Activity level in left auditory cortex predicts behavioral performance in inhibition tasks in children

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Abstract

Sensory processing during development is important for the emerging cognitive skills underlying goal-directed behavior. Yet, it is not known how auditory processing in children is related to their cognitive functions. Here, we utilized combined magneto- and electroencephalographic (M/EEG) measurements to show that child-unique auditory cortical activity at ~250 ms after auditory stimulation predicts the performance in inhibition tasks. While unaffected by task demands, the amplitude of the left-hemisphere response was significantly correlated with the variability of behavioral response time. Since this response is not present in adults, our results suggest divergent brain mechanisms in adults and children for consistent performance in auditory-based cognitive tasks. This difference can be explained as a shift in cognitive control functionality from sensorimotor associations in the auditory cortex of children to top–down regulated control processes involving (pre)frontal and cingulate areas in adults.

Keywords: Auditory processing, MEG, EEG, inhibition, development, cognitive control

Introduction

The development of basic auditory circuits in the brain relies on everyday aural experiences. Converging evidence from studies of both typical and clinical groups has shown the importance of this type of plasticity for efficient auditory functioning (Gordenet al., 2003; Tierney et al., 2015). Auditory sensory processing during development not only enables human communication and language learning, it also plays a role in cognitive and sensorimotor aspects of behavior (Kraus et al., 2012; Siegel et al., 2015). Indeed, the effect of auditory expertise extends into cognitive functions such as attention and cognitive control that rely on auditory processing (Kraus and White-Schwoch, 2015). Presumably, an interaction between auditory, sensorimotor and cognitive processing govern the resulting phenotype of goal directed behavior (Kraus and White-Schwoch, 2015). Given the evident link between auditory and cognitive development, we have surprisingly limited understanding of how the typical development of cortical auditory responses is related to cognitive functions such as cognitive control.

Auditory evoked brain responses measured with electro- and magnetoencephalography (EEG/MEG) have been successfully used to study the development of the central auditory system (Paetau et al., 1995; Johnstone et al., 1996; Ponton et al., 2000; Ponton et al., 2002; Čeponienė et al., 2002; Wunderlich and Cone-Wesson, 2006) and they have been used as a marker for central auditory pathway plasticity (Sharma et al., 2002). Especially interesting from the perspective of auditory development is a sustained activation pattern approximately 250ms after auditory stimulation, as it is typically reported in a wide age range of children but not in adults.

In adults, the resulting waveform from auditory stimulation is a combination of transient positive and negative deflections, which were defined by their order (P1-N1-P2-N2) or latency (e.g. N100) – and a lower letter “m” to indicate their MEG counterparts. In contrast, the most prominent responses in primary school children (~6–12 years) are the P1(m) at around 100ms (Orekhova et al., 2013; Yoshimura et al., 2014) and a sustained activation pattern at ~250 ms (N2m/N250m) (Paetau et al., 1995; Pontont et al., 2000; Ceponiene et al., 2002; Parviainen et al., 2019). The development of the auditory neural activation is best characterized by a gradual dissociation of the earlier, more transient responses (P1/N1), and an attenuation of the later, sustained, response (N250) until it is no longer or barely present in adults (Ponton et al., 2000; Albrecht et al., 2000; Čeponienė et al., 2002; Takeshita et al., 2002; Wunderlich and Cone-Wesson, 2006). The right hemisphere seems to precede the left hemisphere in this developmental trajectory, suggesting faster maturation of the right-auditory cortex and possibly stronger experience-driven plasticity in the left than right hemisphere (Parviainen et al., 2019).

Developmental studies of human auditory processing have merely sketched the age-related changes in timing or strength of activation across the time-line of processing the sensory information. To go beyond the descriptive level, a fundamental question is how the development of activity in these time-windows (i.e. ~100 and 250 ms.) is functionally meaningful for the development of cognitive functions. These two time-windows seem to represent functionally distinct processes. First, they are dissociated by their developmental trajectories (Parviainen et al., 2019). Second, responses in these time-windows show different refractory periods; whereas shortening the inter stimulus interval (ISI) attenuates the earlier response pattern, the later, more sustained response is enhanced (or unaffected) (Takeshita et al., 2002; Karhu et al., 1997).

The child N1(m), emerging during early-mid childhood, seems to correspond relatively straightforward to the adult N1(m) (Čeponienė et al, 1998) and its role in auditory information processing is relatively well known. In short, although the N1(m) primarily reflects sensory and perceptual processing, it is also affected by (selective) attention (Hilyard et al., 1973; Näätänen, 1982). In contrast, the later time-window (i.e. ~200-300ms) shows remarkable differences between adults and children. Indeed, children show an auditory evoked response (i.e. N250m) that is reported even by passive stimulation, using different sound types, and under different attentional conditions (van Bijnen et al., 2019; Parviainen et al., 2019; Albrecht et al., 2000; Takeshita et al., 2002; Johnstone et al., 1996). This response is typically absent in adults. Instead, adults consistently show a response pattern in this time-window only in active tasks and it has been implicated in executive control in the cingulate cortex (Falkenstein et al., 1999; Nieuwenhuis et al., 2003; Huster et al., 2010). Given the apparent relevance of this child-specific response for the developing brain, little is known about its role in the functional development of auditory and related cognitive networks.

This sustained activation pattern has been suggested to reflect increased automatization of information processing (Albrecht et al., 2000; Parviainen et al., 2011), possibly corresponding with the development of (neural) inhibitory control (Čeponienė et al., 2002) or the ability to control attention (Johnstone et al., 1996). However, direct correlational evidence comes only from language studies that have related weaker and/or contracted activity in this time window in typical developing children to a better performance on language tests (Parviainen et al. 2011; Hämäläinen et al., 2013). A direct link between (the maturation of) this sustained response and higher-order cognitive skills such as attention and inhibition has not been established.

In this study, we investigated the later, sustained response in the child brain. More specifically, we explored its developmental trajectory in a cross-sectional design and its sensitivity to task manipulations by varying attentional and inhibitory demands. Most importantly, to improve our understanding of its functional significance, we explored how much this response explained behavioral performance measures of inhibition and attention. In the present study, 78 typically developing children and 16 adults completed three variations of a simple auditory oddball paradigm; a passive oddball task, an active oddball task (press button for deviant tone) and a Go/No-go task (press button for standard tone).

We combined M/EEG recordings and individual MRI's to achieve maximal sensitivity to the spatiotemporal characteristics of maturation-specific activation patterns (Sharon et al., 2007). A combination of M/EEG is uniquely suitable to extract the separate components from the time-varying activation pattern evoked by auditory stimuli, and adding individuals MRI's increases the accuracy of localizing the underlying cortical generators. Importantly for our purpose, while MEG is more sensitive to hemispheric differences, EEG provides a better account of deeper (e.g. cingulate cortex) and radial sources (Baillet, 2017; Gross, 2019).

Materials and Methods

Participants

Participants were Finnish speaking school children (6-14 years) recruited through schools and the National Registry of Finland, and Finnish speaking adults. None of the participants had neurological disorders or were on medication affecting the central nervous system. In total, 78 children and 16 adults participated in this study. Of the 78 children, eleven were excluded: one did not finish the experiment and one had too many errors in the MEG task (>50% errors in at least one block, see below), five had excessive head movements or magnetic interference during MEG/MRI measurements, two objected to go in the MRI scanner, and two showed structural abnormalities in their MRI. No adults were excluded. The data included in this study consisted of 67 children (mean age 10.2 years, SD: 1.4, range: 6–14, 36 boys, 31 girls) and 16 adults (mean age 24.8, SD: 3.4, range: 20–30, 3 men, 13 women). Children were recruited to cover mainly the ages between 8-12 years as previous studies indicated this age range is an important developmental period for our response of interest. All participants had normal hearing as tested with an audiometer. The study was approved by the Ethics Committee of the University of Jyväskylä. An informed consent was obtained from all children and their parents, and the adults in accordance with the Declaration of Helsinki. All participants received compensation for participation (movie ticket or gift card).

Stimuli and Tasks

Auditory stimuli consisted of a 70-ms (10–ms rise/fall time) sine wave tone with a frequency of either 1.0- (standard tone(ST); 70%) or 1.5-kHz (deviant tone(DT); 30%) at 65 dB SPL and were created with the Audacity software® (V2.3.3) (http://audacityteam.org/). A continuous stream of auditory stimuli was presented binaurally with an inter-stimulus interval varying between 1.6 and 2.0–s. The stream always started with the standard tone, and two deviant tones were never presented in a row. The participants completed three tasks: a passive listening task (PL), an auditory Go/No-go (GN) and an auditory oddball task (OB). The stimuli were identical in all three tasks but the instructions on how to respond were different: subjects were asked to ignore the tones (PL), press a button to ST (GN), and press the button to DT (OB). The number of stimuli was different in the PL task compared to the GN and OB: 150 stimuli/block vs. 90 stimuli/block, respectively (figure 1).

