Behavioral/Systems/Cognitive

Event-Related Brain Potential Correlates of Human Auditory Sensory Memory-Trace Formation

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The event-related potential (ERP) component mismatch negativity (MMN) is a neural marker of human echoic memory. MMN is elicited by deviant sounds embedded in a stream of frequent standards, reflecting the deviation from an inferred memory trace of the standard stimulus. The strength of this memory trace is thought to be proportional to the number of repetitions of the standard tone, visible as the progressive enhancement of MMN with number of repetitions (MMN memory-trace effect). However, no direct ERP correlates of the formation of echoic memory traces are currently known. This study set out to investigate changes in ERPs to different numbers of repetitions of standards, delivered in a roving-stimulus paradigm in which the frequency of the standard stimulus changed randomly between stimulus trains. Normal healthy volunteers ($n = 40$) were engaged in two experimental conditions: during passive listening and while actively discriminating changes in tone frequency. As predicted, MMN increased with increasing number of standards. However, this MMN memory-trace effect was caused mainly by enhancement with stimulus repetition of a slow positive wave from 50 to 250 ms poststimulus in the standard ERP, which is termed here "repetition positivity" (RP). This RP was recorded from frontocentral electrodes when participants were passively listening to or actively discriminating changes in tone frequency. RP may represent a human ERP correlate of rapid and stimulus-specific adaptation, a candidate neuronal mechanism underlying sensory memory formation in the auditory cortex.

Key words: **event-related potentials; mismatch negativity; echoic memory; audition; sensory memory; human**

Introduction

Human auditory sensory (echoic) memory is correlated with changes of an event-related potential (ERP), termed mismatch negativity (MMN). MMN is elicited during passive listening to deviant sounds interrupting a sequence of repeated standard stimuli (Näätänen et al., 1978). This suggests that a preattentive echoic memory trace of the preceding stimuli is used as a template against which incoming sounds are compared. MMN increases progressively with the number of standard stimulus repetitions (Sams et al., 1983; Näätänen, 1992; Imada et al., 1993; Javitt et al., 1998), suggesting that MMN reflects the strength of the underlying echoic memory trace, henceforth termed the "MMN memory-trace effect." However, MMN is elicited after a trace for preceding standards has been formed; hence, it only indirectly probes trace strength. A direct correlate of echoic trace formation has not been described in human ERPs.

A candidate neuronal mechanism for echoic memory has been discovered recently in cat primary auditory cortex (A1) (Ulanovsky et al., 2003). Stimulus-specific adaptation (SSA), the reduction in neuronal firing, was observed with repetition of frequent standard sounds, whereas responses to rare frequency deviants did not adapt. However, it is unknown whether SSA correlates with ERP changes during human echoic memory formation. The N1 component of the human auditory evoked potential (AEP) increases with larger frequency differences between tones (frequency specificity) (Näätänen et al., 1988) and decreases with repetition (Butler, 1968; Näätänen and Picton, 1987). However, both effects are affected by interstimulus interval (i.e., refractoriness) (Budd et al., 1998).

Another candidate ERP component was observed in a study that compared the MMN memory-trace effect in schizophrenic and control subjects (Baldeweg et al., 2004). This study revealed a frontocentral positive ERP around the time of the N1 in response to repetition of standards. Here, we characterize such ERP repetition effects that may indeed correlate with formation of echoic memory traces.

The neural mechanisms underlying MMN generation in humans are still not fully understood. It was originally proposed by Näätänen (1984) that MMN represents a change detection mechanism that is functionally and spatially distinct from an afferent input population (N1 generators). Recently, an alternative hypothesis has been proposed, suggesting that MMN is in fact a N1

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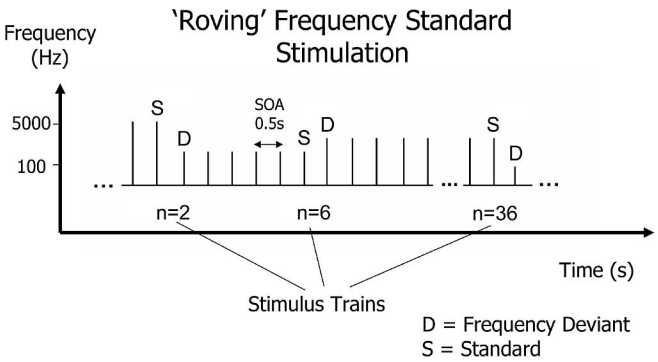

Figure 1. Illustration of the roving standard stimulation used in this study. The stimulus sequence consisted of stimulus trains of a variable number (2, 6, or 36 standard repetitions) of identical standard stimuli (indicated by vertical lines). The frequency varied randomly (between 100 and 5000 Hz) from train to train, as indicated by the different height of the vertical lines. The deviant (D) and the last standard (S) preceding it were used for ERP analysis and to compute MMN difference waves. In two blocks, participants were asked to watch a movie (passive condition), and in two more blocks, they were asked to indicate a change in frequency via button press (active condition). SOA, Stimulus onset asynchrony.

response (Jääskeläinen et al., 2004), which is suppressed and delayed by stimulus-specific adaptation (May et al., 1999), without the existence of separate mismatch neurons [for a critical assessment, see Näätänen et al. (2005)]. Furthermore, there is evidence that MMN consists of at least two components, a "temporal" component, recorded from posterior temporal (mastoid) electrodes, and a "frontal" component, recorded from frontal electrodes (Näätänen and Michie, 1979). The present study examined the topography of ERP changes with standard repetition. We also examined the onset of repetition effects in the latency range of P50, which may index the formation of sensory memory traces at the level of primary auditory cortex. In addition, we tested whether the same ERP changes occur when subjects actively hold frequency information in sensory memory to perform a frequency discrimination task.

