A backward encoding approach to recover subcortical auditory activity

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1. Abstract

Several subcortical nuclei along the auditory pathway are involved in the processing of sounds. One of the most commonly used methods of measuring the activity of these nuclei is the auditory brainstem response (ABR). Due to its low signal-to-noise ratio, ABRs have to be derived by averaging activity evoked by a high number (several thousand) of repetitions of e.g. clicks or tone bursts. To date no approach exists that can be used to non-invasively investigate both auditory brainstem activity following natural sounds (e.g. speech, music) and silent periods, for example, within selective attention tasks. For several cognitive neuroscientific questions this is a severe limitation. We propose that by training a backward encoding model to reconstruct evoked ABRs from electrophysiological data, spatial filters (channel weights) can be obtained that are tuned to auditory brainstem activity. Since these filters can be applied to any other dataset (i.e. generalized) using the same spatial coverage, this could allow for the estimation of auditory brainstem activity from any continuous sensor level data. In this study, we established a proof-of-concept that by employing a backward encoding model generated using a click stimulation rate of 30 Hz we could predict the expected ABR activity recorded via electroencephalography (EEG) from an independent measurement, using a stimulation rate of 9 Hz. By showing that the individually predicted and measured ABRs are highly correlated ($r \sim 0.67$), we laid the necessary foundation to use this paradigm in more naturalistic listening situations.

keywords: auditory brainstem response, magnetoencephalography, electroencephalography, backward encoding, signal reconstruction

2. Introduction

Following mechanoelectrical transduction in the cochlea, neural activity passes through several subcortical nuclei on its way to the primary auditory cortex. Along the ascending auditory pathway these nuclei perform several fundamental computations relevant for sound processing (Ehret & Romand, 1997). However, an abundance of descending pathways exists in the auditory system involving brainstem and even cochlear structures, with a still weakly understood functional role (Terreros & Delano, 2015). With most findings stemming from animal research (for reviews, see Huffman & Henson, 1990; Suga & Ma, 2003; Terreros & Delano, 2015), the availability of tools to study neural activity along subcortical auditory regions in healthy human participants would invaluably broaden our understanding of their functional roles in normal and disordered hearing.

In humans, inference about subcortical auditory activity is usually drawn from the noninvasively measured auditory brainstem response (ABR) – a sequence of evoked potentials recorded via electroencephalography (EEG) that occur within the first 10 ms after acoustic stimulation. The recording consists of five to seven vertex positive waves (Wave I to VII; Jewett & Williston, 1971). By convention, each of these waves has been associated with activity in one or a few subcortical structures along the auditory pathway (Møller, Jho, Yokota, & Jannetta, 1995). As electrical signals also have magnetic properties, an ABR can in principle also be captured using magnetoencephalography (MEG; Lütkenhöner, Lammertmann, Ross, & Pantev, 2000; Parkkonen, Fujiki, & Mäkelä, 2009). However, this has been controversial, given the deep location of brainstem structures and the pronounced sensitivity of MEG to superficial sources (Hari & Salmelin, 2012). Yet, a recent study using concurrent intracerebral and MEG recordings shows that activity in deep subcortical areas (Amygdala, Hippocampus) can indeed be disentangled from the surface MEG activity (Pizzo et al., 2019). In an essential study, Parkkonen et al. (2009) managed to measure a magnetic ABR (mABR) by computing the root-mean-squared (RMS) signal across all magnetometer channels. Using equivalent current dipole models, they offered plausible locations for the specific source origins of the ABR components, showing that activity along the auditory hierarchy is

measurable with MEG. While these results are promising, the general paradigm used to measure (m)ABRs poses strong limitations, in particular due to the low signal to noise ratio (SNR) of brainstem activity on M/EEG sensors, as obtaining them usually requires averaging thousands of simple sounds such as clicks or tone bursts to elicit a clear response. This is especially problematic for researchers interested in the role of brainstem regions in more naturalistic listening tasks (e.g. listening to continuous speech or music) or during silent periods (e.g. a cue-target period in selective attention tasks or in anticipation of upcoming sounds). This makes the availability of tools to further study these neural activity patterns increasingly important.