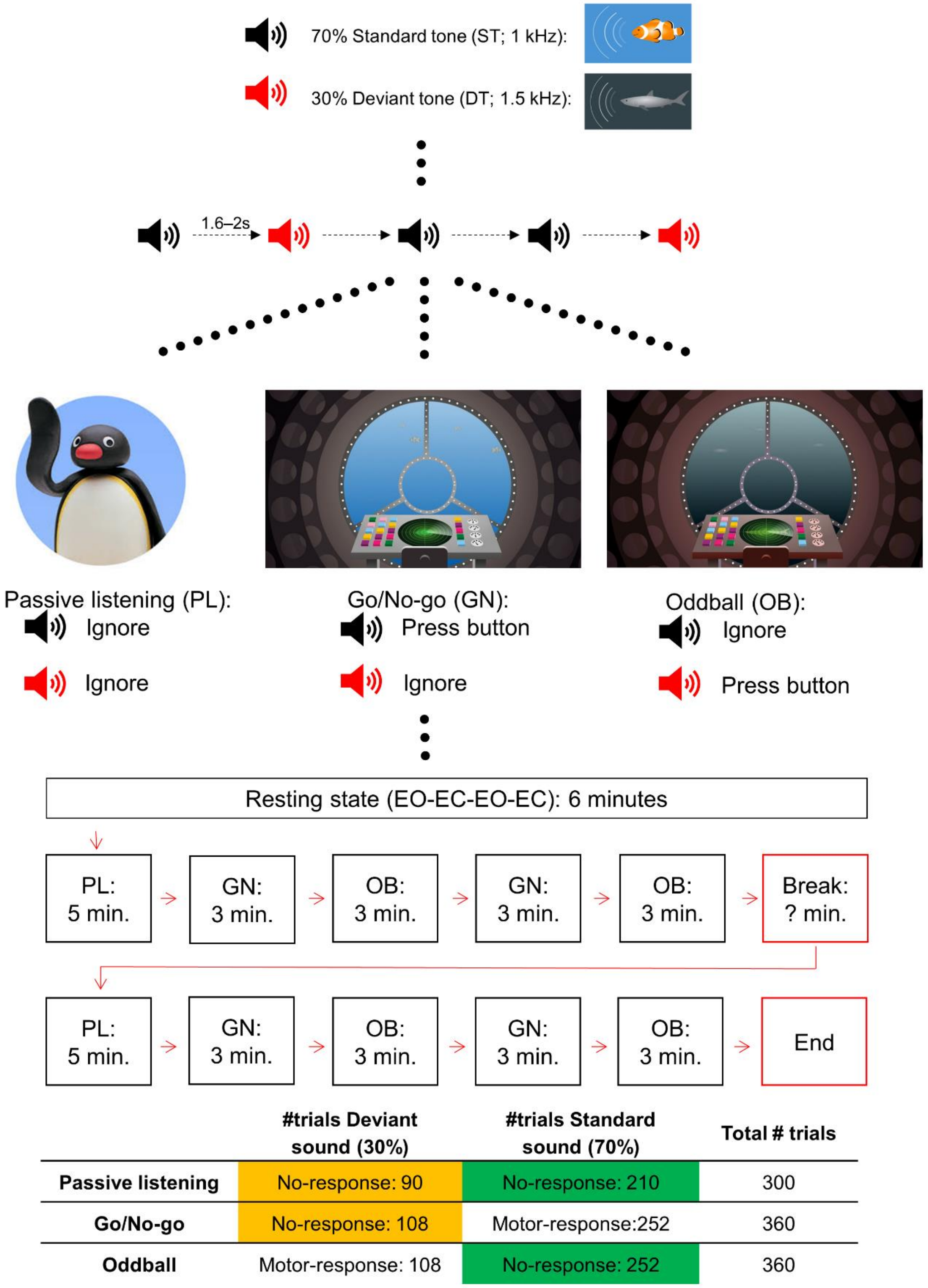
The stimuli were embedded in a game. We created a visual environment resembling a submarine, where the captain gave instructions to the participants “inside” the submarine (Figure 1). Visual stimuli were created by Studio Dennis Parren (www.dennisparren.com) and were there for the sole purpose of engaging the participants. All stimuli were controlled by PsychoPy (V3.2) (Peirce et al., 2019) running on a Linux desktop PC. Auditory stimuli were delivered to the subject through plastic tubes and earpieces using an MEG-compatible hi-fidelity sound system.

Procedure

The experiment was conducted in a child-friendly environment in which the participants were asked to help science by studying the clownfish population. Before the start of the tasks, we measured resting-state activity with two times 1.5 minutes eyes open (EO) and eyes closed (EC). Subsequently, participants were instructed by a captain through movie clips on how to perform the three auditory tasks.

The first PL task started after the captain instructed the participant to ignore the tones while he would look for the clownfish. During this task, the participants watched the silent stop-motion animation series “Pingu”. After the first PL task, the captain explained that the submarine detects fish using sound (i.e., sonar) and that the captain needs help detecting them while he navigates the submarine. The participants were then told that the two tone-pips represented two types of fish (Figure 1); the clownfish (ST) and the shark (DT). First, they were asked to detect the clownfish (GN task) by pressing a button (as quickly as possible) after the ST's. Participants were also instructed to look in the middle of the window (Figure 1) and focus on the sounds.

Twelve practice trials preceded the actual measurement to check whether the participants understood the task. Subsequently, in the OB task they were asked to detect the sharks by pressing a button whenever the DT was presented in order to protect the clownfish. Again, twelve practice trials were included to check whether the participants understood the task. Finally, two blocks of the GN task and OB task, each consisting of 90 trials (27 DT/63 ST), were completed alternately before the break. During the break, we offered participants a snack and drink and a possibility to stretch their legs. After the break, participants completed the same blocks again starting with the PL task followed by two blocks of alternating GN and OB tasks. The complete procedure is shown in Figure 1.



	#trials Deviant sound (30%)	#trials Standard sound (70%)	Total # trials
Passive listening	No-response: 90	No-response: 210	300
Go/No-go	No-response: 108	Motor-response:252	360
Oddball	Motor-response: 108	No-response: 252	360

Figure 1. Experimental design and procedure. Statistical contrasts of interest marked in yellow/green (bottom table).

M/EEG and MRI

The brain responses were recorded using a 306-channel MEG system and the integrated EEG system (Elekta Neuromag® TRIUX™, MEGIN Oy, Helsinki, Finland). M/EEG data were filtered to 0.1–330 Hz and sampled at 1000 Hz. EEG recordings were performed with a 32-channel cap and referenced online to an electrode on the right earlobe. Vertical and horizontal electrooculograms (EOG) were measured to capture eye movements and blinks for offline artifact suppression. EOG electrodes were placed directly below and above the right eye and on the outer canthi of each eye, and a common ground electrode was attached to the collarbone.

Five digitized head position indicator (HPI) coils were placed on the EEG cap to continuously monitor the head position in relation to the sensors of the MEG helmet. The EEG electrodes and HPI coils were digitized relative to three anatomic landmarks (nasion, left and right preauricular points) using the Polhemus Isotrak digital tracker system (Polhemus, Colchester, VT, United States). In addition, ~150 distributed scalp points were digitized to aid in the co-registration with individual magnetic resonance images (MRIs).

T1- and T2-weighted 3D spin-echo MRI images were collected with a 1.5 T scanner (GoldSeal Signa HDxt, General Electric, Milwaukee, WI, USA) using a standard head coil and with the following parameters: TR/TE = 540/10 ms, flip angle = 90º, matrix size = 256 x 256, slice thickness = 1.2 mm, sagittal orientation.

Behavioral assessment

Cognitive skills were tested on a separate visit. The behavioral tests included subtests of Wechsler Intelligence Scales for Children Third edition (Wechsler, 1991) or Wechsler Adult Intelligence Scale and the Stop Signal Task (SST) from the Cambridge Neuropsychological Automated Test Battery (CANTAB). Of the Wechsler Intelligence scale, the following subtests were administered: Similarities, Block Design, Digit Span, Coding and symbol search.

The similarities test is designed to assess verbal reasoning and the development of concepts. The block design subtest is designed to assess an individual's ability to understand complex visual information. Digit span (backward/forward) is designed to measure verbal short-term memory and attention. The coding test is designed to measure speed of processing but is also affected by other cognitive abilities such as learning, short-term memory and concentration. Finally, the symbol search test is designed to measure processing speed but is also affected by other cognitive abilities such as visuomotor coordination and concentration.

In the SST, the participant must respond to an arrow stimulus by selecting one of two options depending on the direction in which the arrow points. The test consists of two parts: in the first part, the participant is first introduced to the test and told to press the left-hand button when they see a left-pointing arrow and the right-hand button when they see a right-pointing arrow. There is one block of 16 trials for the participant to practice this. In the second part, the participant is told to continue pressing the buttons when they see the arrows, but if they hear an auditory signal (a beep), they should withhold their response and not press the button. The task uses a staircase design for the stop signal delay (SSD), allowing the task to adapt to the performance of the participant, narrowing in on the 50% success rate for inhibition. The test is designed to measure response inhibition/impulse control.

Data analysis

MEG data were first processed with the temporal signal space separation (tSSS) and movement compensation options, implemented in the MaxFilter™ program (version 3.0; MEGIN Oy, Helsinki, Finland), to suppress external interference and compensate for head movements (Taulu and Simola, 2006). The data were converted to the mean head position over the whole recording for each individual subject.

M/EEG data were analyzed using MNE-Python (version 0.17) (Gramfort et al., 2014; Gramfort et al, 2013). Continuous M/EEG recordings were low-pass filtered at 40 Hz, EEG data was re-referenced to the average over all EEG channels, and bad channels and data segments were identified and excluded. Epochs of –0.2 to 0.8 s relative to stimulus onset were then extracted and corrected for the baseline (–0.2 to 0s) offset. Epochs were rejected for incorrect responses and large MEG signals (> 4 pT/cm for gradiometers, > 5 pT for magnetometers). Independent component analysis (ICA) was applied to suppress ocular and cardiac artifacts separately for MEG and EEG (Hyvärinen and Oja, 2000). Next, *autoreject*, an automatic data-driven algorithm, was used on the EEG data to repair or exclude bad epochs. We followed procedure introduced by Jas and colleagues (2017). If the algorithm excluded more than 20% of the epochs, manual artifact rejection of the EEG epochs was used instead. Finally, the data were manually checked for obvious artifacts, and the six experimental conditions were averaged separately.

The cortical surface for the source model was constructed from the individual structural MRI with the Freesurfer software (RRID: SCR_001847, Martinos Center for Biomedical Imaging, http://freesurfer.net; Dale et al., 1999; Fischl et al., 1999; Fischl et al., 2001). The M/EEG source space was decimated at 4.9 mm spacing, resulting in ~5000 current locations per hemisphere.

