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Sam van Bijnen

Functional Significance of Auditory Cortex Activation for Cognitive Skills in Children

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF EDUCATION AND
PSYCHOLOGY

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ABSTRACT

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Children and adults show marked differences in their neural processing of auditory information. Most notably, children show a robust, prolonged activation pattern at ~250 ms after auditory stimulation, as measured by electro- and magnetoencephalography (M/EEG). Furthermore, auditory processing during development is crucial in enabling essential skills such as reading, writing, and language learning. Recently, this list of skills that rely on the proper development of the auditory cortex has been extended to include more general cognitive skills such as executive functioning and attention. The current literature has related auditory processes in children, especially in the left hemisphere, to performance on language-related tasks, but the extent of the functional significance of a developing auditory system remains elusive. This dissertation aims to (i) provide a comprehensive account of the functional significance of the prolonged activation pattern in children and (ii) examine the associations between auditory activation and performance on language, attention, and inhibition tasks in children and adults. In study I, source analysis of the activation pattern at ~250 ms showed stronger responses in children with delayed language development compared to typical controls. However, in the clinical group, the left hemisphere activation strength correlated positively with performance on a phonological processing task. Study II investigated the association between auditory activation and attention and inhibition tasks in typical developing children and found that, while the activation strength was unaffected by the task demands, stronger left hemisphere activation was associated with a superior performance on certain inhibition tasks. Finally, study III contrasted the auditory activation patterns of children and adults and investigated their functional significance for response inhibition. We found divergent associations between auditory activation and inhibition task performance in children and adults. Together, the results suggest a functional difference in the auditory processing of adults and children: children seem to rely more strongly on auditory cortical activation until more automatized auditory processing is established in adulthood, which seems especially important for competent language development and inhibitory control.

Keywords: Development, magnetoencephalography (MEG),
electroencephalography (EEG), language, auditory processing, cognition,
response inhibition

TIIVISTELMÄ (ABSTRACT IN FINNISH)

van Bijnen, Sam
Kuuloaivokuoren aktivaation toiminnallinen merkitys lapsen kognitiivisille taidoille
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Lapsilla ja aikuisilla on huomattavia eroja aivojen kuuloinformaation käsittelyssä. Lasten aivoissa nähdään erityinen pitkäkestoinen aivovaste ~250 ms kuuloärsykkeen esittämisen jälkeen elektroenkefalografialla ja magnetoenkefalografialla (M/EEG) mitattuna. Kuulotiedon käsittelyn kehitys on lisäksi merkittävässä roolissa monien taitojen, kuten lukemisen, kirjoittamisen ja kielen oppimisen kannalta. Kuuloaivokuoren kehitys on viime aikoina yhdistetty myös laajemmin kognitiiviseen kehitykseen, mm. toiminnanohjaukseen ja tarkkaavuuteen. Tämänhetkisen tutkimuskirjallisuus osoittaa, että kuulotiedon käsittely erityisesti vasemmalla kuuloaivokuorella on yhteydessä suoriutumiseen kielellisissä tehtävissä, mutta kehittyvän kuulojärjestelmän merkitys laajemmin on epäselvää. Tämän väitöskirjan tavoitteena on (i) selvittää lasten pitkäkestoisen aivoaktivaation toiminnallinen merkitys ja (ii) tutkia kuulotiedon käsittelyn yhteyttä kognitiiviseen suoriutumiseen kielellisissä, tarkkaavuus- ja inhibitiotehtävissä lapsilla ja aikuisilla. Ensimmäisessä osatutkimuksessa aktivaation lähdemallinnus osoitti voimakkaampia vasteita lapsilla, joilla oli viivästynyt kielen kehitys verrattuna kontrolleihin. Tässä kliinisessä ryhmässä vasemman aivopuoliskon aktivaation voimakkuus oli kuitenkin positiivisesti yhteydessä kognitiiviseen suorituskykyyn fonologisen tiedonkäsittelyn tehtävässä. Toisessa osatutkimuksessa selvitettiin kuuloaktivaation yhteyttä tarkkaavuuteen ja inhibitioon tyypillisesti kehittyvillä lapsilla ja havaittiin, että vaikka tehtävän vaatimukset eivät vaikuttaneet aktivaation voimakkuuteen, voimakkaampi aktivaatio vasemmassa aivopuoliskossa oli yhteydessä parempaan suorituskykyyn inhibitiotehtävässä. Kolmannessa osatutkimuksessa verrattiin lasten ja aikuisten kuuloaktivaatiota ja tutkittiin sen toiminnallista merkitystä reaktioinhibitiolle. Kuuloaktivaation yhteys suoriutumiseen reaktioinhibitio-tehtävässä oli lapsilla ja aikuisilla erilainen. Yhdessä nämä tulokset viittaavat toiminnalliseen eroon aikuisten ja lasten kuulotiedon käsittelyssä; lapsen aivot näyttävät nojaavan voimakkaammin kuuloaivokuoren aktivaatioon, kunnes aikuisikään mennessä on muodostunut automatisoituneempi kuulon prosessointiketju. Tällä kuuloaivokuoren aktivaatiolla näyttää olevan tärkeä rooli kielen ja inhibitorisen kontrollin kehityksen kannalta.

