Quantifying the individual auditory and visual brain response in 7- month-old infants watching a brief cartoon movie

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ABSTRACT

Electroencephalography (EEG) continues to be the most popular method to investigate cognitive brain mechanisms in young children and infants. Most infant studies rely on the well-established and easy-to-use event-related brain potential (ERP). As a severe disadvantage, ERP computation requires a large number of repetitions of items from the same stimulus-category, compromising both ERPs' reliability and their ecological validity in infant research. We here explore a way to investigate infant continuous EEG responses to an ongoing, engaging signal (i.e., "neural tracking") by using multivariate temporal response functions (mTRFs), an approach increasingly popular in adult-EEG research. N=52 infants watched a 5-min episode of an age-appropriate cartoon while the EEG signal was recorded. We estimated and validated forward encoding models of auditory-envelope and visual-motion features. We compared individual and group-based ('generic') models of the infant brain response to comparison data from N=28 adults. The generic model yielded clearly defined response functions for both, the auditory and the motion regressor. Importantly, this response profile was present also on an individual level, albeit with lower precision of the estimate but above-chance predictive accuracy for the modelled individual brain responses. In sum, we demonstrate that mTRFs are a feasible way of analyzing continuous EEG responses in infants. We observe robust response estimates both across and within participants from only five minutes of recorded EEG signal. Our results open ways for incorporating more engaging and more ecologically valid stimulus materials when probing cognitive, perceptual, and affective processes in infants and young children.

INTRODUCTION

Neuroimaging studies in healthy human infants are subject to severe constraints, as participants cannot follow verbal instructions, show generally short attention spans, and overall tend to be not very cooperative. As functional magnetic resonance imaging (fMRI) studies are difficult to realize in infants (Ellis & Turk-Browne, 2018), electroencephalography (EEG) continues to be the most popular method to investigate cognitive brain mechanisms in very young children and infants.

To analyze the EEG signal, most studies in infants rely on the use of event-related brain potentials (ERPs). Accordingly, most infant EEG paradigms have been optimized for the computation of ERPs: This method necessitates that a few, carefully selected stimulus conditions are repeated multiple times to elicit and average a stereotypical brain response (i.e., an ERP) that can then be compared between conditions or between individuals. This leads to experimental designs that are often (a) highly unnatural and (b) have difficulties capturing the infants' attention for more than a few minutes.

However, in recent years and with the advent of modern computational possibilities, several new approaches to analyze EEG data have become available in adult EEG research. One such approach is the so-called "neural tracking", which seeks to compute and assess the relationship between the recorded EEG signal and an ongoing stimulus signal. The key ideas here are, first, naturally varying, non-repetitive stimuli, often movies (Bartels, Zeki, & Logothetis, 2008; Hasson, Nir, Levy, Fuhrmann, & Malach, 2004; Nishimoto et al., 2011) or naturally spoken conversation (Broderick, Anderson, Di Liberto, Crosse, & Lalor, 2018; Ding & Simon, 2013; Fiedler, Wöstmann, Herbst, & Obleser, 2019), which have higher ecological validity and arguably engage the participant qualitatively differently than artificial, isolated stimuli (Hamilton & Huth, 2018; Huk, Bonnen, & He, 2018; Matusz, Dikker, Huth, & Perrodin, 2018). Second, a mathematical framework (usually a variant of the general linear model) that allows to either "reconstruct" features of such a natural stimulus based on the ongoing brain response (so-called backward or decoding models), or to "predict" the measured ongoing brain response from features of the stimulus (so-called forward or encoding models; Dayan & Abbott, 2001; Naselaris, Kay, Nishimoto, & Gallant, 2011).

While the use of these advanced EEG analysis approaches has become rapidly mainstream in non-human and adult human neuroscientific research, it is still rare in infant research. This is unfortunate, since they not only have yielded important new insights in adult research and are likely to offer the same potential in infant studies, but they may even

provide higher gains in infancy research, which suffers from notoriously low data quality and quantity. It may for instance reduce attrition rates, as experimental designs can be optimized to be highly engaging for infant participants. Rather than presenting hundreds of repetitions of very similar stimuli, which raises the additional challenge of keeping a non-cooperative participant attending to the screen, participants can be presented with constantly changing, engaging videos in which stimuli are embedded.

Importantly, as in adult work, infant brain research has seen an increased interest in the use of naturalistic settings over the past years. Recent research has for instance demonstrated the feasibility of investigating interpersonal neural coupling in adult-infant-interactions (Leong et al., 2017) or the use of oscillatory brain responses in analyzing responses to dynamic social information (Jones, Venema, Lowy, Earl, & Webb, 2015). While dynamic, naturalistic settings and experimental paradigms yield important new insights into how brains behave and interact in real life rather than an abstract laboratory setting, they inherently pose the additional challenge of hard-to-predict and highly variant sensory input. Being able to directly relate a constantly changing input to ongoing brain responses would therefore also be crucial for the analysis of state-of-the-art ecologically valid experimental designs.

One particularly promising approach to do so is the use of multivariate temporal response functions (mTRFs), which offer a mathematically simple way to link ongoing, continuous environmental signals to simultaneously recorded brain responses. In adults, mTRFs have successfully been used to track the processing of ongoing speech (e.g., Fiedler et al., 2019) as well as ongoing and naturalistic visual input (O'Sullivan, Crosse, Di Liberto, & Lalor, 2017). Furthermore, Kalashnikova et al. (2018) used mTRFs in infants to analyze the processing of ongoing auditory speech signals, reporting a stronger cortical tracking for infant-directed compared to adult-directed speech (Kalashnikova, Peter, Di Liberto, Lalor, & Burnham, 2018).

We here demonstrate the feasibility and utility of a forward encoding modelling combined with non-repetitive complex multisensory stimulation in an infant population. We presented 7-month-old infants with a 4'48'' long age-appropriate cartoon (one episode of the cartoon-show *Peppa Pig*) while recording the EEG. We focused our analysis on the processing of three low-level physical stimulus parameters; the auditory envelope, the motion content, and luminance. All three parameters have been amply investigated in both infants and adults and are known to elicit reliable ERP responses.

The auditory ERP response typically consists of a frontocentral P1–N1–P2–N2 sequence of responses, which can be clearly observed in adults and emerges in infancy and early childhood (see e.g., Wunderlich & Cone-Wesson, 2006, for a review). Compared to adults, infants tend to show a much less pronounced P1–N1 response, and the overall response is dominated by a broad P2 response (Wunderlich, Cone-Wesson, & Shepherd, 2006).

The infant visual ERP to complex stimuli such as objects and faces comprises three main components; the Pb, the Nc, and the Slow Wave (Webb, Long, & Nelson, 2005). In particular, the Nc response, a frontocentral negativity typically observed between 400 and 800 ms after stimulus onset often linked to the allocation of attention has been amply investigated (de Haan, Johnson, & Halit, 2003; Reynolds & Guy, 2012).

