Research Article

Neural Correlates of the Binaural Masking Level Difference in Human Frequency-Following Responses

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Received: 10 February 2016; Accepted: 2 November 2016; Online publication: 28 November 2016

ABSTRACT

The binaural masking level difference (BMLD) is an auditory phenomenon where binaural tone-in-noise detection is improved when the phase of either signal or noise is inverted in one of the ears ($S_{\pi}N_o$ or S_oN_{π} , respectively), relative to detection when signal and noise are in identical phase at each ear (S_oN_o). Processing related to BMLDs and interaural time differences has been confirmed in the auditory brainstem of non-human mammals; in the human auditory brainstem, phase-locked neural responses elicited by BMLD stimuli have not been systematically examined across signal-to-noise ratio. Behavioral and physiological testing was performed in three binaural stimulus conditions: S_oN_o , $S_{\pi}N_o$, and S_oN_{π} . BMLDs at 500 Hz were obtained from 14 young, normal-hearing adults (ages 21–26). Physiological BMLDs used the frequency-following response (FFR), a scalp-recorded auditory evoked potential dependent on sustained phase-locked neural activity; FFR tone-in-noise detection thresholds were used to calculate physiological BMLDs. FFR BMLDs were significantly smaller (poorer) than behavioral BMLDs, and FFR BMLDs did not reflect a physiological release from masking, on average. Raw FFR amplitude showed substantial reductions in the $S_{\pi}N_o$ condition relative to S_oN_o and

S_oN_{π} conditions, consistent with negative effects of phase summation from left and right ear FFRs. FFR amplitude differences between stimulus conditions (e.g., S_oN_o amplitude– $S_{\pi}N_o$ amplitude) were significantly predictive of behavioral $S_{\pi}N_o$ BMLDs; individuals with larger amplitude differences had larger (better) behavioral BMLDs and individuals with smaller amplitude differences had smaller (poorer) behavioral BMLDs. These data indicate a role for sustained phase-locked neural activity in BMLDs of humans and are the first to show predictive relationships between behavioral BMLDs and human brainstem responses.

Keywords: auditory, binaural, binaural masking level difference, frequency-following response, neurophonic, phase locking

Abbreviations: BMLD – Binaural masking level difference; FFR – Frequency-following response; P(C) – Proportion correct; SNR – Signal-to-noise ratio; BAEP – Brainstem auditory evoked potential; MSO – Medial superior olive; IC – Inferior colliculus; ITD – Interaural time difference

INTRODUCTION

Binaural masking level differences (BMLDs) have been used to investigate binaural processing for the past ~60 years (Hirsh 1948; Licklider 1948) and are of interest in clinical populations such as cochlear implant users and aging adults with and without hearing loss (Dubno et al. 2008; Lu et al. 2010). Auditory brainstem processing related to BMLDs was suggested by theoretical models (Durlach 1963; Jeffress 1948), and has been confirmed in studies of animal electrophysiology in the medial superior olive (MSO) and inferior colliculus (IC)

Portions of this work were presented at the American Auditory Society's Annual Scientific and Technology Conference in Scottsdale, AZ, in 2015, and served as partial fulfillment of SH's Au.D. degree requirements.

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(Caird et al. 1991; Du et al. 2009b; Jiang et al. 1997a; McAlpine et al. 1996; Palmer et al. 2000; van der Heijden et al. 2013). In contrast, human literature has largely not found physiological correlates of BMLDs in brainstem auditory evoked potentials (BAEPs) (Fowler and Mikami 1996; Wilson and Krishnan 2005; Wong and Stapells 2004). The frequency-following response (FFR), a BAEP reflecting sustained phase-locked neural activity throughout the brainstem (Smith et al. 1975), may hold potential to relate behavioral and physiological measures of binaural processing using within-subjects designs.

The traditional paradigm for BMLDs is to obtain a tone-in-noise detection threshold for a tone and noise presented at various signal-to-noise ratios (SNRs) when signal and noise are in the same phase to each ear (homophasic or S_0N_0). Detection thresholds are also obtained in antiphasic conditions when either signal or noise are π radians, or 180°, out of phase between the ears, $S_\pi N_0$ and $S_0 N_\pi$, respectively. Binaural release from masking facilitates tone detection at less favorable SNRs in antiphasic conditions. The difference, in decibels (dB), between homophasic and antiphasic detection thresholds indicates the amount of binaural release from masking. Human behavioral BMLDs are approximately 15 dB around 500 Hz and decrease to approximately 3 dB at frequencies above 1500 Hz (Buss et al. 2007; Hirsh 1948; Licklider 1948; Moore 2003; Webster 1951). The decreasing magnitude of the BMLD at higher frequencies is thought to be related to poorer phase-locked representations of fine structure as frequency increases (Bernstein and Trahiotis 1996; Zurek and Durlach 1987). Magnitude of the BMLD is affected by signal frequency, duration, and bandwidth of masking noise, (Bernstein et al. 2006; van de Par and Kohlrausch 1999). BMLDs are thought to rely on neurons related to processing interaural time differences, such as coincidence detectors (for a review, see Litovsky and McAlpine 2010).

An alternate approach to examining binaural release from masking has often been used in human electrophysiology. Rather than finding physiological tone-in-noise detection thresholds, then calculating physiological BMLDs, response amplitude has been compared between homophasic and antiphasic conditions (Hughes et al. 2014; Wilson and Krishnan 2005). If amplitude increases in antiphasic conditions, relative to homophasic amplitude, this reflects a physiological release from masking or unmasking. Larger amplitude increases are interpreted as stronger release from masking. BMLDs require estimates of tone-in-noise detection thresholds in multiple phase conditions, but unmasking studies may use one or few stimulus SNRs without obtaining time-intensive physiological tone-in-noise detection thresholds.

