Research Article

Lateralization and Binaural Interaction of Middle-Latency and Late-Brainstem Components of the Auditory Evoked Response

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ABSTRACT

We used magnetoencephalography to examine lateralization and binaural interaction of the middle-latency and late-brainstem components of the auditory evoked response (the MLR and SN10, respectively). Click stimuli were presented either monaurally, or binaurally with left- or right-leading interaural time differences (ITDs). While early MLR components, including the N19 and P30, were larger for monaural stimuli presented contralaterally (by approximately 30 and 36% in the left and right hemispheres, respectively), later components, including the N40 and P50, were larger ipsilaterally. In contrast, MLRs elicited by binaural clicks with left- or right-leading ITDs did not differ. Depending on filter settings, weak binaural interaction could be observed as early as the P13 but was clearly much larger for later components, beginning at the P30, indicating some degree of binaural linearity up to early stages of cortical processing. The SN10, an obscure late-brainstem component, was observed consistently in individuals and showed linear binaural additivity. The results indicate that while the MLR is lateralized in response to monaural stimuli—and not ITDs—this lateralization reverses from primarily contralateral to primarily ipsilateral as early as 40ms post stimulus and is never as large as that seen with fMRI.

Keywords: middle-latency response, lateralization, binaural interaction, interaural time difference, auditory brainstem response, SN10

INTRODUCTION

The auditory middle-latency response (MLR), with vertex-positive deflections at 13, 30, and 50 ms (P13, P30, P50) and vertex-negative deflections at 19 and 40 ms (N19, N40) (Geisler et al. 1958; Picton et al. 1974; Davis and Hirsh 1979; Ozdamar and Kraus 1983), represents the earliest components of the auditory evoked response (AER) with generators in auditory cortex (AC) (Celesia 1976; Scherg and Von Cramon 1986; Liégeois-Chauvel et al. 1994) and is thus crucial for understanding early cortical processing in audition. Furthermore, the MLR has also been used to assess temporal acuity of auditory cortex (Rupp et al. 2002a), peripheral auditory function (Rupp et al. 2002b; Atcherson and Moore 2014), functional integrity of the ascending auditory pathway (Musiek et al. 1984; Fifer and Sierra-Irizarry 1988; Kraus and McGee 1990; Alain et al. 2013), and depth of anesthesia (Plourde 2006), making it an important tool in both research and clinical settings.

Unlike the primary visual and somatosensory cortices, where afferent projections derive exclusively from the contralateral hemifield (Wall and Dubner 1972; Rodieck 1979) resulting in highly lateralized cortical responses to lateralized stimuli (Buchner et al. 1994; Clark et al. 1994), the primary AC receives

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substantial ipsilaterally derived projections (Brugge 2013). These can be either excitatory or inhibitory, while contralaterally derived projections are thought to be exclusively excitatory (Phillips and Gates 1982). Whether such functional neuroanatomical gradients nevertheless result in lateralized MLRs remains unclear. Although it is well established that *later* components of the auditory evoked response—especially the N1—can be lateralized in response to both monaural (Scherg and Von Cramon 1986; Woldorff et al. 1999; Hine and Debener 2007; Königs and Gutschalk 2012) and lateralized binaural (McEvoy et al. 1993; McEvoy et al. 1994; Palomäki et al. 2005; Johnson and Hautus 2010; Königs and Gutschalk 2012) stimuli, previous studies examining the MLR are inconclusive. While some have reported balance for monaural stimulation (Peters and Mendel 1974; Scherg and Von Cramon 1986; Kileny et al. 1987; Jacobson and Grayson 1988), others have indicated varying degrees of contralateral dominance for the N19 (Woods and Clayworth 1985), the N19-P30 pair (Woods et al. 1987), the P30 and P50 (Mäkelä et al. 1994), or the P50-N100 pair (Pantev et al. 1986), but not for binaural stimuli lateralized by interaural time differences (ITDs) (McEvoy et al. 1994).

Apart from providing new insight into early cortical auditory processing, establishing the laterality of the auditory MLR would assist in understanding the relationship between the dendritic currents measured by M/EEG (Lopes da Silva 2013) and the fMRI BOLD signal, which is thought to reflect a combination of synaptic activity and spiking (Singh 2012). In response to monaural stimulation, fMRI typically shows strong contralateral dominance, often double in amplitude for contralateral compared to ipsilateral stimuli (Scheffler et al. 1998; Woldorff et al. 1999; Jäncke et al. 2002; Langers et al. 2005; Gutschalk and Steinmann 2015). In response to ITD-lateralized sounds, fMRI shows little or no contralateral dominance (Woldorff et al. 1999; von Kriegstein et al. 2008; McLaughlin et al. 2015). Given that the long-latency components of the AER are only slightly lateralized in response to either monaural or lateralized binaural stimuli, and if auditory fMRI activity is more strongly coupled to earlier, faster components of the AER (i.e., the MLR), this would suggest that the MLR might be strongly lateralized in response to monaural sounds.