If we were successful in estimating auditory and visual brain responses using a forward encoding model approach, we expect response functions comparable to classical evoked brain responses. Furthermore, since the combined use of auditory and visual regressors provides more information compared to the use of either regressor alone, we expected a more consistent and reliable response function when using auditory and visual regressors in one model.

Finally, while it is common in adult studies using mTRFs to compute individual response functions based on a subset of the available data, due to the limited amount of data available in the infant cohort we aimed to explore the potential benefit from relying on a "generic" response function (Di Liberto & Lalor, 2017), that is, an average response function computed across participants. Hence, we computed an averaged response function over *n*–1 participants and used this response function to model responses in the *n*th participant (i.e. leave-one-out cross validation). We directly contrasted results obtained with these two approaches on the present data set.

METHODS

Infant participants. Fifty-two 7-month-old infants were included in the final sample (age: 213 ± 8 days [mean ± standard deviation (SD)]; range: 200-225, 24 female). Not untypical for infant studies (Stets, Stahl, & Reid, 2012), an additional 39 infants had been tested but could not be included in the final sample. Note also that directly prior to the experiment reported here, infants had already participated in a 5–10-minute-long ERP experiment on visual emotion perception (see below), further contributing to the drop-out rate since infants often became fussy or tired after the first experiment. In detail, infants were

excluded because they did not watch the complete video (n=24); were too fussy to watch the video at all (n=10); did not contribute at least 100 s of artifact-free data (n=3); had potential neurological problems (n=1); or because of technical problems during the recording (n=1).

All infants were recruited via the maternity ward at the local hospital (Universitätsklinikum Schleswig-Holstein); were born full-term (38–42 weeks gestational age); had a birth weight of at least 2500 g; and had no known neurological deficits. The study was conducted according to the declaration of Helsinki, approved by the ethics committee at the University of Luebeck, and parents provided written informed consent.

Adult reference sample. In addition, we collected data from a reference sample of n = 33 adult participants. Data from n=5 were excluded due to technical difficulties during the recording (n=2) or failure to contribute at least 100 s of artifact-free data (n=3), leading to a final sample of n=28 (mean age: 50 years; range: 21–69, 16 female).

Stimulus. As stimulus material we used one episode (duration 4’48’’, that is, 269 s or 6451 frames) of the cartoon show Peppa Pig (“Peppa Pig–The new car”), an age-appropriate cartoon featuring a family of pigs and their daily life. Sound and visual parameters were not manipulated in any way.

Procedure–Infants. After arrival in the laboratory, parents and infant were familiarized with the environment and parents were informed about the study and signed a consent form. The EEG recording was prepared while the infant was sitting on his/her parent’s lap. For recording, we used an elastic cap (BrainCap, Easycap GmbH) in which 27 Ag/AgCl-electrodes were mounted according to the international 10-20-system. An additional electrode was attached below the infant’s right eye to record the electrooculogram. The EEG signal was recorded with a sampling rate of 250 Hz using a BrainAmp amplifier and the BrainVision Recorder software (both Brain Products).

For the EEG recording, the infant was sitting in an age appropriate car seat (Maxi Cosi Pebble) positioned on the floor. As part of a larger study, a t-shirt was positioned over the chest area of the infants. The t-shirt had either previously been worn by the infant’s mother (n=19) or by the mother of a different same-aged infant (n=14) or had not been worn before (n=19). This modulation was not of main interest to the present study and will not be analyzed or reported here in further detail.

In front of the infant (approximately 60 cm from the infant’s feet), a 24-inch monitor with a refresh rate of 60 Hz was positioned at a height of about 40 cm (bottom edge of the

screen). Left and right of the monitor, loudspeakers (Logitech X-140) were positioned and set to a comfortable level of loudness. When the infant was attending to the screen, the video was started and played without interruption until the end of the episode. The parent was seated approximately 1.5 m behind the infant and was instructed not to interact with the infant during the video. In case the infant became too fussy and started crying during the video, the video was aborted and the infant was excluded from further analysis.

Before this video presentation, infants had been presented with a series of photographs displaying happy and fearful facial expressions as part of the larger, maternal-odor study. Again, the results of this part of the study will not be further analyzed here.

Procedure–Adults. Adult participants were presented with the same "Peppa Pig" movie after they had already participated in one of several unrelated EEG studies. They were informed about the study and signed a consent form. For recording the EEG signal, we used 64 Ag/AgCl active scalp electrodes positioned in an elastic cap according to the international 10-20-system. The EEG signal was recorded with a sampling rate of 1000 Hz using an ActiChamp amplifier and the BrainVision Recorder software (Brain Products).

Adult participants sat in a soundproof and electrically shielded chamber (Desone) in a comfortable chair approximately 1 m away from a 24-inch monitor with a refresh rate of 60 Hz on which the video was presented. Sound was presented from the same loudspeaker models used in the infant study, also positioned left and right to the screen (Logitech X-140).

Analysis. Unless noted otherwise, the analysis protocol was identical for infant and adult data. We analyzed the data using Matlab 2013b (The MathWorks, Inc., Natick, MA), the Matlab toolbox FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011), and the multivariate temporal response function (MTRF) toolbox (Crosse, Di Liberto, Bednar, & Lalor, 2016).

Preprocessing. The data were referenced to the average of all electrodes (mean reference), filtered using a 100-Hz-lowpass and a 1-Hz-highpass filter, and segmented into 1-sec-epochs. To detect epochs contaminated by artifacts, the standard deviation was computed in a sliding window of 200 msec. If the standard deviation exceeds 80 mV at any electrode, the entire epoch was discarded, and if less than 100 artifact-free epochs remained, the participant was excluded from further analysis. An independent component analysis (ICA) was computed on the remaining epochs. Components were inspected visually by a trained coder (S.J.) and rejected if classified as artefactual (infants: 5 ± 2 components per participant [mean ± SD], range 1–10; adults: 26 ± 5, range 11–36). A 1–10 Hz bandpass

filter was applied to the cleaned data. Adult data were downsampled to the infant-data sampling frequency of 250 Hz.

Extraction of stimulus regressors. Regressors characterizing motion, luminance, and the sound envelope were extracted from the stimulus video. Exemplary excerpts of audio, luminance, and motion regressors are shown in Fig 1B.

To compute a regressor of average luminance across all pixels, the weighted sum of the rgb values for each frame was computed using Matlab (Bartels et al., 2008).

To compute a regressor of average motion across all pixels, each video frame was converted to grey-scale, and the difference between two consecutive frames was computed. Then, the mean across all pixels for which this difference was larger than 10 (to account for random noise, see e.g. Jessen & Kotz, 2011; Pichon, de Gelder, & Grèzes, 2009) was computed.