The FFR reflects neural activity generated throughout the auditory brainstem, including the MSO and IC as neural generators (Smith et al. 1975), and it may preserve neural information relevant to BMLDs. Previous FFR studies have demonstrated that interaural time differences are reflected in FFR waveform morphology and decreased response amplitude, but have not related perceptual and physiological findings (Ballachanda and Moushegian 2000; Gockel et al. 2013). Auditory brainstem responses have not revealed B MLD-like, unmasked, or enhanced amplitude (Kevanishvili and Lagidze 1987). Envelope-following responses reflecting primarily brainstem generators revealed average physiological $S_\pi N_0$ and $S_0 N_\pi$ BMLDs of approximately 1 dB when elicited by 500 Hz tones that were sinusoidally amplitude modulated at a rate of 80 Hz (Wong and Stapells 2004). Wong and Stapells (2004) used adaptive bracketing to estimate physiological tone-in-noise detection thresholds and BMLDs; however, trends in amplitude unmasking were not reported. One human FFR paper has reported FFRs to BMLD stimuli. Wilson and Krishnan (2005) reported that the 500 Hz FFR signal-to-noise ratio was enhanced, or unmasked, in antiphasic conditions ($S_\pi N_0$ and $S_0 N_\pi$) relative to homophasic $S_0 N_0$, which is consistent with a release from masking; one or few stimulus SNRs were used per subject, which did not allow physiological tone-in-noise detection thresholds to be determined. In addition, FFR signal-to-noise ratios in S_π conditions were decreased relative to S_0 when tones were presented without noise. Although FFR signal-to-noise ratios in antiphasic conditions became larger relative to homophasic conditions, the observed FFR unmasking was not predictive of behavioral BMLDs. Predictive, within-subjects relationships between behavioral BMLDs and scalp-recorded BAEPs have not been reported in either humans or animals, although single-unit and neurophonic activity mimicking the periodicity of the stimulus, as seen in the FFR, has been associated with processing of BMLDs and interaural time differences (Jiang et al. 1997b; Kuokkanen et al. 2013). Findings of Wilson and Krishnan (2005) indicate that the FFR is capable of reflecting binaural processing related to BMLDs. FFRs to BMLD stimuli and BMLDs obtained using FFR tone-in-noise detection thresholds have potential to study human binaural processing using a type of phase-locked neural activity known to play a role in the processing of BMLDs and interaural time differences in a variety of animal models.

In this study, we examined behavioral and physiological BMLDs in young, normal-hearing human adults. Similar approaches were used in behavioral and physiological conditions; both behavioral and physiological test methods established tone-in-noise detection thresh-

olds by testing across a range of SNRs using a traditional bracketing approach. The purposes of the present study were to (1) obtain physiological BMLDs using FFR tone-in-noise detection thresholds and (2) analyze brain-behavior relationships of the BMLD.

METHODS

Participants

Fourteen young, normal-hearing subjects participated in this study (average age = 22.6 years $\pm$ std.dev.1.3; 12 females). Twelve of these subjects also participated in the electrophysiology conditions. Inclusion criteria included audiometric thresholds ≤ 25 dB HL at octave frequencies of 0.25–8 kHz with interaural asymmetries ≤ 10 dB at each frequency. All subjects included in the study were monolingual native English speakers with normal tympanometric measures, no known history of otological or neurological disease, with less than 7 years of formal musical training, and not currently taking centrally acting prescription medications. All methods and procedures used in this study were approved and in accordance with the International Review Board at James Madison University. Data collection took place over two to three sessions for a total of approximately 9–10 h per subject.

Stimuli

Stimuli for behavioral and physiological conditions were 500 Hz tonebursts presented in one-third octave noise centered on 500 Hz; behavioral BMLDs are larger in narrowband noise than they are in broadband noise (van de Par and Kohlrausch 1999). The narrowband noise was filtered by zeroing out the amplitude of frequencies beyond the passband (445–561 Hz), equivalent to ~ 96 dB/octave. BMLDs are large at 500 Hz, and using this frequency would be expected to elicit both robust behavioral BMLDs and FFRs (Webster 1951; Wilson and Krishnan 2005). Stimulus duration was 250 ms, including a 15-ms rise/fall time with a Hanning window. Onset and offset times were identical for the tones and noise; noise was not presented continuously. Stimuli were generated with a sampling frequency of 44.1 kHz. Tone level was fixed at 70 dB sound pressure level (SPL) for behavioral conditions and was 80 dB SPL for physiological conditions; noise level varied to adjust signal-to-noise ratio. These stimulus levels produce robust behavioral BMLDs and tone-evoked FFRs (Krishnan 2007; Pichora-Fuller and Schneider 1998). Calibration of signal-to-noise ratios was performed using the spectrum level of the noise. Acoustic calibrations of the noise confirmed that the spectrum was flat across the passband. Onset polarity was

condensation for behavioral and physiological measures; equivalent results would be expected with rarefaction polarity. Magnetically shielded ER-3A insert earphones with double-length tubing delivered stimuli to both ears for the physiological and behavioral conditions. All testing was conducted in a double-walled, sound-attenuated booth.

Behavioral BMLD Procedure

Methods for the behavioral BMLDs followed those of Pichora-Fuller and Schneider (1991). Tone-in-noise detection thresholds were obtained for three conditions: S_0N_0 , $S_\pi N_0$, and S_0N_π . Binaural masking level differences were obtained by subtracting the antiphasic threshold from the homophasic threshold. An adaptive two-interval, two-alternative forced choice procedure (2AFC) was used with a two-down, one-up adaptive rule (Levitt 1971). The step size for SNR was 4 dB until the fourth reversal, after which it was 2 dB; each run was terminated after the twelfth reversal. Threshold was estimated as the mean of the last eight reversals. This adaptive procedure targeted the 0.707 proportion correct [P(C)] point of the psychometric function. A custom Matlab program (version R2013B) was developed for this procedure. The subject was instructed to identify which of the two intervals had the tone by using a computer mouse to click on a virtual button. The subject was given immediate feedback on the correctness of their response. A minimum of three runs for each phase condition was collected. Each subject was given at least one practice run to orient them to the task; experimental trials began when the participants demonstrated consistent tracking functions. At least three tracking functions were used to reconstruct a psychometric function for each phase condition (Leek et al. 1992). Logistic fits to reconstructed psychometric functions from each phase condition were used to guide the initial stimulus SNR selection for the FFR conditions and to facilitate comparisons of perception and FFR within the same phase conditions.