Avainsanat: Kehitys, magnetoenkefalografia (MEG), elektroenkefalografia (EEG), kieli, auditorinen prosessointi, kognitio, reaktioinhibitio

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LIST OF ORIGINAL PUBLICATIONS

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Considering the instructions given and the comments made by the co-authors, the author of this thesis contributed to the original publications as follows: designing the experiments (Study II & III), collecting the M/EEG data (Study II & III), analyzing the data, and writing the manuscripts (Study I, II & III).

FIGURES

FIGURE 1 Age distribution of the children in Study II & III 22
FIGURE 2 Experimental design and procedure of studies II & III. 25
FIGURE 3 Butterfly plot of signals recorded by gradiometer sensors to left and right ear stimulation of one participant (top). ECD's were selected in the time-window of interest (window). The bottom figure shows the typical field distribution and dipole orientation (arrows). 28
FIGURE 4 Dipole x and y coordinates in axial plane of each participant (thin lines) in SLI (grey) and TD group (black) as well as their averages (thick lines)..32
FIGURE 5 Grand average time-course of activation of the dipolar sources in the left and right hemisphere plotted separately for contralateral (thick lines) and ipsilateral (thin lines) responses for SLI (grey) and TD (black) group..33
FIGURE 6 Individual (top) and averaged (bottom) strength of activation in the left hemisphere (LH; left) and right hemisphere (RH; middle) in response to ipsi- and contralateral auditory stimulation of children with SLI (grey) and typical language development (black). Hemispheric differences (right) are plotted as the difference in activation strength to contralateral stimulation (i.e., right ear for left hemisphere and vice versa). Whiskers in the bottom figures represent the standard error of the mean (SEM). 34
FIGURE 7 Scatterplot representing the correlation between phonological processing (raw score) and N250m amplitude in the left hemisphere, to contralateral stimulation, for the SLI (grey) and TD (black) group...35
FIGURE 8 Scatterplots of the responses at ~250ms to the No-go tone and intraindividual coefficient of variability (ICV; left), stop-signal reaction time (SSRT; middle) and response accuracy (right)............37
FIGURE 9 Source waveforms in the left and right transverse temporal gyrus for the PL (top) and GN (middle) deviant tones. Top and middle graphs show individual waveforms (gray) and the grand average waveform (red). Bottom graph shows the grand average waveforms of the PL (solid line) and GN (dotted line) and their standard deviation (red shaded area). Child-activity pattern starting at ~200 ms highlighted in gray shaded area. 38
FIGURE 10 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). 39
FIGURE 11 Grand average 3D visualization of the No-go (deviant tone) M/EEG combined source estimates for all children (right) and

adults (left). 3D-plots presented for the two most prominent time-windows of activation in children (120ms and 248ms) and adults (110ms and 216ms). 40

TABLES

TABLE 1 Fixed effects of the model: estimate (standard error(s.e.)), degrees of freedom, t-value, and p-value...34
TABLE 2 Forward selection multiple linear regression analysis using hemisphere, task, age, sex, and behavioral performance as predictors of the brain responses at ~250ms....................................36
TABLE 3 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 (NG) tone as the predictors. 37
TABLE 4 Partial (correcting for age in children only) correlation between the P1-N1-P2-N250 amplitudes of the passive listening (PL) and Go/No-go (GN) tasks in the left (L) and right (R) hemisphere and behavioral measures. Significant correlations marked in bold. 41