To compute a regressor of sound envelope, the audio soundtrack of the video was extracted and submitted to the NSL toolbox, an established preprocessing pipeline emulating important stages of auditory peripheral and subcortical processing (Ru, 2001). The output of this toolbox resulted in a representation containing band-specific envelopes of 128 frequency bands of uniform width on the logarithmic scale with center frequencies logarithmically spaced between 0.1 and 4 kHz. To obtain the broadband temporal envelope of the audio soundtrack, these band-specific envelopes were then summed up across all frequencies to obtain one temporal envelope. Following earlier own and others' approaches, we used the first derivative of the half-wave rectified envelope as the final audio regressor (for details see Fiedler et al., 2017). The result is a pulse-train-like series of peaks where, across frequency bands, the acoustic energy rises most steeply, reflecting "acoustic edges" such as syllable onsets.

Stimulus parameters. As expected for a child-friendly cartoon movie, frame-to-frame fluctuations in luminance were small. On average, the change in luminance from one frame to the next was 0.35 units per frame (range 0–53, median = 0.05). Note that this deviates from previous studies where the entire dynamic range of luminance (i.e., black to white) was used to quantify the temporal response function in the adult EEG response (e.g., Lalor, Pearlmutter, Reilly, McDarby, & Foxe, 2006; Vanrullen & MacDonald, 2012) or in non-human animal electrophysiological responses (Ringach & Shapley, 2004). In contrast, the luminance-derived motion regressor yielded sizable variance, with a mean frame-to-frame change of 38 units (range 0–192, median = 36).

In sum, while variance in the luminance regressor was small, both motion and audio regressors showed considerable and promising degrees of variance.

Lastly, all regressors were downsampled (audio) and interpolated (motion, luminance), respectively, to the EEG sampling frequency of 250 Hz. In all regressors, time periods in which no EEG data was available as a result of artefact rejection during preprocessing were zero-replaced. Finally, EEG data and physical regressors were aligned and available for the linear model analysis.

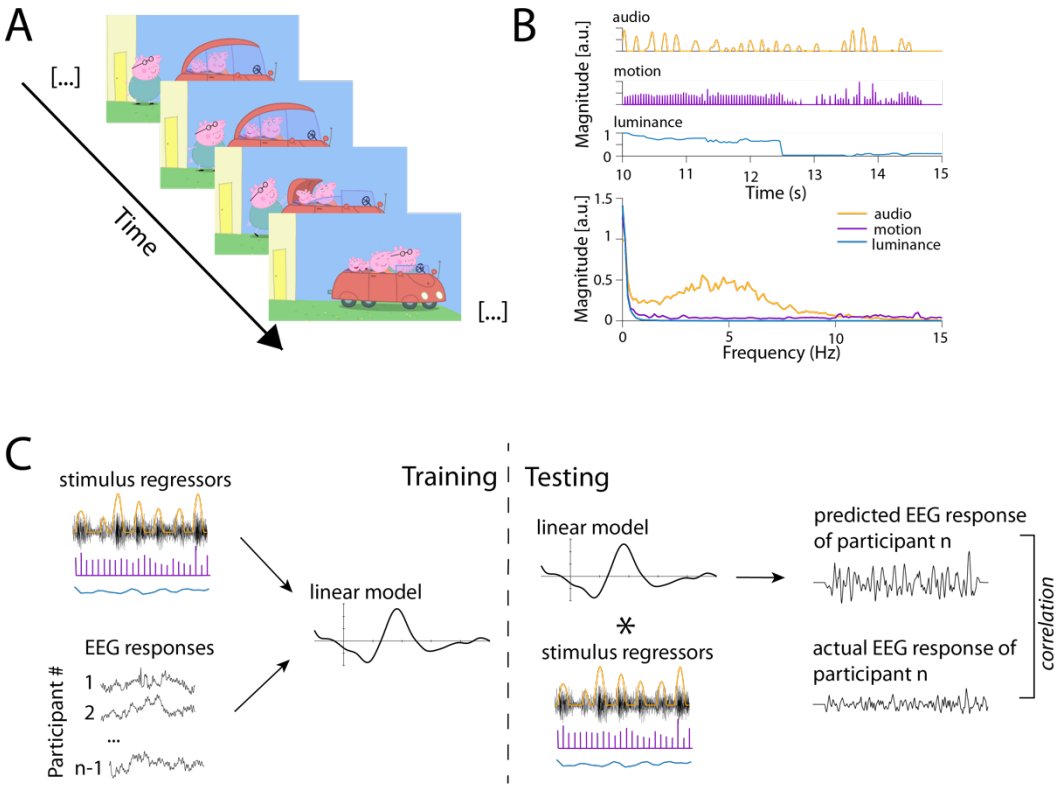

Figure 1. Physical properties of stimulus regressors. A) shows four exemplary stills from the movie used as stimulus material. B) shows an example of a 5-s-long stretch of the audio (orange), motion (purple), and luminance regressors (blue). Below, the frequency spectrum of the stimulus regressors is depicted; while frequencies < 10 Hz appear to be dominant in the audio regressors, no such dominance can be observed for the other regressors. C) shows an overview of the analysis approach. During training, stimulus regressors and the EEG signal of n-1 participants was used to compute a generic response function (left part). During testing, this generic response function was used to predict the EEG response of the nth participant, which was then compared to the actual EEG response of that participant. See main text for further details.

Temporal response functions (TRF). To quantify the degree to which the measures EEG of 7-month-olds (as well as adults) can be expressed as a linear response to stimulus features,

we used regularized regression (with ridge parameter λ) as implemented in the mTRF toolbox (Crosse et al., 2016). The key idea here is to estimate a temporal response function (TRF), that is, a set of time-lagged weights *g,* with which a regressor *s* (here, the physical stimulus features) would need to be convolved (i.e. multiplied and summed) in order to optimally predict the measured EEG response *r*.

More specifically, we used a forward encoding model approach. In a first pass, we aimed to maximize the predictive accuracy of such a model by estimating so-called "generic" models, that is, we predicted the EEG data of an *n*th participant based on a "generic" temporal response function (TRF) from *n-1* participants to the auditory or visual stimulus signal. Since changes in the EEG signal are not likely to occur simultaneously with changes in the stimulus signal but rather with an (unknown) time lag, predictions were computed over a range of time lags between 200 ms earlier than the stimulus signal and 1000 ms later than the stimulus signal.

Choosing the optimal regularization parameter λ. To obtain the optimal regularization parameter λ for each stimulus regressor separately, as well motion and audio simultaneously, we trained the respective model on a variety of λ values between 10^{-5} and 10^{5}, increasing the exponent in steps of 0.5, and used the resulting models to predict the EEG signal for each participant. We then computed the mean response function across *n-1* participants and used this response function to predict EEG response of the nth participant (i.e., *n*-fold leave-one-out crossvalidation). Finally, we computed the predictive accuracy (i.e., Pearson's correlation coefficient *r* between the predicted EEG response and the actual EEG response) for each participant, resulting in one accuracy value for each electrode (27 for infants, 64 for adults) per participant and stimulus parameter for each λ value. For each participant, stimulus parameter, and electrode, we selected the λ value maximizing *predictive* accuracy. Based on these values, we obtained the mean regularization parameter λ value across all electrodes and participants (see Table S1).