Physiological Recordings

A Neuroscan SynAmps RT acquisition system was used to record FFRs from a three-channel recording (Krishnan et al. 2005; Swaminathan et al. 2008). The non-inverting electrode was at Cz (vertex); three inverting electrodes were located at nape-of-the-neck, left earlobe, and right earlobe, with a ground electrode at Fpz. The Cz-to-nape-of-the-neck channel was analyzed and is believed to reflect primarily inferior colliculus activity (Smith et al. 1975). Other nuclei in the auditory brainstem, such as the medial superior olive, also contribute to the FFR and are

important to interaural time difference processing (van der Heijden et al. 2013). Absolute electrode impedances were below 3 k Ω and interelectrode impedances were kept within 1 k Ω . Stimulus onset asynchrony was 533.33 ms. Online activity was filtered 30–3000 Hz. The analysis time window was 0–270 ms, and the analog-to-digital sampling rate was 20 kHz. A minimum of 1000 individual, artifact-free sweeps were collected for each condition. For the FFR recordings, 100 unique versions of the narrowband noise were generated and randomly ordered. Presenting multiple versions of the noise reduces the likelihood that envelope-following responses would be elicited because the envelope would be different for each noise version (e.g., Won et al. 2011). A single stimulus onset polarity was used, which emphasizes phase-locked responses to the fine structure of the 500 Hz carrier frequency (for a review, see Aiken and Picton 2008). Online artifact rejection criteria was ± 30 μ V. The participants were seated in a reclining chair and instructed to relax quietly. There was a 5 min silent period between each FFR condition.

Physiological Analysis

FFR analysis was based on amplitude measurements and phase coherence (Batra et al. 1986; Clinard et al. 2010; Dobie and Wilson 1989; John et al. 1998). Response amplitude represents the averaged magnitude of the neural response, and this metric uses the average waveform. Phase coherence indicates the degree of phase locking to the stimulus frequency and is independent of response amplitude; phase coherence is performed on the non-averaged, sweep-by-sweep data. Consecutive pairs of sweeps were concatenated to achieve a Fast Fourier Transform (FFT) resolution of 1.92 Hz. Stimulus frequency was specified using coherent sampling and constrained the response to one FFT bin (John and Picton 2000). FFR amplitude was obtained from the 500 Hz FFT bin where the averaged response was located. The mean of five FFT bins above and below the response bin (± 10 Hz) was used as a noise estimate. The resulting signal-to-noise ratio from amplitude and noise measures was used as an F-ratio with 2,20 degrees of freedom (Dobie and Wilson 1996). A p value of <0.05 was used as the criterion to determine response presence. FFR amplitude was also normalized for some analyses; an individual's maximum amplitude for a given phase condition (e.g., S_oN_o) served as their reference for normalized amplitude in that specific phase condition.

Phase coherence used non-averaged, concatenated pairs of sweeps and was calculated using phase information from the 500 Hz FFT bin of each sweep pair. This analysis is analogous to the vector strength

metric used in single-unit studies of phase locking (Dobie and Wilson 1989). Phase data were analyzed using the Rayleigh test to assess circular uniformity (Fisher 1993); response presence was indicated by a p value <0.05 . A phase coherence of 1 indicates perfect phase locking and a value of 0 indicates random phase. Custom Matlab programs were created for these analyses. During data collection sessions, frequent control recordings with an occluded earphone removed from the ear were performed and did not detect artifactual responses.

Physiological Procedure

BMLDs were calculated the same way for behavioral and physiological measures; FFR BMLDs were calculated by subtracting an antiphasic FFR detection threshold from the homophasic FFR detection threshold. An adaptive bracketing procedure was used to determine FFR tone-in-noise detection thresholds to the same 250 ms tone-in-noise stimuli from the behavioral task. For each phase condition (e.g., S_oN_o), the initial SNR presented was in the plateau of the average reconstructed psychometric function (e.g., 20 dB SNR) for that individual and descended in 8 dB steps until the response was absent; stimulus SNR then increased by 4 dB. If time permitted, 2 dB steps were then made to determine threshold. Detection threshold was defined as the lowest (poorest) signal-to-noise ratio at which a present response was obtained. The adaptive nature of stimulus SNR selection resulted in some SNRs having fewer data points than others. Figure 1 shows an individual's FFR data across a range of SNRs, with FFR amplitude becoming smaller (poorer) as stimulus SNR becomes less favorable; these FFR data are consistent with a previous report of monaural tone-in-noise FFR amplitude (Marsh et al. 1975).

Statistical Analysis

Statistical analyses were performed in SPSS (version 21) and Matlab (2014B). The repeated measures analysis of variance (ANOVA) used Bonferroni corrections for post hoc p values.

RESULTS

Behavioral BMLDs

A one-way, repeated-measures ANOVA was performed to evaluate effects of phase condition on behavioral BMLDs. Average behavioral BMLDs for $S_{\pi}N_o$ were 10.03 dB ($\pm$ std. error 1.33 dB) and for S_oN_{π} were 8.29 dB ($\pm$ std. error 1.14 dB), consistent with BMLD magnitudes reported in the literature (e.g., Pichora-

FIG. 1. Individual data from a 22-year-old participant elicited using S_oN_o 500 Hz conditions. **a** Examples of response FFTs at various stimulus SNRs tested for the S_oN_o condition. FFR amplitude decreased as the acoustic SNR of the stimulus decreased; response was absent at -12 dB SNR. **b** An FFR waveform that was elicited with a 20 dB SNR.

Fuller and Schneider 1991) (Fig. 2). The main effect of phase condition was not significant [$F_{(1,12)} = 3.037$, $p = 0.107$]. Slightly larger behavioral BMLDs are often observed in the $S_{\pi}N_o$ condition relative to S_oN_{π} (e.g., Pichora-Fuller and Schneider 1991), and these behavioral BMLDs confirm robust behavioral release from masking.

