MEG INDUCED ACTIVATION MEASURES IN DESCRIBING AUDITORY CORTEX MATURATION

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Master's thesis
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August 2015

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MÄKELÄ, NOORA: MEG induced activation measures in describing auditory cortex maturation

Master's thesis, 34 p., 2 appendices

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Psychology

August 2015

Maturational trajectory of stimulus-evoked changes in neural oscillation is still quite unknown in humans. The purpose of this study was to describe maturational changes of auditory processing in induced activation power and phase-locking values. The subjects were children between the age of 6 and 13 years (N=36) and adults (N=11). In this thesis, whole-head magnetoencephalography (MEG) were used to record cortical auditory activation during passive listening. The pure tones stimuli (1000 Hz, 50 ms duration) were monoaurally presented to both ears. Time-frequency analyses were applied using Morlet wavelet transform to stimulus induced power and phase-locking values from the left and the right auditory cortices. For closer examination, measures of the maximum activation were calculated from time-frequency representations.

The results revealed significant differences in rhythmic induced activity and inter-trial phase-locking between children and adults. Adults showed stronger induced power and earlier latencies than children. Also, adults had stronger phase-locking across trials and earlier timing of the maximum phase-locking than those in children. Changes between children in different age groups were not observed. Contralateral ear stimulation evoked stronger, earlier and lower frequency induced responses and also stronger phase-locking than ipsilateral ear stimulation. Further, contralateral dominance was observed in all age groups and only in the right hemisphere.

The findings indicate that the maturation of induced activation is not complete before the age of 13 years. Moreover, results imply that contralateral preference has developed in children at least by the age of 6, and suggest hemispheric differences in neural oscillatory maturation mechanism. The current data proposes that the temporal and spectral induced activation profiles might characterize different developmental trajectories, possibly reflecting age-related differences in neural auditory processing and providing a basis for further examination.

Keyword: development, auditory cortex, oscillation, induced activity, phase-locking analysis, hemispheric asymmetry, magnetoencephalography (MEG)

JYVÄSKYLÄN YLIOPISTO

Psykologian laitos

MÄKELÄ NOORA: MEG induced activation measures in describing auditory cortex maturation

Pro gradu -tutkielma, 34 s., 2 liites

Ohjaaja: Tiina Parviainen

Psykologia

Elokuu 2015

Kuuloaivokuoren ärsykkeisiin liittyvien neuraalisten oskillaatioiden kehitystä ihmisellä ei vielä täysin tunneta. Tämän tutkimuksen tavoitteena on kuvata auditorisen prosessoinnin kehitystä induced-aktivaation ja phase-locking-arvon avulla. Koehenkilöt olivat 6–13,5-vuotiailta lapsia (N=36) sekä aikuisia (N=11). Koko pään kattavaa magnetoenkefalografiaa (MEG) käytettiin nauhoittamaan aivokuoren aktivaatiota passiivisen kuuntelun tehtävän aikana. Osallistujille esitettiin yksinkertaisia siniääniä (1000 Hz, kesto 50 ms) ärsykkeenä erikseen molempiin korviin. Induced-aktivaatiosta ja phase-locking-arvosta laskettiin aika-taajuuskuvat (time-frequency representation) sekä vasemman että oikean hemisfäärin aktivaation mukaan käyttämällä Morlet wavelet -muunnosta. Tarkempaa tutkimista varten aktivaation maksimin voimakkuus laskettiin aika-taajuuskuvan avulla.

Tulokset osoittivat merkittäviä eroja lasten ja aikuisten rytmisen induced-aktivaation ja phase-locking-arvon välillä. Aikuisilla havaittiin voimakkaampi vaste induced-aktivaatiossa ja varhaisemmat latenssit kuin lapsilla. Lisäksi aikuisilla oli lapsiin verrattuna nähtävissä voimakkaampi ja aikaisempi phase-locking-arvo. Tuloksissa ei havaittu eroja eri-ikäisten lapsiryhmien välillä. Kontralateraaliseen korvaan esitetty ärsyke aiheutti voimakkaamman, aikaisemman ja taajuudeltaan matalamman induced-aktivaation sekä voimakkaamman phase-locking-arvon kuin ipsilateraalinen ärsyke. Kontralateraalinen dominanssi oli havaittavissa jokaisessa ikäluokassa ja se näkyi ainoastaan oikeassa hemisfäärissä.

Löydökset osoittavat kuulotiedon käsittelyyn liittyvän rytmisen aktivaation kehityksen olevan keskeneräistä vielä 13 vuoden iässä. Tulokset viittaavat siihen, että kontralateraalinen preferenssi on kehittynyt ainakin 6-vuotiailla lapsilla ja että neuraalisten oskillaatioiden kehittymismekanismissa on eroja vasemman ja oikean hemisfäärin välillä. Tulokset antavat viitteitä siitä, että induced-aktivaation avulla voidaan luonnehtia auditorisen prosessoinnin kypsymisen erilaisia kehityskaaria, jotka todennäköisesti heijastavat ikään liittyviä eroavaisuuksia auditorisessa prosessoinnissa. Nämä tulokset tarjoavat pohjan tulevaisuuden tutkimuksille.

Avainsanat: kehitys, kuuloaivokuori, oskillaatiot, induced aktivaatio, phase-locking analyysi, aivopuoliskojen epäsymmetrisyys, magnetoenkefalografia

CONTENT

INTRODUCTION

Development of the auditory cortex

Brain development in humans is a nonlinear process that reflects structural and functional specialization (Gogtay et al., 2004). Development of the primary functions in the auditory cortex starts before birth (Fujioka, Mourad, & Trainor, 2011; Wunderlich, Cone-Wesson, & Shepherd, 2006) but the development continues to adolescence and extends likely into early adulthood (Tonnquist-Uhlen, Ponton, Eggermont, Kwong, & Don, 2003). Development is accompanied with the maturational process of the different brain systems of the cortex (Basar-Eroglu, Kolev, Ritter, Aksu, & Basar, 1994; Gogtay et al., 2004). These processes include, for example, synaptic pruning, increased synaptic efficacy and changes of the gray and the white matter volume. The anatomical maturation may be reflected in functional development affecting processing efficiency and processing speed (Ruhnau, 2001). By examining the age-related changes in auditory stimulus produced brain activity it is possible to improve our knowledge of the general developmental processes and individual variation in the neural functions (Müller, Gruber, Klimesch, & Lindenberger, 2009; Tonnquist-Uhlen et al., 2003; J. Yordanova & Kolev, 1997).

Human auditory processing consists of multiple different divisions, such as perception, separation, auditory memory and attention. The auditory processing stars at acoustic level when sound information of the audio signals is received and transferred from mechanical into electrical signals. The re-encoded sound information travels through the auditory pathway into the primary auditory cortex, which is located in the superior temporal gyrus of the left and the right hemisphere including to Brodmann areas 41, 42 and 22 (Scott & Johnsrude, 2003). Primary auditory cortex plays a central role in hearing and processing of auditory information. However, functionally human auditory cortex is a complex system and there are many connections with frontal, occipital and parietal lobes. Due to this, auditory cortex undergoes major developmental changes reflecting functional and structural specialization (Shahin, Trainor, Roberts, Backer, & Miller, 2010). Furthermore, auditory maturation is influenced by interactions of environmental and genetic factors (Yan, 2003). In general, structures of the brain related to basic function, for example sensory areas mature early (Gogtay et al., 2004). In turn, higher-order areas associated e.g. with executive function mature later.

The auditory cortex is known to be structurally asymmetric and the left hemisphere, for example, is shown to be typically larger than the right one. The differences between hemispheres has been found both in gross anatomic and also in microstructure level (Devlin et al., 2003; Dorsaint-Pierre et al., 2006), and these are thought to be related to dominance for speech in the left hemisphere (Penhune, Zatorre, MacDonald, & Evans, 1996). Structural asymmetries in cerebral areas have also been found in infants (Dubois et al., 2009). Yet, the role of hemispheric differences and its development is an unsolved issue.

The measurement of functional development

Functional development of the cerebral cortex can be investigated by means of neural activity. Timing is crucial when studying the development of cortical activity. Using non-invasive techniques like magnetoencephalography (MEG) or electroencephalography (EEG) brain activation sequences, such as modulation of cortical rhythm and evoked responses, can be recorded. The presented stimulus activates thousands of synchronously firing pyramidal neurons in the cerebral cortex (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). These activations produce postsynaptic electric currents, which create weak magnetic fields. With MEG, it is possible to measure these cortically generated signals (Hari, Parkkonen, & Nangini, 2010). Both EEG and MEG have the millisecond time resolution that allows exploring brain activation during sensory processing, cognition, motor planning and social interaction in real-time (Hari & Salmelin, 2012). This is an important aspect when studying auditory processing occurring within short time-window.

Brain oscillations are cyclically repeated waveforms of similar duration and shape, which are arising from the human brain (Steriade, 1993). The first recoded rhythmic activity was 10 Hz alpha rhythm over the posterior scalp regions by Berger (1929) and that was, in fact, the first published EEG recording. Afterwards, brain rhythms have been classified based on their frequency content and region of origin. The influence of Berger, the frequency band of the rhythms are traditionally named using Greek letters as delta (1-3 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (around 40 Hz). Furthermore, it is typical to divide the cortical rhythms into spontaneous activity and stimulus evoked rhythms. Spontaneous rhythms are observed without any external stimuli, whereas evoked rhythms are temporary modulated by the external task (Başar, 1998).