These optimal λ parameters were used in the following to train the model, resulting in separate response functions for each stimulus parameter. For each of the three physical stimulus parameters (luminance, motion, audio) we computed a separate model. In addition, we computed a model using both, motion and audio, as regressors ("joint audio-motion model"). We chose not to include luminance in this model, as the regressor for luminance did not yield any reliable model in itself (see results).

Evaluation of temporal response functions. For statistical evaluation of the resulting response functions, we computed a cluster-based permutation test with 1000

randomizations, testing the obtained response functions against zero. A cluster was defined along the dimensions time and electrode position, with the constraint that a cluster had to extend over at least two adjacent electrodes. A type-1-error probability of less than .05 was ensured for all clusters.

In addition, to assess internal validity of our model predictions on an individual basis, we computed three different predictive accuracies per participant. First, for each participant *n*, we computed the correlation between the predicted response generated on a model trained on *n–1* participants and the actual EEG response of *n* ("generic model").

Second, rather than relying on the generic model based on *n–1* participants, we computed an individual response function for each participant ("individual model"). To that end, 80 % of the available data for a given participant were used to train the model, and the resulting response function was then correlated with the response observed in the remaining 20 % of the data.

Third, a *permuted* or null predictive accuracy ("shifted control") was obtained. Before calculating accuracy this way, we shifted the actual EEG response for participant *n* in steps of 2 s (in order to ensure to exceed the potential autoregressive structure of the EEG data) and computed the correlation between the shifted EEG signal and the predicted response, based on the generic model trained on *n–1* participants.

RESULTS

Temporal response function. We computed a generic temporal response function for each stimulus regressor as well as the audio and motion regressor combined (joint audio-motion model).

We observed a clearly defined response function using the audio regressor (Figure 2 for infants and Figure S2 for adults) and the motion regressor (Figure 3 and Figure S3 for adults), while no clear response function could be obtained using the luminance regressor for either infants or adults (Figure S1). While Figures 2 and 3 show the respective response functions obtained from a model which included both regressors (joint audio-motion model), comparable response functions resulted when using either of the regressors in isolation.

Interestingly, the observed response function did not only become visible in the average response function, but also for the vast majority of participants on an individual level (Figure 2B and 3B). Furthermore, note that while a clearly defined response was

visible for both, the audio and motion regressor, the amplitude of the response function for the motion regressor was much smaller compared to the amplitude of the audio response function.

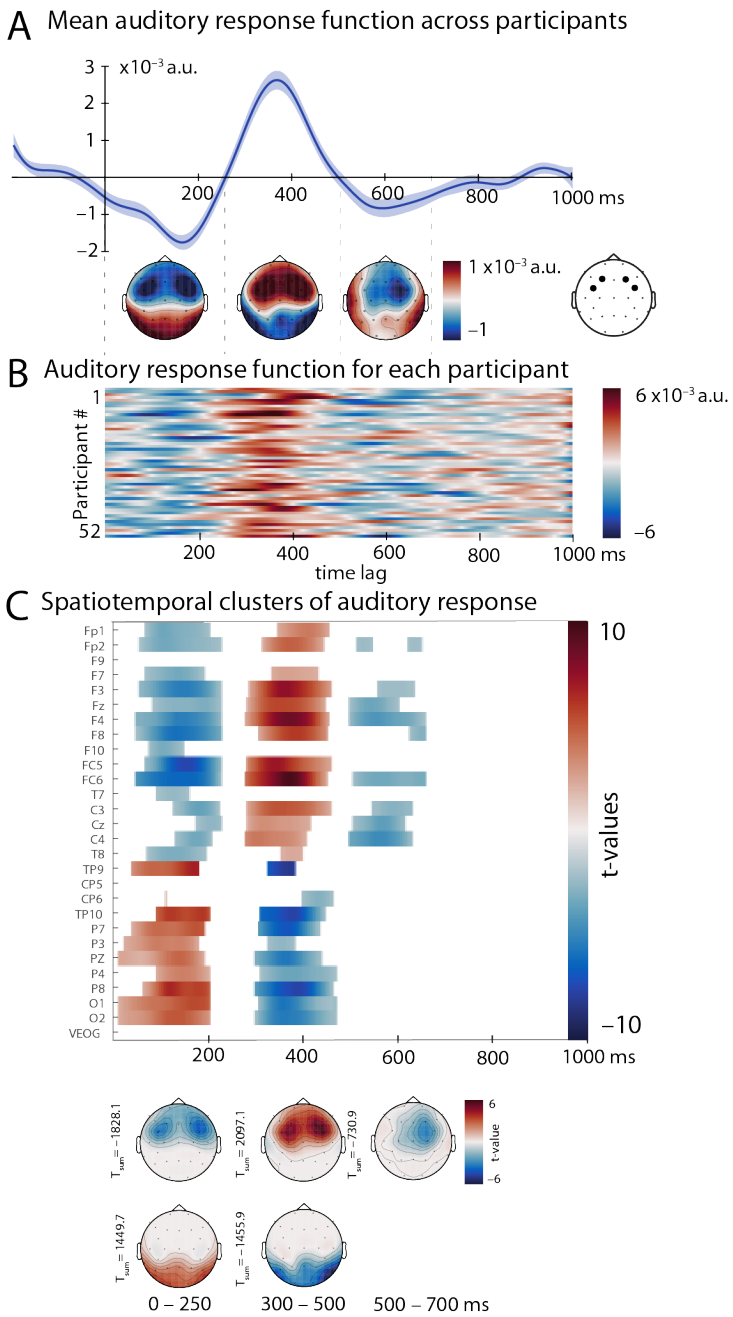

Figure 2. Auditory response function (using motion and audio regressor simultaneously) for infant participants. A) shows the mean mTRF (mean ± within-subject SEM) computed across all participants, averaged over FC5, FC6, F3, and F4, and topographic representations for 0–250 ms, 250–500 ms, and 500–700 ms with electrodes included in the above-shown average marked by black dots. B) shows the auditory response function for each individual infant. C) displays the results of the cluster-based permutation test,

comparing the response function shown in A) and B) to zero. Positive deviations are displayed in red, while negative deviations are shown in blue. In the bottom part of C), the same clusters as in the top part of C) are shown as topographic distributions, along with the summed t-value across the cluster.

Comparing infant and adult brain responses. When directly comparing infant and adult response functions (Figure 4), similarities as well as striking differences emerge. Overall, amplitudes of the response functions are comparable for infants and adults, both showing the already mentioned larger amplitudes for audio regressors and smaller amplitudes for motion regressors. For both, infants and adults, the auditory response function is marked by a prominent frontocentral positivity (250–500 ms for infants, 300–450 ms for adults). While this response appears to be slightly longer for infants, overall, both latency and topography indicate a comparable response for infants and adults. In contrast, the infant auditory response function lacks a second, earlier and more central positivity, which can be observed between 150 and 250 ms in the adult auditory response function.