Physiological BMLDs

One purpose of the present study was to obtain FFR BMLDs using FFR tone-in-noise detection thresholds. Average FFR BMLDs for $S_{\pi}N_o$ were -11.83 dB ($\pm$ std. error 2.77) and for S_oN_{π} were 1.83 dB ($\pm$ std. error 0.87) (Fig. 2). To compare FFR BMLDs across phase conditions, a one-way, repeated-measures ANOVA was

performed. The main effect of phase condition was significant [$F_{(1,11)} = 23.921$, $p < 0.001$, partial $\eta^2 = 0.685$]; FFR BMLDs for $S_{\pi}N_o$ were significantly lower (poorer) than for S_oN_{π} . The small 1.83 dB average FFR BMLD for S_oN_{π} indicates minimal-to-absent release on average, and the -11.83 dB FFR BMLD for $S_{\pi}N_o$ indicates the opposite of a release from masking. Average FFR BMLDs did not indicate a robust release from masking, although the range of FFR BMLDs shows that some individuals showed positive FFR BMLDs in the S_oN_{π} condition.

To evaluate differences between the magnitudes of behavioral BMLDs and FFR BMLDs, a 2×2 repeated measures ANOVA was performed with BMLD as the dependent variable and the factors were test method (perception or physiology) and phase condition (S_oN_{π} or $S_{\pi}N_o$). The main effects were significant for test method [$F_{(1,10)} = 81.485$, $p < 0.001$, partial $\eta^2 = 0.891$] and phase condition [$F_{(1,10)} = 12.005$, $p = 0.006$, partial $\eta^2 = 0.546$]. In addition, the test method $\times$ phase condition was also significant [$F_{(1,10)} = 24.291$, $p = 0.001$, partial $\eta^2 = 0.708$], consistent with trends seen in Figure 2. Behavioral BMLDs were significantly larger (better) than FFR BMLDs. FFR BMLDs were successfully obtained by calculating the difference between detection thresholds, but did not reveal significant physiological release from masking on average.

FIG. 2. **a** Binaural masking level differences for behavioral (filled symbols) and physiological (open symbols) data. **b** Detection thresholds for behavioral (filled symbols) and physiological (open symbols) data. Data points have been slightly shifted along the abscissa to minimize overlapping data points. Error bars are one standard error. Behavioral data indicate a release from masking, but average FFR data do not reflect a release from masking.

Behavioral Detection Thresholds

A one-way, repeated-measures ANOVA was performed to evaluate differences in behavioral tone-in-noise detection thresholds across phase conditions. The main effect of phase condition was significant [$F_{(2,24)} = 39.817$, $p < 0.001$, partial $\eta^2 = 0.768$]. Post

hoc tests showed that behavioral detection thresholds for $S_{\pi}N_o$ and S_oN_{π} were significantly lower (better) than S_oN_o ($p < 0.001$), but not significantly different from each other ($p > 0.05$). Behavioral detection thresholds were lower (better) for antiphase conditions than for the homophase condition, consistent with the expected release from masking in the antiphase conditions (Fig. 2).

Physiological Detection Thresholds

Both behavioral and FFR BMLDs were calculated as the difference between homophase and antiphase tone-in-noise detection thresholds. FFR detection threshold was defined as the lowest (poorest) SNR where a response was present. To better understand the FFR BMLD findings, a one-way, repeated-measures ANOVA was performed to evaluate FFR detection thresholds across phase conditions. Figure 2 shows FFR detection thresholds for each phase condition. A significant main effect of phase condition was revealed [$F_{(1.15,12.64)} = 20.346$, $p < 0.001$, partial $\eta^2 = 0.649$]. Post hoc tests revealed that physiological detection thresholds were not significantly different for S_oN_o and S_oN_{π} ($p = 0.059$), the conditions where the 500 Hz signal was in identical phase across the two ears; this finding is in contrast to behavioral tone-in-noise detection thresholds which improved in both antiphase conditions. However, physiological detection thresholds for S_oN_o and S_oN_{π} were significantly lower (better) than for $S_{\pi}N_o$ ($p < 0.001$), where the signal was 180° out of phase between the ears (Fig. 2). Significantly higher (poorer) $S_{\pi}N_o$ detection thresholds suggest that the amplitude of these sinusoidal-like FFRs are negatively affected when the interaural phase difference of the eliciting tones is 180°.

Detection thresholds represent performance at just one SNR out of the multiple SNRs that were tested. Examining behavioral and physiological data across the entire range of SNRs tested and across the different phase conditions reveals similar trends in behavioral tone-in-noise detection and normalized FFR amplitude. Figure 3 shows both behavioral proportion correct [P(C)] from reconstructed psychometric functions (left axes) and normalized FFR amplitude (right axes) decreasing as SNR becomes less favorable (lower). Average logistic fits in Figure 3d show a behavioral release from masking with fits (solid lines) for S_oN_{π} and $S_{\pi}N_o$ conditions shifted to lower SNRs relative to S_oN_o , while the overlapping fits for normalized FFR amplitude (dotted lines) do not indicate a release from masking. Data from these functions are consistent with robust release from masking for behavioral measures, but not for normalized FFR amplitude.

Relationship Between Behavioral and Physiological BMLDs

Predictive relationships between perceptual and physiological BMLDs were assessed using simple linear regression. Behavioral BMLDs were used as the dependent variable and physiological BMLDs as the independent variable. Scatterplots in Figure 4 illustrate these relationships. Physiological BMLDs were not significantly predictive of behavioral BMLDs for either $S_{\pi}N_o$ or S_oN_{π} [$S_{\pi}N_o$ FFR BMLD $\times$ $S_{\pi}N_o$ behavioral BMLD, $R^2 = 0.16$, $t_{(11)} = 1.370$, $p = 0.201$; S_oN_{π} FFR BMLD $\times$ S_oN_{π} behavioral BMLD, $R^2 = 0.00$, $t_{(10)} = 0.040$, $p = 0.969$]. When the FFR detection threshold was defined as the lowest SNR at which a response was present, the resulting FFR BMLDs did not predict behavioral BMLDs.