An important step in this direction was undertaken by Maddox and Lee (2018). They used a paradigm that views evoked potentials as an impulse response of a linear system. By performing a regression between a rectified speech audio signal and a concurrent EEG recording, they measured an ABR to continuous speech. They showed a high correlation between this speech-derived and a previously measured click-evoked ABR, suggesting that ABRs can be derived from natural speech. Despite being promising, an ongoing sound stimulation is required to derive these ABRs, making the investigation of stimulus-free periods impossible.

Here, we propose a new approach to overcome some of these issues, with the prospect of modeling auditory brainstem activity following naturalistic sounds and within stimulus free periods. We used the signal obtained during a concurrent electric and magnetic ABR recording to generate channel weights that are tuned to putative auditory brainstem activity.

These weights were generated by using the signal captured by the MEG sensors as regressors for a concurrent electric ABR recording. We propose that these weights can be applied to other sensor-level data to estimate ongoing auditory brainstem activity.

In this initial study, we attempt to establish the proof-of-concept that by training a model on a 30 Hz stimulation rate we can predict the dynamics of an ABR from an independent measurement using a different stimulation rate (9 Hz). By showing that the individually reconstructed and measured

ABRs are highly correlated, we laid the necessary foundation to generalize this approach and model auditory brainstem activity also in more interesting and complex listening situations.

3. Materials & Methods

3.1. Subjects

The data analyzed for this study were collected from 14 healthy volunteers (10 males, *M* = 26.71 years; *SD* = 4.38 years) without reported psychiatric, neurological and hearing disorders. The experimental protocol was approved by the ethics committee of the University of Salzburg and all participants gave written informed consent prior to the experiment.

3.2. Stimuli and procedure

Participants listened to a total of 10000 clicks per condition at a sound pressure level of 60 dB. Stimuli were presented binaurally in two separate blocks at a rate of 30 Hz and of 9 Hz. Each click stimulus had a duration of 80 µs. Auditory stimuli were presented inside the MEG helmet through a pneumatic system (SOUNDPixx, Vpixx technologies, Canada) with a stimulation delay of 16.5 ms estimated using a microphone (ER10C, Etymotic Research, US) and an oscilloscope (Rigol DS 1074Z). This delay was compensated by shifting the time axis during the data analysis accordingly. The measurement took in total about 6 minutes for the 30 Hz condition and about 20 minutes for the 9Hz condition. The experimental procedure was programmed using Psychophysics Toolbox 3 (Brainard, 1997) and custom built Matlab routines (Mathworks, Natick, USA).

3.3. Data acquisition

Magnetic brain activity was recorded using a 306-channel whole-head MEG system (TRIUX, Elekta Oy, Finland) with a sampling rate of 10 kHz. The system consists of 204 planar gradiometers and 102 magnetometers. Before entering the magnetically shielded room (AK3B,

Vakuumschmelze, Hanau, Germany), the head shape of each participant was acquired with >300 digitized points on the scalp, including fiducials (nasion, left and right pre-auricular points) with a Polhemus FASTRAK system (Polhemus, Vermont, USA). The ABR was measured with a single electrode located on FpZ based on the electrode placement of the international 10-20 system (Klem, Lüders, Jasper, & Elger, 1999). A ground electrode was placed on the forehead at midline and a reference on the clavicle bone of the participants.

3.4 Data analysis

3.4.1 Preprocessing

The acquired data were preprocessed in MNE-Python (Gramfort et al., 2014). First, an automated algorithm (*autoreject* implemented in MNE Python; Jas, Engemann, Bekhti, Raimondo, & Gramfort, 2017) was used to detect bad MEG channels. This was followed by Maxwell-filtering the data using the Signal Space Separation (SSS) algorithm implemented in MNE-Python (Taulu & Simola, 2006), to suppress external magnetic interference. The Maxwell-filtered and continuous data was then high-pass filtered at 150 Hz and low-pass filtered at 1000 Hz using a zero-phase Hamming window. As muscular activity has an overlapping spectral bandwidth (~20-300 Hz) with our frequency spectrum of interest (Muthukumaraswamy, 2013), another run of autoreject was applied to reject residual bad segments in our data. The epoched data was then further analyzed using the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) and custom built Matlab routines. An auditory brainstem response recorded from the MEG sensors (mABR, Parkkonen et al., 2009) was obtained using the global mean field power of all magnetometers (GMFP, Esser et al., 2006). The electric ABR was computed by averaging the epoched data obtained from a single EEG channel.