The MEG and EEG data were registered to the structural data with MNE coregistration using the fiducial landmark locations, digitized EEG electrode locations and the additional scalp point. A forward solution for the source space was constructed using three-layer BEMs. Conductivity values used for the intracranial tissue (brain, CSF), skull and scalp were set to 0.3, 0.006 and 0.3 for adults and 0.33, 0.0132 and 0.33 for children, respectively. The noise covariance matrix was calculated from the individual epochs 200-ms pre-stimulus baseline, using a cross validation method implemented in MNE. In order to combine data from the MEG gradiometers, MEG magnetometers and EEG electrodes into a single inverse solution, the forward solution matrix and data were whitened using the covariance matrix (Engemann and Gramfort, 2015).

The source currents were examined using a cortically-constrained, depth-weighted ($p = 0.8$) L2 minimum norm estimate (Hämäläinen and Ilmoniemi, 1994) with a loose orientation constraint (0.2). To determine the direction of the source currents, the source components normal to the cortical surface were extracted. The MNE solutions were constructed for each individual subject; source waveforms were computed as the mean value of the source element within region-of-interest (ROI) label 30 (transverse temporal gyrus) as defined by the Desikan-Killiany Atlas (Desikan et al., 2006). Amplitude values of the sustained response were calculated as an average over the 200-325ms time-window after stimulus presentation, which was determined by visual inspection of the grand averages (see Figure 2). Only negative averages were included in the statistical analysis, as we assumed positive values would reflect cortical activity unrelated to our response of interest.

Statistical analysis

As shown in Figure 1 (colored cells in bottom table) we designed the experiment to separately compare the effects of Oddball vs Passive (to focus on attention) and Go/No-go vs Passive (to focus on inhibition). We used the deviant tones (DT) for the comparison between Passive and Go/No-go (GN) and the standard tones (ST) for the comparison between Passive and Oddball (OB). Crucially, for these comparisons the stimuli (ST or DT), probability (30% or 70%) and motor response (None) were identical and the amount of trials close to equal.

A multiple linear regression analysis was performed to test for main effects of age, hemisphere and task. Subsequently, a related samples Wilcoxon Signed-ranks test was used to explore and describe the effects in more detail, as the brain response distributions were heavily skewed (non-negative values were excluded).

Partial correlations (controlling for age) were calculated for behavioral performance measures and the 2x2 (hemi x task) auditory brain responses. We included the following behavioral performance measurements: mean reaction time (RT), intra-individual coefficient of variation (ICV; calculated as SDRT/mean RT), response accuracy (ERR; calculated as square root of error %) from tasks completed inside the scanner, and the stop-signal reaction time (SSRT), which was completed outside the scanner during the behavioral assessment.

Linear regression analyses were performed with the behavioral performance measures as dependent variables. Age was entered first followed by the brain responses as independent variables. All variables in the linear regression model were selected based on the significant partial correlations. All statistical analyses were performed using SPSS statistics 25.

Finally, a bivariate correlation was used to check whether the brain responses were related to any of the subtests of the Wechsler Intelligence Scales for Children (i.e. digit span, symbol coding, symbol search, block design or similarities) to see if we had to control for possible intelligence effects.

Results

Descriptive statistics of cognitive skills and behavioral performance

Descriptive statistics of the children’s performance during the M/EEG experiment and their cognitive skills as per the behavioral assessment session are presented in Table 1.

Table 1. Mean, standard deviation (SD) and range of behavioral performance measures. Reaction times (RT), intra-individual coefficient of variation (ICV) and response accuracy (ERR) gathered from the Go/No-go task (GN) and the Oddball task (OB). Stop-signal reaction time (SSRT) was gathered from the stop-signal task during the behavioral assessment.

	Children			**Adults**		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
Age (years)	10.17	1.44	6-14	24.78	3.38	20-30
M/EEG experiment						
GN RT (ms)	484.20	82.74	328-693	298.50	57.5	221-395
GN ICV	0.4	0.09	0.19-0.56	0.27	0.05	0.2-0.35
GN ERR (√%)	2.54	1	0.53-4.87	1.36	0.62	0-2.17
OB RT (ms)	480.67	82.03	234-728	303.69	53.85	214-420
OB ICV	0.38	0.11	0.18-0.82	0.21	0.04	0.14-0.32
OB ERR (√%)	1.78	0.85	0-3.87	0.7	0.36	0-1.18
Behavioral assessment						
SSRT (ms)	205.94	56.20	87-351	140.81	32.62	80-198
Digit span*	10.55	2.65	5-17	18.06	2.89	14-26
Symbol search*	12	2.58	5-18	36.50	7.84	19-46
Coding*	10.88	2.98	4-19	81.56	9.35	66-103
Block design*	11.61	2.97	4-17	52.63	10.15	36-65
Similarities*	10.39	2.63	2-16	28.38	3.2	24-35

* standardized score for children, raw score for adults

Developmental trajectory of the auditory evoked responses

Figure 2 shows the measured neuromagnetic responses to the standard tones in the passive listening task at MEG sensor level (gradiometers). For visualization purposes, groups were separated by age (< 10 years old, > 10 years old and adults). The main activation in children is a sustained response pattern at around 250ms (N250m) in both hemispheres. The activation pattern of the older children in the earlier time window (~100ms) starts to resemble the adult activation pattern, but only in the right hemisphere. In contrast, the main activation in adults is evoked at around 100ms in both hemispheres.

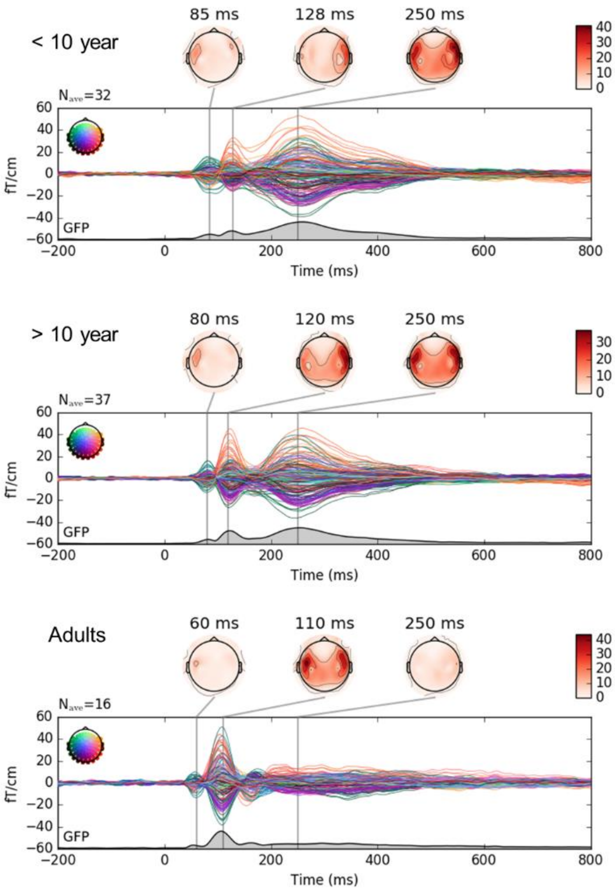


Figure 2. Developmental (age) differences in auditory brain responses to the passive listening (PL) standard tone (ST) as measured by the MEG gradiometers. Groups divided for illustration purposes between children younger than 10 (top), older than 10 (middle) and adults (bottom).

Sustained response at ~250ms in auditory cortex is unique to the child activation pattern

Figure 3 shows the evoked responses between groups in the left and right temporal channels (gradiometers) with tasks overlaid. In general, the effects of age and task on the strength of activation seem to appear in three separable time-windows: (i) transient activity at ~100ms, (ii) a more sustained activation pattern between 200-300ms and (iii) prolonged activity between 400-800ms. From those three time-windows, the sustained activation pattern at ~250ms is unique to children; the earlier activity at ~100ms is the main activation pattern in adults. The later prolonged activity between 400-800ms shows a change between tasks, but not between age groups.