An alternate definition of FFR detection threshold was used to further examine the predictive relationship between physiological and behavioral BMLDs. The behavioral task estimated the 0.707 P(C) point on the psychometric function. To more closely approximate similar definitions of detection threshold across the two test methods, FFR detection thresholds for each individual for each phase condition were alternately defined as the SNR corresponding to 0.707 normalized amplitude. Redefined FFR detection thresholds were more similar across phase conditions (Fig. 5a) than those from the original definition of lowest SNR with a present response (Fig. 2). Although redefining FFR detection thresholds resulted in more positive FFR BMLDs, FFR BMLDs were still significantly poorer than behavioral BMLDs (Fig. 5b). These redefined FFR BMLDs were not significantly predictive of behavioral BMLDs, either [$S_{\pi}N_o$ FFR BMLD $\times$ $S_{\pi}N_o$ behavioral BMLD, $R^2 = 0.02$, $t_{(11)} = -0.412$, $p = 0.689$; S_oN_{π} FFR BMLD $\times$ S_oN_{π} behavioral BMLD, $R^2 = 0.03$, $t_{(10)} = 0.501$, $p = 0.629$] (Fig. 6). Behavioral and physiological BMLD results show contrasting patterns. Behavioral BMLDs indicated robust release from masking, while physiological BMLDs span a much broader range of negative to positive values with only some individual data indicating a release from masking (Figs. 4 and 6). Although FFR BMLDs were calculated using two different definitions of FFR tone-in-noise detection thresholds, they demonstrated poor predictive relationships with behavioral BMLDs.

FFR Amplitude Across Phase Conditions

Physiological tone-in-noise detection thresholds were significantly poorer for $S_{\pi}N_o$ relative to S_oN_o and S_oN_{π} conditions (Fig. 2), indicating that FFR amplitude may be degraded under $S_{\pi}N_o$ conditions. Raw FFR amplitude was systematically affected by stimulus phase condition, particularly $S_{\pi}N_o$. When the 500 Hz signal

FIG. 3. Double y-axis plots showing average data and average logistic fits to reconstructed psychometric functions (left axis, filled symbols, solid lines) and normalized FFR amplitude (right axis, open symbols, dashed lines) for each phase condition. **a–c** Data for individual phase conditions. **d** Average logistic fits are shown for all conditions and demonstrate improved behavioral detection in antiphase conditions, while normalized FFR amplitude trends are

similar across phase conditions. The *solid horizontal line* at 0.707 represents behavioral threshold from the adaptive task, and the *dotted horizontal line* at 0.5 represents chance behavioral performance. Error bars are one standard error; conditions with only one data point have error bars equivalent to zero.

is in identical phase across the two ears, S_oN_o and S_oN_π conditions, consistent amplitude trends and overlapping logistic fits are seen across stimulus SNR (Fig. 7a, c, d). When the 500 Hz signal is 180° out of phase between the ears, the $S_\pi N_o$ condition, there is a substantial decrease in response amplitude (Fig. 7b,

d). Given that the sinusoidal-like, neurophonic nature of the tone-evoked FFR follows the periodicity of the stimulus frequency (Smith et al. 1975; Worden and Marsh 1968), these findings are consistent with scalp-

FIG. 4. Bivariate scatterplots of FFR BMLDs and behavioral BMLDs for $S_\pi N_o$ (**a**) and $S_o N_\pi$ (**b**). Filled symbols indicate an FFR BMLD > 0 dB, and open symbols indicate an FFR BMLD ≤ 0 dB. FFR BMLDs were not predictive of behavioral BMLDs.

FIG. 5. Binaural masking level differences and detection thresholds for behavioral (filled symbols) and physiological (open symbols) conditions, where FFR detection thresholds were redefined as 0.707 normalized amplitude. Behavioral data shown here are the same as those in Fig. 2. Errors bars are one standard error. FFR detection thresholds do not reflect a release from masking when using this alternate definition of physiological detection threshold.

FIG. 6. Bivariate scatterplots of FFR BMLDs and behavioral BMLDs for $S_{\pi}N_o$ (a) and S_oN_{π} (b), where FFR BMLDs were based on 0.707 normalized FFR amplitude detection thresholds, similar to the behavioral definition of detection threshold. Filled symbols indicate an FFR BMLD > 0 dB, and open symbols indicate an FFR BMLD ≤ 0 dB. Redefined FFR BMLDs did not predict behavioral BMLDs.

recorded FFRs from the $S_{\pi}N_o$ conditions reflecting a non-linear summation of neural activity of neurophonics with opposite polarity. Amplitude reductions would be expected in $S_{\pi}N_o$ conditions with phase cancellation, and amplitude enhancements

would be expected from constructive phase summation in S_oN_o and S_oN_{π} conditions.

FFR amplitude differences between phase conditions are further examined in Figure 8. FFR amplitude from $S_{\pi}N_o$ conditions revealed substantial decrements relative to S_oN_o and S_oN_{π} , consistent with negative effects of phase summation. S_oN_o – S_oN_{π} amplitude differences are effectively zero (Fig. 8b, d), consistent with a lack of physiological release from masking or amplitude enhancements (e.g., amplitude unmasking) that would have indicated unmasking in S_oN_{π} tone-evoked FFRs. In contrast, S_oN_o – $S_{\pi}N_o$ and S_oN_{π} – $S_{\pi}N_o$ amplitude differences reveal larger FFR amplitude differences, particularly at higher SNRs, consistent with negative effects of phase summation when the 500 Hz signal is in opposite phases at each ear (Fig. 8a, c, d). Asymmetries in audiometric thresholds were not significantly correlated with the S_oN_o – $S_{\pi}N_o$ FFR amplitude differences ($p > 0.05$). A one-way repeated measures ANOVA evaluated FFR noise differences across phase conditions; FFR noise estimates were not significantly different between the three phase conditions ($p > 0.05$). FFRs elicited in

FIG. 7. Raw FFR amplitudes across stimulus SNR and phase conditions. a–c FFR amplitude for each phase condition. Average (filled symbols) and individual data (open symbols) are shown with average logistic fits (bold lines) and fits to individual data (thin, gray lines). d Average fits from all phase conditions. Some SNRs (e.g., S_oN_o , 14 dB SNR) have only one or a small number of subjects. Error bars are one standard error.