Materials and Methods

Subjects. Forty participants (five females), aged 23–48 years (mean age, 31.2 years; 38 right handed; two left handed), were recruited through advertisement. According to self-report, all participants were free of neurological and psychiatric disorders and had no history of hearing impairment. Informed consent was obtained from each participant. Ethical approval was obtained from the local ethical committee.

Stimuli and design. In all recordings, pure sinusoidal tones were generated with a Neurosoft (El Paso, TX) sound program and delivered binaurally through headphones by the Stim interface system (NeuroScan Labs, Sterling, VA) at a sound pressure level of 80 dB. This experiment was based on an oddball paradigm designed by Cowan et al. (1993) using variable or "roving" standard stimuli instead of one constant standard stimulus (Fig. 1) and modified by Baldeweg et al. (2004). Within each stimulus train, all standard tones were of one frequency and were followed by a train of a different frequency. The first tone of this new stimulus train served as the deviant and the last as the standard. The frequency of a train of repeated standard stimuli altered randomly from the lower frequency limit of 100 Hz to the upper limit of 5000 Hz (from 100 to 1000 Hz in steps of 100 Hz and between 1000 and 5000 in steps of 200 Hz) as used by Haenschel et al. (2000).

Each of the four blocks contained 550 stimuli, including 85 deviants. The number of standard stimulus presentations that occurred in a single stimulus train varied among 2, 6, and 36. The intertrain interval was 0.5 s. Tones were of 200 ms duration with rise and fall times of 10 ms and were presented with a constant stimulus onset asynchrony of 0.5 s. The EEG was recorded in four blocks, with 1 min breaks separating the blocks. Each of the four blocks contained 550 stimuli, which included 85 deviants.

In one-half of the blocks, participants were instructed to ignore the tones and asked to watch a silent movie with subtitles (passive listening). In the remaining two blocks, participants were asked to respond via a button press, with one key-press of the index finger of one hand denoting when the deviant was higher and another press with the index finger of the other hand when the deviant was lower in frequency than the preceding standard tone (active discrimination). Presentation of the four blocks was counterbalanced. To control for the possible influence of handedness, the buttons corresponding to the change of the deviant frequency were counterbalanced across participants. Behavioral performance was monitored on-line. The task was designed to be performed at ceiling level because of the large frequency changes between stimulus trains. Hence, only reaction time (RT) data will be reported.

ERP acquisition and analysis. EEG recordings were acquired with the Scan 4.0 software (NeuroScan Labs) and obtained from 36 scalp locations, consisting of standard 10/20 placement and in addition right and left temporal electrodes using an analog bandpass of 0–100 Hz (6 dB down) and digitized continuously at a sampling rate of 500 Hz. Vertical and horizontal electrooculogram electrodes were placed above and below the right eye and laterally from both eyes. A reference electrode was placed on the nose. EEG data were averaged off-line in intervals from 500 ms before the stimulus and up to 1000 ms after stimulus onset and were baseline corrected from −100 to 0 ms before the stimulus. For the analysis of ERPs, data were filtered between 0.5 and 30 Hz. First, EEG epochs were excluded automatically if amplitudes exceeded ±100 μV and were then visually inspected for more subtle artifacts, such as muscle contamination. MMN waveforms were obtained by subtracting waveforms elicited by predeviant standards from waveforms elicited by deviants. Based on inspection of the grand average data, mean ERP amplitudes were computed in the interval of 80–180 ms, and in addition, peak latencies of N1 and mismatch potentials were determined in the same time window. To examine the early onset of ERP repetition effects, we computed the mean amplitude in a 30–80 ms window around the P50 peak, as well as determined peak amplitude and latency of this primary auditory cortex component at the central electrodes Cz (vertex electrode), C3, and C4 referenced to combined mastoids.

Statistical analysis. Analysis of the standard and deviant ERP amplitude and latencies were performed for the frontocentral electrode Fz and the right mastoid electrode RM. Main effects of stimulus and standard repetition were evaluated using a two- (stimulus; deviant vs standard) by-three (standard repetition; $n = 2$, 6, and 36) repeated-measures ANOVA design. Additional Bonferroni's-corrected *post hoc* tests were performed to examine the direction of interaction effects.