CONTENTS

ABSTRACT
TIIVISTELMÄ (ABSTRACT IN FINNISH)
ACKNOWLEDGEMENTS
LIST OF ORIGINAL PUBLICATIONS
FIGURES AND TABLES
CONTENTS

1 INTRODUCTION 13
  1.1 Auditory development and cognition 14
  1.2 Development of auditory perception 14
    1.2.1 Human auditory system 15
    1.2.2 Development of late auditory evoked brain responses 15
  1.3 Functional significance of (developing) auditory evoked brain responses 16
    1.3.1 Language 17
    1.3.2 Attention & Response Inhibition 18
  1.4 Methodological considerations 18
    1.4.1 Spatio-temporal characteristics of child auditory activation.. 18
    1.4.2 Hemispheric differences 19
    1.4.3 Combined M/EEG 19
  1.5 Aims of the research 20

2 METHODS 21
  2.1 Participants 21
  2.2 Cognitive assessment 22
  2.3 Stimuli, tasks & procedures 23
  2.4 M/EEG and MRI data acquisition 26
  2.5 M/EEG and MRI data analysis 26
  2.6 Statistical analysis 30

3 RESULTS 32
  3.1 Study I: Left hemisphere enhancement of auditory activation in language impaired children 32
  3.2 Study II: Activity level in left auditory cortex predicts behavioral performance in inhibition tasks in children 35
  3.3 Study III: Divergent associations between auditory activation and inhibition task performance in children and adults 39

4 DISCUSSION 42
  4.1 Study I: Left hemisphere enhancement of auditory activation in language impaired children 42

  - 4.2 Study II: Activity level in the left auditory cortex predicts behavioral performance in inhibition tasks in children 43
  - 4.3 Study III: Divergent associations between auditory activation and inhibition task performance in children and adults 43
  - 4.4 Functional significance of the child auditory response for language and cognitive control processing.. 44
  - 4.5 Hemispheric differences in language processing and response inhibition 47
  - 4.6 Strengths, limitations, and future directions 49

YHTEENVETO (SUMMARY)...52

REFERENCES...55

ORIGINAL PAPERS

1 INTRODUCTION

Auditory processing during critical developmental stages contributes strongly to typical language learning. Recently, this framework was extended to include its importance for the development of executive functions (Kraus et al., 2012; Kraus & White-Schwoch, 2015). Unraveling the neurobiology of auditory cognition during different developmental stages presents substantial challenges. First, auditory skills and neural plasticity have an intricate symbiotic relationship, as neural response properties throughout the auditory system have been observed to change following auditory experience (Sharma et al., 2002), which in turn drives our performance on auditory learning tasks (Strait et al., 2015; Tierney et al., 2015). Second, the developmental changes in the auditory system further add to the complexity. These developmental changes can consist of the neuroanatomical properties of the auditory system but also, and likely more importantly, the functional reorganization of the auditory cortical regions.

This dissertation aims to shed light on the importance of auditory activation in the developing brain. Of particular interest is activation, which previous studies have shown to be prominent in the child's brain but is evidently "lost" during development. This activity has been used as an indication of auditory maturation as previous studies associated stronger activity, especially in the left hemisphere, with less developed language skills. However, it is unlikely that this activity is simply an anomaly that fades with the maturation of the auditory cortex and provides no benefits for the developing brain. This dissertation focuses on contrasting the auditory activity of typical developing children, children with delayed language development, and adults in auditory-based (cognitive) tasks to illuminate the importance of activation of the basic auditory circuits for cognitive functions.

1.1 Auditory development and cognition

Auditory development utilizes naturally occurring and external forces (i.e., nature and nurture) for optimizations throughout the auditory circuitry. In turn, this interaction between genetics, (mal)adaptations, disease, and experience influences our perception of the auditory world around us. Consequently, brain development and experience-dependent plasticity are inseparable and the main drives behind developing auditory cognitive skills.