FIG. 8. Raw FFR amplitude differences between phase conditions as a function of stimulus SNR. **a–c** Average (filled symbol) and individual data (open symbols) for the $S_oN_o-S_{\pi}N_o$, $S_oN_o-S_oN_{\pi}$, and $S_oN_{\pi}-S_{\pi}N_o$ amplitude differences, respectively. **d** Average amplitude

differences are shown for conditions with at least three subjects; data points have been slightly offset along the abscissa to minimize overlapping data points. Error bars are one standard error.

$S_{\pi}N_o$ conditions may be analogous to adding two sinusoids of the same frequency with a near 180° phase difference. More response attenuation would be expected if the system had more synchronous phase locking across the two stimulated ears; effects of binaural FFR phase summation in individuals with greater neural synchrony would likely result in larger amplitudes for S_oN_o conditions and greater amplitude attenuation in the $S_{\pi}N_o$ conditions. Variability in the $S_oN_o-S_{\pi}N_o$ amplitude differences may suggest that some individuals have greater inter-ear synchrony and therefore greater effects of FFR phase summation, while other individuals would have smaller $S_oN_o-S_{\pi}N_o$ amplitude differences potentially related to poorer inter-ear synchrony.

Amplitude Differences Predict Behavioral BMLD

If the magnitude of response attenuation from S_oN_o and S_oN_{π} conditions to $S_{\pi}N_o$ conditions was indicative of inter-ear neural synchrony, it is plausible to expect

a relationship between those amplitude reductions and the behavioral binaural masking level difference. FFR amplitude differences of $S_oN_o-S_{\pi}N_o$ and $S_oN_{\pi}-S_{\pi}N_o$ were significantly predictive of behavioral $S_{\pi}N_o$ BMLDs [$S_oN_o-S_{\pi}N_o$ amplitude difference $\times S_{\pi}N_o$ behavioral BMLD, $R^2 = 0.77$, $t_{(5)} = 3.673$, $p = 0.021$; $S_oN_o-S_oN_{\pi}$ amplitude difference $\times S_{\pi}N_o$ behavioral BMLD, $R^2 = 0.99$, $t_{(4)} = 14.674$, $p < 0.001$]. One outlier was excluded from the linear regression analyses because this individual would not be considered to have a behavioral release from masking with a BMLD < 3 dB (e.g., Jiang et al. 1997b) and regression diagnostics confirm this point as an outlier. Individuals with larger amplitude decrements had more robust behavioral release from masking, and those individuals with smaller amplitude decrements had less robust behavioral release from masking (Fig. 9). FFR amplitude differences were significantly predictive of behavioral BMLDs, indicating a relationship between the phase-locked FFR and behavioral binaural release from masking.

FIG. 9. Bivariate scatterplots of FFR amplitude differences from 12 dB SNR conditions and behavioral $S_{\pi}N_0$ BMLDs. R^2 values and lines of best fit include participants with at least a 3 dB behavioral BMLD; the open datum point in each panel was excluded from regression analysis. FFR amplitude differences were significantly predictive of behavioral $S_{\pi}N_0$ BMLDs.

Phase Coherence Measures

FFRs were also analyzed using phase coherence, which relies on sweep-by-sweep, non-averaged phase information, is independent of amplitude, and is analogous to vector strength used in invasive recordings (Dobie and Wilson 1989). In this sample of young, normal-hearing adults, phase coherence and raw FFR amplitude performed nearly identically. Relationships between amplitude (dependent variable) and phase coherence (independent variable) across all stimulus SNRs were examined using simple linear regression; separate analyses were performed for each of the three phase conditions. Regression findings for S_0N_0 , $S_{\pi}N_0$, and S_0N_{π} revealed high R^2 values of 0.94, 0.86, and 0.92, respectively ($p < 0.001$). Phase coherence findings are not reported separately here because of the high R^2 values between the two measures and their high degree of similarity in the statistical analyses.

DISCUSSION

The magnitude of FFR amplitude decrements in $S_{\pi}N_0$ conditions (e.g., $S_0N_0-S_{\pi}N_0$) was significantly predictive of behavioral $S_{\pi}N_0$ BMLDs, suggesting a previously unreported relationship between scalp-recorded neurophonic responses and binaural release from masking. Physiological release from masking, in the form of enhanced or unmasked amplitude to $S_{\pi}N_0$ and S_0N_{π} antiphasic conditions, is often observed in human cortical responses but was not evident in the present study of brainstem responses. FFR amplitudes were equivalent when the 500 Hz signal was in phase at each ear (S_0N_0 and S_0N_{π}); substantial FFR amplitude reductions were observed when the 500 Hz signal was in

opposite phase at each ear ($S_{\pi}N_0$), likely related to phase summation effects at the level of scalp electrodes. Behavioral measures indicated robust release from masking, consistent with the literature.

Phase Condition Affected FFR Amplitude

FFR amplitude followed the trend of behavioral performance, $P(C)$, decreasing as SNRs became less favorable (Fig. 3). However, FFR amplitudes from antiphasic conditions were not enhanced relative to homophasic amplitudes, on average (Figs. 3, 7, and 8). In conditions where the 500 Hz tone was in phase at each ear, S_0N_0 and S_0N_{π} , FFR amplitudes were nearly identical (Fig. 8d). In contrast, when the 500 Hz tones were in opposite phase at each ear, $S_{\pi}N_0$, substantial amplitude reductions were observed relative to S_0N_0 and S_0N_{π} amplitudes (Figs. 7d and 8d). Amplitude reductions in the $S_{\pi}N_0$ conditions are consistent with scalp-recorded FFRs reflecting the summed response energy from each ear. These patterns of amplitude across phase condition are inconsistent with expected psychophysical findings of the release from masking (Figs. 3 and 7). Similar FFR amplitude reductions related to binaural interaction have been reported between S_0 and S_{π} conditions, without noise, where each recording was made at an individual SNR, rather than across a range of SNRs (Wilson and Krishnan 2005). When FFR-eliciting stimuli are in opposite phases at the left and right ears, the scalp-recorded FFR can reflect a phase summation, or cancellation, that can reduce response amplitude.