For the motion response function, both infants and adults show two frontal / frontocentral positivities (250– 450 and 700–900 ms for infants and 250–350 and 450–550 ms for adults). Hence, infants and adults show a comparable response, though the infant response appears to be much slower and less temporally modulated.

Cluster-based permutation test. We computed a cluster-based permutation test comparing the temporal response function obtained using the motion, luminance, and audio regressor as well as the motion and audio regressor simultaneously. We did not observe any significant cluster using the luminance regressor for either infants or adults. In contrast, we did obtain multiple significant clusters, indicating a positive or negative deviation from zero, for the motion and audio regressor, both when included separately as well as in combination (see supplementary material for a full list of the results of the cluster-based permutation test using audio and motion regressor separately as well as in combination for infants and adults, Figure 2C and 3C for infant results and S2C and S3C for adult results). The resulting clusters confirm the deflections observed in the auditory and motion response function (Figure 2A and 3A, respectively).

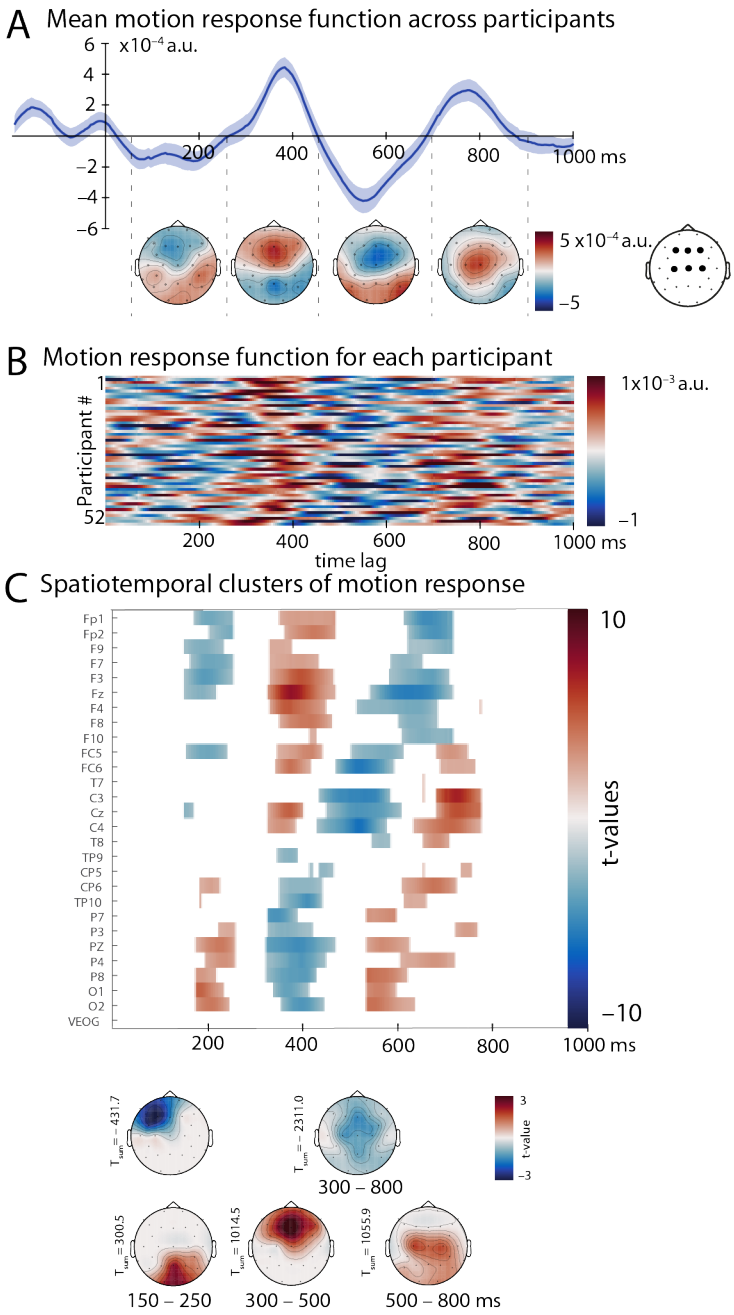

Figure 3. Motion response function (using motion and audio regressor simultaneously) for infant participants. A) shows the mean mTRF (mean ± SEM) computed across all participants, averaged over F3, Fz, F4, C3, Cz, and C4, and topographic representations for 50–250 ms, 250–450 ms, 450–700 ms, and 700–900 ms with electrodes included in the above-shown average marked by black dots. B) shows the motion response function for each individual infant. C) displays the results of the cluster-based permutation test, comparing the response function shown in A) and B) to zero. Positive deviations are displayed in red, while negative deviations are shown in blue. In the bottom part of C), the same clusters as in the top part of C) are shown as topographic distributions, along with the summed t-value across the cluster.

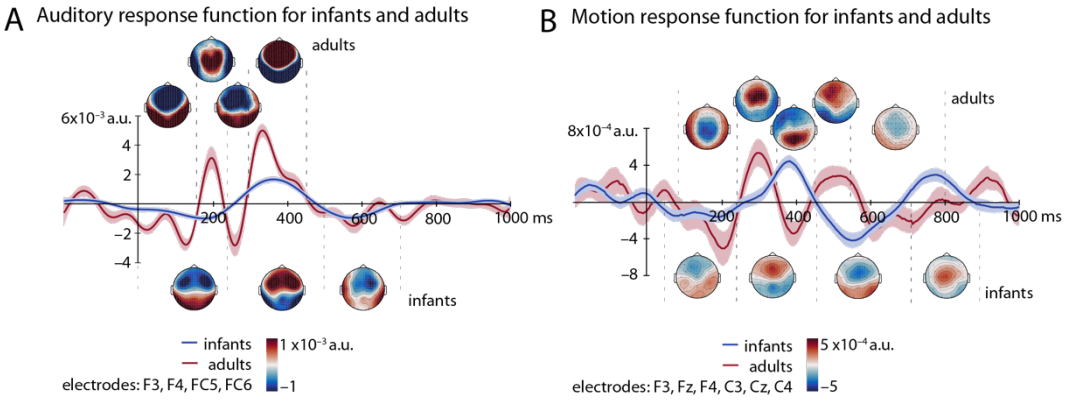

Figure 4. Comparison of infant and adult response functions. Mean mTRF for infant (in blue) and adult (in red) participants are shown for the audio regressor (A) and the motion regressor (B). The infant response functions and topographical representations are identical to those shown in Fig 2A and 3A for audio and motion regressors, respectively. Responses are averaged across the same electrodes for adults and infants, namely FC5, FC6, F3, and F4 for A) and F3, Fz, F4, C3, Cz, and C4 for B). The topographic representations of adult responses correspond to those in the supplementary material, namely 50–150 ms, 150–250 ms, 250–300 ms, and 300–450 ms for A) and 50–250 ms, 250–350 ms, 350–450 ms, 450–550 ms, and 550–800 ms for B).