Utilizing whole-head magnetoencephalography in 10 normal-hearing listeners, we reexamined lateralization of the MLR in response to both monaural and binaural, ITD-lateralized click stimuli. After it was found that the SN10—a late, infrequently observed midbrain response (Davis and Hirsh 1979; Hashimoto 1982)—was consistently present in our listeners, we used this response in conjunction with those from cortex to examine another discrepancy between fMRI

and M/EEG data. Specifically, early components of the AER tend to show binaural responses that are approximately equal to the sum of their monaural counterparts, i.e., little to no binaural interaction (but see Riedel and Kollmeier 2002; Riedel and Kollmeier 2006; Junius et al. 2007), while later components tend to show sub-additivity (Pratt 2013). In contrast, the lone fMRI study examining this question showed monaural activity that was itself larger than its binaural counterpart—i.e., strong sub-additivity—at every structure examined, down to and including the inferior colliculus (IC) (Krumbholz et al. 2005). We therefore evaluated if the later brainstem response potentially shows a pattern that is more similar to fMRI results.

METHODS

Ethics Statement

All procedures were approved by the Institutional Review Board at the University Hospital Heidelberg in accordance with the Declaration of Helsinki, and all participants provided written informed consent prior to participation.

Listeners

Eleven healthy listeners with no reported history of hearing disorders were recruited for the study (five males; 20–43 years of age, mean 25.6). One female listener was excluded from analysis due to low signal-to-noise ratio of the averaged evoked responses, leaving five male and five female listeners in the remaining analyses.

Stimuli and Procedure

All sound stimuli were generated in MATLAB (The Mathworks, Natick, MA) and stored as 32-bit wav files at a sampling rate of 48 kHz. The digital sound files were converted to analog waveforms by an on-board sound card (RME DIGI96/8 PAD) and freestanding DA converter (RME ADI-8 DS, RME, Haimhausen, Germany) controlled by SoundMexPro software (SoundMexPro, Oldenburg, Germany) in the MATLAB environment. The analog stimuli then passed through a programmable attenuator (TDT PA5) before being amplified (TDT HB7, Tucker-Davis Technologies, Alachua, FL, USA) and presented to listeners via ER-3 insert earphones (Etymotic Research, Elk Grove Village, IL, USA). Note that our choice of ER-3 earphones effectively low-pass filtered our click stimuli at approximately 3 kHz—this is unlikely to have affected our results.

The stimuli used in the study were sequences of clicks with interclick intervals ranging between 97 and 137 ms. Each click consisted of four “up” samples at a sampling rate of 48 kHz with one of five conditions: (1) monaural left, (2) monaural right, (3) dichotic with a $-604.17\text{-}\mu\text{s}$ ITD (29 samples at 48 kHz), (4) dichotic with a $604.17\text{-}\mu\text{s}$ ITD, or (5) diotic. The left- and right-leading ITD stimuli were used to determine whether perceived lateralization or lateralization, *per se*, is the crucial factor underlying lateralized MLRs. Six thousand instances of each click condition were presented to each listener in random order, split across two blocks (3000 instances per condition per block). The recording time needed for each block was approximately 30 min, for a total recording time of approximately 1 h. Stimuli were presented at 96-dB peak-equivalent SPL, which was indicated by pilot studies to be a comfortable listening level.

Data Acquisition

MEG was recorded using a whole-head system comprised of two orthogonal planar gradiometers at each of 61 locations around the head (Ahonen et al. 1993) and digitized at a sampling rate of 1000 Hz with an online band-pass filter between 0.03 and 330 Hz. Stimulus trigger pulses were produced by the remaining six channels of the same eight-channel sound card used to present the sound stimuli and recorded by the MEG acquisition system. Thus, temporal resolution of stimulus-locked averaging was limited only by the 1000-Hz sampling rate of the MEG acquisition. Prior to the MEG session, the locations of 32 points around the head, referenced to the coordinate system defined by three cardinal points (left and right preauricular points and the nasion), were digitized using the Polhemus tracker system (Colchester, VT, USA). Participants' head position within the dewar was measured by four head position-indicator coils placed on the left and right mastoids and forehead. During the recording, participants watched a silent movie of their choosing and were instructed to remain as still as possible.

Preprocessing

MEG data were analyzed using BESA 5.1 (BESA GmbH, Gräfelfing, Germany). Bad channels, *i.e.*, channels with either no signal or excessive noise, were rejected by visual inspection. The data were then divided into epochs spanning from 10 ms before to 70 ms after click onset and binned according to click condition; epochs containing large artifacts were automatically rejected using a gradient criterion ($<2\%$ of all epochs, on average). The epochs were then baseline corrected by subtracting the mean

signal in the baseline period (at 0 ms and from 0 to 10 ms for brainstem and cortical responses, respectively) and averaged. A grand average comprised of all conditions was additionally created for both source analysis (see below) and display purposes.