Results

MMN memory-trace effect during passive listening

The grand mean ERPs to standards and deviants after 2, 6, and 36 standard repetitions are illustrated in Figure 2 (left) and the corresponding difference waves in Figure 3 (left). As predicted, during passive listening, deviant tones evoked a negativity at frontal electrodes and a mismatch positivity at mastoid electrodes, followed by a frontocentral P3a component at ~250 ms. ERPs to standards and deviants were differently affected by repetition (stimulus-by-repetition effect; $F_{(2,78)} = 4.9$; $p = 0.01$) (Fig. 2). Although no significant change occurred in the deviant negativity with increasing repetition (*post hoc* effect of repetition; $F_{(2,78)} = 2.1$; $p = 0.13$) (Table 1), there were marked changes in the ERP to the standard ($F_{(2,78)} = 12.6$; $p < 0.001$). Thus, the predicted increase of MMN difference wave amplitude with repetition ($F_{(2,78)} = 3.79$; $p = 0.03$) (Fig. 3, left, Table 2) was mainly caused by changes in the standard ERP. These changes took the form of a reduction in N1 amplitude superimposed on a slower positive wave. This repetition positivity (RP) commenced with the P50 component and lasted until 250 ms poststimulus (Fig. 4). For illustration, difference waves were computed between the stan-

dard ERP to $n = 36$ and to $n = 2$ repetitions (Fig. 4*C*), showing a bilateral frontocentral scalp distribution of the RP (Fig. 5), with no visible inversion at mastoid electrodes. It is possible, though, that the standard ERP for $n = 2$ may contain a residual MMN to either the preceding train of standards or to the deviant (Sams et al., 1983). Therefore, an additional difference wave was computed subtracting the ERP after $n = 6$ repetitions from that after $n = 36$ repetitions (Fig. 4*C*). This difference wave was of very similar onset latency and duration, and the scalp potential distribution appears indistinguishable from that of the $n = 36$ minus $n = 2$ wave (Fig. 5). This suggests that RP is unlikely to be determined solely by the presence of a residual MMN. The RP was consistently observed across study participants with only 1 of 40 subjects not showing a visible ERP repetition effect. Also, the frontocentral topographical distribution of RP appeared reproducible across individuals and studies (Baldeweg et al., 2004, 2005).

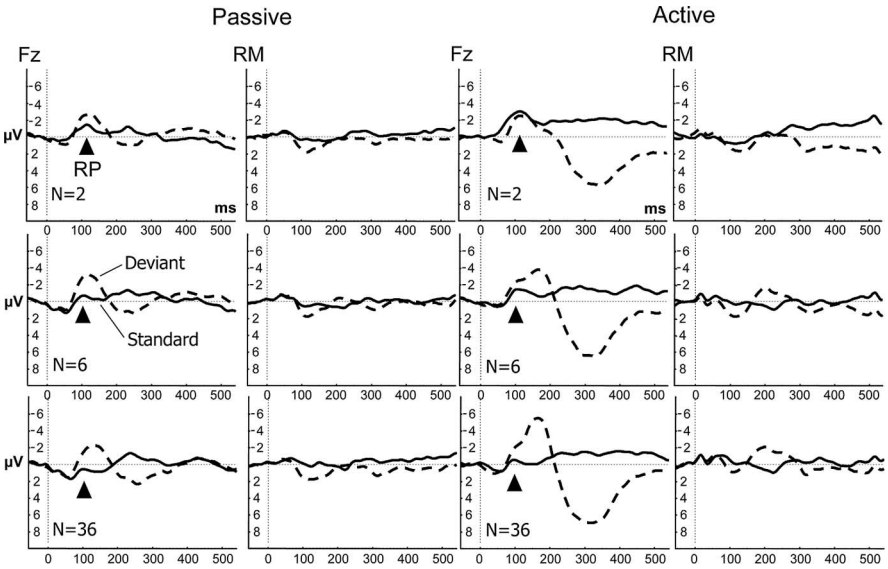

Figure 2. ERPs during passive and active discrimination. The standard (black lines) and deviant (dashed lines) responses are shown after 2 (top), 6 (middle), and 36 (bottom) standard repetitions for the passive (left) and active (right) conditions for central frontal and for right mastoid electrodes. The arrowheads indicate where RP can be seen. Note also the increase in P50 amplitude to both standards and deviants. There is a significant decrease in N1 latency to standards and increase in the latency of the deviant negativity with repetition.

Although significant positive polarity mismatch potentials were elicited at both mastoid electrodes (stimulus effect for RM; $F_{(1,39)} = 42.6$; $p < 0.001$), standard repetition had no effect on the mean standard and deviant ERP amplitudes ($F_{(2,78)} = 2.04$, $p = 0.140$; and $F_{(2,78)} = 0.97$, $p = 0.380$, respectively) (Table 1) nor on the mean mismatch amplitude ($F_{(2,78)} = 2.51$; $p = 0.09$) (Table 2) at these posterior electrodes. Thus, repetition effects were only visible over frontocentral electrodes, without the inversion of polarity across the superior temporal plane, characteristic for the supratemporal auditory N1 component (Vaughan and Ritter, 1970). Thus, in agreement with previous studies using different deviant probabilities (Sams et al., 1983; Sato et al., 2000; Paavilainen et al., 2003), no memory-trace effect (i.e., probability effect) was observed in the temporal (mastoid) mismatch component.