This dissertation argues that auditory brain development is grounded in two important principles: first, the automatization of auditory processing, as the brain becomes more synchronized and efficient at processing auditory information with age (Albrecht et al., 2000). Second, this lack of automatization is behaviorally relevant. Traditionally, the relevance of auditory development in humans has been studied in relation to arguably the most significant accomplishment of the developing brain: language acquisition. Other important skills include auditory or perceptual learning that underlies a variety of basic to more complicated auditory tasks (e.g., frequency discrimination and speech-in-noise). However, the beneficial effects of experience-related tuning of the auditory system do not stop at these auditory functions. Indeed, automated sound processing in the adult brain is also linked to cognitive and executive functioning skills (Kraus & White-Schwoch, 2015; Krizman et al., 2012). Similarly, in children, the benefits of music training transfer to nonauditory abilities such as attention, working memory, and response inhibition (Habibi et al., 2018; Strait et al., 2015). Importantly, this suggests that not only do the development of auditory and cognitive processes coincide, but auditory experience has an independent influence on the relevant cognitive processes.

An important question is if and how immature processing of sound in the auditory cortex is relevant for cognitive functions and how this contrasts with adult processing. Given the evident importance of auditory sensory development for cognitive skills, we have a surprisingly limited understanding of how the (developing) auditory cortex aids it.

1.2 Development of auditory perception

Studies have shown that auditory perception already begins well before birth (Hepper & Shahidullah, 1994; Lecanuet & Schaal, 1996). With continuing development after birth, the brain becomes especially attuned to perceptual, memory, and semantic functions that aid language skills and enjoyable auditory experiences such as listening to music. Importantly, neural development is the foundation of (the development of) the human auditory system, which is dependent on everyday aural experiences and communication in childhood. Auditory evoked brain responses measured with electro- and magnetoencephalography (EEG/MEG) have been successfully used to study the development of the central auditory system (Čeponienė et al., 2002; Johnstone et al., 1996; Paetau et al., 1995; Ponton et al., 2000; Ponton et al., 2002; Wunderlich & Cone-Wesson, 2006), and they have been used as a marker for central auditory pathway plasticity (Sharma et al., 2002).

1.2.1 Human auditory system

Human sound processing starts when receptor cells in the cochlea known as hair cells transduce changes in air pressure into electrical signals and transmit it to the brain. First, continued changes in air pressure caught by the external ear travel through the ear canal and vibrate the tympanum (eardrum). The auditory ossicles (malleus, incus & stapes) convey these vibrations to the cochlea. The stapes' vibrations push against the oval window and stimulates the cochlea. Because the cochlea consists of fluid-filled compartments, these vibrations create changes in fluid pressure that causes the basilar membrane to move. The transduction of the movement of the basilar membrane into electrical signals occurs in the organ of corti, the receptor organ of the inner ear. The organ of corti sits on top of the basilar membrane and contains the hair cells. The movement of the hair cells initiate the mechanoelectrical transduction.

Three main pathways relay the electrical responses to the brain for interpretation: the dorsal and intermediate acoustic stria, and the trapezoid body. The hair cells connect to axons in the cochlear component of the vestibulocochlear nerve that terminate in the dorsal and ventral cochlear nuclei at the medullo-pontine junction on the ipsilateral side. The first bilateral interactions occur via the trapezoid body, which sends its input to the ipsi- and contralateral superior olivary complex. The superior olivary nuclei, together with axons from cochlear nuclei via the contralateral dorsal acoustic stria and ipsilateral intermediate acoustic stria, project to the inferior colliculus in the midbrain via the lateral lemniscus. Each lateral lemniscus receives information from both ears but projects to the ipsilateral inferior colliculus. The lateral lemnisucus relays information to primarily the contralateral medial geniculate nucleus of the thalamus, with a secondary pathway to the ipsilateral side. Axons of the geniculate terminate in the primary auditory cortex located in the medial transverse temporal gyrus (Heschl's gyrus) within the lateral sulcus. The signals reach the cortical areas within the first 10ms after sound onset (Shvarts & Mäkelä, 2020). As the time after sound onset increases, the signal propagates from the brain stem nuclei to primary and secondary auditory areas in the lateral sulcus (sylvian fissure), planum temporale and lateral temporal cortex.