Certain event may cause either increases or decreases of signal power in certain frequency band, called event-related synchronization (ERS) or event-related desynchronization (ERD) (Pfurtscheller & Lopes da Silva, 1999). Also, different oscillations have been suggested to associate with specific behavioral states. For example, the lower alpha is modulated as a result of attentional processes (Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998), whereas high-frequency gamma rhythms have been linked with information processing and attention (Tallon-Baudry & Bertrand, 1999). Different frequency bands and spatial information of their origin can indicate numerous cognitive and sensory processes (Fujioka & Ross, 2008). Although, various cognitive functions can be associated with distinct frequencies, the functional role and developmental status of brain oscillation is yet not entirely understood.

Functional development of the auditory cortex has been investigated mainly by means of auditory evoked potentials (AEP). AEPs are event related potentials (ERP) evoked by auditory stimulation (Picton, Hillyard, Krausz, & Galambos, 1974). Using ERP technique, certain stimulus or event is presented multiple times, and these individual responses to each stimulus presentation are averaged to given category of stimuli (see, Luck, 2005). In the averaging processing, it is assumed, that the activation of interest is time-locked to the external stimulus. In other words, responses are constant from trial to trial. AEP are believed to express auditory processing in the different stages (Picton et al., 1974) and average activation is thought to reflect the cognitive processes evoked by stimulus (Bastiaansen & Hagoort, 2003). However, while averaging signals cancels out the background noise, also some information are lost. Therefore, it is required that also other methods are used to quantify different indicators of neuronal development in the brain (Pfurtscheller & Lopes da Silva, 1999; Tallon-Baudry & Bertrand, 1999; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Time-frequency domain analysis allows investigating also auditory rhythmic activity that is not strictly phase-locked to stimulus unlike averaged AEP. By analyzing the temporal changes of cortical rhythms in different frequency bands, it is possible to evaluate stimulus-related changes in time-frequency representation (TFR) profiles by versatile way.

Indeed, stimulus-related MEG/EEG cortical auditory responses may differ in their phase-relationship to the event (David, Kilner, & Friston, 2006). These different forms of activation are called evoked and induced oscillation. Evoked oscillations are phase-locked to the stimulus, whereas the phase of an induced activation can vary from trial to trial. In other words, evoked activity occurs with the same phase and latency from one trial to another (Bastiaansen & Hagoort, 2003). Therefore, phase-locked oscillation can be detected in the average ERP (Roach & Mathalon, 2008). Non-phase-locked induced oscillation, however, are eliminated when the evoked response is calculated by traditional time-averaged methods (Tallon-Baudry & Bertrand, 1999). It has been suggested that these two different types of activities have differences in their functional meaning and distinct underlying neural mechanism (Bastiaansen & Hagoort, 2003; Hsiao, Wu, Ho, & Lin, 2009; Pfurtscheller & Lopes da Silva, 1999; Shahin et al., 2010; Thut, Miniussi, & Gross, 2012). For that reason, these two components should be separated. Studying these different types of activations may provide information about neurophysiological dynamics involved in neural representation and stimulus processing (Müller et al., 2009).

Previous MEG and EEG studies of auditory development

The maturational status of the brain has an influence on auditory stimulus processing (Fujioka & Ross, 2008). Earlier developmental studies recorded by EEG are commonly focused investigating AEP waveforms. Adults AEP waveform consists of a positive-negative-positive sequence, typically labeled as P_1 component at 50 ms, N_1 component at 100 ms, P_2 component around 200 ms and a small N_2 component after this (Mäkelä, Hämäläinen, Hari, & McEvoy, 1994; Picton et al., 1974). Along with maturation, they go through marked changes in their waveform morphology, latencies and amplitudes (Eggermont, 1992; Wunderlich et al., 2006). In children, the P_1 and N_2 peaks dominate the auditory waveform (Ceponiene, Rinne, & Näätänen, 2002), and N_1 component is not regularly present until 9 years of age and older (Ponton, Eggermont, Kwong, & Don, 2000).

Besides EEG, also MEG offers a good means to investigate maturational dynamics of neural coding. The main benefit of MEG is that magnetic fields are minimally attenuated or distorted by meninx, skull and the scalp, unlike electric signal measuring by EEG (Hämäläinen et al., 1993). Therefore the spatial accuracy and source localization is better in MEG than in EEG. Also, spectral power measures between children and adults should not be influenced by differences in skull thickness. MEG allows the precise estimation of the timing related to the auditory stimulus differences and also cortical areas localization associated in information processing and, consequently, combines both great temporal accuracy and adequate spatial accuracy. However, magnetic fields observed outside the head is influenced by the orientation of the neuronal currents with respect to the skull (Hämäläinen et al., 1993). MEG is more sensitive to tangential oriented sources, whereas the radial oriented currents are not commonly detected by MEG. Moreover, MEG mostly ignores signals from deep sources and therefore it is suited for investigating development of cortical auditory mechanism. In addition, MEG is well suited to examining of functional hemispheric differences (Pantev, Ross, Berg, Elbert, & Rockstroh, 1998). Further, MEG does not require focusing and maintaining attention in stimulus and this method can be used to study neural processing even in small children. Therefore, MEG was an e an excellent tool to use in this study.

Indeed, with whole-head MEG system the activity from both hemispheres can be recorded simultaneously (Mäkelä et al., 1994), which allows studying the functional asymmetries noninvasively (Pantev et al., 1998). Previous MEG and fMRI studies have shown that monaurally presented sound stimuli evoked larger and earlier latency responses to contralateral stimulation than to ipsilateral stimulation in adults (Jäncke, Wustenberg, Schulze, & Heinze, 2002; Mäkelä et al., 1993; Pantev et al., 1998). However, the contralateral dominance and its development in auditory processing of children are yet not entirely understood. There are few previous ERP studies related to functional asymmetry of auditory development. Using MEG, it has been found that in school-age children the N_1 component was often more adult-like in right hemisphere than the left (Parviainen, Helenius, Poskiparta, Niemi, & Salmelin, 2011), and the latency for children of the right hemisphere shortened faster than in the left hemisphere (Kotecha et al., 2009). These result suggested that the right hemisphere may lead the maturation.

Although the brain development has been examined using ERPs, the maturation of stimulus induces neural oscillations in auditory cortex is yet largely unknown in humans. On the other hand, it is known that spontaneous EEG activity undergoes considerable changes from childhood to adulthood (Basar-Eroglu et al., 1994; Petersen & Eeg-Olofsson, 1971). The EEG activity in the lower frequencies (delta, theta) seems to decrease with age, while the dominance of higher frequency bands (alpha, beta) increases (Gasser, Verleger, Bacher, & Sroka, 1988; Matthis, Scheffner, Benninger, Lipinski, & Stolzis, 1980). Considering these changes in spontaneous brain rhythms it is likely that also the analysis of stimulus induced oscillatory activity might provide a meaningful method to examine developmental changes in the event-related information processing (J. Yordanova & Kolev, 1997). Recent studies associated in event-related activity in children have found that phase-locking was lower in children than in adults and showed to increase by age (Fujioka & Ross, 2008; Müller et al., 2009; Shahin et al., 2010; J. Yordanova & Kolev, 1997), which are thought to related to maturation and learning. Moreover, Yordanova and Kolev (1996, 1997) found differences in time-structure and amplitudes in theta, alpha and beta frequencies in children aged 6 to 11 compared from those in adults using auditory-oddball task. Also, it has been suggested that auditory-oddball task related whole power would decrease from childhood to old age (Müller et al., 2009).

The main focuses of the present study is to examine the development of stimulus induced oscillatory activity in the auditory cortex from childhood to adulthood. The maturational changes in MEG activity are suggested to reflect of increase information processing efficacy (Fujioka & Ross, 2008). Maturation in myelination, synaptic elimination and increasing synaptic efficacy is related the development of information processing (Eggermont, 1992). It has also been speculated that age-related rhythmic changes could reflect different neural coding mechanism in auditory perception (Müller et al., 2009). Maturational differences in the functional properties of auditory processing can provide valuable information about typical development of central nervous system (Tonnquist-Uhlen et al., 2003). By characterizing the course of functional auditory maturation in healthy individuals, it may provide better understanding for studying both normal and abnormal development.

Aims of the study

The aim of this study was to investigate developmental differences in the event-related changes in rhythmic activation in the auditory cortex. We compare both induced activation power and phase-locking value in children from three different age groups and adults during passive listening.

In this study, we have two main questions. First, we wanted to investigate what kind of maturational changes happens in the auditory processing when measuring the cortical rhythms from typically developing children between 6 and 13.5 years of age. We compared children's oscillatory responses with those of adults. Second, we examined whether there are differences between contralateral and ipsilateral auditory processing. Importantly, many studies focus on mean difference between age groups. However, children at the same age may show a large variability. Our purpose is to survey the variation within the age group and compare the variation of children and adults to each other.

Our expectation was that responses of the induced power and the phase-locking value would change with age. According to previous studies, it can be supposed that induced power should decrease with age whereas phase-locking should become stronger (Müller et al., 2009). It has been shown in the previous ERP-studies that adults have preferences to contralateral ear stimulation, which is shown as shorter peak latencies and stronger peak amplitudes than ipsilateral stimulation in both hemispheres (Mäkelä et al., 1993). We expected that the contralateral preference shows also in rhythmic processing at least in adults group. Finally, we assumed that individual variation within the age groups might be rather huge especially in children group. The present study is exploratory in nature and its aim is to investigate how do different measures of induced activation reflect maturation.

MATERIALS AND METHODS

Subjects

Subjects were thirty-seven children and eleven adults with normal hearing and no history of neurological disease. All subjects were right-handed native speakers of English and recruited in the Oxford area in the UK. Child participants were volunteers acquired from local schools and adults were university students from the University of Oxford, obtained via a mailing list. Due to disrupted data, one of the child participants was discarded. Therefore, the final data analysis consisted of 36 children aged 6–13.5 years and 11 adults aged 19–26 years. Children were divided into three groups by age: group A (n = 13, 2 females, age range = 6–7.5 years), group B (n = 11, 6 females, age range = 9–10.5 years) and group C (n = 12, 8 females, age range = 12–13.5 years). Group D consist adults (n = 11, 6 females, age range = 19–26 years).