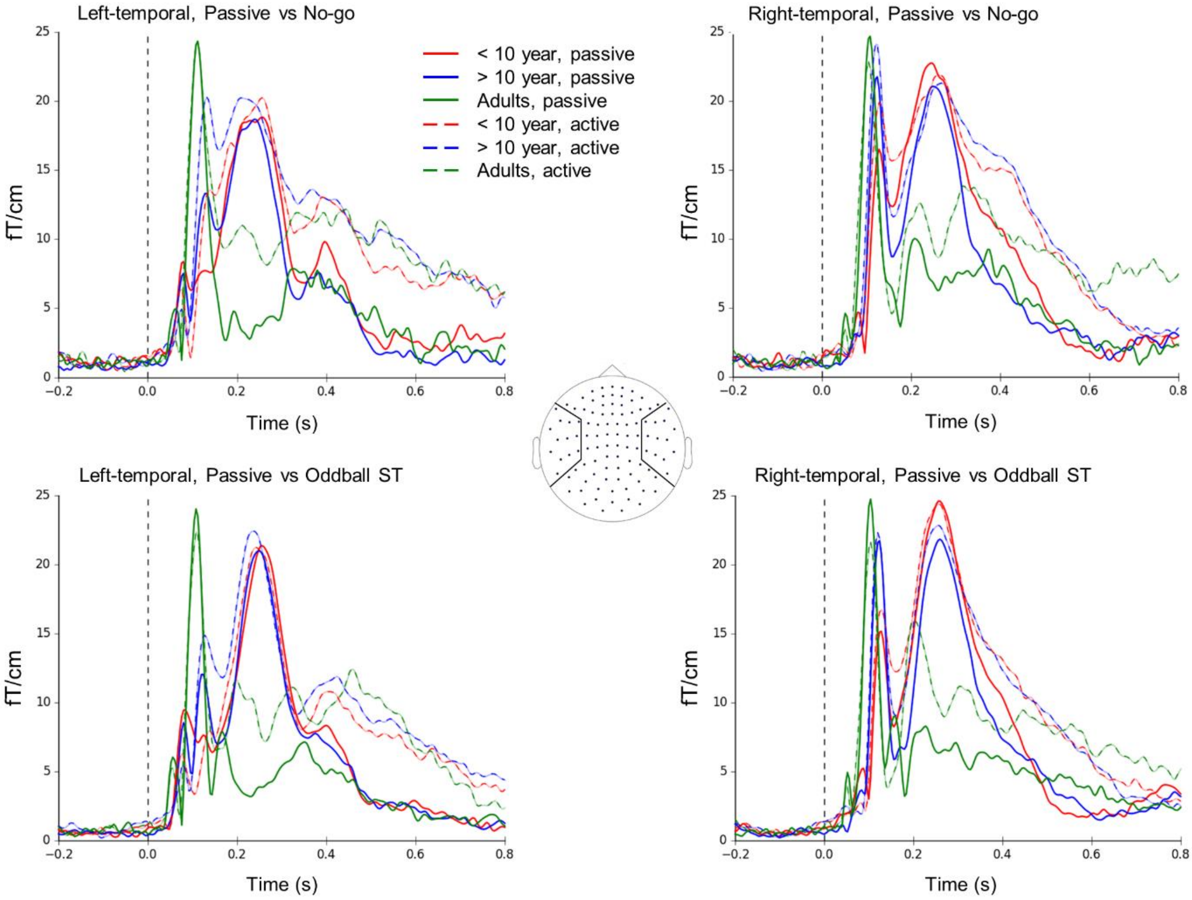


Figure 3. MEG Gradiometer sensor-level averaged auditory brain responses for the different conditions. Selected channels for the averages depicted in the center (left- and right-temporal gradiometers). Groups divided between < 10-year-old's (red), > 10-year-old's (blue) and adults (green). Top figures depict the passive (solid lines) and No-go (dotted lines) averages in the left and right hemisphere. Bottom figures depict the passive (solid lines) and oddball standard tone (ST) (dotted lines) averages in the left and right hemisphere.

The maximum activation in children, emerging around 250ms appears to be similar across tasks including passive listening. In contrast, adults do not show a similar response in the auditory cortex in any of the tasks. Indeed, combined M/EEG source localization of the responses show marked differences between adults and children (figure 4). The peaks in the child waveform are all localized in the temporal regions irrespective of task.

In contrast, the source localization in adults depends on stage of processing: the early peak at 100ms reflects activation in the temporal regions and the later activation ~200-300ms reflects activation in the medial regions of the cerebral cortex (e.g. cingulate cortex). As the responses in children vs. adults in the 250-ms time-window reflect activation of different brain regions, their strength is not directly comparable. Moreover, the response pattern at ~250ms in the auditory cortex looks to be unique to the child brain (figure 4&5). Therefore, we did not directly contrast adults and children for this activation pattern. In the statistical analysis we focused on the strength of activation around ~250ms after stimulus presentation in children's transverse temporal gyrus. As per our experimental design, we discuss the PL vs GN and PL vs OB separately (see methods and figure 1).

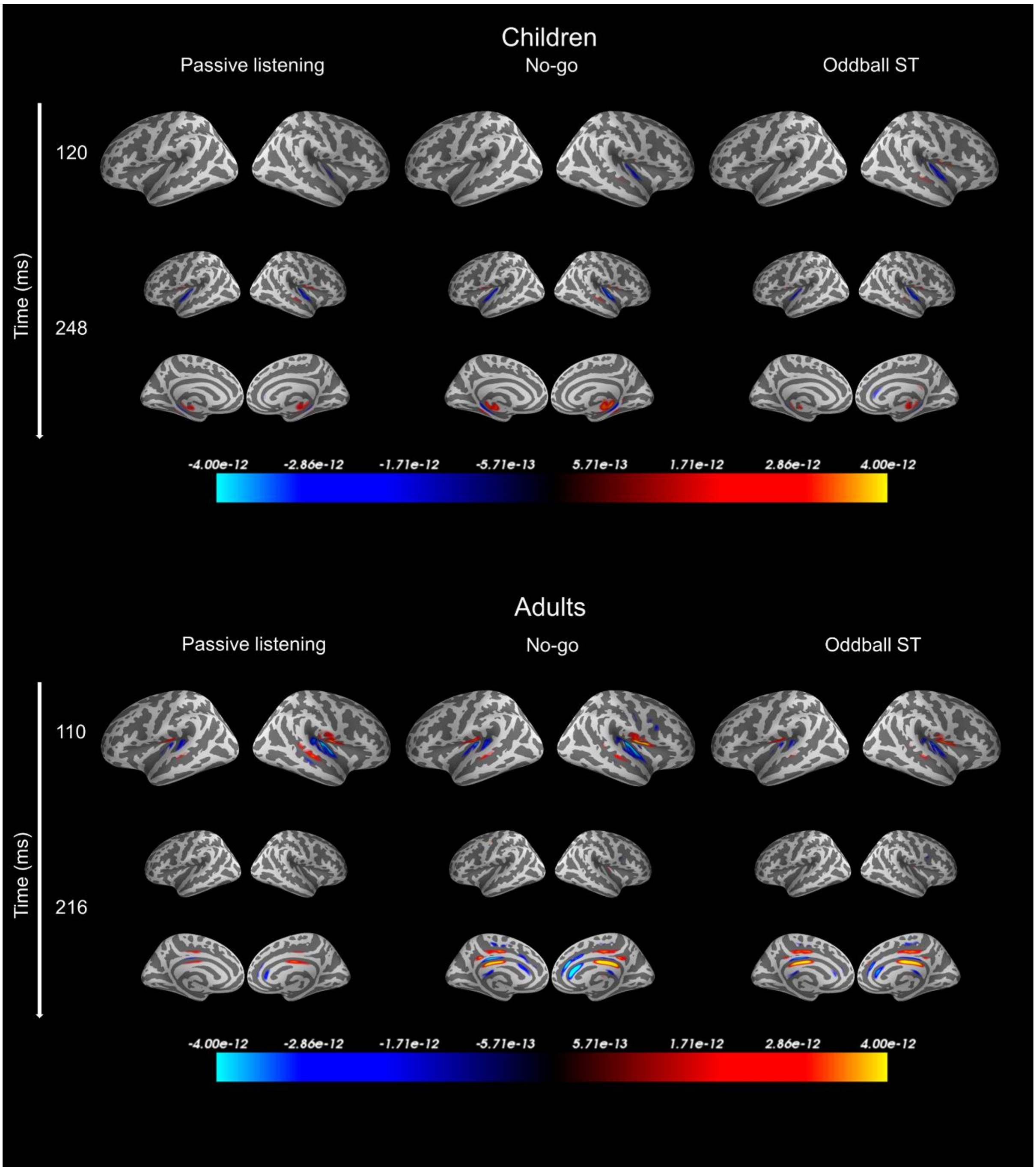


Figure 4. Grand average 3D visualization of the M/EEG combined source estimates for all children (top) and adults (bottom). 3D-plots presented for the two most prominent time-windows of activation in children (120ms and 248ms) and adults (110ms and 216ms). Conditions separated from left to right: Passive listening (standard tone(ST)), No-go (deviant tone) and Oddball (ST).