1.2.2 Development of late auditory evoked brain responses

The sequence of brain responses to auditory stimulation has originally been characterized using EEG scalp recordings as a waveform with positive and negative peaks, with the nomenclature focused on the order of the peaks (P1-N1-P2-N2) or latency (e.g., N100, N250) and a lower case "m" to indicate their MEG counterparts. The components of this waveform are divided into two categories:

exogenous (obligatory) and endogenous (cognitive). This waveform, however, is not a single phenomenon but rather the sum of temporally and spatially overlapping neural activity from various cortical sources at the selected measurement sites (Wunderlich & Cone-Wesson, 2006).

The development of auditory neural activation is best characterized by a gradual dissociation of the earlier, more transient responses (P1/N1), and an attenuation of the later (~200-300ms), prolonged, activity until it is no longer or barely present in adults (Albrecht et al., 2000; Čeponienė et al., 2002; Orekhova et al., 2013; Paetau et al., 1995; Ponton et al., 2000; Sussman et al., 2008; Takeshita et al., 2002; Wunderlich & Cone-Wesson, 2006; Yoshimura et al., 2014). The right hemisphere precedes the left hemisphere in this developmental trajectory, suggesting faster maturation of the right auditory cortex (Parviainen et al., 2019).

The development of the auditory evoked responses coincides with a substantial anatomical and functional reorganization of the auditory cortex, most notably with axonal maturation in the superficial layers (Moore & Jr, 2007). By age eleven or twelve, axon density reaches adult-like maturity, corresponding with the emergence of the N1 (Moore & Jr, 2007; Ponton & Eggermont, 2001). Maturation during this stage is argued to broaden communication between the auditory cortices as well as their cortical interaction within the same hemisphere (Moore & Jr, 2007). Interestingly, around the time this reorganization of the auditory cortex is reported to be complete, at age 12, the N250m typically starts to decrease (Čeponienė et al., 2002; Ponton et al., 2000; Takeshita et al., 2002; Wunderlich & Cone-Wesson, 2006).

The attenuation of this auditory response in the child brain suggests it is an important signature of (auditory) brain maturation. Nevertheless, it has been less intensively studied, perhaps because the N1(m) is the most dominant response in adults (Näätänen & Picton, 1987). Similarly, the P1(m) in children received more attention, possibly because it is argued to be the most dominant response in children (Orekhova et al., 2013), especially during the early years. Some have also argued the child N2(50) corresponds to the adult N2 (Čeponienė et al., 2002). However, given that the adult N2 is present only during active attentional processing and not during passive stimulation (Parviainen et al., 2006), it is more likely this reflects a child-unique neural response that is functionally meaningful for the developing brain.

1.3 Functional significance of (developing) auditory evoked brain responses

Developmental studies of human auditory processing have merely sketched the age-related changes in timing or strength of activation across the timeline of auditory activation. 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. The activity in these time-windows is mostly obligatory, which means it is dependent on the auditory properties of the stimuli and the auditory pathway's integrity. However, attention and the cognitive status of the listener can affect their latency and amplitude (Wunderlich & Cone-Wesson, 2006).

In adults, exogenous activity in the early time window is thought to reflect conscious sound detection (Näätänen & Picton, 1987) and can be affected by attention and experience (e.g., music). Interestingly, adults show a remarkable shift from exogenous to endogenous activation at around 200–250 ms after stimulation, as under passive listening circumstances this auditory cortical pattern is typically absent in adults (Sussman et al., 2008; Ruhnau et al., 2011; Takeshita et al., 2002). Instead, adults consistently show activation in this time window only in active tasks, and it has been implicated in cognitive control in the cingulate cortex (Falkenstein et al., 1999; Huster et al., 2010; Nieuwenhuis et al., 2003). Accordingly, the consensus of the timeline of auditory neural processing posits that the early transient peaks reflect stimulus-dependent processing, while the post-200-ms activation is thought to signify cognitive or evaluative aspects. In contrast, children show a robust and prolonged (obligatory) activation pattern around 250 ms after stimulation in the auditory cortex, with possible relevance for language, attention, and inhibition skills.

1.3.1 Language

The auditory system is adapted early in child development to optimally process spoken language, even without knowledge of its specific characteristics. As this relies on everyday aural experience (Gordon et al., 2003; Tierney et al., 2015), many studies have looked at auditory evoked responses and their relation to language learning and disorders.