Research protocol

Current thesis is a part of a research project of auditory language perception in the maturating brain. The total research procedure consists of three separate paradigms using words, syllables and pure tone as stimuli. In this study, only the pure tones experiment is reported. The Central University Research Ethics committee of University of Oxford has approved the study and it was funded by the Academy of Finland.

Two research sessions were performed during the study. Subjects were tested behaviorally to define linguistic and non-linguistic abilities during the first session, and a magnetoencephalography (MEG) measurement was performed during the second session.

Behavioral tests

All participants completed the behavioral test battery. The linguistic and non-linguistic skills were tested using two subtests, Vocabulary and Matrix Reasoning, of the third edition of the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1974). The Test of Word Reading Efficiency, Towre (Torgesen et al. 1999) was performed to examine the phonemic decoding and the sight word recognition. According the present tests, all children and adults had typical reading skills, language related abilities and verbal short-term memory.

Auditory stimuli

The stimuli of the study were 1000 Hz pure tones with duration of 50 ms including 15 ms fade-in and fade-out time. The tones were created in Adobe Audition and controlled with the Presentation program (Neurobehavioral System Inc., San Francisco, CA). The sounds were monaurally presented through insert earphones to the subject's ears and tones were delivered alternately either to the left or the right ear. The inter-stimulus intervals (ISI) varied randomly from 800 to 1200 ms. The stimulus intensity was set 65 dB above individual sensation thresholds. The participants were instructed to sit still and watch silent cartoons without paying attention to the sound stimuli.

Recordings

During the recording, the subjects were sitting with the head leaning on the back of the magnetometer helmet. It was confirmed that the participants did not wear anything magnetic. The measurements were carried out in a magnetically shielded room at the Oxford Centre for Human Brain Activity (OHBA) at the Warneford Hospital in the Oxford. MEG recordings were performed using a 306-channel Neuromag VectorView^{TM} whole-head neuromagnetometer (Elekta Neuromag, Helsinki, Finland). Helmet consists of 122-channels, each sensor site containing of two planar gradiometers and one magnetometer. Planar gradiometers measure the change in magnetic field on orthogonal direction and show maximum signal directly above an active cortical area (Hämäläinen et al., 1993). Therefore, the signals from the planar gradiometers were used for data analyses.

Because of eye movements and blinks, which produce disturbance to the measured MEG signals, the vertical and horizontal eye motion were recorded using EOG (Electro-oculography) and the artefacts were rejected from the further analysis. For the purpose of monitor the positon of the each subject's head, four head position indicator (HPI) coils were attached behind the ears and to the forehead. The positions of these coils within the MEG helmet were determined using 3D-digitizer (Polhemus, Colchester, VT) with respect to three individual anatomical landmarks (left and right pre-auricular reference points and nasion) prior to the measurement. In the beginning of the recording, small currents were sent to the indicator coils and head position was quantified by measuring the produced magnetic field. Head position can be monitored continuously throughout the recording and this continuous head position indicator (cHPI) can be used to compensate for effects of the head movement on the MEG data (Wehner, Hämäläinen, Mody, & Ahlfors, 2008). In case of young children move their heads during the test, the cHPI was engaged.

The MEG signals were sampled at 600 Hz and bandpass filtered at 0.03 – 0.330 Hz. The data were processed with the signal space separation (SSS) method (Taulu, Simola, & Kajola, 2004) using MaxFilter^{TM} software. The process improves the signal-to-noise ratio of the recorded data by compensating external interference and sensor artifacts. In case of cHPI was used for subject, movement compensation was used whit SSS and the temporal extension of SSS (tSSS) was applied. On average 97 epochs were gathered from each subject.

Data analysis

The raw MEG-data were processed using functions provided by MNE Python project. First, time-frequency representations on topographies for MEG sensors were plotted in all gradiometer channels. It is known that auditory stimulation evoke activation over the temporal regions and especially the channels located over the superior temporal gyrus. We used this information when selecting the channels for closer examination. For further analysis, we chose symmetrically one channel in left and one channel in the right hemisphere in the auditory cortex that showed approximately the largest signal. Topography of the power and phase-locking values were used to identify the channels in the left and the right hemispheres. Phase-locking values provided clearer picture of the distribution of activation and they were used to detect channels of interest along the scalp. Typically the induced activation showed also the strongest signals in these sensors. In majority of the cases, the channels were the same across subjects (channel 242 in the left hemisphere and channel 1332 in the right hemisphere) and therefore these were used in the analysis for all individuals.

Time-frequency representations (TFRs) were calculated separately for each participant for induced power and phase-locking values in both hemispheres (left and right auditory cortices) and for both ear stimuli (left and right), using a Morlet wavelet transform (wavelet width 7). Fourier transformation can determine frequencies well but it doesn't consider changes over time (Quian Quiroga, Sakowitz, Basar, & Schurmann, 2001). However, wavelet analyses provide information of when and how the frequency content of a MEG waveforms changes over time (Samar, Bopardikar, Rao, & Swartz, 1999). Since we wanted to investigate the event-related changes in rhythmic activity, the Morlet wavelet transform were used. Also the TFRs and evoked responses averaged across participants from different age groups were calculated. Our purpose was to examine the rhythmic activity with a large frequency scale, considering the changes both in slow- and high-frequency bands. Therefore, the frequency band of interest was selected to 7–60 Hz and time window -300–1000 ms.

Al in all, two different TFR were computed: *stimulus induced changes in power* and *phase-locking between trials.* Non-phase-locked induced power is not revealed in traditional averaging methods that are used to detect evoked responses (David et al., 2006). In induced power, wavelet transformation was first computed to each trial and then average of the time-frequency decompositions over trials were calculated. In this way, it is possible to find out rhythmic changes in the auditory cortex in which the temporal relationship with sound onset is loose (Tallon-Baudry & Bertrand, 1999). Instead of induced power, phase-locking value is representing phase difference across single trial response, which reflects how systematically the stimulus evokes same response in time across trials. In other words, phase-locking value describes the range to which phase values becomes clustered over trials. The phase-locking value was quantified by first averaging MEG signals over trials and then oblige to the time-frequency power representation to give an event-related response.

Five different measures were identified from these time-frequency representations:

(I) *Strength of the Maximum Induced Power* reflects how strong the amplitude of the induced power is in its maximum point.

(II) *Timing of the Maximum Induced Power* shows in what moment in time the induced power is the strongest.

(III) *Frequency of the Maximum Induced Power* reflects the strongest induced power.

(IV) *Strength of the Maximum Phase-Locking* demonstrates how strong the inter-trial phase-locking is.

(V) *Timing of the Maximum Phase-Locking* shows when the inter-trial phase-locking achieves its maximum value.

The measures were calculated using the MNE Python script (provided by Tuomas Puoliväli). The size of 10 ms and 10 Hz time-frequency window was used to locate induced power and phase-locking value maximum in time and space. Because the measures were defined 10 ms x 10 Hz window, the numerical value of each variable was shown in range of ten units (for example 7 – 17 Hz). For statistical analysis and more accurate examination, the mean values were calculated.