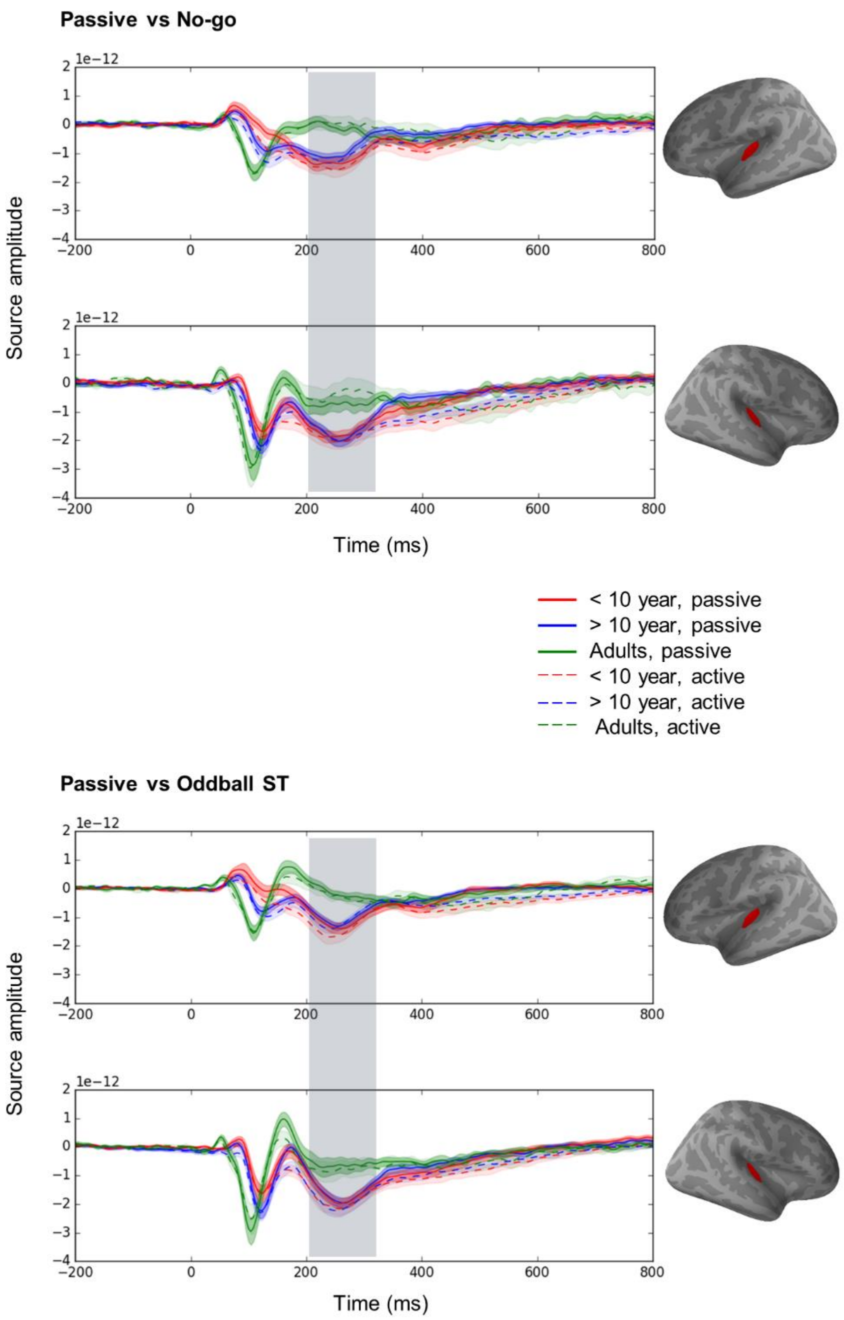


Figure 5. M/EEG combined Source estimates in the left and right transverse temporal gyrus (red area). Waveforms are an average of the entire area. Groups divided between < 10-year-old's (red), > 10-year-old's (blue) and adults (green). Top two figures depict the passive (solid lines) and attention (oddball standard tone) (dotted lines) waveforms in the left (top) and right (bottom) hemisphere. Bottom two figures depict the passive (solid lines) and inhibition (No-go deviant tone) (dotted lines) waveforms in the left (top) and right (bottom) hemisphere. Shaded areas around the waveform represent the standard error of the mean (SEM). Window is an approximation of the timepoints included in the calculation of the average.

Passive vs Go/No-go task comparison

Right hemisphere shows generally stronger activation at ~250ms independent of task

The multiple linear regression model, as shown in Table 2 revealed that hemisphere, but not age or task, was a significant predictor of the strength of activation. The Wilcoxon Signed-ranks test showed stronger activation in the right compared to the left hemisphere in both the PL and GN task. In the PL task the activation strength was 32% stronger in the right (*Mdn* = -15.18, IQR = [-8.85 – -21.81]) compared to the left hemisphere (*Mdn* = -10, IQR = [-5.35 – -13.6]), Z = -3.39, p = .001. Similarly, in the GN task the activation strength was 26% stronger in the right (*Mdn* = -16.82, IQR = [-9.57 – -24.18]) compared to the left (*Mdn* = -11.29, IQR = [-5.6 – -17.58]) hemisphere, Z = -3.35, p = .001.

Table 2. Multiple linear regression analysis using hemisphere, task and age as predictors of the brain responses at ~250ms.

	B	***SE B***	**Standardized beta**	**ΔR2**
Step 1				
Constant	-27.80	4.96		
Hemisphere	4.82	1.19	0.25*	0.08
Task	-1.18	1.19	-0.06	ns
Age	0.77	0.42	0.11	ns

*Note: B = Unstandardized beta, SE B = standard error for the unstandardized beta, ΔR2 = R2 change. *p < 0.05.*

There was no significant effect of task on the activation strength. In general, the GN task showed non-significant stronger activation compared to the PL task. In the left hemisphere there was 13% stronger activation in the GN task (*Mdn* = -11.29, IQR = [-5.6 – -17.58]) compared to the PL task (*Mdn* = -10, IQR = [-5.35 – -13.6]), Z = -1.67, p = .095. In the right hemisphere, responses were 5% stronger in the GN task (*Mdn* = -16.82, IQR = [-9.57 – -24.18]) compared to the PL task (*Mdn* = -15.18, IQR = [-8.85 – -21.81]), Z = -0.82, p = .415.

Figure 6 shows the individual data points used the analysis as well as the average (line) and standard deviation (bar) for each condition.

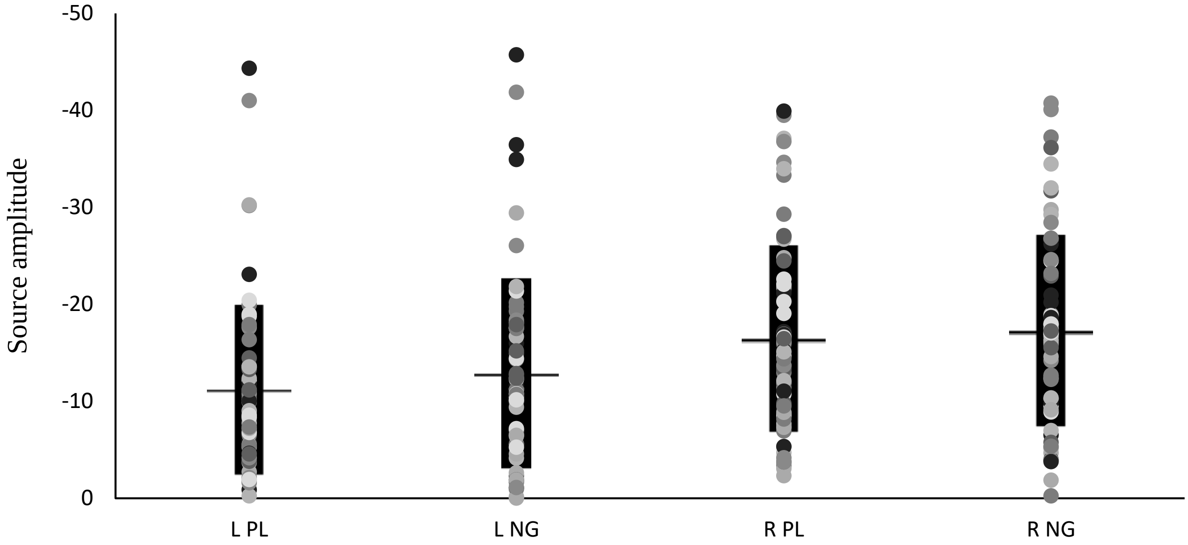


Figure 6. Individual data points (dots), average (horizontal line) and standard deviation (black bar) for the conditions: passive listening (PL) deviant tone and No-go (NG) deviant tone in the left (L) and right (R) hemisphere.

Left hemisphere auditory responses at ~250ms predicts behavioral performance on inhibition tasks

A correlation analysis did not reveal any relationships between the brain responses and the subtests of the Wechsler Intelligence Scales for Children. As such, no control for general intelligence was added to the partial correlation analysis. Table 3 shows the result of a bootstrapped (10.000 samples) partial correlation (controlled for age) which revealed significant positive correlations between amplitudes in the left hemisphere (irrespective of task) and performance measures on both the Go/No-go (MEG inhibition task) and the SSRT (during behavioral assessment). Stronger left-hemisphere activation was related to lower intra-individual variability (ICV) in reaction times, lower error rate (ERR) and smaller stop-signal reaction times (SSRT).

More specifically, in the PL task, a stronger left-hemisphere response amplitude was related to decreased ICV (r = .479, 95%CI = [.195 - .661], p = .000) and SSRT (r = .331, 95%CI = [.113 - .543], p = .02 and ERR (r = .314, 95%CI = [-.026 – .553], p = 0.028). Similarly, in the GN task, a stronger left-hemisphere response amplitude to the No-go tone was related to decreased ICV (r = .467, 95%CI = [.185 - .685], p = .001), decreased ERR (r = .343, 95%CI = [.022 - .587], p = 0.016), and decreased SSRT (r = .292, 95%CI = [.022 - .533], p = 0.041).

Table 3. Bootstrapped (10.000 samples) partial correlation (controlled for age) between de brain responses and behavioral performance measures. Significant correlations marked in bold.

	RT	**ICV**	**ERR**	**SSRT**
L PL	-0.024	**0.479****	**0.314***	**0.331***
R PL	0.157	-0.033	0.037	0.162
L GN	-0.019	**0.467****	**0.343***	**0.292***
R GN	0.035	0.077	0.036	0.231

*Note: RT = reaction time, ICV = intra-individual coefficient of variability, ERR = response accuracy, SSRT = stop signal reaction time. *p < 0.05, **p < 0.01.*

Subsequently, linear regressions were used to predict the performance measures using age and the selected brain responses. The brain responses to different tasks in the same hemisphere were highly correlated, and there was no significant effect of task, so we used the brain responses measured during the Go/No-go. As shown in Table 4, the amplitude of the auditory response in the left hemisphere (to No-go tone) was a significant predictor of intra-individual variability of reaction time, error rate and stop-signal reaction time. Figure 7 shows the corresponding scatterplots.

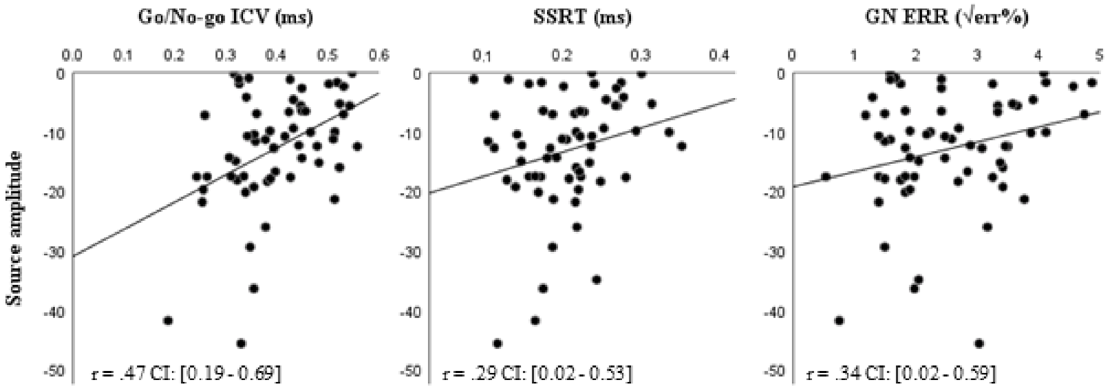


Figure 7. Scatterplots of the responses at ~250ms to the No-go tone and the behavioral performance measures: intraindividual coefficient of variability (ICV; left), stop-signal reaction time (SSRT; middle), and response accuracy (right).