Source Analysis

The 32 digitized head points were used to approximate the position of a spherical head model for each listener. The source configuration used to model the grand-averaged MEG waveforms in each listener consisted of three equivalent current dipoles, one in each auditory cortex on the superior temporal plane and one in the midbrain fixed to be just below the approximate location of the inferior colliculi using the BESA template brain (Table 1). The cortical dipoles were fit to the peak of the P30—a vertex-positive (in EEG) component of the MLR occurring approximately 30 ms post stimulus—after inspection of sensor-level waveforms indicated that it was the largest and most consistent component across listeners. Subsequently, the orientation of the midbrain dipole (whose location was fixed) was fit to the peak of the SN10, an infrequently observed negativity occurring at 10 ms post stimulus. The resulting dipole models were then used to construct spatially filtered source waveforms for all conditions in all listeners and saved as ASCII files for further analysis using Python. Note that the polarity of our cortical source waveforms is in reference to the surface of auditory cortex, which is also consistent with how such potentials are typically recorded at the vertex in EEG.

The data were then low-pass filtered at 150 Hz using a zero phase-shift, second-order Butterworth filter, detrended, and baseline corrected. For detrending, the epoch-length linear trend (as determined by a least-squares fit to the data) was subtracted from each epoch. The amplitudes and latencies of each of four successive MLR peaks in the cortical source waveforms were then measured in the following intervals: N19 (15–25 ms), P30 (25–35 ms), N40 (35–45 ms), and P50 (45–55 ms). As no high-pass filter was used, amplitudes for each component were referenced to the immediately preceding component (*i.e.*, P13–N19, N19–P30, P30–N40, and N40–P50), which was necessary for putatively negative-going components that were positive if surrounded by large positive components (the N40, in particular). Finally, the amplitude and latency of the SN10 in the midbrain source was measured as the negative peak occurring between 5 and 15 ms post stimulus.

To examine whether the resulting midbrain activity might instead have reflected unaccounted-for cortical activity, we also analyzed the data using a classical two-dipole model (one source in each AC). The resulting

Table 1

Talairach coordinates (in mm) for the two AC sources and dipole orientation for the midbrain source. Mean $\pm$ s.e.m. (standard error of the mean across listeners). Note that i_{hat} , j_{hat} , and k_{hat} denote vector strengths (with values ranging from zero to one) away from the sagittal, coronal, and axial planes, respectively

	x	y	z	i_{hat}	j_{hat}	k_{hat}
Left AC	-44.3 ± 1.7	-23.7 ± 3.1	5.6 ± 3.8	0.01 ± 0.06	0.64 ± 0.06	0.72 ± 0.04
Right AC	44.4 ± 2.3	-23.0 ± 2.2	8.0 ± 1.9	-0.06 ± 0.05	0.56 ± 0.07	0.77 ± 0.04
Midbrain	0	-35.2	-15.9	0.01 ± 0.08	0.70 ± 0.00	-0.66 ± 0.02

AC source waveforms were nearly identical to those from the three-dipole model (data not shown). Thus, we present only the results from the three-dipole model.

Lateralization Indices

To quantify the amount of lateralization exhibited by the MLR, we computed lateralization indices for each component pair in each of two ways. The first, which is consistent with the index used by previous literature, was defined for each ear as the difference between the right and left AC responses, i.e., $\text{Lat}_{\text{Ear}} = (|\text{Right AC}| - |\text{Left AC}|) / (|\text{Right AC}| + |\text{Left AC}|)$. The second is defined in each hemisphere as the response elicited by the ipsilateral stimulus subtracted from that elicited by the contralateral stimulus, divided by their sum, i.e., $\text{Lat}_{\text{Hemi}} = (|\text{Contra}| - |\text{Ipsi}|) / (|\text{Contra}| + |\text{Ipsi}|)$. By computing lateralization within a hemisphere across the two ears, this latter index eliminates confounds of hemispheric asymmetry, which can be quite strong for tonal stimuli in auditory cortex (with typically right-ear > left-ear responses) due in large part to anatomical differences resulting in differing amounts of field cancellation (Shaw et al. 2013).

Binaural Difference Responses

To examine binaural interaction in both cortical and subcortical waveforms, we computed binaural difference waveforms by subtracting the mean of the responses to binaural conditions from the sum of responses to monaural conditions (van Olphen et al. 1978; Dobie and Norton 1980; Levine 1981; Wrege and Starr 1981). The binaural difference response gives an indication of the linear additivity of monaural responses, and prominent deflections in the binaural difference response are thought to reflect neuronal activity specific to binaural stimulation (Dobie and Berlin 1979; Gaumond and Psaltikidou 1991). To quantify the binaural difference response, we computed average amplitudes within 2.5 ms of each of three grand average peaks in both the cortical and subcortical waveforms. For the cortex (midbrain), these peaks were at 12, 27, and 53 ms (10, 19, and

34 ms). Note that the waveforms from left and right AC were collapsed prior to computing these amplitudes.