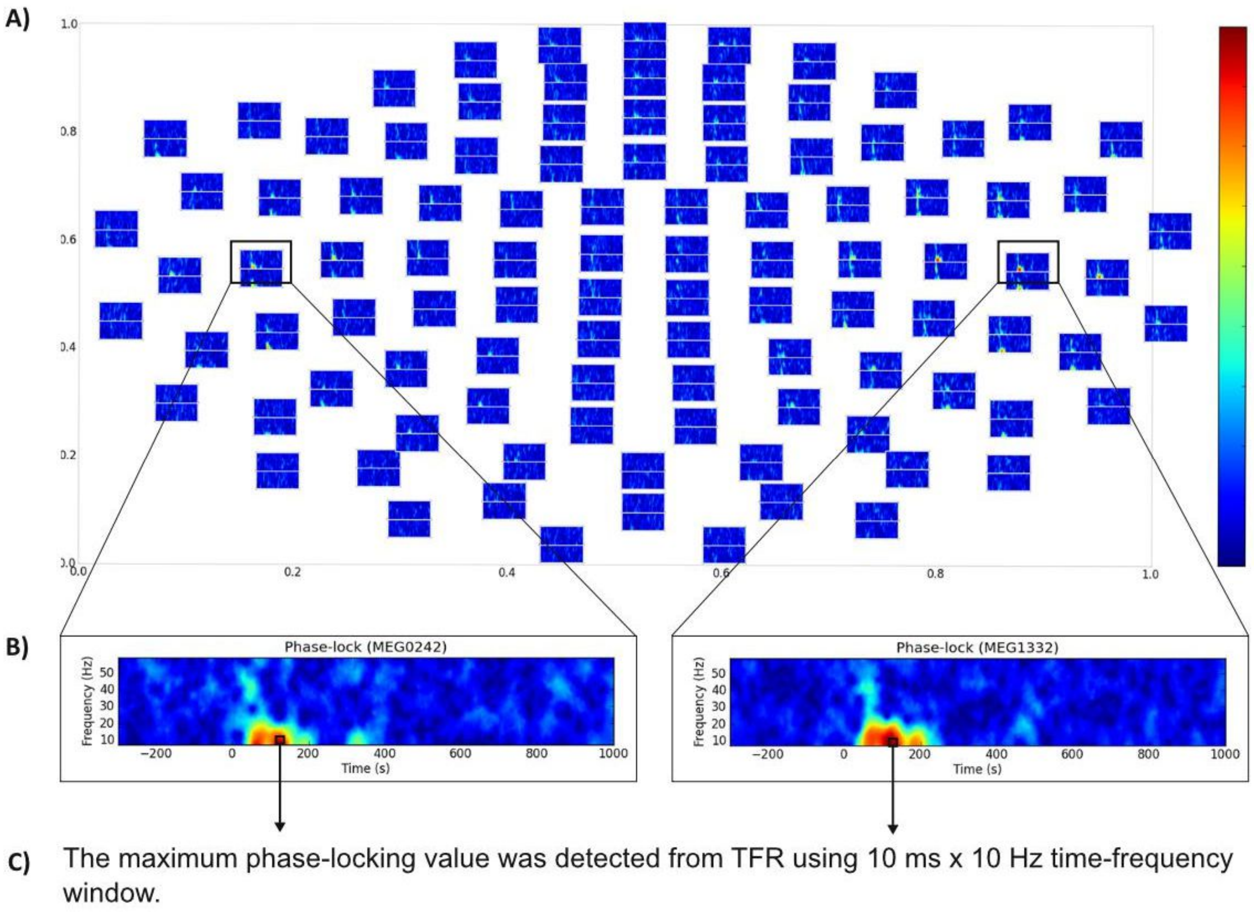


FIGURE 1. *An example of how to determine the channel of interest for closer examination and localize the maximum value from TFR. A) Plotted topographic distribution of the time-frequency phase-locking values. By means of them one channel from the left (channel 242) and one channel from the right (channel 1332) temporal lobe were chosen for closer analysis. B) Time-frequency representation (TFR) with changes phase-locking values as a function of time in response of left ear sound stimuli. Red color indicates of maximum value whereas blue color represents the minimum value. C) Maximum phase-locking value was calculated from TRF using the MNE Python script.*

Statistical analysis

The statistical analyses were done using IBM Statistics SPSS 20 (SPSS Inc., Chicago, IL). For general overview of the results, box plot distribution was used. A repeated measures analysis of variance (ANOVA) was performed to compare induced power and phase-locking values between hemispheres, stimulated ear and age groups. Hemisphere (left and right) and ear (left and right) were set as the within-subject factors and group (A, B, C and D) as the between-subjects factor. The five measures were strength of the maximum induced power, timing of the maximum induced power, frequency of the maximum induced power, strength of the maximum phase-locking and timing of the maximum phase-locking. To investigate age group differences more specifically with pairwise comparison, post-hoc tests using Bonferroni correction were employed. According to the Shapiro-Wilk test of normality, some of the variables were not completely normally distributed. However, when the distributions of the variables were analyzed graphically, the assumption of normality appeared to be reasonable. The Greenhouse-Geisser corrections were applied if the sphericity was violated according to the Mauchly's Test of Sphericity. Nonetheless, it must be noted the relatively small sample size in each age group. The level of statistical significance was set at $p >$ .05.

RESULTS

General overview of the results

Figure 2 illustrates the distribution of strength, timing and frequency of the maximum induced power and strength and timing of the maximum phase locking in the different age groups. A visual analysis of the box plot graph implies that adults had stronger maximum induced power than children whereas timing of the maximum induced power seems to shorten with age. According to the box plots, there seems to be larger variation in strength of the maximum induced power in adult group compared to those in children. However, the variation in timing of activation within adult group is relatively smaller than in children group. That means the maximum value of the induced power appears in a narrow time-window (approximately within 100 ms) in adults. Based on figure 2, the distribution in frequency of the maximum induced power seems to be quite large in young children. However, the mean value appears around 10 Hz for contralateral response especially in older groups. In this regard, the variation within adults group appears to be quite small.

The visual examination between box plots of the phase-locking values indicate that phase-locking between trials seems to increase with age and it seems to be earlier in adults than in children. The timing of the maximum phase-locking is focused at the 50 - 150 ms in adult group. Overall, the variation within the age groups seems to be relatively constant.

All in all, preliminary visual analysis of the box plot distributions suggest that there are age related changes in different age groups in strength and timing of the maximum induced power and phase locking. Moreover, figure 2 indicates that contralateral ear stimulation evokes different response than ipsilateral stimulation. The statistical analyses were performed to investigate these preliminary results more closely.

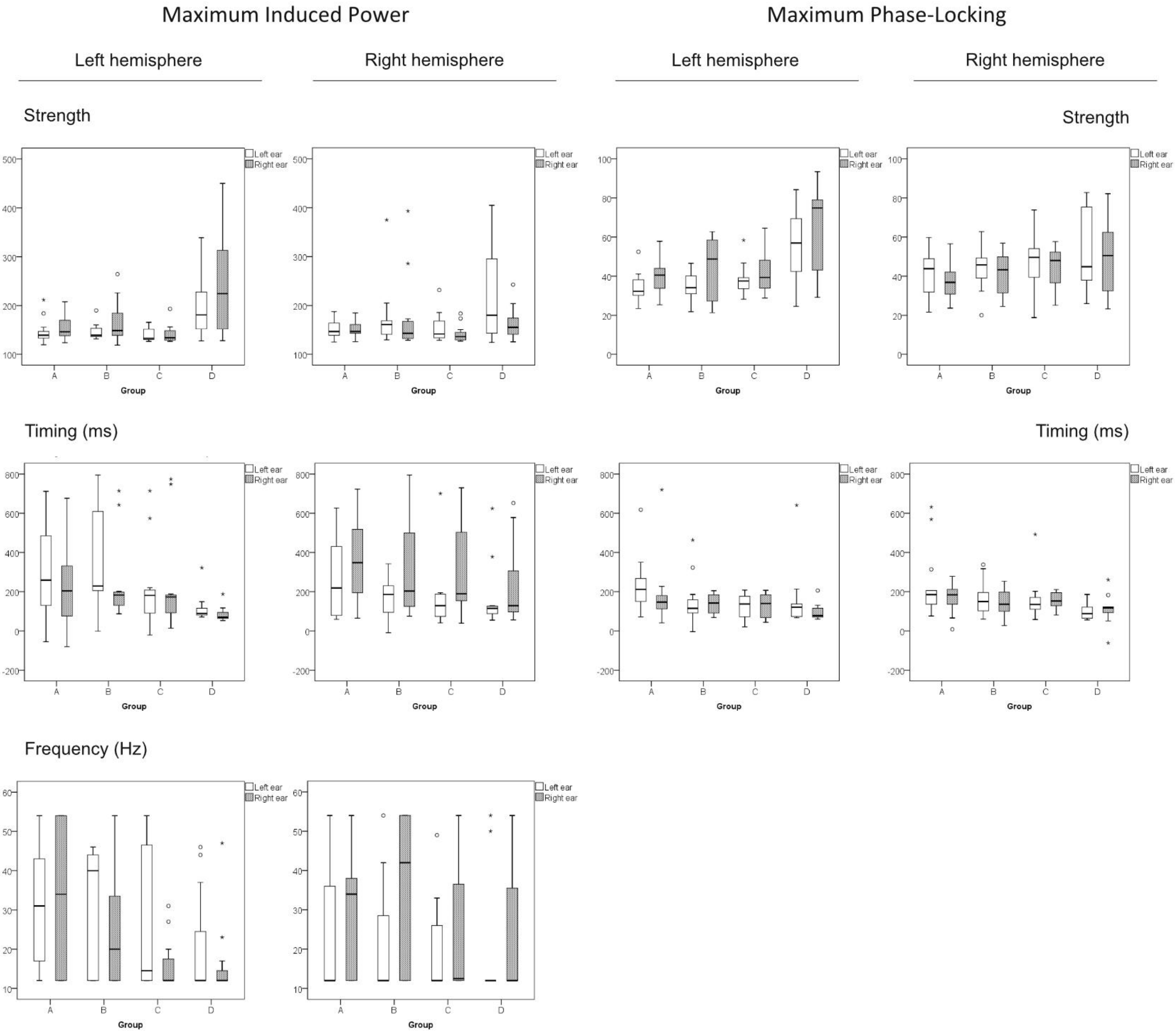


FIGURE 2. *Box plot distribution of strength of the maximum induced power, timing of the maximum induced power, frequency of the maximum induced power, strength of the maximum phase-locking and timing of the maximum phase-locking in different age group; 6 – 7.5 years (A), 9 – 10.5 (B), 12 – 12.5 years (C) and adults (D) in left and right ear stimulation in both hemispheres.*

Differences across age groups in induced power

TABLE 1. *Strength, timing and frequency of the maximum induced power (mean +-SD) in different age groups; 6 – 7.5 years (A), 9 – 10.5 (B), 12 – 12.5 years (C) and adults (D) in left and right ear stimulation in both hemispheres.*

	Maximum Induced Power							
	Left ear				Right ear			
Response type	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D
	Left hemisphere							
Strength	146.36 +- 25.37	146.64 +- 17.51	139.59 +- 13.87	199.62 +- 71.25	154.58 +- 24.59	166.80 +- 45.05	141.04 +- 19.24	265.52 +- 156.16
Time (ms)	305.54 +- 240.87	349.0 +- 267.87	221.91 +- 211.04	117.55+- 71.68	222.08 +- 237.42	248.36 +- 217.05	230.00 +- 255.28	85.63 +- 39.97
Frequency (Hz)	30.85 +- 13.91	30.90 +- 15.49	27.42 +- 18.40	20.27 +- 14.33	32.77 +- 19.06	25.09 +- 17.13	15.75 +- 6.68	16.63 +- 10.65
	Right hemisphere							
Strength	151.75 +- 18.75	176.96 +- 69.16	153.68 +- 30.55	223.10 +- 99.02	151.41 +- 17.35	179.91+- 83.69	141.69 +- 18.58	164.23 +- 34.56
Time (ms)	266.08 +- 196.70	166.90 +- 110.80	169.08 +- 176.58	173.18 +- 172.89	365.92 +- 228.17	335.72 +- 277.11	294.08 +- 236.36	233.81 +- 207.40
Frequency (Hz)	25.46 +- 16.55	22.09 +- 14.91	19.83 +- 11.79	19.27 +- 16.21	29.23 +- 15.81	33.55 +- 20.91	23.58 +- 16.92	24.63 +- 17.13

Strength of the Maximum Induced Power

Table 1 shows the mean and standard deviation values in strength, timing and frequency of the maximum induced power. There was a statistically significant interaction between ear, hemisphere and group in strength of the maximum induced power (F (3, 43) = 5.23 $p = .004$). Results indicate that the left and the right ear stimuli evoke different amplitude in the left and the right hemisphere. This interaction between ear and hemisphere, however, appears differently in different age groups. When repeated measure ANOVA was performed on the each age group separately, there was a significant interaction between ear and hemisphere (F (1, 10) = 7.86 $p = .019$) only in adults group (group D). In children groups (A-C) there were no statistically significant effects. A further examination in adults group revealed that there were a significant main effect of ear in strength of the maximum induced power in the left hemisphere (F (1, 10) = 5.90 $p = .036$), and also in the right hemisphere (F (1, 10) = 5.92 $p = .035$). The contralateral ear stimulus evoked a stronger response in the left and the right hemisphere in adults group (see table 1 and figure 3).