Children’s main obligatory evoked responses (P1 and N250) diverge between speech and non-linguistic stimuli (Čeponienė et al., 2008; Hämäläinen et al., 2013), highlighting their importance for speech sound discrimination and language function. In addition, in children with language disorders like dyslexia or specific language impairment (SLI, also known as developmental language disorder, DLD), the auditory waveform is delayed, being similar to that of younger typically developing children (McArthur & Bishop, 2004). If their reading is compensated (e.g., improved through interventions), their brain responses are like those of same-aged controls (Sharma et al., 2006).

The child-unique activation pattern at ~250 ms post-stimulation has been reported to increase with stimulus repetition in typical developing children, suggesting a role in neural models of (language) learning and memory trace formation (Čeponienė et al., 2005; Karhu et al., 1997). This is consistent with recent research that has linked increased or prolonged activation in this time window, particularly in the left hemisphere, to poorer performance on language tasks (Hämäläinen et al., 2013; Parviainen et al., 2011). Together, this suggests that activation in this time window is an indicator of language or auditory development. However, given that this activation is minimal in adults and stronger activation is typically related to poorer performance, it is still unclear what the functional significance of this activation pattern in children is, both in terms of language processing and more general cognitive processing.

1.3.2 Attention & Response Inhibition

The prolonged activation pattern in children 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 inhibition (Čeponienė et al., 2002) or the ability to control attention (Johnstone et al., 1996). However, an empirical link between (the maturation of) this prolonged activity pattern and cognitive skills such as attention and response inhibition has not been established.

Response inhibition can be defined as the ability to withhold a dominant behavioral response to stimuli. It refers to ignoring certain stimuli that compete for attention and enable goal-directed behavior. The Go/No-Go task is the most widely used motor response inhibition task due to its simplicity and validity. However, depending on the performance measure (e.g., reaction time, accuracy), it likely gauges the variance of more rudimentary processes beyond purely motor response inhibition, like attention. Therefore, it is not only necessary to understand which measures improve during development but especially which measures most strongly relate to the brain responses elicited by these tasks.

1.4 Methodological considerations

Different methodological choices are likely a crucial factor in explaining existing discrepancies between studies of auditory, language and cognitive development. I discuss why comparing children and adults is more difficult than one might think, particularly in the context of auditory stimuli, and highlight the advantages of combining magneto- and electroencephalography.

1.4.1 Spatio-temporal characteristics of child auditory activation

Isolating neurophysiological signatures in the child's auditory waveform is challenging because the peaks and troughs overlap considerably in space and time. For example, the emerging N1(m) in primary school children (~6—11 years) can be difficult to detect using sensor-level analysis because the final waveform is a mixture of the preceding (P1) and next component (N250). To reliably separate and extract neural signatures that reflect distinct processes and have divergent developmental trajectories, it is necessary to include source information. When the underlying neural generators of these main components in the child waveform are modelled with equivalent current dipoles (ECDs), they reflect currents with an anterosuperior direction (P1(m)) and an inferior-posterior direction (N250(m) and N1(m)) (Yoshimura et al., 2014; Paetau et al., 1995; Ponton et al., 2000; Parviainen et al., 2011). In addition, children show hemispheric differences in the basic auditory response properties (Parviainen et al., 2019), further adding to the difficulty of drawing conclusions from these neurophysiological signatures.

1.4.2 Hemispheric differences

The auditory cortices receive input from both ears. However, contralateral input (i.e., from the opposite ear) is prioritized, as is evidenced by stronger activation in the hemisphere contralateral to the stimulated ear compared to the ipsilateral ear (Mäkelä et al., 1993; Pantev et al., 1998; Parviainen et al., 2019; Salmelin et al., 1999). The strength of auditory activation is typically lateralized in both adults and typical developing children (Johnson et al., 2013; Orekhova et al., 2012; Parviainen et al., 2019; Yoshimura et al., 2014). In general, the neurophysiological responses are stronger in the right hemisphere compared to the left hemisphere. While the importance of this hemispheric preference has been established in adults (Boemio et al., 2005), in children, hemispheric differences might be able to explain inconsistent results between studies and may provide pivotal information for understanding (a)typical development.