Statistical Analysis

Peak amplitudes and latencies were evaluated using a repeated-measures analysis of variance (ANOVA) framework in R (<http://www.r-project.org/>). When appropriate, additional ANOVAs and post hoc paired comparisons were performed (see the “Results” section). In order to balance and simplify the statistical analysis, the peak amplitude and latency values from the diotic control condition were excluded after it was found that they did not differ from either of the ITD-lateralized binaural conditions. Subsequently, for the cortical sources, the peak amplitude values from each of the four component pairs (P13-N19, N19-P30, P30-N40, and N40-P50) were entered into separate three-way ANOVAs with hemisphere (left vs. right), type (monaural vs. binaural), and side (contralateral vs. ipsilateral) as factors. The same analysis on latency values was performed but on individual components rather than component pairs. The peak and latency values from the midbrain source were evaluated for the SN10 component only, using a one-way ANOVA with condition as the lone factor. For peaks in the binaural difference waveforms, single-sample, two-sided *t* tests were used to evaluate whether each peak was significantly different from zero.

RESULTS

Grand-average source waveforms displayed the characteristic components of the MLR, including the P13, N19, P30, N40, and P50 (Fig. 1). All conditions elicited nearly identical responses, with the exceptions being (i) the qualitatively different response elicited by the monaural, ipsilateral stimulus (I_{Mon}) and (ii) the larger N19 elicited by binaural vs. monaural stimuli, particularly in right AC. Visual inspection of the blue, I_{Mon} , waveform in Figure 1C suggests that the difference between this waveform and those elicited by the remaining

Fig. 1. Paradigm and cortical source waveforms. **A** Stimulus conditions and experimental design. **B** Grand-average source locations/orientations overlaid onto BESA's template brain/head surface. **C** Auditory cortex source waveforms for the grand average (all conditions collapsed; *top panels*) as well as each condition separately (*bottom panels*). Five main peaks of the MLR are visible: P13, N19, P30, N40, and P50. The *solid (dashed) traces* show the

waveforms for the monaural (binaural) conditions. The response to the diotic click stimulus is not shown, after it was found that it did not differ from either of the remaining binaural conditions. C_{Mon} contralateral monaural stimulus, I_{Mon} ipsilateral monaural stimulus, C_{Bin} contra-leading binaural stimulus, I_{Bin} ipsi-leading binaural stimulus.

three conditions manifested itself as (i) a smaller (relative to the preceding P13), delayed N19; (ii) a smaller, earlier P30; (iii) an N40, or at least a stronger one; and (iv) a larger P50.

Cortical Sources—Amplitude

To quantify these effects, we computed peak amplitudes and latencies for each of the four components (component pairs, in the case of amplitude) and conditions (Fig. 2A). The most consistent effect was a stronger overall response in right AC compared to left AC, consistent with previous reports (main effect of hemisphere for each component pair, cf. Table 2). An additional main effect of type was observed for the P13-N19 and N19-P30. This seems real for the P13-N19 given that both monaural stimuli elicited smaller responses than either binaural stimuli (Fig. 2A, leftmost panel). For the N19-P30, however, this effect (as well as a main effect of side) was likely driven exclusively by the smaller response to the I_{Mon} condition; the C_{Mon} stimulus elicited a response

nearly as large as either binaural stimuli. This was confirmed by a significant two-way interaction between type and side. For the P13-N19, we additionally observed a significant hemisphere-by-type interaction, suggesting that the difference between monaural and binaural responses was larger in one hemisphere. This was confirmed by subsequent two-way ANOVAs (one for each hemisphere), where it was found that the binaural/monaural difference in the P13-N19 amplitudes was larger and more robust in right AC, though both were significant (left AC: $F_{1,9}=7.6$, $P<0.05$; right AC: $F_{1,9}=42.8$, $P<0.0005$). For the P30-N40 pair, no significant effects were observed apart from the main effect of hemisphere. For the N40-P50 pair, we observed a significant type-by-side interaction, here driven by *larger* I_{Mon} responses compared to the other conditions (Fig. 2A, right-most panel).

Because one of the primary reasons for conducting the study was to examine MLR lateralization, we additionally performed paired amplitude comparisons, in each AC and for each

Fig. 2. Cortical amplitude (A) and latency (B) quantifications for each of the four component pairs (for amplitude) or components (for latency). Error bars denote standard error of the mean across

listeners. Legend as in Fig. 1. For display purposes, values were collapsed across hemispheres but analyzed separately statistically.

component pair, between the contralaterally and ipsilaterally evoked responses for the monaural conditions. This analysis indicated significant lateralization in each AC for the N19-P30 (left AC: $T_9=2.7$, $P<0.05$, right AC: $T_9=4.6$, $P<0.01$), the N40-P50 (left AC: $T_9=2.6$, $P<0.05$, right AC: $T_9=2.9$, $P<0.05$), and a trend in right AC for the P13-N19 ($T_9=2.0$, $P=0.075$).

To further quantify MLR lateralization, we computed a lateralization index for each component pair in each of two ways (see the “Methods” section), the first defined for each ear (Lat_{Ear}) and the second defined for each hemisphere (Lat_{Hemi} ; cf. Table 3). For the Lat_{Ear} index, positive values indicate that responses are stronger in right AC, while negative values indicate larger responses in left AC. It is apparent from this index that right AC responses were generally larger than left AC responses, consistent with previous auditory MEG studies using tonal stimuli. For the Lat_{Hemi} index, positive values indicate that responses are stronger

in response to contralateral stimulation; negative values indicate responses that are stronger in response to ipsilateral stimuli. Here, the earlier component pairs had positive values indicating larger responses elicited by contralateral stimuli. This trend was reversed for the N40-P50 pair, reflecting larger ipsilaterally driven responses at those latencies. Differences between left and right AC lateralization indices were never statistically significant. As the latter index avoids the typical right > left asymmetry and thus yields values that are more consistent and easier to interpret in the context of lateralization, we focus our later discussion on it.