3.4.2 Backward modeling

In order to reconstruct auditory brainstem activity from the MEG a backward encoding model was built using the signal captured by the MEG sensors as regressors for a concurrent electric ABR recording. This was achieved by performing a ridge regression between the electric ABR and the data obtained from the magnetometers by utilizing the mTRF toolbox (Crosse, Di Liberto, Bednar, & Lalor, 2016). A "leave-one-out" cross-validation procedure was implemented and the regularization parameter (λ) that produced the highest correlation coefficient between the EEG and MEG signal at a 30 Hz stimulation rate was selected. Instead of the usual trial-to-trial based cross-validation approach, sub averages (per 100 trials) were built to speed up processing and account for the low SNR of brainstem activity. Afterwards the backward model was trained by utilizing the mTRF toolbox (Crosse et al., 2016) to perform a ridge regression between the signal captured by the MEG and EEG to generate channel weights for each training time point **(Figure 1, Backward modeling)**. By applying these weights to a new MEG measurement, a matrix with the time generalized "activation" for each testing/training time point is created **(Figure 1, Signal extraction)**. Analogous to classification-based decoding approaches (King & Dehaene, 2014), we assume that this temporal generalization can be interpreted as the presence of an activation pattern during a training period (e.g. the pattern contributing to a specific ABR wave) at a corresponding testing time. While this approach could be flexibly applied to any other paradigm, we sought to establish an important proof-of-principle for this approach: that is, we tested whether backward models obtained from magnetometers during one ABR measurement using a 30 Hz stimulation rate could correctly predict the ABR obtained from an independent measurement using a 9 Hz stimulation rate **(Figure 1, Evaluation)**. In order to compare the reconstructed signal with the measured signal, an overall correlation coefficient between both signals was computed for each subject individually.

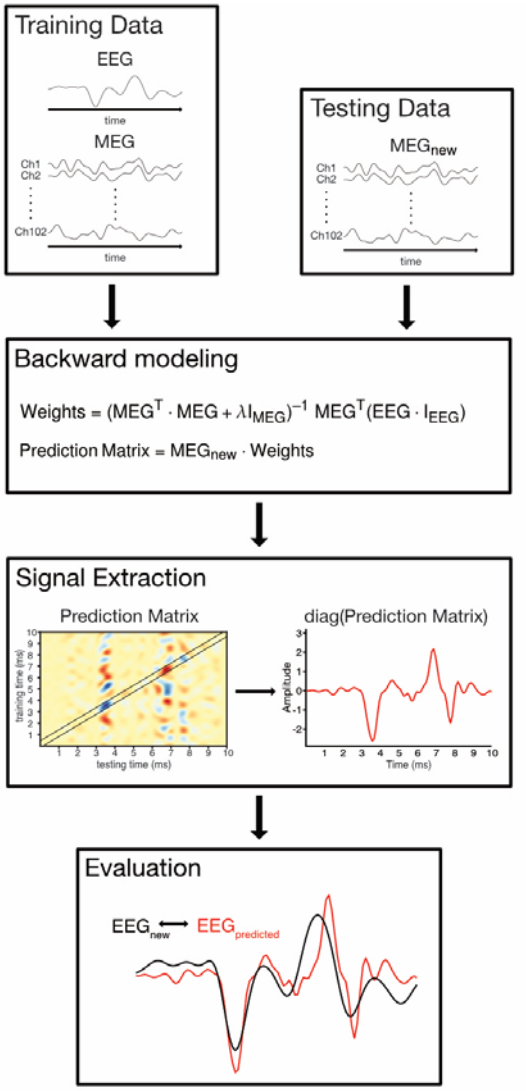

Figure 1: *A backward modeling approach used to reconstruct auditory brainstem activity. MEG sensors were asserted as regressors for a concurrent electric ABR recording. The thereby generated weights were then used in a new measurement to reconstruct brainstem activity from the MEG recording. This activity was extracted by taking the diagonal from the Prediction Matrix. Here, the quality of the Prediction was evaluated by correlating the reconstructed ABR with the actual signal evoked by a different stimulation rate (9Hz).*