There was also a statistically significant effect of group in the strength of the maximum induced power (F (3, 43) = 5.96 *p = .002*). Pairwise comparison showed that the maximum induced power was stronger in adult than in children in group A and C (D>A p = .006, D>C p = .002; see table 1 and figure 3). However, between group D and B the difference was not significant. Furthermore, there were no significant differences between children of different age group.

In conclusion, adults had stronger maximum induced power than children in group A and C. In adults, contralateral stimulation evoked stronger response than ipsilateral stimulation in both hemispheres.

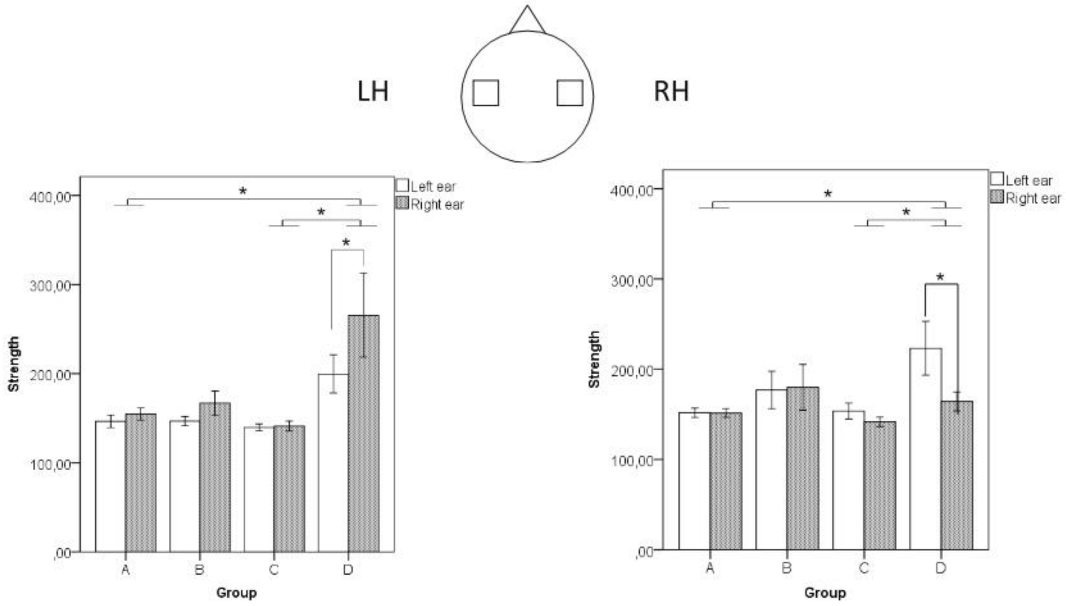


FIGURE 3. *Mean strength of the maximum induced power (+- SEM) after left and right ear stimulation for the age groups in left and right hemispheres. Significance level of p < .05.*

Timing of the Maximum Induced Power

When examining timing of the maximum induced power, there was a statistically significant interaction between ear and hemisphere (F (1, 43) = 6.72 *p = .013*). In the right hemisphere, there was a significant main effect of ear in timing of the maximum induced power (F (1, 43) = 7.26 *p = .010*). The left ear stimulation evoked earlier response than the right ear stimulation (see table 1, figure 4). However, there was no effect of ear in timing of the maximum induced power in the left hemisphere. It must be noted that the standard deviations of the induced power timing are wide and the individual variations within groups are fairly large especially in children (see table 1 for SD and figure 2).

The differences between age groups were statistically significant (F (1, 43) = 3.37 *p = .027).* Pairwise comparison suggests that the maximum induced power evoked later in group A than in group D (p = .031, see table 1 and figure 4). The same trend can be seen between group B and D (figure 4), although the difference only approached the significance effect (p = .093). Difference between group C and D was not significant.

In conclusion, induced responses appeared significantly earlier for contralateral ear in all age groups but only in the right hemisphere. Also, younger subjects had longer latencies and the latency seemed to approach adult values by increasing age.

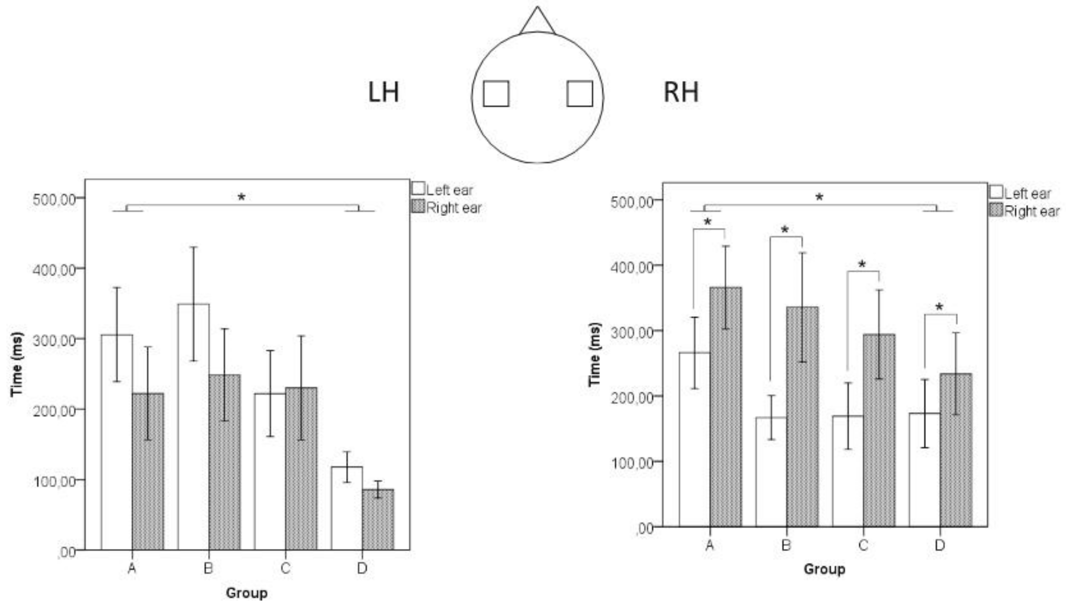


FIGURE 4. *Mean time (ms) of the maximum induced power (+- SEM) after left and right ear stimulation for the age groups in left and right hemispheres. Significance level of p < .05.*

Frequency of the Maximum Induced Power

The repeated measures ANOVA revealed a significant interaction between ear and hemisphere in frequency of the maximum induced power (F (1, 43) = 7.92 *p = .007*), indicating that the frequency effect of stimulated ear is different in the left and the right hemispheres. In the right hemisphere, there was a significant main effect of ear in frequency of the maximum induced power (F (1, 43) = 4.59 *p = .038*) and in the left hemisphere, the main effect of ear approached a significance result (F (1, 43) = 2.86 *p = .098*). The contralateral ear stimulation appears to evoke lower frequency response than the ipsilateral ear stimulation (see table 1, figure 5).

According to figure 5, the frequency of the maximum induced power seems to lower with age and the group effect approached statistically significant value (F (1, 43) = 2.69 *p = .058*). However, in the pairwise comparison the difference between age groups were not statistically significant.

In conclusion, contralateral stimulation caused lower frequency responses than ipsilateral stimulation in the right hemisphere and almost significantly in the left hemisphere. There was a tendency towards lower frequencies in older subjects.