Cortical Sources—Latency

The statistical pattern of results for component latencies is summarized primarily by a type-by-side interaction for the N19, P30, and N40 components, driven by (i) a later N19 and (ii) earlier P30s and N40s

Table 2
Component pair amplitude and latency statistics

	Amplitude				Latency			
	P13-N19	N19-P30	P30-N40	N40-P50	P13-N19	N19-P30	P30-N40	N40-P50
Hemi (L vs. R)	7.9*	6.2*	5.5*	19.2**	2.9, n.s.	0.9, n.s.	3.4	1.0, n.s.
Type (M vs. B)	29.4***	20.6**	0.8, n.s.	1.5, n.s.	4.1	8.7*	25.3**	0.2, n.s.
Side (C vs. I)	2.0, n.s.	14.6**	0.9, n.s.	10.7*	20.2**	2.9, n.s.	22.0**	0.0, n.s.
Hemi × type	11.8*	0.8, n.s.	0.6, n.s.	0.1, n.s.	1.6, n.s.	1.8, n.s.	0.2, n.s.	0.1, n.s.
Hemi × side	1.2, n.s.	0.1, n.s.	0.2, n.s.	0.9, n.s.	0.5, n.s.	0.1, n.s.	0.4, n.s.	0.3, n.s.
Type × side	2.0, n.s.	19.3**	0.1, n.s.	8.9*	13.8**	3.5	9.8*	0.7, n.s.
3-way interaction	1.5, n.s.	0.1, n.s.	0.2, n.s.	0.5, n.s.	0.9, n.s.	0.0, n.s.	0.3, n.s.	0.0, n.s.

The value in each cell represents an F value with 1 and 9 ° of freedom in the numerator and denominator, respectively (i.e., $F_{1,9}$), reflecting the fact that there were two levels in each factor and 10 participants. Hemisphere: right vs. left. Type: monaural vs. binaural. Side: contralateral vs. ipsilateral

· $P<0.1$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$

Table 3

Lateralization indices for each source and component pair from the monaural conditions. By ear, a positive (negative) index indicates that the response was stronger in right (left) AC. By hemisphere, a positive (negative) index indicates that the response was stronger in response to contralateral (ipsilateral) stimulation

	<i>P13-N19</i>	<i>N19-P30</i>	<i>P30-N40</i>	<i>N40-P50</i>
Lat_{Ear}				
Left ear	0.39 ± 0.10 $T_9 = 3.2^*$	0.35 ± 0.07 $T_9 = 4.7^{**}$	0.20 ± 0.07 $T_9 = 2.5^*$	0.02 ± 0.11 $T_9 = 0.14$, n.s.
Right ear	-0.02 ± 0.17 $T_9 = -0.10$, n.s.	-0.14 ± 0.06 $T_9 = -2.2^*$	0.06 ± 0.10 $T_9 = 0.53$, n.s.	0.49 ± 0.05 $T_9 = 7.7^{***}$
Lat_{Hemi}				
Left AC	0.19 ± 0.15 $T_9 = 1.2$, n.s.	0.25 ± 0.09 $T_9 = 2.7^*$	0.07 ± 0.09 $T_9 = 0.73$, n.s.	-0.26 ± 0.11 $T_9 = -2.3^*$
Right AC	0.26 ± 0.13 $T_9 = 1.9^*$	0.24 ± 0.05 $T_9 = 4.8^{**}$	0.08 ± 0.09 $T_9 = 0.88$, n.s.	-0.22 ± 0.07 $T_9 = -2.9^*$

We did not observe any significant differences between the left and right AC indices, indicating similar bias in each AC for either contralateral (in the case of the N19 and/or P30) or ipsilateral (N40 and/or P50) responses. T values below each index indicate whether it differed significantly from zero

$^*P < 0.1$; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

for the I_{Mon} condition (cf. Table 2); no significant latency effects were observed for the P50 (Fig. 2B).

Midbrain Source

Figure 3 shows the midbrain grand-averaged source orientation (panel A) and waveform (panel B, upper panel), the waveforms for each of the four conditions averaged separately (panel B, lower panel), and amplitude and latency quantifications (panels C and D, respectively). The SN10 is clearly present as a negative deflection in the waveforms around 10 ms and was highly consistent across individuals in terms of both dipole orientation and

waveform morphology. Two-way ANOVAs computed on the peak amplitude and latency values for the SN10 indicated that amplitude was significantly larger for binaural vs. monaural stimulation ($F_{1,9} = 50.9$, $P < 0.0001$); there was no significant effect of latency ($F_{1,9} = 1.4$, n.s.). Neither amplitude nor latency was significantly affected by whether the stimulus was presented to the left or right ear, and there were no significant interactions. Later deflections were also clearly present in the midbrain source at 18, 22, and 33 ms. As we neither hypothesized their occurrence nor set out to examine them, and given their temporal overlap with active cortical sources, we did not analyze