Table 4. Linear regression analysis using the behavioral performance measures as the dependent variable, age was entered first in the model, followed by the auditory responses in the left hemisphere to the No-go tone as the predictors.

Performance measure	**Step**	**Standardized Beta**	**∆ R2**
ICV	1. Age	-0.248	0.036
	2. Left auditory NG	0.459	**0.207****
ERR	1. age	-0.319	**0.078***
	2. Left auditory NG	0.304	**0.091***
SSRT	1. age	-0.438	**0.160****
	2. Left auditory NG	0.295	**0.086***

*Note: ICV = intra-individual coefficient of variability, ERR = response accuracy, SSRT = stop signal reaction time. *p < 0.05, **p < 0.01 significance of R2 change.*

Passive vs Oddball task comparison

Right hemisphere shows generally stronger activation at ~250ms independent of task

Similar to the PL vs. GN comparison, the multiple linear regression model revealed that hemisphere, but not age or task, was a significant predictor of the strength of activation (see

Table 5). The Wilcoxon Signed-ranks test showed significant stronger activation in the right compared to the left hemisphere in both the PL and OB task. The hemisphere effect was similar between tasks, with activation strength 29% stronger in the right (*Mdn* = -15.19, IQR = [-8.63 – -21.76]) compared to the left hemisphere (*Mdn* = -10.15, IQR = [-6.04 – -15.67]) in the PL task, Z = -3.329, p = .001, and 31% stronger in the right (*Mdn* = -18.27, IQR = [-10.4 – -22.56]) compared to the left hemisphere (*Mdn* = -10.82, IQR = [-6.8 – -16.11]) in the OB task, Z = -4.24, p = .000.

Table 5. Multiple linear regression analysis using hemisphere, task and age as predictors of the brain responses at ~250ms.

	B	***SE B***	**Standardized beta**	**ΔR2**
Step 1				
Constant	-26.77	4.33		
Hemisphere	5.12	1.08	0.29*	0.1
Task	-0.69	0.58	-0.08	ns
Age	0.6	0.38	0.09	ns

*Note: B = Unstandardized beta, SE B = standard error for the unstandardized beta, ΔR2 = R2 change. *p < 0.05.*

There was no significant effect of task. In the left hemisphere, activation strength was 8% stronger in the OB task (*Mdn* = -10.82, IQR = [-6.8 – -16.11]) compared to the PL task (*Mdn* = -10.15, IQR = [-6.04 – -15.67]), Z = -1.56, p = 0.119. In the right hemisphere, activation strength was 11% stronger in the OB (*Mdn* = -18.27, IQR = [-10.4 – -22.56]) compared to the PL task (*Mdn* = -15.19, IQR = [-8.63 – -21.76]), Z = -3.42, p = .001.

Figure 8 shows the individual data points used the analysis as well as the average (line) and standard deviation (bar) for each condition.

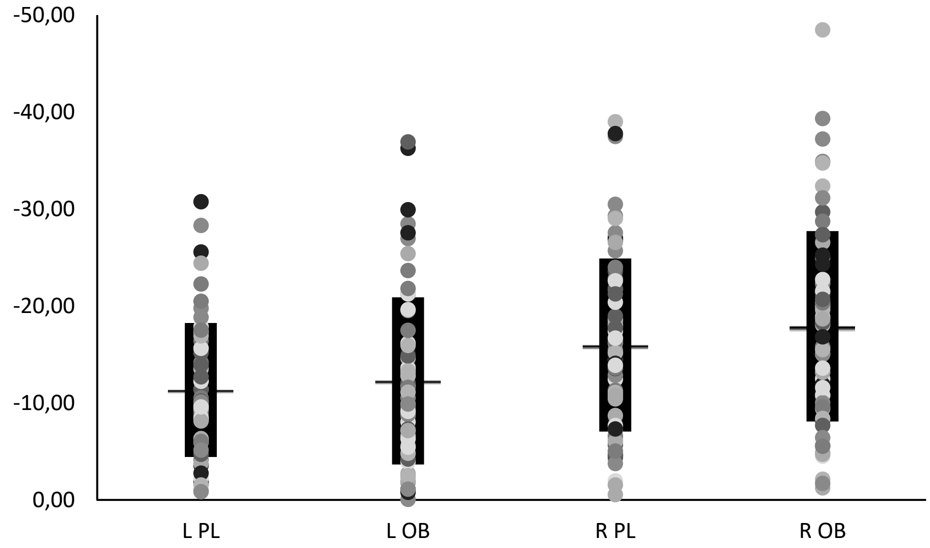


Figure 8. Individual data points (dots), average (horizontal line) and standard deviation (black bar) for the conditions: passive listening (PL) standard tone and oddball (OB) standard tone in the left (L) and right (R) hemisphere.

Left hemisphere auditory responses at ~250ms predicts stop-signal reaction time

A correlation analysis showed no consistent relationships between the brain responses and the subtests of the Wechsler Intelligence Scales for Children; PL standard tone in the right hemisphere correlated with symbol search score (r = .261, p = .03) and the PL standard tone in the left hemisphere correlated with coding score (r = -.259, p = .04). No control for general intelligence was added to the partial correlation analysis. Table 6 shows the result of a bootstrapped (10.000 samples) partial correlation (controlled for age) revealed significant positive correlations between amplitudes in left hemisphere during the OB task and SSRT. Stronger activation in the left hemisphere during the OB task were related to smaller SSRT's (r = 0.355, 95%CI = [0.142 – 0.560], p = 0.008).

Table 6. Bootstrapped (10.000 samples) partial correlation (controlled for age) between de brain responses and behavioral performance measures. Significant correlations marked in bold.

	RT	ICV	ERR	SSRT
L PL	-0.153	0.252	0.194	0.251
R PL	0.087	0.042	0.025	0.224
L OB	0.033	0.234	0.230	**0.355****
R OB	0.143	0.086	0.028	0.238

*Note: RT = reaction time, ICV = intra-individual coefficient of variability, ERR = response accuracy, SSRT = stop signal reaction time. *p < 0.05, **p < 0.01.*

As shown in Table 7, the linear regression model revealed that the strength of the auditory response in the oddball task was a significant predictor of the SSRT (p = 0.019).

Table 7. Linear regression analysis using the behavioral performance measures as the dependent variable, age was entered first in the model, followed by the auditory responses in the left hemisphere to the No-go tone as the predictors.

Performance measure	Step	Standardized Beta	Δ R2
SSRT	1. age	-0.469	**0.160****
	2. Left auditory OB	0.282	**0.075***

*Note: SSRT = stop signal reaction time. *p < 0.05, **p < 0.01 significance of R2 change.*

Discussion

In this study we assessed the developmental trajectory and functional significance of a robust, obligatory and sustained response pattern at ~250ms (N250m). Our data demonstrate that this activation pattern is uniquely prominent in the child brain; adults show an activation pattern in this time-window only in the active tasks and in different brain regions than children (i.e. medial regions of the cerebral cortex vs. auditory cortex, respectively). Surprisingly, and contrary to some earlier studies, age did not seem to affect the strength of activation in this time window. Perhaps this suggests a non-linear decrease during development of this auditory response with age, as it is absent in adults. This was also indicated by previous studies with a wider age range than the present study, which found an initial increase in activation strength until children reached the age of 11, after which a gradual decrease was reported (Ponton et al., 2000; Ponton et al., 2002). In the present study, the strength of activation in children in this time-window was unaffected by task demands, but the strength of activation in the left hemisphere was associated with superior performance on inhibition tasks and measures of cognitive control.

Our results confirm that (i) the N250m does not reflect a delayed adult N1m, nor does it correspond to the activation around 200ms in adults in active tasks (N2m) but instead is a developmentally specific auditory evoked brain response (Albrecht et al., 2000; Ponton et al., 2000, 2002; Takeshita et al., 2002; Parviainen et al., 2011; Parviainen et al., 2019) and that (ii) this sustained response pattern is part of general and automatic, circuit level, processing in auditory areas of the child brain (Parviainen et al., 2019). We expand on these findings by illuminating its functional significance for cognitive skills.

The strength of the sustained response in the left, but not right, hemisphere was most consistently associated with performance on inhibition tasks. Left-hemisphere response strength explained 20.7%, 9.1% and 8.6% of unique variance of the ICV, response accuracy and SSRT respectively. We focus on the ICV and the sustained response during No-go trials, as the other results are likely different, less sensitive, measures of the same effect (i.e. one underlying effect is the most parsimonious explanation of our results).

The ICV reflects temporal variation in cognitive performance and it has been extensively studied in attention-deficit/hyperactivity disorder (ADHD) (de Zeeuw et al., 2008; van Belle et al., 2015). Intrasubject variability has long ago been put forward as an endophenotype of ADHD, the characteristic lapses of intention and attention in ADHD are thought to be a result of deficits in temporal processing that result in higher intrasubject intertrial variability (Castellanos and Tannock, 2002). Importantly, the auditory cortex coordinates activity with intricate timing. Indeed, the evoked responses reflect the auditory system’s ability to consistently respond with the same timing to each stimulus presentation. The behavioral importance of temporal processes is further supported by our and other studies’ finding that ICV is a much better predictor of inhibitory success (% successful inhibition) (r = .740) than traditional measures of reaction time (r = -.076) (Bellegrove et al., 2004; de Zeeuw et al., 2008, van Belle et al., 2015). Combined, these results suggest that ICV is an important measure of cognitive control that possibly relies on the auditory cortex’s ability to consistently respond to the presented stimulus.