Wilson and Krishnan (2005) reported enhanced 500 Hz FFR SNRs in antiphasic conditions relative to homophasic conditions in young, normal-hearing humans but did not report physiological BMLDs, predictive relationships, or record FFRs across a range of stimulus SNRs; stimulus SNRs were not always identical across homophasic and antiphasic stimulus conditions, and amplitude unmasking may have been influenced by variability in the acoustic SNR. Results from the present study showed equivalent FFR detection thresholds between S_0N_0 and S_0N_{π} conditions (Figs. 2 and 5) and do not indicate an FFR amplitude enhancement indicative of unmasking in antiphasic conditions (Figs. 3, 7, and 8).

BMLD findings differed between behavioral and physiological conditions. Both positive and negative FFR BMLDs were observed and only positive behavioral BMLDs were observed. A range of positive and negative physiological BMLDs is consistent with neurophysiological studies in animals (Jiang et al. 1997b; Palmer et al. 2000). It is possible that the acoustic reflex may have been elicited with stimuli used in the present study. Acoustic crossover related to interaural attenuation may have also occurred, but would have

been at very low sensation levels (<20 dB SL) below the intensity threshold for FFR presence (for a review, see Krishnan 2007).

Amplitude Differences Predicted Behavioral BMLDs

Behavioral $S_{\pi}N_o$ BMLDs were successfully predicted by FFR amplitude differences (Fig. 9). These amplitude differences, $S_oN_o-S_{\pi}N_o$ and $S_oN_{\pi}-S_{\pi}N_o$, are presumably related to FFR phase summation from left and right ear stimulation. The size of this amplitude difference may be related to the quality of phase locking. Larger FFR amplitude is typically interpreted as indicating more synchronous phase locking, and in cases of monaural stimulation or binaural homophasic stimulation (e.g., S_oN_o) this interpretation is consistent with the literature. In binaural stimulus conditions where the eliciting tone is antiphasic ($S_{\pi}N_o$), smaller amplitude FFRs may also be consistent with more synchronous phase locking, because FFRs elicited by $S_{\pi}N_o$ stimuli reflect simultaneous responses of opposite phases from left and right ears. Individuals with higher inter-ear neural synchrony would be likely to have higher S_oN_o FFR amplitudes, and those individuals would be likely to have larger degrees of FFR amplitude reduction in the $S_{\pi}N_o$ condition where the 500 Hz stimulus is in opposite polarities in each ear. If the summed neurophonic activity reflected in the $S_{\pi}N_o$ FFR reflects a summation of sinusoidal-like responses 180° out of phase, then amplitude reduction would likely be proportional to the degree of inter-ear synchrony. Predictive qualities of these amplitude differences are illustrated by high R^2 values (Fig. 9) and are consistent with cross-correlation. Individuals with the largest behavioral BMLDs had the largest amounts of FFR amplitude reduction ($S_oN_o-S_{\pi}N_o$ and $S_oN_{\pi}-S_{\pi}N_o$), and individuals with the smallest behavioral BMLDs had the smallest amounts of amplitude reduction. If such inter-ear synchrony is apparent in scalp-recorded FFRs, it may be plausible to expect similar processing at the inputs of individual neurons, such as coincidence detectors. Variations in the number of neurons tuned to interaural phase differences of 0 and π radians may also contribute to these findings.

Stimulus SNR selection was adaptive in the present study; use of fixed SNRs across individuals would have increased the number of data points available for comparison at a given SNR. FFR BMLDs were not predictive of behavioral BMLDs, whether FFR BMLDs were determined using detection thresholds based on the lowest SNR at which responses were present or based on 0.707 normalized FFR amplitude. Both positive and negative FFR BMLDs were observed, indicating unmasking and the lack of unmasking, respectively. This pattern of both positive and nega-

tive physiological BMLDs has also been observed in single-unit studies of BMLD-related activity in the IC and MSO when S_oN_o detection thresholds are compared to those of either $S_{\pi}N_o$ or S_oN_{π} (Jiang et al. 1997b; Langford 1984; McAlpine et al. 1996; Palmer et al. 2000). Behavioral BMLDs and physiological FFR BMLDs were not strongly correlated and demonstrated different trends. However, FFR amplitude differences did predict behavioral BMLDs and are consistent with a role for phase-locked neural activity in the perception of binaural unmasking.

There are a number of factors that may contribute to this brain-behavior relationship. Non-auditory factors such as memory, attention, and motivation influence perceptual measures. Perceptual measures may also involve the full auditory pathway from auditory nerve to cortex. In contrast, many physiological measures, such as the FFR, reflect a particular type of neural activity elicited in a limited region of the auditory system. These limitations must be considered when comparing behavioral and physiological measures, even when a within-subject design is used and stimuli are nearly identical between behavioral and physiological measures as they were in the present study. FFR amplitude differences were significantly predictive of behavioral BMLDs, which may be consistent with the auditory system performing a subtraction procedure between left and right ear input as proposed by a model of binaural hearing (Durlach 1963). The type of neural coding may also differ between the FFR, reflecting phase-locking, and all types of neural coding available in the central auditory nervous system during BMLD processing (e.g., rate coding).

Stimulus paradigms differed between the behavioral and physiological tasks and may have influenced the brain-behavior relationship. During the behavioral task, stimulus SNR varied along an adaptive track and stimulus presentations included tone-in-noise as well as noise-only presentations, using a traditional two-interval, two-alternative forced choice procedure. During the physiological task, tone-in-noise stimuli were repeatedly presented at the same signal-to-noise ratio, which is necessary to obtain an adequate signal-to-noise ratio in the averaged evoked potential waveform. Participants were also resting or asleep during the physiological conditions. These differences in test procedures place different demands on processing in the auditory system and may have contributed to the poor predictive relationships between behavioral BMLDs and FFR BMLDs.