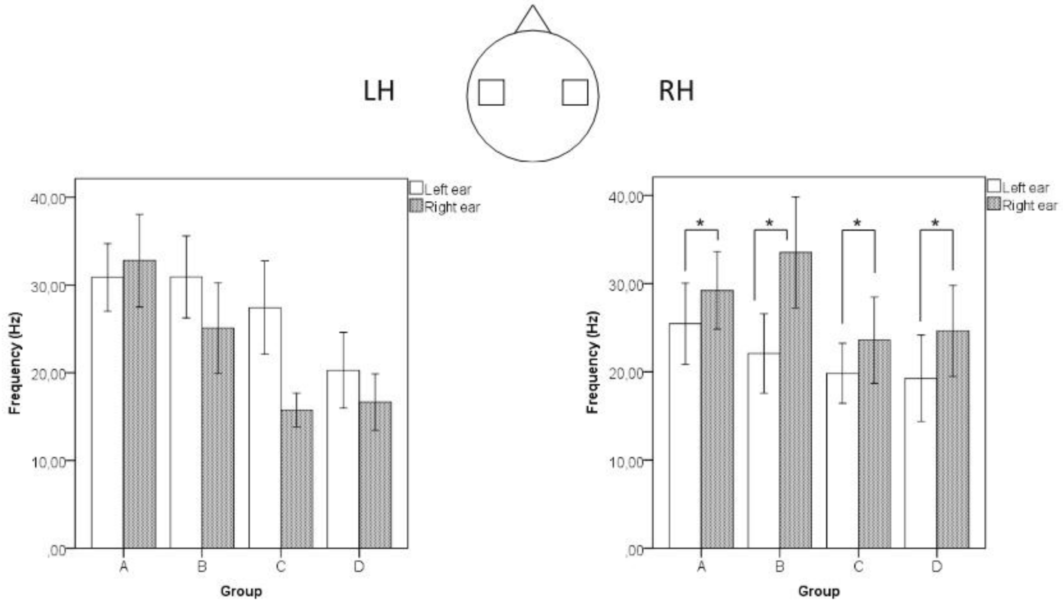
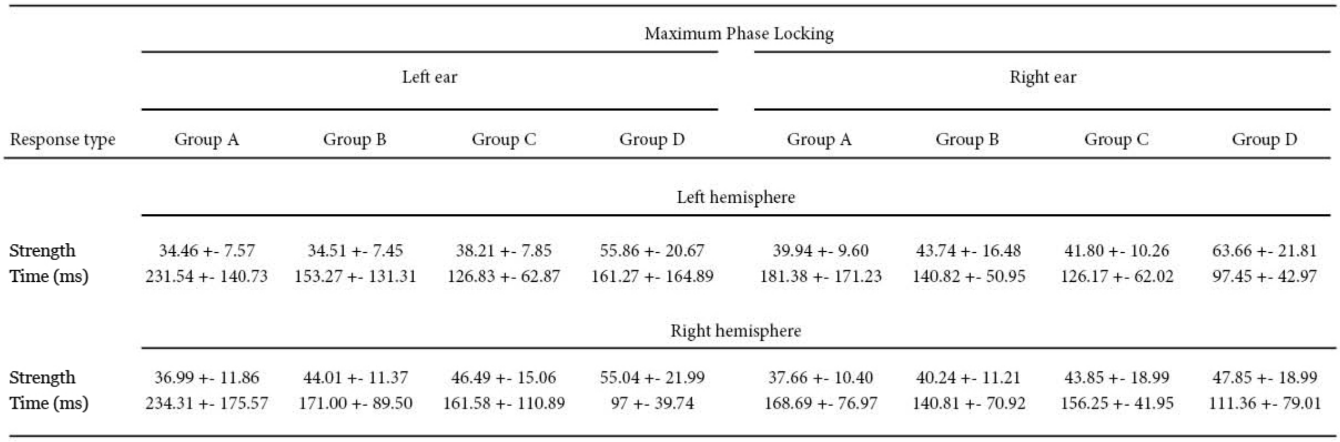


FIGURE 5. *Mean frequency (Hz) of the maximum induced power (+- SEM) after left and right ear stimulation for the age groups in left and right hemispheres. Significance level of p < .05.*

Differences across age groups in phase-locking value

TABLE 2. *Strength, timing and frequency of maximum phase-locking (mean +- SD) in different age groups; 6 – 7.5 years (A), 9 – 10.5 (B), 12 – 12.5 years (C) and adults (D) in left and right ear stimulation in both hemispheres.*



	Maximum Phase Locking							
	Left ear				Right ear			
Response type	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D
	Left hemisphere							
Strength	34.46 +- 7.57	34.51 +- 7.45	38.21 +- 7.85	55.86 +- 20.67	39.94 +- 9.60	43.74 +- 16.48	41.80 +- 10.26	63.66 +- 21.81
Time (ms)	231.54 +- 140.73	153.27 +- 131.31	126.83 +- 62.87	161.27 +- 164.89	181.38 +- 171.23	140.82 +- 50.95	126.17 +- 62.02	97.45 +- 42.97
	Right hemisphere							
Strength	36.99 +- 11.86	44.01 +- 11.37	46.49 +- 15.06	55.04 +- 21.99	37.66 +- 10.40	40.24 +- 11.21	43.85 +- 18.99	47.85 +- 18.99
Time (ms)	234.31 +- 175.57	171.00 +- 89.50	161.58 +- 110.89	97 +- 39.74	168.69 +- 76.97	140.81 +- 70.92	156.25 +- 41.95	111.36 +- 79.01

Strength of the Maximum Phase-Locking

According to repeated measures ANOVA, there was a statistically significant interaction between ear and hemisphere in strength of the maximum phase-locking (F (1, 43) = 19.94 *p = .001*), which indicates that the left and the right ear stimuli evoke different strength of the phase-locking in the left and the right hemispheres. A further examination showed that there were significant main effects of ear in strength of the maximum phase-locking in the left hemisphere (F (1, 43) = 19.99 *p = .001*) and in the right hemisphere (F (1, 43) = 6.10= *.018)*. The phase-locking for the contralateral stimulation seems to be stronger than for the ipsilateral response (see table 2 and figure 6). Left ear stimulation evoked stronger phase-locking than right ear stimulation in the right hemisphere whereas right ear stimulation evoked stronger phase-locking than left ear stimulation in the left hemisphere (see table 2 and figure 6). The age groups differed statistically significantly (F (1, 43) = 6.32= *.001)* and pairwise comparison indicated that adults group (group D) differs from group A (p = .001), group B (p = .010) and group C (p = .029). The phase-locking appears to be stronger in the adults than in the children (See table 2 and figure 6).

Overall, there was stronger phase-locking for contralateral ear stimulation than ipsilateral ear stimulation and it showed in both hemispheres in all age groups. Adults showed also stronger phase-locking than children but differences between children groups were not observed.

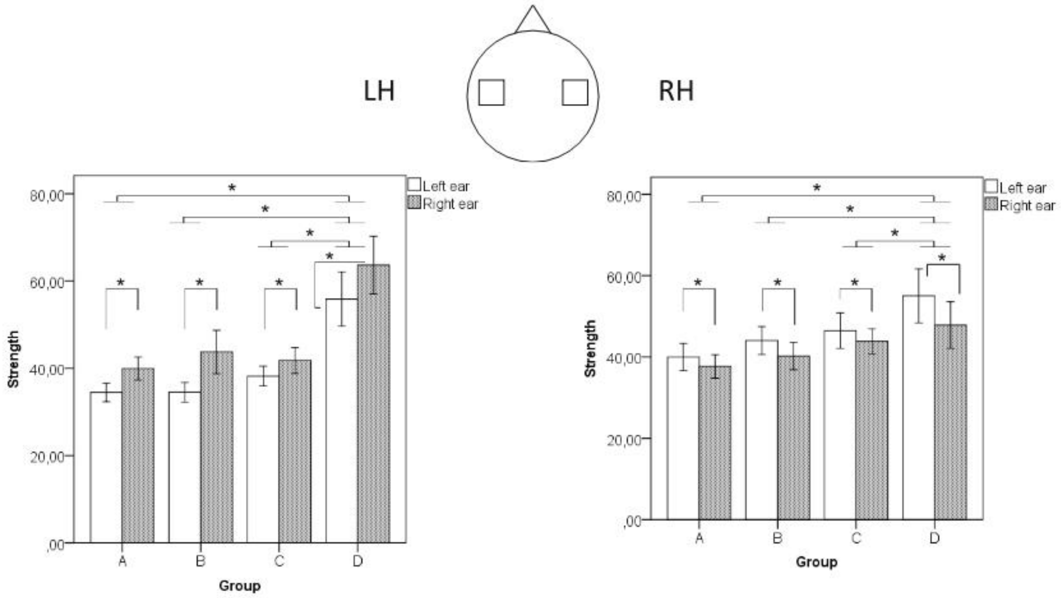


FIGURE 6. *Mean strength of the maximum phase-locking (+- SEM) after left and right ear stimulation for the age groups in left and right hemispheres. Significance level of p < .05.*

Timing of the Maximum Phase-Locking

When examining timing of the maximum phase-locking, ANOVA showed neither statistically significant interaction nor main effect between variables. However, the differences between age groups were statistically significant (F (1, 43) = 5.02 *p = .005).* Pairwise comparison revealed that the group A differs from group D (p = .003) and the difference between group A and C approach significance (p = .067). In the group A, timing of the phase-locking was later than in the adult group (D) (see table 2 and figure 7). Group B and C did not differ from adults. In conclusion, maximum phase-locking emerged earlier in older subjects.