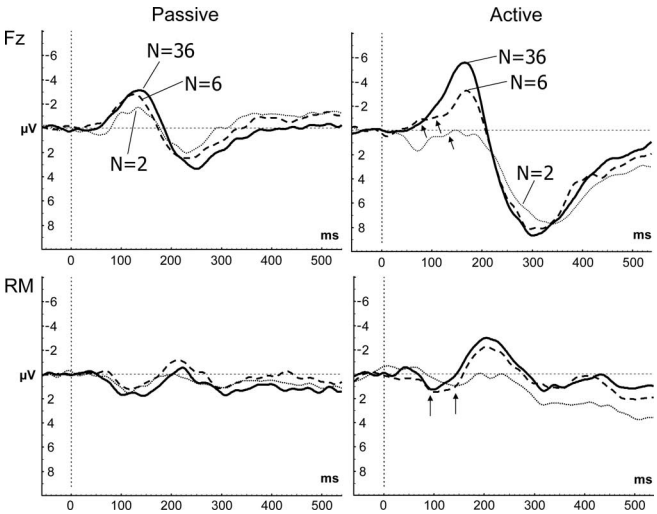

Figure 3. MMN difference waves. The MMN difference waves for 2 (dotted lines), 6 (dashed lines), and 36 (black lines) standard repetitions in the passive (left) and the active (right) conditions are shown for central frontal and the right mastoid electrode. The arrows indicate the shortening of the onset latency into the P50 latency range.

Repetition and stimulus effects in the P50 latency window

Although it is not possible to accurately infer the location of ERP generators from scalp potential distribution, it is nevertheless possible to use the early onset latency of RP to estimate the likely generators in the superior temporal plane. Intracerebral AEP recordings from human Heschl's gyrus (HG) (Liegeois-Chauvel et al., 1991, 1994) identified the primary auditory responses (N13, P17, N26) in the medial part of HG (AI), and the mid-latency responses (MLR; 30–90 ms) were found along the medial to lateral extent of HG. The RP clearly developed around the latency of P50, which originates in the lateral part of AI, with a first peak at 70 ms and extending into the time window of N1 and P2. These latter components are localized in secondary auditory cortex in lateral HG and planum temporale as well as in the cortex anterior to HG. Figure 4 shows repetition effects in the latency range of the MLR components, although components other than the P50 could not be reliably identified as a result of the limitations of the present experiment [for reference, see Dyson et al. (2005)]. A marked repetition effect is visible for P50 for both mean amplitude ($F_{(2,38)} = 25.5$; $p < 0.001$) and peak amplitude ($F_{(2,38)} = 31.9$; $p < 0.001$) measurements and to a lesser degree also for the preceding positivity (a slow envelop of P17 and P30; not measured here). This response is best seen at the vertex electrode when using an average mastoids reference (Figs. 4*B*, 5), in agreement with the topography of primary auditory responses (Dyson et al., 2005). The onset latency at 50 ms strongly suggests a primary auditory cortex origin of the early RP, a finding also in agreement with the origin of SSA (Ulanovsky et al., 2003).

Furthermore, this P50 repetition effect also allowed us to examine the controversial issue of the contribution of new afferent input to MMN (Näätänen et al., 2005) at the level of primary auditory cortex. No stimulus main effect (i.e., a difference in P50 between standards and frequency deviants) was found (mean amplitude, $F_{(1,38)} = 0.124$, $p = 0.727$; peak amplitude, $F_{(1,38)} = 0.303$, $p = 0.585$), suggesting that early afferent responses within primary auditory cortex do not significantly contribute per se to

Table 1. Mean ERP amplitude (80–180 ms; in microvolts) and peak latency (in milliseconds) to standard and deviant stimuli

	Mean amplitude				Latency			
	STD		DEV		STD		DEV	
	Fz	RM	Fz	RM	Fz	RM	Fz	RM
Passive								
$n = 2$	−0.68 (0.30)	0.33 (0.17)	−1.61 (0.25)	1.16 (0.18)	129 (4.46)	122 (5.83)	118 (3.54)	135 (7)
$n = 6$	−0.18 (0.22)	0.26 (0.17)	−1.81 (0.25)	0.99 (0.21)	130 (5.63)	117 (5.78)	123 (3.96)	118 (6.84)
$n = 36$	0.88 (0.23)	−0.11 (0.13)	−1.29 (0.26)	1.28 (0.20)	133 (5.36)	116 (5.43)	131 (3.41)	111 (6.2)
Active								
$n = 2$	−3.96 (0.54)	1.38 (0.40)	−1.44 (0.34)	0.89 (0.24)	120 (4.05)	134 (6.44)	132 (4.29)	140 (6.68)
$n = 6$	−0.36 (0.24)	0.31 (0.17)	−2.10 (0.31)	0.61 (0.23)	125 (4.85)	115 (5.63)	144 (5.26)	152 (6.18)
$n = 36$	0.13 (0.27)	−0.53 (0.20)	−2.99 (0.38)	0.14 (0.27)	121 (5.66)	110 (8.08)	156 (4.14)	159 (5.18)

The SEM is shown in parentheses. The effect of standard repetition ($n = 2$, 6, and 36) is shown for the passive and active discrimination conditions, separately for frontal and mastoid electrodes. STD, Standard; DEV, deviant.