Generic vs. individual response functions. The results discussed above rely on a generic model computed based on data from *n–1* participants in order to predict the *n*th participant (see Di Liberto & Lalor, 2017). An alternative approach (and in fact preferable, if enough data for per subject is available; e.g., Fiedler et al., 2019; O'Sullivan et al., 2017) computes an individual model based on a subset of an individual's data and compare the resulting predictions to the remaining data.

As expected, individual models showed a larger variance compared to the generic model (Figure 5–7; see S4 and S5 for data from adult participants), but both, generic model and individual model result in correlations clearly above zero (with the exception of luminance, where no reliable prediction was possible for either mode, see Figure 5C).

When both, audio and motion regressor were included (Figure 6), the generic model resulted in a higher correlation compared to the individual model for infant participants ($t(51)=3.76$, $p<.001$); 37 participants showed a higher correlation with the generic model while only 15 participants showed a higher correlation with the individual model. When using only the motion regressor (Figure 5B), the correlations were also higher for the generic compared to the individual model ($t(51)=3.50$, $p<.001$), while for the auditory regressor (Figure 5A), this difference was less pronounced ($t(51)=1.82$, $p=.07$).

As a control analysis, a generic model using temporally shifted (i.e., purposefully misaligned) versions of the actual EEG signal (1,000 iterations) did yield substantially lower predictive accuracy values.

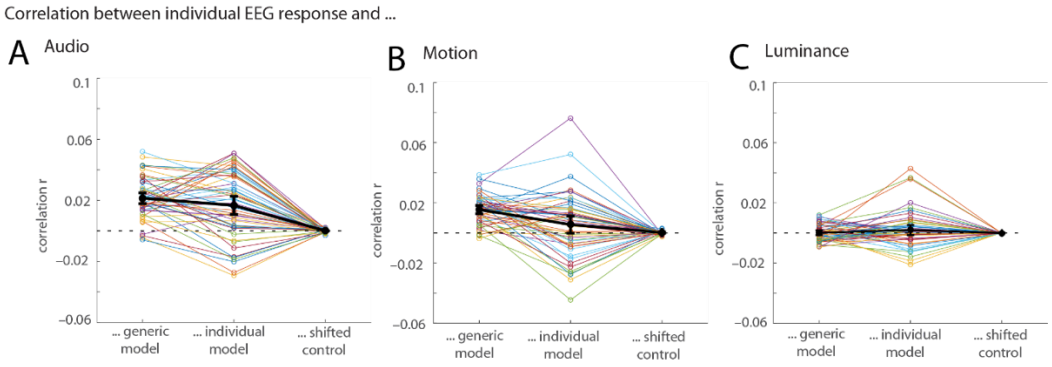

Figure 5. Predictive Accuracy (r) between model and EEG response for infant participants. The recorded individual EEG response was correlated with three different parameters using Pearson's correlation coefficient for the audio regressor (A), motion regressor (B), and luminance regressor (C). On the left, the correlation between the recorded EEG responses of participant n and the response predicted by the generic model based on the remaining n-1 participants is shown for each participant. In the middle, the correlation between the model trained on the first 80 % of the data available for each participant and used to predict the remaining 20 % from that participant and the actual EEG response recoded from that participant is shown. The right column shows the correlation between the prediction generated by the generic model and the recorded EEG data shifted in a circular way in steps of 2 s as a control condition (averaged over all possible shifts). Correlations are shown for each infant participant (in colors) as well as the mean correlation with 95% CI (confidence interval) across all participants (in black).

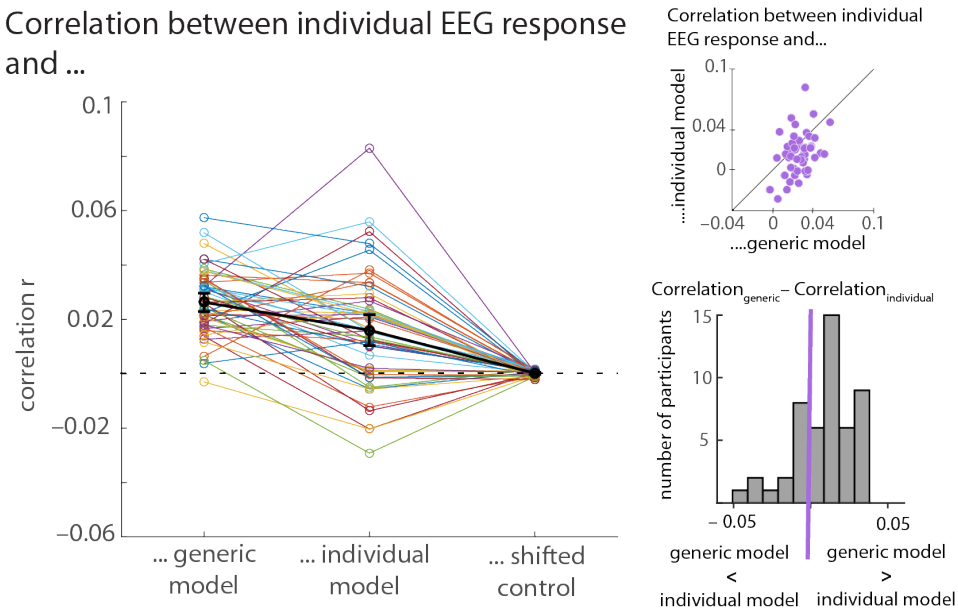

Figure 6. Predictive accuracy for modelled and observed EEG response for infant participants in a joint audio–motion model. The left part of the figure shows the correlation (based on Pearson's correlation coefficient) between the recorded EEG signal and the EEG responses predicted based on the generic model (left column), the individual model (middle column), and a shifted control condition (right column, see text). The two plots on the right hand visualize a comparison between the generic and the individual model. In the top plot, each purple dot indicates the difference between the correlation with the generic model and the correlation with the individual model. Hence, a purple dot in the right bottom part of the graph indicates an individual with a higher correlation for the generic compared to the individual model, while a purple dot in the top left part indicates an individual with a higher correlation for the individual compared to the generic model. The bottom plot displays the same information in a bar graph; individuals having a higher correlation for the generic model have a positive difference and hence fall to the right of the zero-threshold marked in purple while those with a higher correlation for the individual model have a negative difference and fall to the left of the zero-threshold.