Fig. 3. Midbrain source analysis and amplitude/latency quantifications. **A** Average source orientation. **B** Grand-averaged source waveforms collapsed across all conditions (top panel) and for each of the five stimulus conditions separately (bottom panel). The SN10 is clearly visible as a negative-going deflection at ~10 ms. R_{Mon} right-ear monaural stimulus, L_{Mon} left-ear monaural stimulus, R_{Bin} right-

leaded binaural stimulus, L_{Bin} left-leading binaural stimulus. Question marks denote components of questionable source origin. **C**, **D** SN10 amplitude and latency quantifications for all conditions. Legend same as in **B**. Error bars denote standard error of the mean across listeners.

them in detail. However, we return to them in the discussion.

Binaural Difference Responses

Binaural difference responses are shown in Figure 4. For the cortical sources, three positive-going peaks in binaural difference waveforms (gray traces) can be observed, peaking at 12, 27, and 53 ms. Because the binaural difference responses from left and right AC were similar, we averaged them before computing peak amplitudes and statistics. The resulting peaks at 27 and 53 ms were significantly different from zero (27 ms: $T_9=5.5$, $P<0.001$; 53 ms: $T_9=4.0$, $P<0.01$). There was also a trend for the peak at 12 ms ($T_9=1.9$, $P=0.09$), though a supplemental analysis using narrower band-pass filters (20–150 Hz as opposed to 0–150 Hz) did not reveal such a peak in the binaural difference waveforms (Fig. 5). Although there is likely substantial binaural interaction at around the time of the N40 given the fact that the I_{Mon} condition was the only condition to definitely elicit this deflection (cf. Fig. 1C), this interaction does not manifest itself in the binaural difference waveform given the facts that (i) the response of the I_{Mon} condition is phase advanced relative to any of the other conditions and (ii) the I_{Mon} and C_{Mon} traces are of opposite polarities at this latency. The binaural interaction at this latency appears stronger if we apply a 20-Hz high-pass filter to the waveforms and results in a significant peak in the binaural difference waveform at 39 ms ($T_9=-4.2$,

$P<0.01$). Finally, although the amplitudes of the later two peaks (at 27 and 53 ms) appear similar, it is worth noting that the binaural difference response itself (gray traces) was larger than the mean binaural response (dashed pink traces).

The N19 appeared to behave in a fundamentally different, supra-additive manner. That is, the N19 peak of the binaural mean response is more negative than the N19 of the sum of the two monaural conditions. In our opinion, this likely reflects either (i) the fact that peaks at both 12 and 27 ms (likely corresponding to the P13 and P30) show sub-additivity, perhaps making the N19 of the monaural sum artificially positive, or (ii) the difficulty in obtaining sufficient SNR for these early, small components. Indeed, when using the same 20-Hz high-pass filter that was used to evaluate the N40, the 12-ms peak in the binaural difference waveform is not statistically different from zero ($T_9=0.4$, n.s.), and the binaural difference waveform is completely flat until the P30 latency, suggesting linear additivity of the N19.

For the midbrain source, no significant difference was observed in the latency range of the SN10 ($T_9=0.51$, $P=0.62$). In contrast, two later peaks at 19 and 34 ms were both significantly different from zero (19 ms: $T_9=2.8$, $P<0.05$; 34 ms: $T_9=4.4$, $P<0.01$). However, given the difficulty of measuring deep brain activity with MEG and the fact that these later peaks co-occurred with cortical sources, it is not clear whether they truly arose from the midbrain.

Fig. 4. Binaural difference (BD) responses for the cortical (A) and subcortical (B) sources and their amplitude quantifications (C, D). The binaural response is the average of the two binaural ITD conditions (C_{Bin} and I_{Bin} for A, R_{Bin} and L_{Bin} for B), and the monaural sum response is the sum of the two monaural

conditions ($C_{\text{Mon}} + I_{\text{Mon}}$ for panel A, $R_{\text{Mon}} + L_{\text{Mon}}$ for panel B). Note that both the peak amplitudes shown in panel C and the associated statistical tests were computed after collapsing across the two hemispheres.

Fig. 5. Cortical source waveforms and binaural difference responses after applying a 20-Hz HPF. **A** Grand-average (*top panels*) and individual condition (*bottom panels*) source waveforms (**B**). Corresponding binaural difference responses.

DISCUSSION

The present findings demonstrate a robust contralateral dominance of the P30 in response to monaural stimulation but no significant lateralization for ITD-lateralized stimulation. Unexpectedly, the subsequent N40 and P50 peaks showed ipsilateral instead of contralateral dominance. Furthermore, the data show that the SN10, an infrequently observed brainstem response, can be reliably recorded with MEG using tailored source analysis methods.