Table 2. Mean MMN amplitude (80–180 ms; in microvolts) and peak latency (in milliseconds)

	Mean amplitude		Latency	
MMN	Fz	RM	Fz	RM
Passive				
$n = 2$	−1.04 (0.39)	0.94 (0.19)	125 (4.44)	120 (3.37)
$n = 6$	−1.80 (0.30)	0.74 (0.24)	124 (3.73)	129 (3.96)
$n = 36$	−2.25 (0.35)	1.44 (0.25)	128 (3.35)	130 (4.08)
Active				
$n = 2$	0.49 (0.51)	0.62 (0.32)	133 (4.97)	136 (4.91)
$n = 6$	−1.76 (0.50)	0.77 (0.28)	146 (5.23)	117 (3.15)
$n = 36$	−3.37 (0.39)	0.18 (0.28)	157 (3.23)	116 (4.22)

The SEM is shown in parentheses. The effect of standard repetition ($n = 2$, 6, and 36) is shown for the passive and active discrimination conditions, separately for frontal and mastoid electrodes.

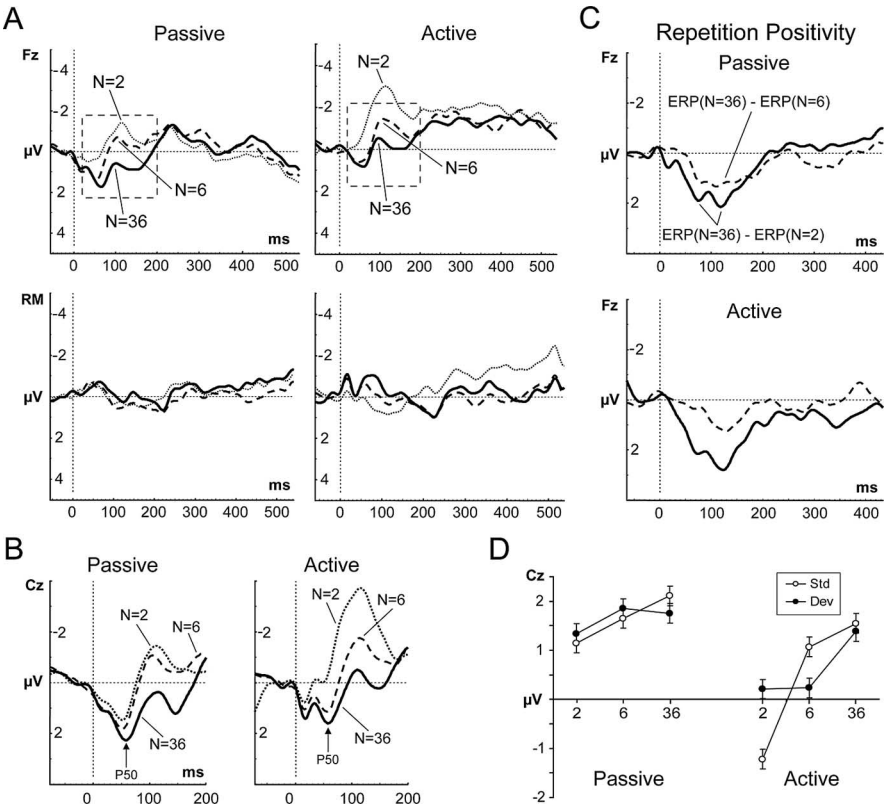

Figure 4. The RP. ***A***, The standard ERP after 2, 6, and 36 repetitions for the passive (left) and active (right) conditions for central frontal and right mastoid electrodes. The inset indicates time window for enlarged early ERP shown in ***B***. ***B***, The enlarged early part showing the standard after 2, 6, and 36 repetitions for the passive (left) and active (right) conditions for vertex electrode. ***C***, The difference wave between the standard after 36 and 2 (black line) and 36 and 6 (dashed line) repetitions for the passive (top) and active (bottom) condition are shown for electrode Fz. ***D***, P50 mean amplitude after 2, 6, and 36 repetitions for the passive (left) and active (right) conditions for Cz. Std, Standard; Dev, deviant. Error bars represent SE.

the observed MMN. In contrast, the stimulus effect in the P50 window was dependent on the number of standard repetitions (stimulus-by-repetition interaction effect for P50 mean amplitude; $F_{(2,37)} = 10.1$; $p < 0.001$) (Fig. 4*D*). The P50 to deviants was larger after $n = 2$ standards (i.e., a repetition effect) but smaller after $n = 6$ and 36 (a mismatch effect). This suggests that the early detection of a deviant stimulus is also dependent on a comparison with a memory trace of the standard. Our data therefore imply that increasing strength of this trace leads to more rapid mismatch detection starting from 50 ms onwards, visible also in the shortening of the onset latency of mismatch-difference waves (Fig. 3, arrows) into the P50 latency range.