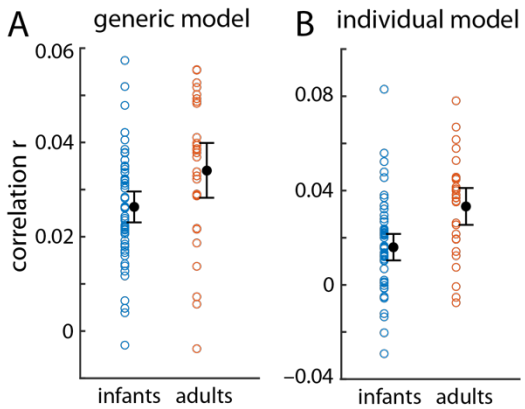

Figure 8. Predictive accuracy for infants and adults in a joint audio–motion model. A) shows the individual correlations using Pearson's correlation coefficient for infants (blue) and adults (orange) using the generic model. B) shows the individual correlations using Pearson's correlation coefficient for infants (blue) and adults (orange) using the individual model. Mean accuracies with 95 % confidence intervals are shown in black.

Discussion

We investigated the use of a variant of forward encoding models (multivariate temporal response functions, mTRFs) to analyze infant brain responses to a continuous complex audiovisual stimulus, namely a 5-minute cartoon movie. We observed clearly defined response patterns to both the auditory as well as the motion content, but no predictive response function for changes in luminance was found.

Our results demonstrate that the simultaneous acquisition of individual brain responses to different sensory modalities is possible in the infant brain, opening new avenues for ecologically valid multisensory research paradigms in developmental neuroscience. Furthermore, our results suggest that a generic model derived from a larger

set of unrelated infant data is as good or slightly better compared to an individual model in predicting the individual brain response, especially in cases where only limited data is available. This points to the further utility of such an approach in developmental and at-risk populations.

Motion and Audio. For both, motion and audio information in the cartoon movie, we found a clearly defined response in both infants and adults. The observed responses are largely consistent with patterns typically reported in more traditional event-related brain potentials. The frontocentral negativity between 450 and 700 ms for instance observed in the infant brain responses linked to the motion regressor corresponds in timing, shape, and topography to the Nc component, an infant ERP component that can routinely be observed in visual paradigms and has been linked to attention allocation (Webb et al., 2005). Likewise, the bifocal frontal positivity observed in the infants' brain response linked to the auditory envelope shows a strong similarity to the commonly reported P2 response in infant auditory brain responses (Wunderlich et al., 2006).

The direct comparison of infant and adult brain responses (Figure 4) may provide insight into the developmental changes. In response to the auditory envelope, both infants and adults show a prominent frontal negativity peaking around 400 ms. Notably, however, the adults show an additional central positivity around 200 ms, which is missing in the infant response. This corroborates and replicates known developmental changes commonly observed in auditory evoked responses when comparing infants and adults (Wunderlich & Cone-Wesson, 2006). Considering the motion response, the correspondence between infant and adult response is less straight-forward. While the adult response is characterized by two frontocentral positivities, one peaking around 300 ms and the other around 500 ms, the infant response is dominated by one frontocentral peak around 400 ms.

Importantly, we used both, generic response functions as well as individual response functions to predict the EEG signal. When using both, the motion and the auditory regressor, performance was significantly better for the generic compared to the individual model. When using only the auditory regressor, the same pattern was visible but the difference only marginally significant. Note, however, that both, generic and individual models generated predictions that were significantly above chance level. This demonstrates two important things. First, five minutes of EEG recording are sufficient to compute reliable models, both on an individual level as well as across participants as a generic model. This is not only true for EEG data obtained from healthy adults but also for data obtained from populations providing notoriously noisy signal, such as infants. Second, brain responses across participants, both infants and adults, are sufficiently similar to

generate a model that can successfully predict a new infant's brain response, yielding even better outcomes compared to the individual model.

Limitations and future studies. The present study provides an important step and proof of feasibility for using mTRFs to analyze infant EEG data in response to complex and dynamic audiovisual stimulus material. This offers a whole host of new possibilities in the investigation of infant's brain responses in their natural environment.

One important feature of the present study is that we used the unmanipulated cartoon video material. While this makes for an ecologically valid and easy-to-obtain stimulus, it comes with the caveat of a lack of control for stimulus properties. Notably, while we did observe a clear-cut response to the motion and the auditory regressor, we did not find a reliable response to the changes in luminance. The most likely explanation for this discrepancy is the lack in variance in the luminance content. While the motion and the auditory regressor showed large-amplitude changes throughout the video (e.g., average motion change between frames = 38 units), average luminance of this cartoon movie remained fairly constant (average luminance change between frames = 0.35 units). Previous studies targeting neural responses to luminance change (in adults) typically used considerably more pronounced black–white contrast (Lalor et al., 2006; Vanrullen & MacDonald, 2012). Hence, the luminance changes in the stimulus material were likely too small to elicit any robust change in brain response. Future studies explicitly varying the luminance content are therefore necessary to investigate the applicability of mTRFs to other visual stimulus parameters in infants.

Also, we operationalized motion as change in pixel from one frame to the next. This means that the motion regressor not only reflected the actual motion of the objects and persons depicted in the video but also cuts in the video. For the present purpose, we did not differentiate between these two possibilities of motion.

Building upon the present results, a next step would therefore be to purposefully manipulate such parameters. By using stimulus material designed to encompass a larger variance in luminance and/or no cuts in the video, it should for instance be possible to observe brain response to changes in luminance and motion responses that can be clearly linked to actual motion rather than video cuts. Such an approach could for instance provide valuable new insights into the processing of biological motion (Marshall & Shipley, 2009; Reid, Hoehl, & Striano, 2006).

Furthermore, in the present study, we did not contrast different conditions, neither within infant nor between different groups of infants. Having demonstrated the feasibility

of using encoding models to model brain responses for this type of complex audiovisual stimuli, the next step would certainly be to utilize this approach to investigate differences in processing between (a) different types of stimulation or (b) different groups of infants.

A first step in using mTRFs to contrast different continuous stimulus signals has been done by Kalashnikova et al. (2018), who compared the processing of infants vs. adult directed speech in 7-month-olds. Future studies could encompass more complex naturalistic scenarios, using for instance audiovisual video material. More importantly, mTRFs can also be used to investigate brain responses in live interactions, in which the live input the infant receives is recorded and used as a regressor in the subsequent analysis. Such an approach would provide an important tool in investigating the neural bases of social interactions.

Conclusion. The present data demonstrate that forward encoding models based on the multivariate temporal response function (mTRF) pose a valuable and versatile tool in quantifying and disentangling complex audiovisual brain responses and the according perceptual processes in infancy. Our results open way for applications to a variety of research areas not only in early development, but also in other special populations characterized by short attention spans and low cooperativeness, including research in severely impaired neurological patients. New paradigms could not only entail complex multisensory perception, but extend to dynamic social interactions. As such, mTRF approaches to infant data analysis will allow developmental researchers to devise more engaging and thereby more easily applicable experimental set-ups for infancy research.

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DATA ACCESSIBILITY.