To rule out that the weights generated during training will not reconstruct an ABR-like response independent of the measured input data, a reconstruction from "noise" was performed and compared to the original reconstruction. The noise was created by shuffling all time points in the averaged signal on each MEG sensor 1000 times. For each shuffle an overall correlation coefficient between the predicted and the original signal was computed. Finally, the correlation coefficients

were z-transformed, averaged, re-transformed (Corey, Dunlap, & Burke, 1998) and compared to the correlation coefficient obtained from the real data using a Fisher r-to-z test.

4. Results

4.1 Correlations between electric and magnetic recordings reveal a rich spatio-temporal-dynamic activity.

The averaged and filtered MEG and EEG signals reveal a sequence of responses peaking between 0 and 10 ms. **Figure 2** provides a comparison between electrical and magnetic recordings. The magnetic ABR was obtained as in Parkkonen et al. (2009) by taking the grand average (root-mean-squared) across all magnetometer channels and subjects. For the electric ABR the signal obtained from a single EEG electrode (on FpZ) was averaged across all subjects. The electric ABR shows clear deflections that can be associated with wave III (4-5ms) and wave V (6-7ms) based on their timing. While similar peaks for these time courses can be noted for the magnetic ABR, the overall signal appears to have a more complex structure compared with the electric signal. However, when correlating the EEG signal across all magnetometer channels and subjects, the resulting topographies of correlation coefficients show that a varying set of magnetometers can be associated with the electric ABR **(Figure 2)**.

This suggests that MEG and EEG pick up similar information that is fundamental for backward modeling attempts and that a rapidly changing generator structure underlies the measured ABR. Descriptively, the correlation topographies are suggestive of a more complex generator configuration than the "moving single (or two-symmetric) dipole" notion commonly assumed in ABR measurements. This could include cortical contributions that would also be captured by a single EEG channel as used in conventional measurements; however, this analysis was not in the scope of the present paper (see discussion). Illustrating the rich spatio-temporal dynamic is important, as it gets lost when assessing an ABR from a single EEG channel or an RMS measure across all magnetometers.