Effect of attention on the MMN memory-trace effect

RTs to target stimuli in the active discrimination condition were not significantly different between target responses for the different number of standard presentations [$n = 2$ repetitions, 0.63 s (SD, 0.25); $n = 6$ repetitions, 0.61 s (SD, 0.17); $n = 36$ repetitions, 0.62 (SD, 0.21)].

Similar to the passive listening condition, there was a stepwise increase with repetition in mean standard ERP amplitude in the time window of 80–180 ms during active discrimination ($F_{(2,78)} = 43.63$; $p < 0.001$). However, in contrast to passive listening, the response to deviants increased significantly ($F_{(2,78)} = 6.24$; $p < 0.005$), which was, however, partially attributable to the overlapping N2b component (Figs. 2, 3; Table 1).

Furthermore, amplitudes of both standard as well as deviant ERPs recorded from mastoid electrodes showed a significant repetition effect ($F_{(2,78)} = 14.95$, $p < 0.001$; and ($F_{(2,78)} = 13.09$, $p < 0.001$, respectively) (Fig. 2), which was not seen during passive listening. However, the mean amplitude of the mastoid mismatch

difference wave was not significantly affected by repetition ($F_{(2,78)} = 1.34$; $p = 0.27$) and was also not significantly different between active and passive conditions ($F_{(1,39)} = 3.48$; $p = 0.07$) (Table 2).

There was a marked effect of attention on the mastoid mismatch latency (condition-by-repetition effect; $F_{(2,78)} = 9.32$; $p < 0.001$). This was because of a progressive shortening of mismatch latency with increasing repetition during active discrimination ($F_{(2,78)} = 6.75$; $p = 0.002$), which was not seen during passive listening (Table 2).

The comparison of RP difference waves between conditions (Fig. 4*C*) showed similarities in polarity and overall wave shape. The mean RP amplitude was enhanced by attention at electrodes Fz (condition; $F_{(1,39)} = 21.87$; $p < 0.001$) and RM ($F_{(1,39)} = 4.21$; $p = 0.047$).

Furthermore, we examined the effect of attention in the early P50 time window, in view of such effects in the 20–50 ms latency range observed previously (Woldorff et al., 1993). The P50 was smaller during active compared with passive attention ($F_{(1,39)} = 31.1$; $p < 0.001$), possibly because of an overlapping slow negative wave. However, the magnitude of the P50 repetition effect (Fig. 4*B*,*D*) was larger in the active condition ($F_{(2,38)} = 8.8$; $p = 0.001$). In addition, attention also influenced the early detection of a deviant stimulus. The point at which the repetition effect on the P50 deviant response (i.e., a larger P50 to the deviant compared with standard) switched into a mismatch effect (i.e., a smaller P50 to deviants than to standards; see above) was influenced by attention (Fig. 4*D*), with the switch occurring after fewer repetitions ($n = 6$) under active compared with passive (at $n = 36$) attention, as indicated by a condition-by-stimulus-by-repetition effect ($F_{(2,37)} = 6.4$; $p = 0.004$).