Data will be made available upon publication.

BIBLIOGRAPHY

Bartels, A., Zeki, S., & Logothetis, N. K. (2008). Natural vision reveals regional specialization to local motion and to contrast-invariant, global flow in the human brain. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhm107

Broderick, M. P., Anderson, A. J., Di Liberto, G. M., Crosse, M. J., & Lalor, E. C. (2018). Electrophysiological Correlates of Semantic Dissimilarity Reflect the Comprehension of Natural, Narrative Speech. *Current Biology*. https://doi.org/10.1016/j.cub.2018.01.080

Crosse, M. J., Di Liberto, G. M., Bednar, A., & Lalor, E. C. (2016). The Multivariate Temporal Response Function (mTRF) Toolbox: A MATLAB Toolbox for Relating Neural Signals to Continuous Stimuli. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2016.00604

Dayan, P., & Abbott, L. (2001). *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems.* Cambridge, MA: MIT Press.

de Haan, M., Johnson, M. H., & Halit, H. (2003). Development of face-sensitive event-related potentials during infancy: a review. *International Journal of Psychophysiology*, *51*(1), 45–58. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14629922

Di Liberto, G. M., & Lalor, E. C. (2017). Indexing cortical entrainment to natural speech at the phonemic level: Methodological considerations for applied research. *Hearing Research*. https://doi.org/10.1016/j.heares.2017.02.015

Ding, N., & Simon, J. Z. (2013). Adaptive Temporal Encoding Leads to a Background-Insensitive Cortical Representation of Speech. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.5297-12.2013

Ellis, C. T., & Turk-Browne, N. B. (2018). Infant fMRI: A Model System for Cognitive Neuroscience. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2018.01.005

Fiedler, L., Wöstmann, M., Graversen, C., Brandmeyer, A., Lunner, T., & Obleser, J. (2017). Single-channel in-ear-EEG detects the focus of auditory attention to concurrent tone streams and mixed speech. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2552/aa66dd

Fiedler, L., Wöstmann, M., Herbst, S. K., & Obleser, J. (2019). Late cortical tracking of

ignored speech facilitates neural selectivity in acoustically challenging conditions. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.10.057

Hamilton, L. S., & Huth, A. G. (2018). The revolution will not be controlled: natural stimuli in speech neuroscience. *Language, Cognition and Neuroscience*. https://doi.org/10.1080/23273798.2018.1499946

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., & Malach, R. (2004). Intersubject Synchronization of Cortical Activity during Natural Vision. *Science*. https://doi.org/10.1126/science.1089506

Huk, A., Bonnen, K., & He, B. J. (2018). Beyond Trial-Based Paradigms: Continuous Behavior, Ongoing Neural Activity, and Natural Stimuli. *The Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.1920-17.2018

Jessen, S., & Kotz, S. A. (2011). The temporal dynamics of processing emotions from vocal, facial, and bodily expressions. *NeuroImage*, *58*(2), 665–674.

Jones, E. J. H., Venema, K., Lowy, R., Earl, R. K., & Webb, S. J. (2015). Developmental changes in infant brain activity during naturalistic social experiences. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21336

Kalashnikova, M., Peter, V., Di Liberto, G. M., Lalor, E. C., & Burnham, D. (2018). Infant-directed speech facilitates seven-month-old infants' cortical tracking of speech. *Scientific Reports*. https://doi.org/10.1038/s41598-018-32150-6

Lalor, E. C., Pearlmutter, B. A., Reilly, R. B., McDarby, G., & Foxe, J. J. (2006). The VESPA: A method for the rapid estimation of a visual evoked potential. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2006.05.054

Leong, V., Byrne, E., Clackson, K., Georgieva, S., Lam, S., & Wass, S. (2017). Speaker gaze increases information coupling between infant and adult brains. *Proceedings of the National Academy of Sciences*. https://doi.org/10.1073/pnas.1702493114

Marshall, P. J., & Shipley, T. F. (2009). Event-related potentials to point-light displays of human actions in 5-month-old infants. *Developmental Neuropsychology*. https://doi.org/10.1080/87565640902801866

Matusz, P. J., Dikker, S., Huth, A. G., & Perrodin, C. (2018). Are we ready for real-world neuroscience? *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_e_01276

Naselaris, T., Kay, K. N., Nishimoto, S., & Gallant, J. L. (2011). Encoding and decoding in fMRI. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.07.073

Nishimoto, S., Vu, A. T., Naselaris, T., Benjamini, Y., Yu, B., & Gallant, J. L. (2011). Reconstructing visual experiences from brain activity evoked by natural movies. *Current Biology*. https://doi.org/10.1016/j.cub.2011.08.031

O'Sullivan, A. E., Crosse, M. J., Di Liberto, G. M., & Lalor, E. C. (2017). Visual Cortical Entrainment to Motion and Categorical Speech Features during Silent Lipreading. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2016.00679

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*, 156869.

Pichon, S., de Gelder, B., & Grèzes, J. (2009). Two different faces of threat. Comparing the neural systems for recognizing fear and anger in dynamic body expressions. *NeuroImage*, *47*, 1873–1883.

Reid, V. M., Hoehl, S., & Striano, T. (2006). The perception of biological motion by infants: An event-related potential study. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2005.10.080

Reynolds, G. D., & Guy, M. W. (2012). Brain-behavior relations in infancy: Integrative approaches to examining infant looking behavior and event-related potentials. *Developmental Neuropsychology*. https://doi.org/10.1080/87565641.2011.629703

Ringach, D., & Shapley, R. (2004). Reverse correlation in neurophysiology. *Cognitive Science*. https://doi.org/10.1016/j.cogsci.2003.11.003

Ru, P. (2001). *Multiscale Multirate Spectro-Temporal Auditory Model*. University of Maryland College Park.

Stets, M., Stahl, D., & Reid, V. M. (2012). A meta-analysis investigating factors underlying attrition rates in infant ERP studies. *Developmental Neuropsychology*, *37*(3), 226–252. https://doi.org/10.1080/87565641.2012.654867

Vanrullen, R., & MacDonald, J. S. P. (2012). Perceptual echoes at 10 Hz in the human brain. *Current Biology*. https://doi.org/10.1016/j.cub.2012.03.050

Webb, S. J., Long, J. D., & Nelson, C. A. (2005). A longitudinal investigation of visual event-related potentials in the first year of life. *Dev Sci*, *8*(6), 605–616.

https://doi.org/10.1111/j.1467-7687.2005.00452.x

Wunderlich, J. L., & Cone-Wesson, B. K. (2006). Maturation of CAEP in infants and children: A review. *Hearing Research*. https://doi.org/10.1016/j.heares.2005.11.008

Wunderlich, J. L., Cone-Wesson, B. K., & Shepherd, R. (2006). Maturation of the cortical auditory evoked potential in infants and young children. *Hearing Research*. https://doi.org/10.1016/j.heares.2005.11.010