl's gyrus, possibly in the frontal cortex (±42, 9, 10 for left stimuli and ±42, 9, 31 for right stimuli) accounted for 92.8 and 86.9% of the late-phase MMN scalp distributions for left and right deviants, respectively.

For reference, we fitted dipoles to the target-stimulus N1 peak. The N1 was best fitted (94.4%) by bilaterally symmetric dipoles near the anterior part of Heschl's gyrus (±42, 0, 17).

Discussion

Our goals were to consider the possibility of multiple generators in the MMN elicited by spatial deviants, and to consider the degree to which the MMN response is lateralized with respect to the side of stimulation.

Our data are consistent with previous studies and suggest that the MMN is comprised of at least two generators, with a posterior generator becoming active earlier than a more-anterior generator (Deouell et al. 1998; Giard et al. 1990; Näätänen and Michie 1979; Rinne et al. 2000; but see Yago et al. 2001). Despite this consistent converging evidence, a need remains for a statistical test applied not to scalp voltages, but to the

Fig. 2 Dipole locations for left and right deviants. **a** Generators of the early-phase (*red*) and late-phase (*blue*) MMN and the target-stimulus N1 (*green*), superimposed on the Montreal Neurological Institute representative brain. Slice is in plane with the early-phase MMN generator. **b** The same dipoles plotted on the corresponding saggital slice
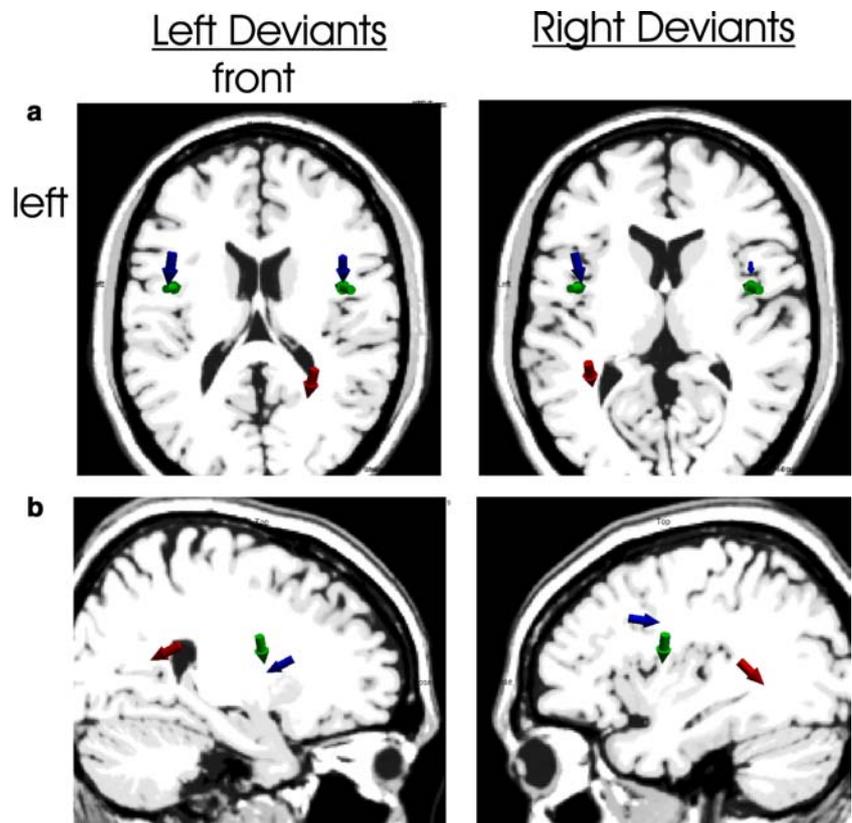
fitted dipole parameters. Unfortunately, fitting dipoles to individual participant's EEG data often proves problematic in MMN paradigms due to the necessarily small number of deviant stimuli. This prevented a direct statistical test of, for example, x, y and z coordinates. Alternative statistical approaches continue to be the topic of investigation in this field.