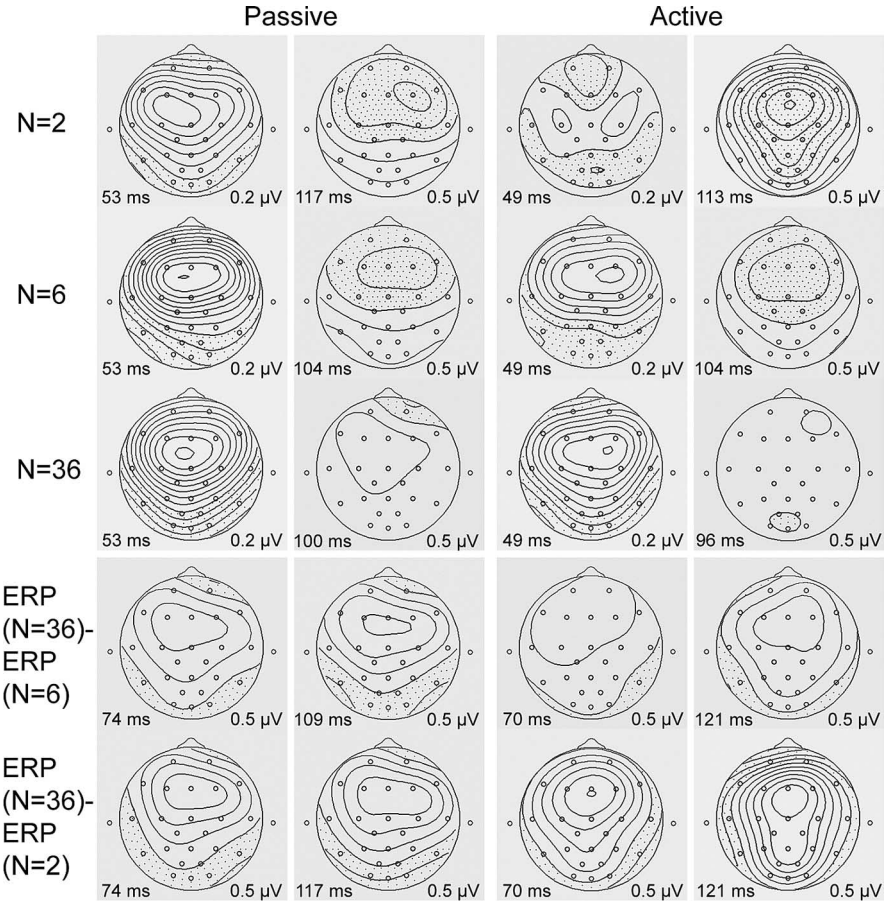

Figure 5. The scalp topography of the standard ERP and RP during passive and active discrimination. Top, Scalp potential maps are shown for the standard ERP after $n = 2$ (first row), 6 (second row), and 36 (third row) repetitions at two time points: P50 at 53 ms and N1 at ~110 ms. Bottom, Scalp topography of RP difference wave between the standard after 36 and 6 [fourth row; ERP ($n = 36$) − ERP ($n = 6$)] and 36 and 2 [fifth row; ERP ($n = 36$) − ERP ($n = 2$)] repetitions. Maps are shown for the peaks at 70 and ~120 ms, as indicated by arrows in Figure 4*C*. Isopotential lines are separated by 0.2 and 0.5 μV. White areas indicate positive polarity, and dotted areas indicate negative-polarity amplitudes. Maps are displayed using a common average reference montage.

Discussion

Summary of findings

This study investigated changes in ERPs associated with the formation and strengthening of echoic memory traces, which precede MMN generation. ERP changes correlated with repetition of standard stimuli were observed as a positive polarity wave (RP) from the frontocentral scalp between 50 and 250 ms poststimulus. Although significant mismatch potentials to stimulus change were detected from both frontal and temporal electrodes, only the frontal component was affected by stimulus repetition. RP accounted for most of the mismatch-negativity magnitude associated with the memory-trace effect in this experiment. Hence, the frontal mismatch component was predominantly sensitive to stimulus-specific adaptation, whereas the temporal component was relatively insensitive to such effects and might represent a true mismatch (i.e., change) detector, as postulated by Näätänen (1984). Furthermore, comparable RP potentials were also found during active tone discrimination, supporting a functional role of RP-associated mechanisms in sensory memory.

ERP correlates of auditory stimulus representation

Näätänen and Winkler (1999) distinguished three main forms of auditory sensory representations in distinct, temporally overlapping processing stages: (1) the afferent activation pattern, reflected by brainstem auditory-evoked potentials (BAEP), (2) sensory feature traces, and (3) sensory stimulus representations of the integrated auditory stimulus represented by MMN. In contrast to BAEP, the first long-latency components P50 and N1 index the retention of a stimulus-specific code over a prolonged period of time (i.e., form a feature trace). Our findings are compatible with two studies that examined the effect of repetition within varying acoustic stimulation. Dyson et al. (2005) observed repetition effects in the latency range of the MLR (P30, P50, N70, and P90). Näätänen and Rinne (2002) identified a late negativity and they too observed an earlier positivity in the time range of the N1 when random frequency sounds were occasionally repeated.

The RP had its onset at around the latency of the P50 and extended beyond the time window of the P2 to ~250 ms poststimulus. Hence, RP does reflect not only changes in a single ERP component such as N1, which is known to be sensitive to stimulus frequency and shows amplitude decrement with stimulus rep-

etition (Näätänen 1992). In addition, the N1 component exhibits a broader frequency tuning than MMN (Näätänen et al., 1988; Näätänen, 1992). It is nevertheless possible that the neurons contributing to N1 generation could acquire better frequency resolution through stimulus repetition, as shown for SSA in AI neurons (Ulanovsky et al., 2004).

The P50 and P2 peaks likewise show amplitude decrements with stimulus repetition, although with different recovery cycles (Erwin and Buchwald, 1986; Lu et al., 1992; Javitt, 2000). One possibility is that RP originated from a combined modulation of P50, N1, and P2 potentials, rather than from a separate ERP component. The decrements in P50 and P2 at short interstimulus intervals, observed with constant stimuli, suggest that refractoriness effects would diminish the RP, unlike the enhancement observed here. However, if repetitions within changing auditory stimuli were investigated, P30 and P50 were enhanced with repetition (Dyson et al., 2005), in agreement with our findings.

It is not known currently which forms of auditory sensory representation are reflected by RP. By virtue of its time course overlapping with P50, N1, and P2 peaks, including the typical latency range of MMN, it could index sensory memory operations on individual feature traces (frequency in this experiment) as well the integrated stimulus representation. So far, the latter is supported by its prolonged time course (until 400 ms poststimulus in Fig. 4), as well as its modulation by top-down mechanisms, evident when subjects performed an overt discrimination task. It is not yet known whether auditory features other than frequency give rise to such RP effects and whether masking stimuli would affect the development of RP, as is the case for MMN (Winkler et al., 1993).