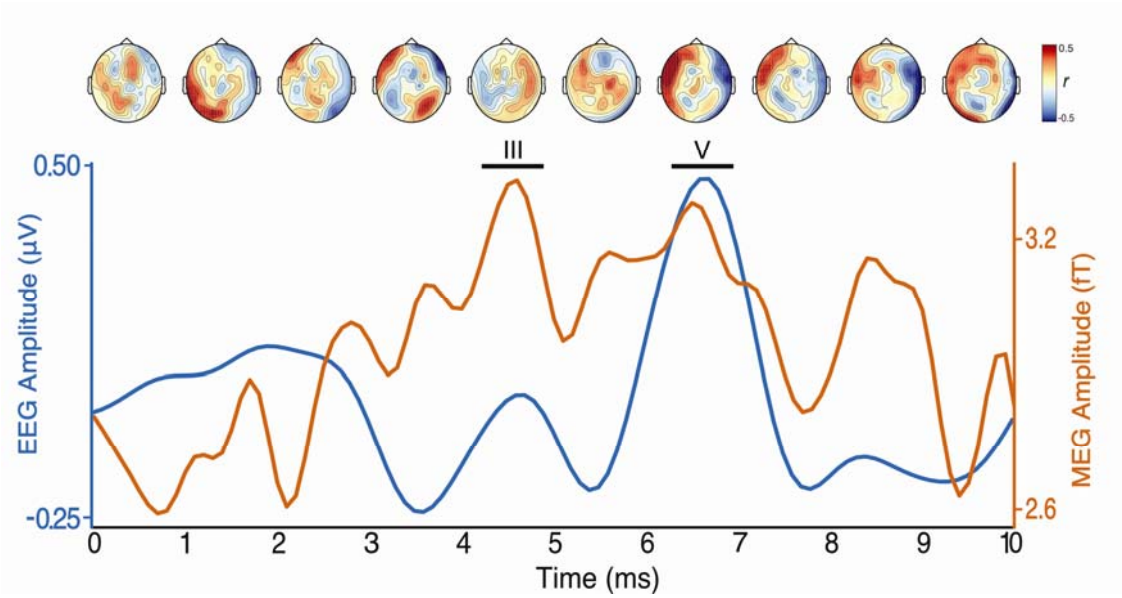

Figure 2: *Grand average of the ABR across all subjects collected using MEG and EEG. The signals were collected in response to 10000 click stimuli at a rate of 30 Hz. The magnetic ABR (red) was obtained by taking the root-mean-squared signal across all magnetometer channels. The topographies are displaying the temporal evolution of correlation coefficients between the signal captured by the EEG electrode (blue) and the 102 magnetometers across all subjects. Each topography indicates a time interval of 1 ms starting between 0-10 ms.*

4.2 Reconstructed brainstem activity is highly correlated with measured electric auditory brainstem activity.

As the measured magnetic ABR might be influenced by a rapidly changing generator structure (**Figure 2**), we performed a ridge regression between the signal captured by the MEG and EEG to generate channel weights for each training time point (**Figure 1, Backward modeling**) to "tune" the MEG to putative brainstem activity. Our long-term goal following this proof-of-concept is to expand this approach to model auditory brainstem activity also in more interesting and complex listening situations.

In this study these channel weights were applied to an independent ABR measurement (i.e. testing dataset) with a different stimulus frequency to predict the electrical ABR via backward encoding from the whole-head MEG data. This modeled activity was then correlated with the actually measured electric ABR. The results show a strong correlation between the measured and reconstructed activity on a single-subject level (**Figure 3a**), with a median correlation coefficient of $r = 0.676$, $p < 0.001$. In order to exclude the possibility that the generated weights will reproduce an ABR-like response independent of the measured signal, we randomized the MEG data by shuffling all time points in the averaged signal on each MEG sensor (1000 times) before applying the channel weights to reconstruct the ABR. This reconstruction from randomized data was then correlated to the measured EEG activity. Finally, the correlation coefficients resulting from this permutation approach were compared to the previously empirically obtained correlation coefficients by means of a Fisher r-to-z test. The results show the reconstruction from the real data was more strongly correlated to the actually measured EEG signal in all participants (**Figure 3c**). The difference between the correlations derived from real and randomized data was significant in 13 out of 14 participants. For the one participant for whom the difference was not significant, we found on closer inspection that the polarity of the ABR was inverted compared with the first measurement. We assume that the change in polarity can be attributed to reference problems, as differences in referencing can cause waveforms of opposite polarity in ABR recordings (Minaya & Atcherson, 2015).