The anatomical and temporal differences between these two generators, evidenced by both topographic and source analysis, is more distinct in the present study than in previous studies. This is perhaps because of the spatial nature of the deviants used here. A preponderance of source analysis studies suggests that MMN generators due to *non-spatial* deviants (frequency, duration, intensity, etc.) are always anterior to the N1 generator. There are some exceptions worth noting, however: Levänen et al. (1996) and Molholm et al. (2005) report magnetoencephalographic (MEG) and functional magnetic resonance imaging (fMRI) evidence, respectively, of right posterior parietal activation by non-spatial deviants. Phonetic stimuli may also be important exceptions that engage left posterior regions (Rinne et al. 1999). The present study finds *symmetrical* posterior generators of the spatial MMN. It is possible that a considerably more posterior generator of the early-phase MMN elicited by *spatial* deviants reduces temporal and physical overlap of the early and late generators and could account for the more prominent distinction between these in our study.

The distinctions between early/late and posterior/anterior components of the spatial MMN are accompanied also by a difference in the pattern of lateralization. Whereas the earlier phase was strongly lateralized and could be well accounted for by a single dipole contralateral to the deviant stimulus, the later phase was less lateralized and required bilaterally symmetric dipoles to obtain a plausible solution. These data are consistent with previous reports of contralaterality of the MMN (Deouell et al. 1998; Giard et al. 1990; Kaiser et al. 2000; Nager et al. 2003; Takegata et al. 2001). We find no evidence, however, to support suggestions of asymmetric involvement of the right hemisphere (Kasai et al. 1999; Levänen et al. 1996; Paavilainen et al. 1991). Again, this may be because of differences between the spatial deviants used in the present study and non-spatial deviants used in previous studies. Kaiser et al. (2000, 2001) reported an asymmetry in dipole latencies: leftward-deviant stimuli elicited a right-hemisphere dipole that was stronger and earlier than the left-hemisphere dipole. Rightward-deviant stimuli elicited a stronger left-hemisphere dipole, but no latency difference was evident. In our study, we found virtually identical latencies for MMN peaks elicited by left- and right-side deviants. Possibly, their MEG measurements were sensitive to neural activity that is subtly different from our EEG measurements.

Previous investigators (Näätänen and Alho 1997; Schröger andrent from our EEG measurements. Wolff 1996; Schröger 1997a,b) have described the spatial-deviant MMN as being a complex comprised of a sensory-related and a memory-related component. It is possible that the early posterior MMN phase described here is sensory related while the later anterior phase is memory related. This idea is supported by the observation that the earlier phase arises predominantly in the hemisphere contralateral to the deviant and *ipsilateral* to the standard on which the memory-trace was based. It is unlikely, however, that the early-phase MMN reported here can be accounted for by refractoriness of the N1 generator(s) arising in or near the primary auditory cortex, since the early-phase MMN dipole differed from the N1 dipole in both its location and orientation. We cannot rule out that refractoriness of neurons outside of primary auditory cortex could contribute to the observed negative deflection of deviant-stimulus ERPs, a proposal also recently advanced by Jääskeläinen et al. (2004) to account for the anterior tendency of MMN responses. Interestingly, such neurons would have to exhibit some location specificity, as this was the only feature on which standards and deviants differed.

An anatomical distinction between spatial and non-spatial MMN generators, or even the existence of spatially specific refractoriness, is of particular relevance to a recently advanced model of auditory cortex in which spatial and non-spatial information are respectively segregated into posterior "where" and anterior "what" pathways (Rauschecker and Tian 2000). Our localization of at least one component of the *spatial* MMN to a region posterior to the N1 generator in primary auditory cortex and near the temporo-parietal junction is consistent with this model and with previous research. For example, temporo-parietal neurons in monkey cortex have spatial tuning properties (Leinonen et al. 1980; Tian et al. 2001) and functional imaging studies have demonstrated activation or modulation of temporo-parietal and inferior parietal regions during spatial auditory tasks such as localization (Alain et al. 2001; Bushara et al. 1999; Weeks et al. 1999; Zatorre et al. 2002), the perception of auditory motion (Griffiths et al. 2000; Lewis et al. 2000) and focusing of spatial attention (Tata and Ward 2005). Our data suggest a promising approach in the effort to characterize the functional architecture of human auditory cortex. We are optimistic that a careful within-subjects comparison of early MMN responses to spatial and non-spatial deviants will reveal important general principles of organization within the auditory system.