Neural generators of RP

The onset of RP in the latency range of P30 and P50 strongly implicates the primary auditory cortex in its generation. Based on a latency comparison with intracranial generators of late AEP components (N70, N1, and P2), the generation of the later part of RP from 70 ms onwards could involve the lateral HG (AII), planum temporale, and the cortex anterior to HG (Liegeois-Chauvel et al., 1991, 1994; Godey et al., 2001). Furthermore, generators within the frontal cortex cannot be excluded, because of the reciprocal connectivity of auditory parabelt regions with lateral and medial frontal regions (Romanski et al., 1999).

Indeed the frontal scalp distribution of the later part of RP has been observed previously (Baldeweg et al. 2004, 2005), with no clear evidence for a polarity inversion below the Sylvian fissure. This implicates neural generators distinct from primary auditory cortex. However, because of the ambiguity of the inverse problem, invasive recordings are required to confirm this. Similarly, mismatch potentials recorded from temporal (mastoid) and frontal electrodes partially may originate from different sources, despite the polarity inversion typical for a single dipole source in the superior temporal plane. This was based on studies of MMN scalp topography (Giard et al., 1990, 1995; Baldeweg et al., 1999, 2002; Rinne et al., 2000) and developmental changes (Gomot et al., 2000) and intracranial recordings in humans (Baudena et al., 1995; Halgren et al., 1995; Kropotov et al., 1995; Liasis et al., 2001; Rosburg et al., 2005). This dissociation was also visible here, showing ERP repetition effects in frontal but not in temporal electrodes in the passive condition.

Adaptation effects and MMN generation

The hypothesis that MMN could result from differential adaptation of superior temporal N1 generators (Jääskeläinen et al., 2004) has been thoroughly examined recently by Näätänen et al. (2005). Our data are in agreement with Näätänen et al. (2005) that separate mechanisms account for N1 and MMN by showing that the time course of RP and MMN extends well beyond that of N1. This is also supported by human intracranial identification of separate N1 and MMN generator sites (Rosburg et al., 2005). Our data show that rapid SSA may underlie echoic memory-trace formation (see also Ulanovsky et al., 2003) by identifying an ERP component (RP), which accounts for most of the MMN memory-trace effect. The original mismatch hypothesis is also supported by identifying a temporal component that is relatively resistant to adaptation effects and that may hence represent a true mismatch detector. Furthermore, the repetition and stimulus effects in the P50 latency range support the notion that new afferent inputs at the level of AI do not contribute to MMN per se (Näätänen et al., 2005) but only in interaction with a strong memory trace.

Neurophysiology of auditory sensory memory

The neurophysiological basis of sensory memory and change detection can be investigated in detail only in animal models (Javitt, 2000). Indeed, the neuronal mechanism of SSA identified in the auditory cortex of the cat shows the characteristic differential response to probabilistic (oddball) stimuli, as identified in human MMN recordings (Ulanovsky et al., 2003, 2004). The remarkable agreement with the present study is the identification of rapid and stimulus-specific adaptation of neural responses to repeated standards, whereas the response to deviants did not change with repetition. Some of the long-term adaptation effects displayed by those auditory neurons (Ulanovsky et al., 2004) may also have a counterpart in human ERP changes (enhanced P50 and P2) across a time scale of a few minutes (Baldeweg et al., 1999) and up to days (Atienza et al., 2002).

The neurophysiological model proposed by Näätänen (1992) and modified by Javitt et al. (1996) assumed that repeating stimuli lead to an increase in tonic inhibition of supragranular auditory neurons that are sensitive to the frequency of the standard stimulus while simultaneously decreasing the level of inhibition of neurons not sensitive to this frequency. Our results are compatible with increasing suppression of neuronal activity coding the frequency of the standard, because increasing RP could be correlated with the suppression of neuronal activity observed in cat auditory cortex. However, this interpretation regarding its neurophysiological basis remains speculative. In contrast, we did not find evidence for the notion of release from inhibition of all other neurons in the time window of the mismatch response [i.e., the correlate of a sensory-memory system according to Näätänen (1992)], because no significant repetition effect was observed for the negativity elicited by deviants in the 80–180 ms time window (Ulanovsky et al., 2003, 2004).

Previously, we found stimulus-specific adaptation effects on oscillatory EEG activity before and after the occurrence of MMN (Haenschel et al., 2000). In future studies, it will be important to investigate the relationship between ERPs and oscillatory neuronal activity (Doheny et al., 2000) during sensory memory formation.

The present data may help to shed some light on the nature of MMN deficits in schizophrenia, in which MMN has proven to be a robust biological marker of disease duration and severity (Javitt, 2000; Umbricht and Krljes, 2005). The major part of this MMN deficit is caused by selective attenuation of the frontal MMN component (Baldeweg et al., 2002; Sato et al., 2003; Todd et al., 2003). The loss of adaptive properties of this frontal component

(including RP) is correlated robustly with measures of cognitive impairment and social dysfunction in chronic schizophrenia (Baldeweg et al., 2004; Light and Braff, 2005). Unraveling the processes of auditory plasticity that enable such rapid sensory adaptation may also shed light on the neuronal and molecular mechanisms underlying this severe mental illness.

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