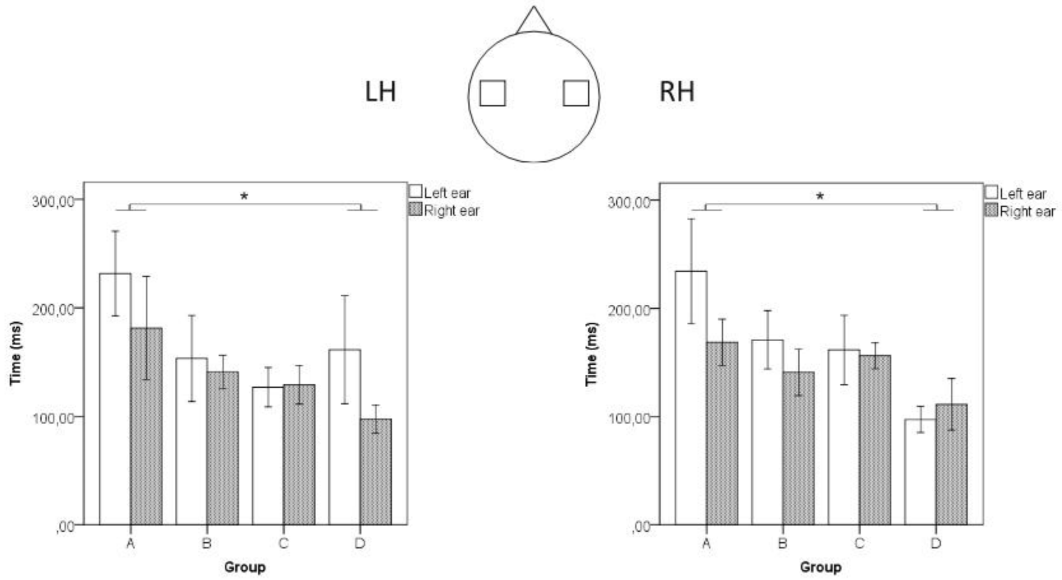


FIGURE 7. *Mean time (ms) of the maximum phase-locking (+- SEM) after left and right ear stimulation for the age groups in left and right hemispheres. Significance level of p < .05.*

DISCUSSION

The present study investigated auditory evoked oscillatory MEG activity in the auditory cortex from 6–13.5 years old children and adults. The aim of the study was to first, assess maturational changes in the neural coding by means of event-related induced power and phase-locking value measures during passive listening. Second, we examined the lateralization and interhemispheric differences in children and adults as regards the side of stimulation. We analyzed five different measures derived from time-frequency representation of stimulus induced changes in power and phase-locking between trials: (I) *Strength of the Maximum Induced Power,* (II) *Timing of the Maximum Induced Power,* (III) *Frequency of the Maximum Induced Power* (IV) *Strength of the Maximum Phase-Locking* and (V) *Timing of the Maximum Phase-Locking.*

The main findings were that there seems to be age-related changes in overall induced power and phase-locking value. However, the main difference appears to be between 6–13 years old children and adults, implying that the maturation of induced activation is not complete before the age of 13 years. Moreover, the results indicated that contralateral ear stimulation evokes different response than ipsilateral stimulation. Contralateral preference was observed in all age groups, even in children age of 6, and it showed only in the right hemisphere. Overall, the development of induced activation power and phase-locking value seems to follow different maturational trends in different power measures, likely reflecting distinct neural aspects of auditory processing.

General maturational changes in induced power and phase-locking value

Maturational changes in oscillatory induced activation were investigated by means of strength, timing and frequency of the maximum induced power. As was expected, younger subjects showed longer induced power latencies than adults. Changes in timing of the maximum induced power indicate that adults have more constant time-structure, whereas children showed more variation in power activation time (see figure 2). This result is in line with previous studies (Fujioka & Ross, 2008; Müller et al., 2009; J. Yordanova & Kolev, 1997; J. Y. Yordanova & Kolev, 1996). Moreover, some of the previous ERP studies have proposed that latencies and amplitudes decrease linearly throughout childhood (Albrecht, Suchodoletz, & Uwer, 2000; Ceponiene et al., 2002; Gruber, Klimesch, Sauseng, & Doppelmayr, 2005), whereas other studies have reported more step-like changes (Kotecha et al., 2009; Ponton et al., 2000). We found the main difference between 6 year old children and adults, implying that the developmental course of induced activation timing may not decrease linearly with age. On the other hand, is has been proposed that spontaneous oscillatory activities maturates much slower speed than evoked responses (see, Fujioka & Ross, 2008; Gasser et al., 1988). The spontaneous rhythmic activity may reflect to non-phase-locked induced activation.

Against our hypothesis, we observed that the maximum induced activity was stronger in adults than in children age around 6 and 13 years old (group A and C). Surprisingly, 9 to 10 years children (group B) showed no difference comparing to adults. On the contrary, previous studies have found that whole power would decrease by age in general (Müller et al., 2009) and reported lower single-sweep amplitude to auditory stimuli in adults than in children. (J. Yordanova & Kolev, 1996; 1997). Two possible explanations come to mind. First, the current result may be explained by the variation in strength and timing of the activation within age groups. Adults showed larger within-subject variation in strength of the maximum induced power than children (see figure 2). However, the variation in timing of the activation within adult group is relatively smaller than in children group. That means the maximum value of the induced power appears in narrow time-window (approximately under 100 ms) in adults. In other words, the induced power seems to achieve its maximum systematically in a specific point in time in adults and, consequently, showed strong MEG activation. In children, there seems to be more variation in timing of the maximum induced power, which can be associated with a small variation in induced power strength. Second, measured induced power may be a reflection of a strong phase-locking value in adults. Evoked activity is tightly phase-locked to the auditory stimuli and it can be detected into average ERP (Tallon-Baudry & Bertrand, 1999). Because oscillatory activation is focused around 100 ms in adults and the phase-locking value is quite strong, the phase-locking activation and average ERP can be seen as a reflection of a strong induces activation power. By examining the time-frequency representations of stimulus induced changes in power in different age-groups (appendix 1), it is tempting to speculate that children have more general induced power and overall induced activity decrease with age. However, our statistical analyzing methods do not support this outcome.

Furthermore, our results indicate that older participants had tendency towards lower frequency. The findings suggests that children have more variation in different frequency range, whereas in adults, the induced power seems to focus around 10 Hz especially in contralateral response (see figure 2). On the other hand, it must be noted that small variation within adults may affect the statistical analysis. In earlier studies, alpha band responses have been associated with increased information processing (J. Y. Yordanova & Kolev, 1996) and attention (Klimesch et al., 1998). The spontaneous alpha response is usually developed by the age of 3 (Basar-Eroglu et al., 1994). Also, Shanin et al. (2010) have proposed that phase-locking in different frequency bands mature in different time and reflects distinct features of sound processing. They found that higher frequencies matured later than lower frequencies. There could be, indeed, differences in developmental trends between different oscillatory frequency bands that may reflect maturation of cortical sound processing. On the other hand, we didn’t examine event-related synchronization or desynchronization of specific frequency band in this study. Based on current results, there are no accurate data to estimate information processing function relating oscillatory frequencies development.

Also, maturational changes in inter-trial phase-locking value were estimated by means of strength and timing of the maximum phase-locking. Expectedly, the phase-locking value proved to be stronger in adults than in children supporting the hypothesis about developmental differences in auditory processing. Furthermore, we found that the maximum phase-locking was earlier in adults than in young children. The same effect was shown in timing of the maximum induced power. The results are in line with previous ERP studies that have shown children having longer-lasting auditory responses than adults (Ceponiene et al., 2002; Eggermont, 1992; Mäkelä et al., 1993).

Surprisingly, we observed no statistically significant differences between the ages of 6–13 neither in strength nor timing of the maximum phase-locking. The results indicate that the general time structure of auditory responses varied remarkably across trials in children. In adults, the phase difference across trials was highly stable, which was seen as a strong phase-locking value. However, even the oldest children showed differences in inter-trial phase-locking value compared to adult group. Yordanova and Kolev (1996; 1997) have shown similar findings in alpha and theta response system between 6 to 11 year old children and adults. Also, previous AEP studies have found that the developmental time course of the auditory cortex extend into adolescence (Ponton et al., 2000). Our result suggests that even 13 year old children have immature phase-locking responses.

It has been proposed that induced activation power and inter-trial phase-locking are related to underlying differences in neural dynamics (Pfurtscheller & Lopes da Silva, 1999; Bastiaansen & Hagoort, 2003). Phase-locked evoked activity is supposed to reflect the summary of post-synaptic potentials of cortical pyramidal neurons (Bastiaansen & Hagoort, 2003), whereas induced power is thought to indicate changes in dynamic communication between and within brain structures (Pfurtscheller & Lopes da Silva, 1999). Strong induced power means that a remarkable number of neural unit are simultaneously active (Varela et al., 2001) and it may reflect the energy cost of cell assemblies. Then, the decrease of overall induced power in adults could be an index of a faster auditory information processing. On the other hand, high amplitude induced power has been assumed to reflect top-down mechanism of sensory processing (Hsiao et al., 2009; Tallon-Baudry & Bertrand, 1999). Based on this assumption, the current findings of strong induced activation power in adults may be a reflection of an effective auditory information processing and the cognitive stage of the brain. In addition, previous developmental AEP studies have indicated that age-related changes in magnitude and timing of AEP waveform are mostly result of increased myelination and synaptic efficiency (Eggermont, 1992; Wunderlich et al., 2006). Also, maturation of the grey and the white matter volume is thought to affecting auditory processing efficiency and speed (Gogtay et al., 2004; Ruhnau, Herrmann, Maess, & Schroger, 2011). The age-related induced activation changes observed in this paper may be a result from the structural maturation of the brain and neural coding organization at the cellular level. It has also been assumed that synaptic pruning of synaptogenesis may be related to changes in the oscillatory phase-locking (Shahin et al., 2010). Pruned synapses in neural network are supposed to fire more synchronously increasing neural efficiency, which can be seen in strong phase-locking in adults.

Differences between contralateral and ipsilateral processing

The results of the current study imply that there are contralateral preference in rhythmic auditory processing in both children and adults. We found, first, that contralateral stimulation evoked stronger induced power response than ipsilateral stimulation in adults group in both hemispheres. Second, induced power showed earlier response for contralateral ear stimulation in all ages compared to ipsilateral stimulation. However, this was seen only in the right hemisphere. Third, lower frequency responses were produced by contralateral stimulation in all age group, but only in the right hemisphere. Fourth, phase-locking value appears to be stronger for contralateral stimulation than in ipsilateral one in both hemispheres and in all ages.