First, it has been proposed that abnormalities in hemispheric specialization underlie neurodevelopmental disorders (de Guibert et al., 2011; Johnson et al., 2013). Children with atypical (language) development generally show a lack of lateralization, possibly due to delayed maturation. Furthermore, the right hemisphere precedes the left in its developmental trajectory, suggesting maturation differences in the auditory cortices. Finally, in addition to functional changes to the auditory cortices, anatomical hemispheric (developmental) differences also play a role. Indeed, numerous studies have reported white and gray matter structural differences underlying neurodevelopmental disorders (Herbert et al., 2005; Jäncke et al., 2007; Lee et al., 2013). The structural development of the auditory cortex affects the strength of activation as measured by MEG and EEG, as a study reported that a more convoluted auditory cortex produces stronger cancelation effects, resulting in a lower measured EEG and MEG signal (Shaw et al., 2013).

Importantly, typical EEG-ERP analysis is unable to adequately address these concerns (spatio-temporal characteristics and hemispheric differences). Together, this emphasizes that, to expand our understanding of the neurodevelopmental aspects underlying our cognitive skills (or problems therein), we need to adopt a more comprehensive approach to analysis, incorporating both temporal and spatial characteristics of activation.

1.4.3 Combined M/EEG

MEG can easily distinguish between sources in the auditory cortex due to its high spatial and temporal resolution by decomposing the magnetic field distribution to the underlying current sources. By utilizing the components' source information, MEG can reliably compare activation in the left- and right-hemisphere auditory cortices. With its poor spatial sensitivity, EEG will have limited capacity to reveal differences between hemispheres, as electrical potentials originating in the auditory cortices summate at the vertex, generating a single maximum on the head surface (Hari & Puce, 2017). However, unlike EEG, the sensitivity of MEG decreases with increasing source depth and radial orientation (Baillet, 2017; Gross, 2019). Thus, a combination of M/EEG is uniquely suitable to extract the separate components from the time-varying activation pattern evoked by auditory stimuli and localize the underlying cortical generators.

1.5 Aims of the research

The aim of this dissertation was to reveal the functional significance of auditory activation in children. While the maturation of auditory neural responses has been the subject of numerous studies, it is unclear how and if these changes reflect behaviorally meaningful changes. Specifically, this dissertation aims to illustrate the association between the maturation of the auditory cortex and its relevance for cognitive skills such as language, inhibition, and attention.

In **Study I**, we utilized magnetoencephalography data to map the source activity variation of the N250m auditory response in children with typical and atypical language development using equivalent current dipole (ECD) models. By correlating the N250m to behavioral performance on language tasks, we investigated its functional significance for language development. We hypothesized that children with specific language impairment would have stronger N250m responses. There were no predefined hypotheses for the behavioral performance measures. Instead, they were used to analyze post-hoc correlations.

Study II employed combined electro- and magnetoencephalography (M/EEG) and individual structural magnetic resonance imaging (sMRI) to assess age differences in, and explore the behavioral significance of, the child's N250 auditory response. We investigated the source model of the (obligatory or exogenous) N250m response in typical developing children in different variations of a simple auditory oddball paradigm. We also related it to behavioral performance measures of response inhibition to explore its functional significance.

The third study looked at whether there were differences in auditory responses between typical developing children and adults, as well as whether earlier auditory responses (< 250 ms post-stimulation) in children were related to inhibitory performance. Using the same techniques as in Study II (M/EEG and sMRI), we compared the auditory responses of typical developing children to those of adults. We further assessed the brain-behavior associations of adults and children to see if children are different from adults in their associations between auditory brain responses and behavioral performance measures.

2 METHODS

2.1 Participants

Participants from Study I were part of a larger study by Helenius and colleagues (2014). Study I consisted of a clinical (SLI) group (n = 10, 3 females) and a typical developing (TD) group (n = 10, 3 females). The TD group had a mean age of 9.5 years (SD = 0.26) and the SLI group a mean age of 9.6 years (SD = 0.56). Participants in this study were recruited through a larger study aiming to highlight the etiology, linguistic development, and prognosis of SLI in the City of Vantaa, Finland (Hannus et al., 2013; Isoaho, 2012). The children in the SLI group had been diagnosed at the Helsinki University Central Hospital prior to school entry. Participants were native Finnish speakers, with one child in the SLI group having a bilingual background. An informed consent was obtained from all subjects and/or their legal guardians, in agreement with the prior approval of the Helsinki and Uusimaa Ethics Committee at the Helsinki University Hospital. The experiments were approved by the Helsinki and Uusimaa Ethics committee and the methods were conducted in accordance with guidelines and regulations.