Our results indicate that the brain mechanisms that, in auditory based tasks, help achieve a consistent performance is remarkably different between children and adults. Most notably, the No-go activation in the 200-325ms time-window shows clear differences: whereas the adult major activation peak was localized to the medial regions of the cerebral cortex (e.g. cingulate cortex), children’s strongest activation pattern was located in the auditory cortex. Importantly, our findings are in line with earlier fMRI study’s and M/EEG studies in adults that emphasize the importance of both the 200-300 time-window and the cingulate cortex in inhibition and cognitive control (Nieuwenhuis et al., 2003; Huster et al., 2010; Falkenstein et al., 1999; Smith et al., 2007; Botvinick et al., 2004; Chambers et al., 2009). In contrast to the mature brain, our data show that children rely strongly on activation in the auditory cortex during the 200-300 time-window, independent of task demands.

Our results further suggest that the amplitude waveforms during auditory inhibition tasks (e.g. Go/No-go or SST) in children and adults are incomparable. This is relevant especially for EEG studies with limited spatial sensitivity; electrical potentials originating in the auditory cortices summate at the vertex, generating one maximum on the head surface (Hari and Puce, 2017). Consequently, even though the main current source underlying the measured signal is different between adults and children, typical EEG-ERP analysis will have limited capacity to reveal this difference, and may also erroneously transfer spatial differences into amplitude effects. Taken together, these results suggest that in order to move forward in understanding the neurodevelopmental underpinnings of improvement in cognitive skills (or problems therein), we need to adopt a more comprehensive approach in analysis incorporating both temporal and spatial characteristics of activation.

Our claim that children and adults employ different neural mechanisms to achieve a consistent performance is in line with previous fMRI studies. In adults, both reduced response variability and improved top-down cognitive control have been directly related to greater anterior cingulate gyrus (ACG) activity (Bellgrove et al., 2004; van Belle et al., 2015) and focal damage to the frontal lobes impairs the stability of cognitive performance (Stuss et al., 2003). In one fMRI study, younger subjects (7-15 years) showed differences from older subjects (15-24 years) in the relationship between dorsal ACG activity and response variability: in older subjects increased dorsal ACG activity was related to a reduction in response variability, whereas in the younger group dorsal ACG activity did not relate to this measure of cognitive control (van Belle et al., 2015). Intriguingly, Simmonds and colleagues (2007) reported that, in typically developing children (8-12 years), instead of cingulate activity, lower variability was associated with activation in the rostral supplementary motor area (pre-SMA) in a Go/No-go task.

The exact neurobiological underpinnings that underlie this difference between adults and children are unclear and should be the subject of further investigation. Our results together with earlier findings indicate a shift from sensorimotor associations in the child brain to more emphasis on cognitive control processes in the adult brain. In the present study, the strength of the sustained response in children showed a positive correlation with inhibitory performance measures, and thus seems to aid the inhibitory performance in children. Similarly, a recent study investigating the auditory no-go in non-human primates identified a sustained response in the auditory cortex to reflect sensorimotor representations important for behavioral inhibition (Huang et al., 2019).

Even though the right hemisphere shows stronger responses, the left hemisphere responses show the meaningful behavioral association in children. We surmise this relates to the different developmental trajectories of the auditory cortices. The left auditory cortex has been known to mature slower than the right (Paetau et al., 1995; Parviainen et al., 2019). In addition, auditory responses in the right-hemisphere has been more strongly linked with genetic regulation compared to the left-hemisphere (Renvall et al., 2012). This protracted development of the left hemisphere arguably provides a time window where the brain can flexibly employ its resources which should be useful in the everchanging environment of the child brain. Indeed, others have argued for stronger experience-driven plasticity in the left-hemisphere (Renvall et al., 2012; Parviainen et al., 2019). However, handedness has also been shown to affect hemispheric dominance of neuromagnetic responses to sounds (Kirveskari et al., 2006) and as such our reported effect might depend on handedness. An important remaining question is whether our reported relationship depends on the auditory cortex that is contralateral to the hand used to respond, or a mechanism unique to the left hemisphere.

A range of issues can impact the accuracy of M/EEG source reconstruction in children (e.g. head movements, distance to sensors, suboptimal cortical surface reconstruction and forward/inverse solutions and M/EEG-MRI co-registration errors). We conducted the experiment and analyzed the data following the generally accepted guidelines and detailed instructions (Gross et al., 2013; Jas et al., 2018). Furthermore, we combined M/EEG and individual MRI’s in a relatively large sample of children, reducing the influence of possible irregular confounds. Although the benefits of combining MEG and EEG have been laid out extensively (Sharon et al., 2007; Aydin et al., 2015; Baillet, 2017; Gross, 2019), its complementarity has been rarely used for theory development.

To conclude, we provide unique evidence that the child-specific auditory activation in the left-hemisphere at around 250ms is functionally meaningful for performance on inhibition tasks. We claim that the mechanisms underlying cognitive control are different in children and adults with more emphasis on sensorimotor associations in children. Interestingly, the association between activation strength and performance measures are limited to the left-hemisphere. We presume this reflects the experience-driven plasticity which is more strongly linked to the left-hemisphere.

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References

Albrecht, R., Suchodoletz, W. v, and Uwer, R. (2000). The development of auditory evoked dipole source activity from childhood to adulthood. Clinical Neurophysiology 111, 2268–2276. doi: 10.1016/S1388-2457(00)00464-8

Aydin, Ü., Vorwerk, J., Dümpelmann, M., Küpper, P., Kugel, H., Heers, M., Wellmer, J., Kellinghaus, C., Haueisen, J., Rampp, S. et al. (2015). Combined EEG/MEG can outperform single modality EEG or MEG source reconstruction in presurgical epilepsy diagnosis. PloS one, 10(3), e0118753. doi: 10.1371/journal.pone.0118753

Baillet, S. (2017). Magnetoencephalography for brain electrophysiology and imaging. Nature Neuroscience 20, 327–339. doi: 10.1038/nn.4504

van Belle, J., van Raalten, T., Bos, D.J., Zandbelt, B.B., Oranje, B., and Durston, S. (2015). Capturing the dynamics of response variability in the brain in ADHD. NeuroImage: Clinical 7, 132–141. doi: 10.1016/j.nicl.2014.11.014

Bellgrove, M. A., Hester, R., and Garavan, H. (2004). The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia, 42(14), 1910-1916. doi: 10.1016/j.neuropsychologia.2004.05.007

van Bijnen, S., Kärkkäinen, S., Helenius, P., and Parviainen, T. (2019). Left hemisphere enhancement of auditory activation in language impaired children. Scientific Reports 9, 9087. doi: 10.1038/s41598-019-45597-y

Botvinick, M.M., Cohen, J.D., and Carter, C.S. (2004). Conflict monitoring and anterior cingulate cortex: an update. Trends in Cognitive Sciences 8, 539–546. doi: 10.1016/j.tics.2004.10.003

Castellanos, F.X., and Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3, 617–628. doi: 10.1038/nrn896

Čeponienė, R., Cheour, M., and Näätänen, R. (1998). Interstimulus interval and auditory event-related potentials in children: evidence for multiple generators. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 108(4), 345-354. doi: 10.1016/S0168-5597(97)00081-6

Čeponienė, R., Rinne, T., and Näätänen, R. (2002). Maturation of cortical sound processing as indexed by event-related potentials. Clinical Neurophysiology 113, 870–882. doi: 10.1016/S1388-2457(02)00078-0

Chambers, C.D., Garavan, H., and Bellgrove, M.A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neuroscience and Biobehavioral Reviews 33, 631–646. doi: 10.1016/j.neubiorev.2008.08.016

Dale, A.M., Fischl, B., and Sereno, M.I. (1999). Cortical surface-based analysis I: segmentation and surface reconstruction. Neuroimage. 9:179–194. doi: 10.1006/nimg.1998.0395

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P et al., (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage, 31(3), 968-980. doi: 10.1016/j.neuroimage.2006.01.021

Engemann, D. A., and Gramfort, A. (2015). Automated model selection in covariance estimation and spatial whitening of MEG and EEG signals. NeuroImage, 108, 328-342. doi: 10.1016/j.neuroimage.2014.12.040

Falkenstein, M., Hoormann, J., and Hohnsbein, J. (1999). ERP components in Go/Nogo tasks and their relation to inhibition. Acta psychologica, 101(2-3), 267-291. doi: 10.1016/S0001-6918(99)00008-6

Fischl B., Sereno M.I., and Dale, A.M. (1999a). Cortical surface-based analysis II: inflation, flattening, and a surface-based coordinate system. Neuroimage. 9:195–207. doi:

Fischl B., Sereno, M.I., Tootell, R.B., and Dale, A.M. (1999b). High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum. Brain Mapp. 8:272–284. doi: 10.1002/(SICI)1097-0193(1999)8:4<272::AID-HBM10>3.0.CO;2-4

Gordon, K.A., Papsin, B.C., and Harrison, R.V. (2003). Activity-Dependent Developmental Plasticity of the Auditory Brain Stem in Children Who Use Cochlear Implants. Ear and Hearing 24, 485–500. doi: 10.1097/01.AUD.0000100203.65990.D4

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Parkkonen, L., and Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. Frontiers in neuroscience, 7, 267. doi: 10.3389/fnins.2013.00267

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Parkkonen, L., and Hämäläinen, M. S. (2014). MNE software for processing MEG and EEG data. Neuroimage, 86, 446-460. doi: 10.1016/j.neuroimage.2013.10.027

Gross, J., Baillet, S., Barnes, G. R., Henson, R. N., Hillebrand, A., Jensen, O., Jerbi, K., Litvak., V., Maess, B., Oostenveld, R. et al. (2013). Good practice for conducting and reporting MEG research. Neuroimage, 65, 349-363. doi: 10.1016/j.neuroimage.2012.10.001

Gross, J. (2019). Magnetoencephalography in Cognitive Neuroscience: A Primer. Neuron, 104(2), 189-204. doi: 10.1016/j.neuron.2019.07.001

Hämäläinen, J.A., Guttorm, T.K., Richardson, U., Alku, P., Lyytinen, H., and Leppänen, P.H.T. (2013). Auditory Event-Related Potentials Measured in Kindergarten Predict Later Reading Problems at School Age. Developmental Neuropsychology 38, 550–566. doi: 10.1080/87565641.2012.718817:

Hämäläinen, M. S., and Ilmoniemi, R. J. (1994). Interpreting magnetic fields of the brain: minimum norm estimates. Medical and biological engineering and computing, 32(1), 35-42. doi: 10.1007/BF02512476

Hari, R., and Puce, A. (2017). MEG-EEG Primer. Oxford University Press.