In line with previous ERP findings (Jäncke et al., 2002; Mäkelä et al., 1993; Pantev et al., 1998), the contralateral dominance was shown clearly in our study. Mäenpää (2013) has also reported similar results concerning AEP activation in children between aged 6 and 13 years. The reason of this effect is the anatomical structure of the auditory pathway (Pantev et al., 1998). In the current study, the contralateral dominance was shown in earlier induced activation responses, lower frequencies and stronger inter-trial phase-locking in all age groups compared to ipsilateral responses. To our knowledge, this is the first study investigating contra- and ipsilateral oscillatory responses in children. The findings suggest that the contralateral preference has developed in children at least the age of 6. Though, the amplitude of contralateral induced activation was stronger than ipsilateral induced activation only in adults groups. This may imply that oscillatory response measured by strength of the maximum induced power is immature in children even in 13 years old. On the other hand, it has been proposed that monoaurally presented stimuli might be transmitted with higher efficiency to the contralateral auditory cortex than the binaurally presented information (Jäncke et al., 2002). Therefore, further investigation with binaural stimulation is needed.

Contralateral dominance was observed only in the right hemisphere measured by timing and frequency of the maximum induced power. The results indicate that there could be some functional asymmetry between hemispheric auditory processing. In addition, current data suggest that the right hemispheres may advance the cortical development. Induced activation time decreased quite linear with age in right hemisphere, whereas time variation between age groups was more mutable in the left hemisphere (see figure 4). Also, there were differences in frequency responses between two hemispheres (see figure 5). In other words, more adult-like response type were observed in the right hemisphere than in the left one. However, earlier studies have shown controversial evidence from maturational changes between the left and the right hemispheres. Pang et al. (1998) observed the syllables related mismatch negativity in 8 mount old infants only over the left temporal side, and concluded that the left hemisphere may lead the maturation. When studying alpha desynchronization in children aged 4 to 6 years, Fujioka and Ross (2008) showed longer-lasting and larger ERD in the left auditory cortex. However, Gasser et al. (1988) found no hemispheric asymmetry across age in the topographic distribution while studying resting oscillatory activity. On the other hand, previous ERP studies have found more mature response in the right hemisphere (Kotecha et al., 2009; Parviainen et al., 2011), which may support the suggestion the faster development of the right hemisphere. In present study, the stimuli were presented alternately to the right and the left ear. Because of this, the asymmetry of the left and the right auditory processing cannot be explained only by contralateral versus ipsilateral stimulation. Instead, our results may well express developmental differences between the hemispheres.

Interestingly, the hemispheric asymmetries in timing and frequency of the maximum induced power were observed in all age groups, both 6 year old children to adults. In adults, it has also been reported that auditory evoked responses, such as the 40-Hz steady state response or the N_1 component, are stronger in the right auditory cortex compared to the left one (Ross, Herdman, & Pantev, 2005; Shaw, Hämäläinen, & Gutschalk, 2013). Also, recent MEG study has found that phase-locking value of alpha and theta activities showed larger in the right hemisphere than in the left hemisphere (Hsiao et al., 2009). It has been suggested that due the underlying anatomy, sensory processing of sound information is right-lateralized (Ross et al., 2005). Right-hemispheric dominance can be seen in the development of hemispheric specialization. Clearly, further study to test this assumption is necessary as no other developmental data displaying lateralization of event-related induced oscillatory activity are presently available.

Evaluation of the study

There are a few limitations in this study. First, the size of the data in each age group was quite small. This might affect the reliability of the statistical test results. With larger sample size, there could be more statistically significant results. Also, there are quite many outliers in the present data, which can also affect the results. However, the sample size is comparable to earlier developmental auditory rhythmic studies. Second, the age range between children groups could be too minor compared to adults. Now, we investigated children between 6 to 13 years old. In the future, it would be interesting to broad age rage also to infants and adolescents and investigate more precise developmental course from young children to old age. For example, alpha frequency component in the evoked auditory response do not have development children under 3 years old (Basar-Eroglu et al., 1994), which may reflect the induced activation and inter-trial phase-locking. Moreover, our data showed contralateral preference even in 6 years old children. Including younger children to the data, it could be possible to investigate when the preference of contralateral ear stimulation is emerged.

In current study, we chose only one MEG channel from both hemispheres for closer examination. However, event-related induced activity may not be seen as systematically in one MEG channel compared to the phase-locking value. In addition, induced activation is not necessarily so strongly lateralized and therefore the possible hemispheric asymmetry found in one auditory MEG channel could be obscure. Further work to test the maturation of interhemispheric induced activation on a larger scale is needed.

Another limitation could be related to the data analysis used in this study. Our statistical analysis were based on the maximal induced activation power calculated from time-frequency representations. Previous studies have observed children having more non-phase-locked induced activity and it is suggested to appear more randomly than those of adults (Müller et al., 2009; J. Y. Yordanova & Kolev, 1996; 1997). However, it is difficult to estimate the overall induced activation by measuring only the maximum power. As discussed earlier, the measured strength of the maximum induced power may influenced by the narrow time variation in adults. Another methodological limitation may relate to calculating the induced activation power. In current paper, wavelet is first computed to each trial and then average TFR over trials is determined. By using this method, also the strong phase-locking value affects the final results. Further work is needed to separate non-phase-locked induced oscillation and phase-locked evoked oscillation more accuracy from each other.

Conclusions

Taken together, the present study shows that event-related auditory induced activation power undergoes thorough maturational changes from childhood to adulthood. We observed stronger induced power and earlier latencies in adults compared to children. Also, phase-locking value was stronger in adults than in children and earlier in older subjects. The differences in phase-locking values observed in children between the age of 6 and 13 years and adults imply that the maturation of auditory oscillatory system is not totally complete at the age of 13. Our findings indicate that stimulus induced activity is functionally involved in auditory perception and age-related changes may reflect development of the underlying cerebral mechanism. Moreover, the results revealed the contralateral preferences in adults as well as in children age of 6 years and older. There are also indication of lateralization on event-related oscillatory activity both children and adults. The current exploratory study provides a basis for further examination. Indeed, it appears that different induced activation power components maturates in different time and reflect developmental trajectories in the auditory cortex. However, more research is needed to investigate the relations of these different maturational mechanisms.

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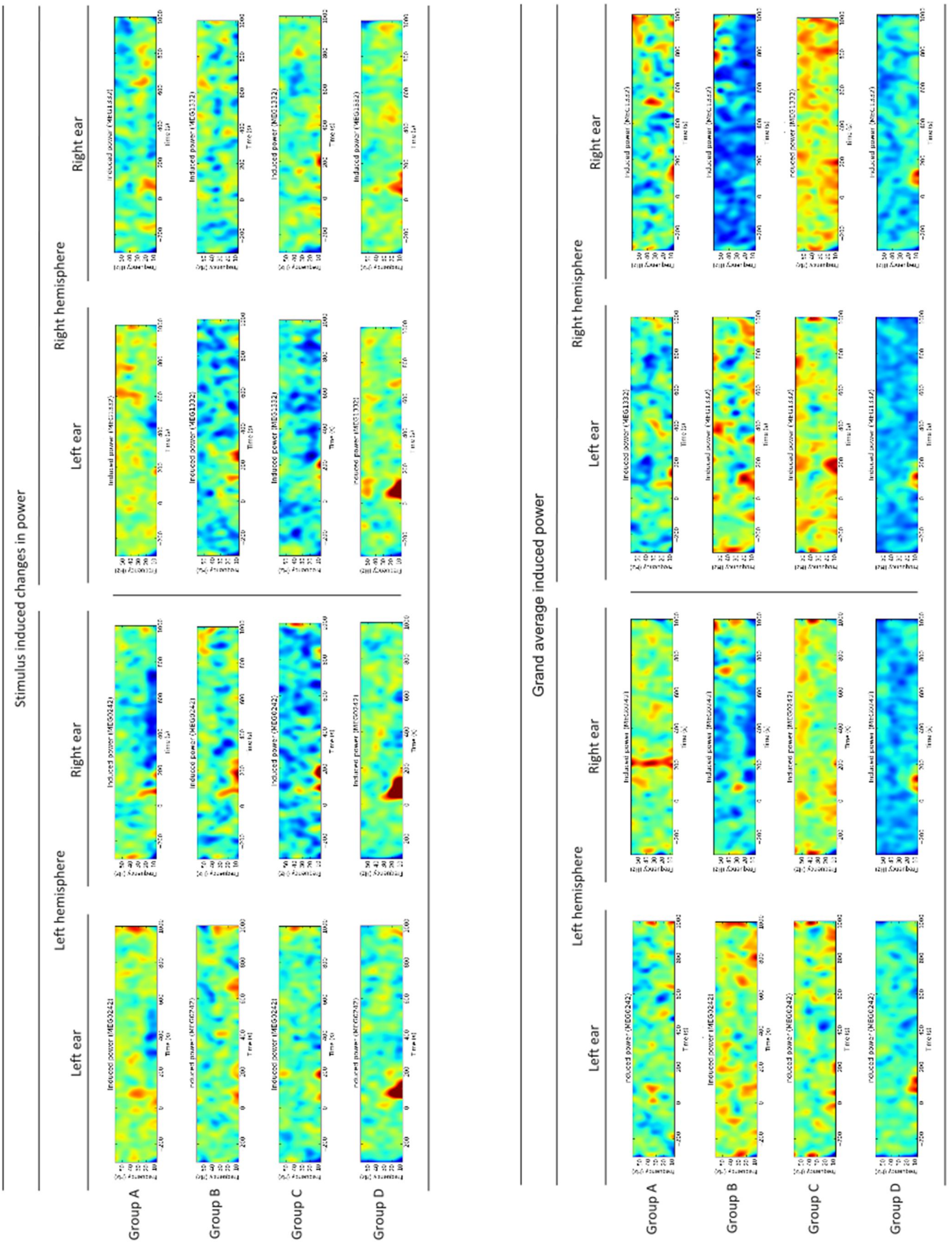
APPENDIX 1

TFR of stimulus induced changes in power for individual frequency bands in subjects from different age groups and grand average induced power in different age groups



APPENDIX 2

TFR of phase-locking between trials for individual frequency bands in subject from different age groups and grand average phase-locking value in different age groups