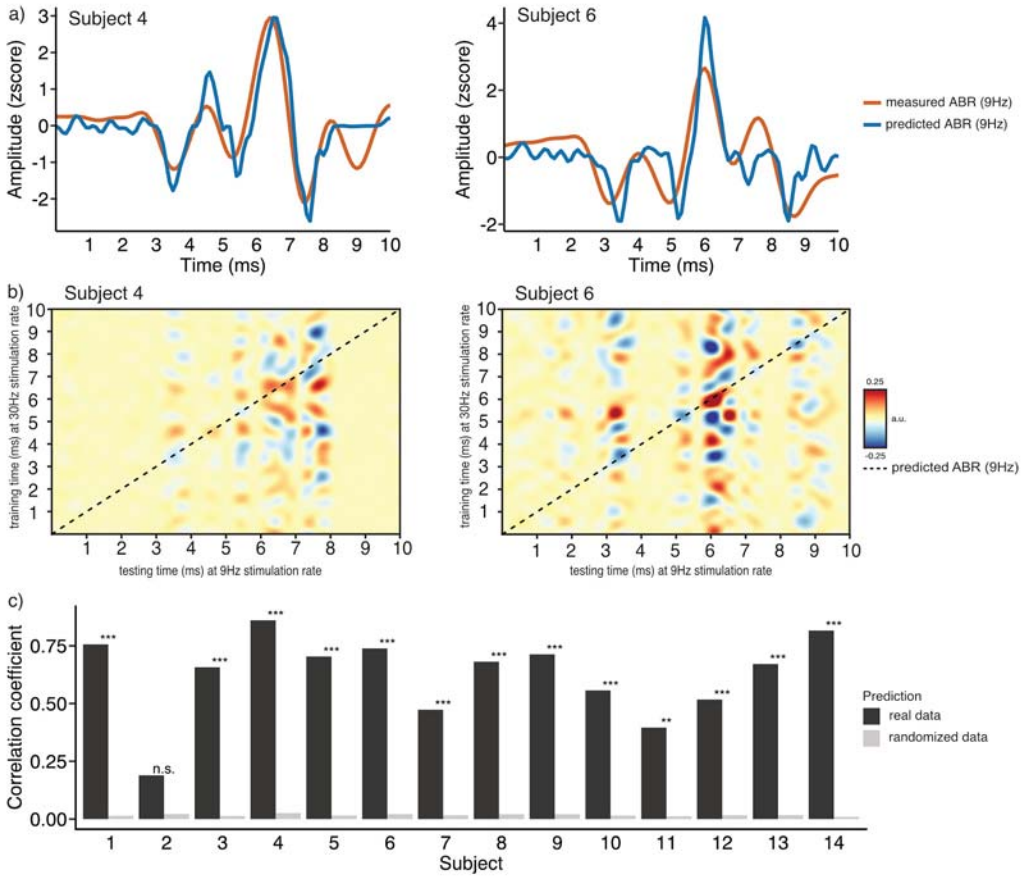

Figure 3:*(a) The reconstructed brainstem activity (blue) for two subjects (4, 6) based on previously computed weights, nicely tracks the actually measured brainstem activity (red). (b) Temporal generalization matrix for the same two subjects. The dashed diagonal line marks the data used for signal reconstruction. (c) Correlation coefficients on single subject level between the individually measured signal and its prediction (black) and between randomized signal and its prediction (grey). Significant differences between the prediction on the real and randomized data are indicated by asterisks.*

Apart from the high correlation between the reconstructed ABR (the diagonal of the temporal generalization matrix) and the measured electric ABR **(Figure 1, Evaluation)**, distinct off-diagonal patterns can be noted on the temporal generalization matrices in **Figure 3b**.

This time generalized "activation" for each testing/training time point **(Figure 1, Signal extraction)** appears to be especially strong around the time course of wave V. Based on the assumption that a

rich spatio-temporal dynamic underlies the magnetic ABR (**Figure 2**), this result could indicate a much broader activation of structures along the ascending auditory pathway than commonly assumed for wave V (putatively lateral leminiscus/inferior colliculi (Møller et al., 1995)).

5. Discussion

In this proof of concept study, we introduce a new approach to capture auditory brainstem activity using a combination of EEG and MEG. Since the presented approach incorporates a (time-) generalization step by applying it to a new dataset, it has the potential to enable the modeling of brainstem activity also in more naturalistic auditory scenarios (e.g. listening to continuous speech or music) and perhaps even during silent periods (e.g. a cue-target period in selective attention tasks). So far this has been problematic, as deriving auditory brainstem activity requires averaging activity evoked by thousands of simple sounds to uncover the signal produced by brainstem regions, resulting in a highly artificial measurement environment. Our approach circumvents this issue by using the signal obtained during a MEG recording as regressors for a concurrent electric ABR measurement. Through this backward encoding approach, channel weights that are responsive to activity from putative auditory brainstem structures are generated (**Figure 1**). We propose that these channel weights can be applied to any other dataset using the same sensor coverage. Analogous to classification-based decoding approaches (King & Dehaene, 2014), we assume that the temporal generalization matrix resulting from the application of the channel weights to a new dataset can be interpreted as the presence of an activation pattern generated during a training period (e.g. the pattern contributing to a specific ABR wave) at a corresponding testing time (e.g. cue target period in selective attention tasks).