References

Alain C, Woods DL, Knight RT (1998) A distributed cortical network for auditory sensory memory in humans. Brain Res 81:23–37

Alain C, Arnott SR, Hevenor S, Graham S, Grady CL (2001) "What" and "where" in the human auditory system. Proc Natl Acad Sci USA 98(21):12301–12306

American Electroencephalographic Society (1994) Guidelines for standard electrode position nomenclature. J Neurophysiol 11:111–113

Bushara KO, Weeks RA, Ishii K, Catalan M-J, Tian B (1999) Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans. Nat Neurosci 2:759–766

Deouell LY, Bentin S (1998) Variable cerebral responses to equally distinct deviance in four auditory dimensions: a mismatch negativity study. Psychophysiology 35:745–754

Deouell LY, Bentin S, Giard MH (1998) Mismatch negativity in dichotic listening: evidence for interhemispheric differences and multiple generators. Psychophysiology 35:355–365

Deouell LY, Bentin S, Soroker N (2000) Electrophysiological evidence for an early (pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect. Brain 123:353–365

Giard M, Perrin F, Pernier J, Bouchet P (1990) Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 27:627–640

Griffiths TD, Green GGR, Rees A, Rees G (2000) Human brain areas involved in the analysis of auditory movement. Hum Brain Mapp 9:72–80

Jääskeläinen IP, Ahveninen J, Bonmassar G, Dale AM, Ilmoniemi RJ, Levänen S, Lin FH, May P, Melcher J, Stufflebeam S, Tiitinen H, Belliveau JW (2004) Human posterior auditory cortex gates novel sounds to consciousness. Proc Natl Acad Sci USA 101:6809–6814

Kaiser J, Lutzendberger W (2001) Location changes enhance hemispheric asymmetry of magnetic fields evoked by lateralized sounds in humans. Neurosci Lett 314:17–20

Kasai K, Nakagome K, Itoh K, Koshida I, Hata A, Iwanami A, Fukuda M, Hiramatsu KL, Kato N (1999) Multiple generators in the auditory automatic discrimination process in humans. Neuroreport 10(11):2267–2271

Kaiser J, Lutzenberger W, Birbaumer N (2000) Simultaneous bilateral mismatch response to right- but not leftward sound lateralization. Neuroreport 11(13):2889–2892

Leinonen L, Hyvarinen J, Sovijarvi ARA (1980) Functional properties of neurons in the temporo-parietal association cortex of awake monkey. Exp Brain Res 39:203–215

Levänen S, Ahonen A, Hari R, McEvoy L, Sams M (1996) Deviant auditory stimuli activate human left and right auditory cortex differently. Cereb Cortex 6:288–296

Lewis JW, Beauchamp MS, DeYoe EA (2000) A comparison of visual and auditory motion processing in human cerebral cortex. Cereb Cortex 10(9):873–888

Molholm S, Martinez A, Ritter W, Javitt DC, Foxe JJ (2005) The neural circuitry of pre-attentive auditory change-detection: an fMRI study of pitch and duration mismatch negativity generators. Cereb Cortex 15:545–551

Näätänen R (1992) Attention and brain function. Erlbaum, Hillsdale, NJ

Näätänen R, Alho K (1997) Higher-order processes in auditory-change detection. Trends Cogn Sci 1(2):44–45