Physiological BMLDs in Brainstem Activity

In non-human mammals, physiological BMLDs and amplitude enhancements indicative of binaural

unmasking have been recorded in single units of the auditory brainstem (Du et al. 2009a; Jiang et al. 1997b; for a review, see Litovsky and McAlpine 2010), as well as the auditory cortex (Caird et al. 1991; Gilbert et al. 2015; Guo and Burkard 2003; Jiang et al. 1997a; McAlpine et al. 1996). Analyses of BMLD activity in the IC and auditory cortex of animals have focused more on firing rate than on phase locking, for reasons related to the restricted frequency range of phase locking in those regions (Rouiller et al. 1979; Steinschneider et al. 1980; Winer et al. 2005). In humans, physiological BMLDs and amplitude enhancements related to unmasking have largely been absent from the auditory brainstem response and the middle latency response (Kevanishvili and Lagidze 1987; Tanis and Teas 1974). In contrast, human cortical responses have reflected BMLD and unmasking, consistent with human perception and the animal physiology literature (Epp et al. 2013; Fowler and Mikami 1992; Fowler and Mikami 1996; Hughes et al. 2014; Ishida and Stapells 2009; Sasaki et al. 2005; Wong and Stapells 2004). The majority of these human studies have used brief, transient stimuli that best elicit onset responses, but do not necessarily reflect stimuli used in psychophysical BMLD tasks. Potential reasons why the current study found predictive brain-behavior relationships, where previous studies have not, may include the use of similar stimuli in behavioral and physiological conditions, as well as using a wide range of stimulus SNRs; these stimuli were long enough to elicit sustained, phase-locked responses in contrast to the transient stimuli often used to elicit onset responses such as the auditory brainstem response. Neural coding changes from the inferior colliculus to cortex (e.g., Belliveau et al. 2014; Winer et al. 2005), and while the perception of BMLD and unmasking may not directly rely on neurophonic activity, as reflected in the FFR, this neural activity may reflect binaural processing in the central auditory system.

Neurophonics and Binaural Processing

Neurophonic activity, such as that reflected in the phase-locked postsynaptic potentials of the FFR, has been associated with physiological processing of BMLDs and interaural time differences (ITDs) in animal data (Du et al. 2009a; Franken et al. 2015; Kuokkanen et al. 2013; Sullivan and Konishi 1986) and computational modeling (e.g., Gilbert et al. 2015; Goldwyn et al. 2014). Human FFR waveform morphology is affected by stimuli with ITDs (Ballachanda and Moushegian 2000), and FFR amplitude unmasking to BMLD stimuli has been reported (Wilson and Krishnan 2005). In addition, physiological and modeling studies in the nucleus

magnocellularis and nucleus laminaris of the barn owl have examined an intracellular membrane potential that oscillates at the stimulus frequency (e.g., 500 Hz) and has been termed the “sound analog potential” (Ashida et al. 2013a; Ashida et al. 2013b; Ashida et al. 2012; Funabiki et al. 2011). These studies have shown that rate-ITD functions and sound analog potential amplitude-ITD functions demonstrate similar trends (Ashida et al. 2013a; Ashida et al. 2012; Funabiki et al. 2011); sound analog potential amplitude is directly proportional to average firing rate of nucleus laminaris neurons (Funabiki et al. 2011). Further, linear summation of left and right ear responses of cells at the MSO and nucleus laminaris predicts binaural responses to ITD stimuli (Kuokkanen et al. 2013; van der Heijden et al. 2013). Results from the current study are consistent with these non-human studies when considering its amplitude findings across phase conditions.

FFR amplitudes in this study were maximal at 0° interaural phase difference, S_0N_0 and S_0N_π , and minimal at 180° , $S_\pi N_0$. Amplitude reductions seen in the $S_\pi N_0$ scalp-recorded FFRs of the present study may reflect, in part, a summation of monaural responses, and is potentially related to reduced input to or output of coincidence detectors, though scalp recordings likely record activity from neurons tuned to a wide range of ITDs. Neurophonic amplitude differences that contrast between BMLD stimulus conditions may be used in ITD processing and possibly contribute to behavioral release from masking. Studies of the FFR binaural interaction component indicate that binaural interaction is a non-linear process (for a review, see Wilson and Krishnan 2005). In addition, precisely timed neural inhibition (Brand et al. 2002; Myoga et al. 2014) and binaural excitatory/inhibitory response properties of neurons (e.g., Langford 1984) may also be contributing factors to these FFR amplitude differences.

Temporal jitter, or variance in phase locking, is thought to contribute to reduced (poorer) behavioral BMLDs in older adults, even those without hearing loss (Pichora-Fuller and Schneider 1992), and this population has degraded phase-locked representation of frequency (Clinard et al. 2010). Results from the current study indicate that individual variability in the quality of phase-locked frequency representation contributes to behavioral BMLD variance in young, normal-hearing adults. Various populations, such as cochlear implant users (Kan and Litovsky 2015; Lu et al. 2010) and individuals with corrected unilateral aural atresia (Gray et al. 2009) have binaural deficits; approaches reported from the present study may help to explain individual differences in binaural performance.

CONCLUSIONS

Scalp-recorded FFRs reflect sustained phase-locked activity that was related to behavioral binaural release from masking. FFR amplitude differences between stimulus phase conditions, related to binaural interaction and phase summation, were significantly predictive of behavioral BMLDs. This new finding of a physiological correlate of BMLDs in subcortical human responses may be useful to investigate binaural processing in disordered populations. FFR BMLDs, however, were not predictive of behavioral BMLDs. These findings support a role of phase-locked, neurophonic responses in human binaural hearing.

ACKNOWLEDGMENTS

Funding for this experiment was provided, in part, by a research grant from James Madison University's College of Health and Behavioral Studies (CGC). Non-financial support was provided by NIH-NIDCD #U24 DC012079, which provided no direct or indirect funds to support this research. The authors also wish to thank several anonymous reviewers for their constructive comments.

Author's Contributions CC and SH designed the research. CC, SH, and MS performed research. CC and SH analyzed data. CC and SH wrote the paper.

COMPLIANCE WITH ETHICAL STANDARDS

All methods and procedures used in this study were approved and in accordance with the International Review Board at James Madison University.

Conflict of Interest The authors declare that they have no conflict of interest.

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