Generators and Lateralization of the MLR

Like many previous M/EEG, intracranial, and lesion-effect studies, our data clearly implicate primary auditory cortex as the main generator of the MLR (Celesia 1976; Kraus et al. 1982; Özdamar et al. 1982; Scherg and Von Cramon 1986; Liégeois-Chauvel et al. 1994; Hashimoto et al. 1995; Kuriki et al. 1995; Gutschalk et al. 1999; Godey et al. 2001; Rupp et al. 2002b; Yvert et al. 2005; Parkkonen et al. 2009). Lateralization of the MLR in response to monaural stimulation, however, has historically been controversial, with some EEG studies reporting lateralization (Woods and Clayworth 1985; Woods et al. 1987; Cacace et al. 1990; Kaseda et al. 1991) and others

reporting balance (Peters and Mendel 1974; Scherg and Von Cramon 1986; Kileny et al. 1987; Jacobson and Grayson 1988). Consistent with human intracranial recordings (Celesia 1976), MEG has shown lateralization, both of the P30 (Mäkelä et al. 1994; Yvert et al. 2001) and the related auditory steady-state response (ASSR) (Ross et al. 2005; Gutschalk et al. 2012), which reflects overlapping middle-latency responses (Gutschalk et al. 1999; Bohórquez and Ozdamar 2008).

Based on the present data, the P30 evoked by monaural clicks seems clearly lateralized, with a contralateral-greater-than-ipsilateral amplitude difference of approximately 40 % (i.e., a lateralization index of 0.25), consistent with previous ASSR data (Ross et al., 2005; Gutschalk et al., 2012). Numerically, the N19 showed similarly contralateral responses (cf. Table 3). However, these effects did not reach statistical significance, perhaps due to the relatively small size of the component and the difficulty in obtaining a clean baseline. Thus, N19 lateralization may well be somewhat smaller or larger than that observed here. The latter is suggested by the high-passed filtered data (Fig. 5), which enhances contralateral dominance of the N19 while attenuating contralateral dominance of the P30. Similar differences in data-analysis setups might have biased whether the N19 (Woods and Clayworth 1985) or

P30 (Mäkelä et al. 1994) was found to be contralaterally dominant previously.

Somewhat unexpected was the finding of ipsilateral dominance of the subsequent N40 and P50 components. To our knowledge, such an inverse lateralization effect has only been observed as a numerical trend for the N40 (Woods and Clayworth 1985) and in a subset of participants for the P50 (Mäkelä et al. 1994), and others have found the opposite effect, i.e., N40 and P50 responses that were larger for monaural stimuli presented contralaterally (Pantev et al. 1986; Mäkelä et al. 1994; Yvert et al. 2001). Such variable results for the later MLR components could in part be due to the presence of multiple P50 generators (Yvert et al. 2001), with some showing contralateral dominance and others showing ipsilateral dominance. The version of the P50 measured by a given study is likely related to details of the acoustic stimulation used.

While contralaterally dominant MLR responses might be expected given contralateral dominance of excitatory projections in the ascending auditory pathway, the ipsilateral dominance we observed for the N40/P50 is less intuitive. One explanation could be that the N40/P50 receives different input than the P30, perhaps inhibition from subcortical nuclei (Glendenning et al. 1992; Stecker et al. 2015) or excitation from the opposite hemisphere via the corpus callosum. Evidence for the latter idea comes from a recent MEG/fMRI study using 8-Hz steady-state responses, which reflects overlapping P50s (Gutschalk and Steinmann 2015). Though not the case in all participants, that study observed a trend for larger ipsilaterally driven responses that was reversed in a participant with callosal agenesis. Interestingly, the P50 (but not the P30) evoked by monaural stimulation is suppressed in the presence of a contralateral masking noise (Ozdamar and Bohórquez 2008), further suggesting that the P50 receives different input than the P30.

Note that we are not suggesting that different components reflect either exclusively excitatory or inhibitory post-synaptic potentials (PSPs); indeed, excitation and inhibition occur simultaneously in auditory cortex, at least in rodents (Wehr and Zador 2003). Accordingly, the remaining dissociation of stronger contralateral dominance in fMRI as compared to MEG might reflect a greater relative sensitivity of fMRI towards either excitatory PSPs or high-frequency synaptic activity, i.e., high gamma, an aspect of neural activity that is known to correlate strongly with the BOLD signal (Mukamel et al. 2005; Singh 2012) and which is difficult to observe with M/EEG. While detailed microelectrode data on this issue are lacking, what data are available show multiple laminar response profiles in primary auditory cortex of awake nonhuman primates (Reser et al. 2000;

Steinschneider et al. 2008), suggesting that the phenomenon is likely complex and multi-faceted.