Hillyard, S. A., Hink, R. F., Schwent, V. L., and Picton, T. W. (1973). Electrical signs of selective attention in the human brain. Science, 182(4108), 177-180. doi: 10.1126/science.182.4108.177

Huang, Y., Heil, P., and Brosch, M. (2019). Associations between sounds and actions in early auditory cortex of nonhuman primates. ELife 8, e43281. doi: 10.7554/eLife.43281

Huster, R.J., Westerhausen, R., Pantev, C., and Konrad, C. (2010). The role of the cingulate cortex as neural generator of the N200 and P300 in a tactile response inhibition task. Human Brain Mapping 31, 1260–1271. doi: 10.1002/hbm.20933

Hyvärinen, A., and Oja, E. (2000). Independent component analysis: algorithms and applications. Neural networks, 13(4-5), 411-430. doi: 10.1016/S0893-6080(00)00026-5

Jas, M., Engemann, D., Bekhti, Y., Raimondo, F., and Gramfort, A. (2017). Autoreject: Automated artifact rejection for MEG and EEG data. NeuroImage, 159, 417-429. doi: 10.1016/j.neuroimage.2017.06.030

Jas, M., Larson, E., Engemann, D. A., Leppäkangas, J., Taulu, S., Hämäläinen, M., and

Gramfort, A. (2018). A reproducible MEG/EEG group study with the MNE software: recommendations, quality assessments, and good practices. Frontiers in neuroscience, 12. doi: 10.3389/fnins.2018.00530

Johnstone, S.J., Barry, R.J., Anderson, J.W., and Coyle, S.F. (1996). Age-related changes in child and adolescent event-related potential component morphology, amplitude and latency to standard and target stimuli in an auditory oddball task. International Journal of Psychophysiology 24, 223–238. doi: 10.1016/S0167-8760(96)00065-7

Karhu, J., Herrgård, E., Pääkkönen, A., Luoma, L., Airaksinen, E., and Partanen, J. (1997). Dual cerebral processing of elementary auditory input in children. Neuroreport, 8(6), 1327-1330.

Kirveskari, E., Salmelin, R., and Hari, R. (2006). Neuromagnetic responses to vowels vs. tones reveal hemispheric lateralization. Clinical neurophysiology, 117(3), 643-648. doi: 10.1016/j.clinph.2005.11.001

Kraus, N., and White-Schwoch, T. (2015). Unraveling the Biology of Auditory Learning: A Cognitive–Sensorimotor–Reward Framework. Trends in Cognitive Sciences 19, 642–654. doi: 10.1016/j.tics.2015.08.017

Kraus, N., Strait, D.L., and Parbery-Clark, A. (2012). Cognitive factors shape brain networks for auditory skills: spotlight on auditory working memory. Annals of the New York Academy of Sciences 1252, 100–107. doi: 10.1111/j.1749-6632.2012.06463.x

Näätänen, R. (1982). Processing negativity: An evoked-potential reflection. Psychological bulletin, 92(3), 605. doi: 10.1037/0033-2909.92.3.605

Nieuwenhuis, S., Yeung, N., Van Den Wildenberg, W., and Ridderinkhof, K. R. (2003).

Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. Cognitive, affective, and behavioral neuroscience, 3(1), 17-26. doi: doi.org/10.3758/CABN.3.1.17

Orekhova, E.V., Butorina, A.V., Tsetlin, M.M., Novikova, S.I., Sokolov, P.A., Elam, M., and Stroganova, T.A. (2013). Auditory Magnetic Response to Clicks in Children and Adults: Its Components, Hemispheric Lateralization and Repetition Suppression Effect. Brain Topogr 26, 410–427. doi: 10.1007/s10548-012-0262-x

Paetau, R., Ahonen, A., Salonen, O., and Sams, M. (1995). Auditory evoked magnetic fields to tones and pseudowords in healthy children and adults. Journal of Clinical Neurophysiology, 12, 177–185. doi: 10.1097/00004691-199503000-00008

Parviainen, T., Helenius, P., Poskiparta, E., Niemi, P., and Salmelin, R. (2011). Speech perception in the child brain: Cortical timing and its relevance to literacy acquisition. Human Brain Mapping 32, 2193–2206. doi: 10.1002/hbm.21181

Parviainen, T., Helenius, P., and Salmelin, R. (2019) Children show hemispheric differences in the basic auditory response properties. Human Brain Mapping. doi: 10.1002/hbm.24553

Peirce, J. W., Gray, J. R., Simpson, S., MacAskill, M. R., Höchenberger, R., Sogo, H., Kastman, E., Lindeløv, J. (2019). PsychoPy2: experiments in behavior made easy. Behavior Research Methods. doi: 10.3758/s13428-018-01193-y

Ponton, C., Eggermont, J.J., Khosla, D., Kwong, B., and Don, M. (2002). Maturation of human central auditory system activity: separating auditory evoked potentials by dipole source modeling. Clinical Neurophysiology 113, 407–420. doi: 10.1016/S1388-2457(01)00733-7

Ponton, C.W., Eggermont, J.J., Kwong, B., and Don, M. (2000). Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. Clinical Neurophysiology 111, 220–236. doi: 10.1016/S1388-2457(99)00236-9

Renvall, H., Salmela, E., Vihla, M., Illman, M., Leinonen, E., Kere, J., and Salmelin, R. (2012). Genome-wide linkage analysis of human auditory cortical activation suggests distinct loci on chromosomes 2, 3, and 8. Journal of Neuroscience, 32(42), 14511-14518. doi: 10.1523/JNEUROSCI.1483-12.2012

Sharma, A., Dorman, M.F., and Spahr, A.J. (2002). A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. Ear and Hearing 23, 532–539. doi: 10.1097/01.AUD.0000042223.62381.01

Sharon, D., Hämäläinen, M.S., Tootell, R.B.H., Halgren, E., and Belliveau, J.W. (2007). The advantage of combining MEG and EEG: Comparison to fMRI in focally stimulated visual cortex. NeuroImage 36, 1225–1235. doi: 10.1016/j.neuroimage.2007.03.066

Simmonds, D.J., Fotedar, S.G., Suskauer, S.J., Pekar, J.J., Denckla, M.B., and Mostofsky, S.H. (2007). Functional brain correlates of response time variability in children. Neuropsychologia 45, 2147–2157. doi: 10.1016/j.neuropsychologia.2007.01.013

Smith, J.L., Johnstone, S.J., and Barry, R.J. (2007). Response priming in the Go/NoGo task: the N2 reflects neither inhibition nor conflict. Clin Neurophysiol 118, 343–355. doi: 10.1016/j.clinph.2006.09.027

Stuss, D. T., Murphy, K. J., Binns, M. A., and Alexander, M. P. (2003). Staying on the job: the frontal lobes control individual performance variability. Brain, 126(11), 2363-2380. doi: 10.1093/brain/awg237

Takeshita, K., Nagamine, T., Thuy, D.H.D., Satow, T., Matsuhashi, M., Yamamoto, J., Takayama, M., Fujiwara, N., and Shibasaki, H. (2002). Maturational change of parallel auditory processing in school-aged children revealed by simultaneous recording of magnetic and electric cortical responses. Clin Neurophysiol 113, 1470–1484. doi: 10.1016/S1388-2457(02)00202-X

Taulu, S., and Simola, J. (2006). Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. Phys. Med. Biol. 51, 1759. doi: 10.1088/0031-9155/51/7/008

Tierney, A.T., Krizman, J., and Kraus, N. (2015). Music training alters the course of adolescent auditory development. Proceedings of the National Academy of Sciences 112, 10062–10067. doi: 10.1073/pnas.1505114112

Wunderlich, J.L., and Cone-Wesson, B.K. (2006). Maturation of CAEP in infants and children: A review. Hearing Research 212, 212–223. doi: 10.1016/j.heares.2005.11.008

Yoshimura, Y., Kikuchi, M., Ueno, S., Shitamichi, K., Remijn, G.B., Hiraishi, H., Hasegawa, C., Furutani, N., Oi, M., Munesue, T., et al. (2014). A longitudinal study of auditory evoked field and language development in young children. NeuroImage 101, 440–447. doi: 10.1016/j.neuroimage.2014.07.034

de Zeeuw, P.D., Aarnoudse-Moens, C., Bijlhout, J., König, C., Uiterweer, A.P., Papanikolau, A., Hoogenraad, C., Imandt, L., Been, D.D., Sergeant, J.A., et al. (2008). Inhibitory Performance, Response Speed, Intraindividual Variability, and Response Accuracy in ADHD. Journal of the American Academy of Child and Adolescent Psychiatry 47, 808–816. doi: 10.1097/CHI.0b013e318172eee9