In this proof-of-concept study, we validated this approach by using these weights to reconstruct the expected brainstem activity from the magnetometers in another ABR measurement with a different stimulation rate (9 Hz). This reconstructed response was then compared with the measured response showing that both were very highly correlated. This validation marks a first step prior to

using this method to model brainstem activity within complex and natural auditory scenarios (e.g. continuous speech, music).

Here, a comparison or combination with the approach brought forward by Maddox and Lee (2018) would be interesting. They succeeded in measuring brainstem activity following continuous speech by asserting the rectified speech audio signal as the regressor for their EEG recording. Using a similar approach, by cross-correlating the fundamental waveform of continuous speech with the recorded EEG signal, Forte, Etard, & Reichenbach (2017) found a distinct peak at ~9 ms. This evoked activity was modulated by attention, leading the authors to suggest a mechanism of selective attention at the level of the brainstem. However, with occurrences of early auditory cortical activity between 8-10 ms at least some thalamocortical contributions are likely (Liégeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994; Brugge et al., 2009). While these results are promising, in both cases a continuous sound stimulation is required to measure brainstem activity, making the recording of stimulus-free periods impossible. Our approach could be used to shed light on the involvement of auditory brainstem activity during these periods (e.g. cue target) as the generated model weights can be applied to MEG data that were recorded in absence of auditory input to create a temporal generalization model that is putative of an activation pattern corresponding to auditory brainstem activity.

Apart from validating this approach, we found evidence that is suggestive of a rich spatio-temporal generator structure underlying typical ABR recordings. By correlating the signal collected with a single EEG electrode across magnetometers and subjects, we show that a time-varying set of MEG sensors is very responsive to the electric ABR. The resulting topographies of correlation coefficients imply that MEG and EEG pick up similar information and that a rapidly changing generator structure underlies the measured ABR. However, this rich spatio temporal dynamic gets lost when assessing an ABR in the traditional way by using only a single EEG electrode or taking the RMS across channels. The rich correlation topographies raise the question if the single EEG electrode used to record the ABR also captures activity from a more complex (cortico-brainstem) network, which is in

contrast to the traditional single (or symmetric) dipole(s) moving along the ascending auditory pathway.

Since ABRs are usually employed in clinical settings, the latter issue could have far-reaching consequences. However, it is beyond the scope of this proof-of-concept study and requires further research. At this stage we can only speculate what contributes to the spatially rich patterns in our study. Repetitive auditory stimulation at a fixed rate (which is standard in the ABR field; see e.g. Hall (2007)) are known to elicit steady-state responses that can be observed in cortical and subcortical areas (for a review, see Picton, John, Dimitrijevic, & Purcell, 2003). Thus, an influence resulting from the continuous and highly predictable stimulation is plausible. To date, studies that used pseudo-random stimulation rates (Thornton & Slaven, 1993; Holt & Özdamar, 2014; Maddox & Lee, 2018) to investigate whether periodic and randomized click trains evoked differences in the ABR could not find any notable effects. However, in these studies only single channel EEG recordings were used to assess the effects of varying stimulation rates on the ABR. These effects might be more accurately captured using multichannel M/EEG recordings, as auditory steady-state responses can be widely recorded over the scalp (Picton et al. 2003) with different polarities across hemispheres (Johnson, Weinberg, Ribary, Cheyne, & Ancill, 1988). This also implies that auditory steady state responses might account for some of the measurement problems faced previously when using MEG to investigate brainstem activity.

6. Conclusion

In this study, we used a combination of MEG and EEG to create a backward encoding model that can be used to reconstruct auditory brainstem activity. We validated this approach by using the weights generated during an ABR measurement with a 30 Hz stimulation rate to predict the expected EEG ABR activity from the MEG in another measurement with a different stimulation rate (9 Hz). The results of this proof-of-concept study illustrate that the backward encoding model can be generalized to an independent dataset to predict an ABR with high accuracy. The power of

(time-) generalizing the backward encoding model to different datasets (using the same sensor coverage) could in principle enable the modeling of auditory brainstem activity in other, more interesting listening situations. The further development of this approach may enhance our understanding of auditory processing by making the potential contributions of subcortical structures measurable in a non-invasive fashion.

7. Competing Interests

The authors declare no competing financial interests.

8. Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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