Measuring the SN10 with MEG

Though it appeared consistently across participants in our data, prior MEG evidence for the SN10 is sparse (Hashimoto et al. 1995; Kuriki et al. 1995). It is more commonly observed with EEG (Picton et al. 1974; Davis and Hirsh 1979; Dobie and Norton 1980; Woods and Clayworth 1985; Tawfik and Musiek 1991; McPherson and Starr 1993) and likely arises from the midbrain given that (i) human intracranial recordings near the inferior colliculus show such a response (Hashimoto 1982; Møller and Jannetta 1982; Kadoya et al. 1998) and (ii) there are no simultaneous deflections in the cortex, either in the present study or in thalamic or cortical potentials recorded intracranially (Yvert et al. 2002). To our knowledge, only one previous MEG study has provided direct evidence of a response at 10 ms (Kuriki et al. 1995) and in only two of four participants. However, the source of that deflection was localized to the same vicinity as the other MLR components. The reason the SN10 was consistently observed in the present study may have to do with the fact that the location of our midbrain dipole was fixed and only its orientation fit. This, combined with the fact that the two cortical dipoles accounted for most of the activity arising from AC, perhaps allowed us to pull out midbrain activity that produces only minor field deflections outside the head.

Binaural Additivity

While binaural difference waves revealed that the SN10 showed near-linear summation, the P30 and subsequent waves of the MLR showed increased proclivity for binaural interaction, as in previous studies (Pratt 2013). In fact, the waveforms elicited by binaural and contralateral monaural stimuli were almost identical, resulting in a binaural difference response whose morphology was very similar to the response elicited by ipsilateral monaural stimuli. The N19 was the only cortical component that increased significantly for binaural vs. contralateral, monaural stimulation. In the binaural difference waves, however, there remained a sustained displacement around the N19 latency. The N19 thus appears to be more linear than the P30, though likely not as linear as the SN10, baseline issues notwithstanding. Later deflections of the midbrain source appeared very binaural, though it is difficult to say with certainty that these deflections are not thalamic (Yvert et al. 2002) or projections of unaccounted-for cortical activity (Scherg and Von Cramon 1986; Gutschalk et al.

1999) given that they co-occur with active cortical sources. However, intracranial potentials with similar latencies and morphology as the first of these deflections (at 18 ms), and perhaps the second (at 22 ms), have been observed in the human IC (Hashimoto 1982).

Taken together, these results are broadly consistent with previous M/EEG studies (Dobie and Norton 1980; Debruyne 1984; Woods and Clayworth 1985; McPherson et al. 1989; McPherson and Starr 1993; Polyakov and Pratt 1995; Junius et al. 2007), though our data generally show a larger increase of interaction with component latency. The long-latency N1 response, not measurable in the present study due to the short ISI, shows yet more interaction (Pantev et al. 1986; Königs and Gutschalk 2012). This would seem to suggest a hierarchy of binaural interaction (Pratt 2013). However, fMRI work has observed substantial binaural interaction down to the IC (Krumbholz et al. 2005), with individual monaural responses themselves as large or larger than binaural responses. While wave V of the ABR also shows binaural interaction, the interaction is small relative to the size of the peak (Riedel and Kollmeier 2002; Riedel and Kollmeier 2006; Junius et al. 2007). The binaural interaction of putative later midbrain components subsequent to the SN10 would therefore better match with the fMRI results, because the interaction would be stronger based on the source activity in this study, but the nature of these waves remains speculative at this point. Thus, instead of an anatomical hierarchy, currently available data suggest that monaural and binaural information is processed in parallel at various nuclei throughout the auditory pathway, with monaural information being reflected by the linear or near-linear additivity of the SN10 and N19 and binaural information marked by BOLD activity as well as wave V (and possibly late midbrain components). However, details of the N19's binaural additivity and the nature of late-brainstem waves remain to be determined.

Spatial Representation in the Auditory Pathway

The lone factor determining MLR morphology in our data was the presence or absence of stimulation in the contralateral ear. This suggests that the representation of acoustic space, per se, in primary auditory cortex is such that it does not strongly manifest itself in the population-level activity reflected by the MLR. This is consistent with previous M/EEG studies, in which the MLR has shown sensitivity neither to ITDs (McEvoy et al. 1994) nor to externalized percepts generated by head-related transfer functions (Junius et al. 2007). It is also consistent with human fMRI data, which has shown that primary auditory cortex is highly sensitive to both ear of stimulation (Woods

et al. 2010; Stecker et al. 2015; Gutschalk and Steinmann 2015) and interaural level differences (ILDs) (McLaughlin et al. 2015; Stecker et al. 2015), but not ITD (von Kriegstein et al. 2008; McLaughlin et al. 2015). Although ITD sensitivity has been found in human auditory cortex, it is generally located in more posterolateral areas (von Kriegstein et al. 2008; McLaughlin et al. 2015) and in long- as opposed to middle-latency components of the AER (McEvoy et al. 1993; Salminen et al. 2009; Salminen et al. 2010; Magezi and Krumbholz 2010; Gutschalk et al. 2012) (for reviews, see Salminen et al. 2012; Gutschalk 2014). In any case, the population-level representation of ITD at the level of the midbrain might be fundamentally different from that found in primary AC (Thompson et al. 2006; von Kriegstein et al. 2008; Belliveau et al. 2014; Vonderschen and Wagner 2014; Yao et al. 2015), though this is in need of further clarification.

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COMPLIANCE WITH ETHICAL STANDARDS

Ethics Statement All procedures were approved by the Institutional Review Board at the University Hospital Heidelberg in accordance with the Declaration of Helsinki, and all participants provided written informed consent prior to participation.

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