Näätänen R, Michie PT (1979) Early selective-attention effects on the evoked potential: a critical review and reinterpretation. Biol Psychol 8:81–136

Näätänen R, Winkler I (1999) The concept of auditory stimulus representation in cognitive neuroscience. Psychol Bull 125(6):826–859

Näätänen R, Tervaniemi M, Sussman E, Paavilainen P, Winkler I (2001) 'Primitive Intelligence' in the auditory cortex. Trends Neurosci 24(5):283–288

Nager W, Kohlmetz C, Joppich G, Möbes J, Münte TF (2003) Tracking of multiple sound sources defined by interaural time differences: brain potential evidence in humans. Neurosci Lett 344:181–184

Paavilainen P, Karlsson M-L, Reinikainen K, Näätänen R (1989) Mismatch negativity to change in spatial location of an auditory stimulus. Electroencephalogr Clin Neurophysiol 73:129–141

Paavilainen P, Alho K, Reinikainen K, Sams M, Näätänen R (1991) Right hemisphere dominance of different mismatch negativities. Electroencephalogr Clin Neurophysiol 78:466–479

Picton TW, Alain C, Otten L, Ritter W, Achim A (2000) Mismatch negativity: different water in the same river. Audiol Neurootol 5:111–139

Rademacher J, Morosan P, Schormann T, Schleicher A, Werner C, Freund HJ, Zilles K (2001) Probabilistic mapping and volume measurement of human primary auditory cortex. Neuroimage 13:669–683

Rauschecker JP, Tian B (2000) Mechanisms and streams for processing of "what" and "where" in auditory cortex. Proc Natl Acad Sci USA 97:11800–11806

Rinne T, Alho K, Alku P, Holi m. Sinkkonen J, Vrtanen J, Bertrand O, Näätänen R (1999) Analysis of speech sounds is left-hemisphere predominant at 100–150 ms after sound onset. Neuroreport 10:1113–1117

Rinne T, Alho K, Ilmoniemi R, Virtanen J, Näätänen R (2000) Separate time behaviors of the temporal and frontal mismatch negativity sources. Neuroimage 12:14–19

Scherg MS, Vajsar J, Picton TW (1989) A source analysis of the late human auditory evoked potentials. J Cogn Neurosci 1(4):336–355

Schröger E (1997a) On the detection of auditory deviations: a pre-attentive activation model. Psychophysiology 34:245–257

Schröger E (1997b) Response from Schröger. Trends Cogn Sci 1(2):45–46

Schröger E, Wolff C (1996) Mismatch responses of the human brain to changes in sound location. Neuroreport 7:3005–3008

Takegata R, Huotilainen M, Rinne T, Näätänen R, Winkler I (2001) Changes in acoustic features and their conjunctions are processed by separate neuronal populations. Neuroreport 12:525–529

Tata MS, Ward LM (2005) Spatial attention modulates activity in a posterior "where" auditory pathway. Neuropsychologia 43:509–516

Tian B, Reser D, Durham A, Kustov A, Rauschecker JP (2001) Functional specialization of rhesus monkey auditory cortex. Science 292:290–293

Weeks RA, Aziz-Sultan A, Bushara KO, Tian B, Wessinger CM, Dang N, Rauschecker JP, Hallet M (1999) A PET study of human auditory spatial processing. Neurosci Lett 262:155–158

Woldorff MG, Tempelmann C, Fell J, Tegeler C, Gaschler-Markefski B, Hinrichs H, Heinze H-J, Scheich H (1999) Lateralized auditory spatial perception and the contralaterality of cortical processing as studied with functional magnetic resonance imaging and magnetoencephalography. Hum Brain Mapp 7:49–66

Yago E, Escera C, Alho K, Giard MH (2001) Cerebral mechanisms underlying orienting of attention towards auditory frequency changes. Neuroreport 12(11):2583–2587

Zattore RJ, Bouffard M, Ahad P, Belin P (2002) Where is 'where' in the human auditory cortex? Nat Neurosci 5(9):905–909