Study II consisted of school-aged (7 years in Finland) children (6–14 years). Study III contained the same children but also included sixteen adults. Figure 1 depicts the age distribution of the children in Studies II and III. Participants were recruited through schools and the National Registry of Finland and were screened for neurological disorders and medication affecting the central nervous system. While 78 children participated in Studies II and III, eleven were excluded for varying reasons: one did not finish the experiment, one had too many errors in the MEG task (> 50% errors in at least one block, see Fig. 1), five had excessive head movements or magnetic interference during MEG/MRI measurements, two objected to going in the MRI scanner, and two showed structural abnormalities in their MRI. The data included in this study consisted of sixty-seven children (mean age 10.2 years, SD: 1.4, range: 6–14, 36 boys, 31 girls). Children were recruited to cover mainly the ages between 8 and 12 years, as previous studies indicated this age range is an important developmental period for our activation pattern of interest. All participants had normal hearing as assessed with an audiometer. Studies II & III were approved by the Ethics Committee of the University of Jyväskylä. In accordance with the Helsinki Declaration, all children, their parents, and adults provided informed consent.

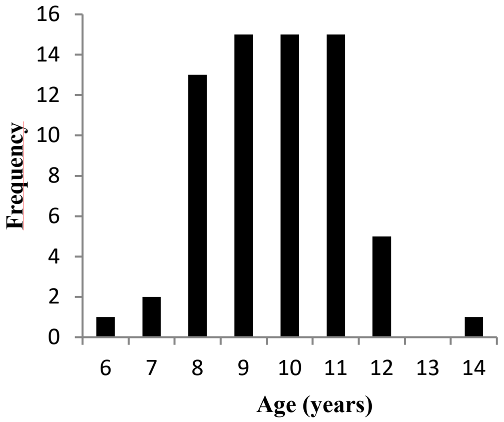


FIGURE 1 Age distribution of the children in Study II & III

2.2 Cognitive assessment

In Study I, subjects were tested on a concise neuropsychological test battery tapping non-linguistic reasoning (block design), vocabulary, verbal short-term memory, and reading-related skills. The main purpose of the behavioral testing was to provide cognitive profiles for both groups, not to diagnose SLI, as the SLI subjects had been diagnosed earlier. In the block design test, the subject is required to copy a pattern from a figure using colored blocks to assess their ability to understand complex visual information. Verbal short-term memory was assessed using the digit span forward subtest (Wechsler, 1991), the sentence repetition tests (Korkman et al., 1997), and phonological encoding and decoding with the pseudoword repetition test (NEPSY). In these tests, the subjects must repeat a sequence of numbers, pseudowords, or complete sentences. A measure of oral reading speed was obtained from the silent reading of sentences (Lindeman, 1998) and reading aloud a narrative passage (the number of words read in 1 minute). The sentence reading test (ALLU; Lindeman, 1998) consists of twenty trials composed of a picture that matches one of the four written sentences. The task is to identify as many correct picture-sentence pairs as possible in 2 min and the total score is the number of correctly identified sentences. Naming speed was estimated as the time to name color squares, digits (RAN; Denckla & Rudel, 1976) or color squares, letters, and digits in a 5 × 10 matrix43 (RAS; Wolf, 1986).

Phonemic awareness was assessed using the phonological processing subtest of NEPSY (Korkman et al., 1997).

For Studies II and III, the behavioral tests included subtests of the Wechsler Intelligence Scales for Children, Third Edition (Wechsler, 1991) 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 (SyS) 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, the participant is 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 sixteen trials for the participant to practice. 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 and narrowing in on the 50% success rate for inhibition. The test produces a Stop-Signal Reaction Time (SSRT), which refers to the duration of inhibiting an initiated response.

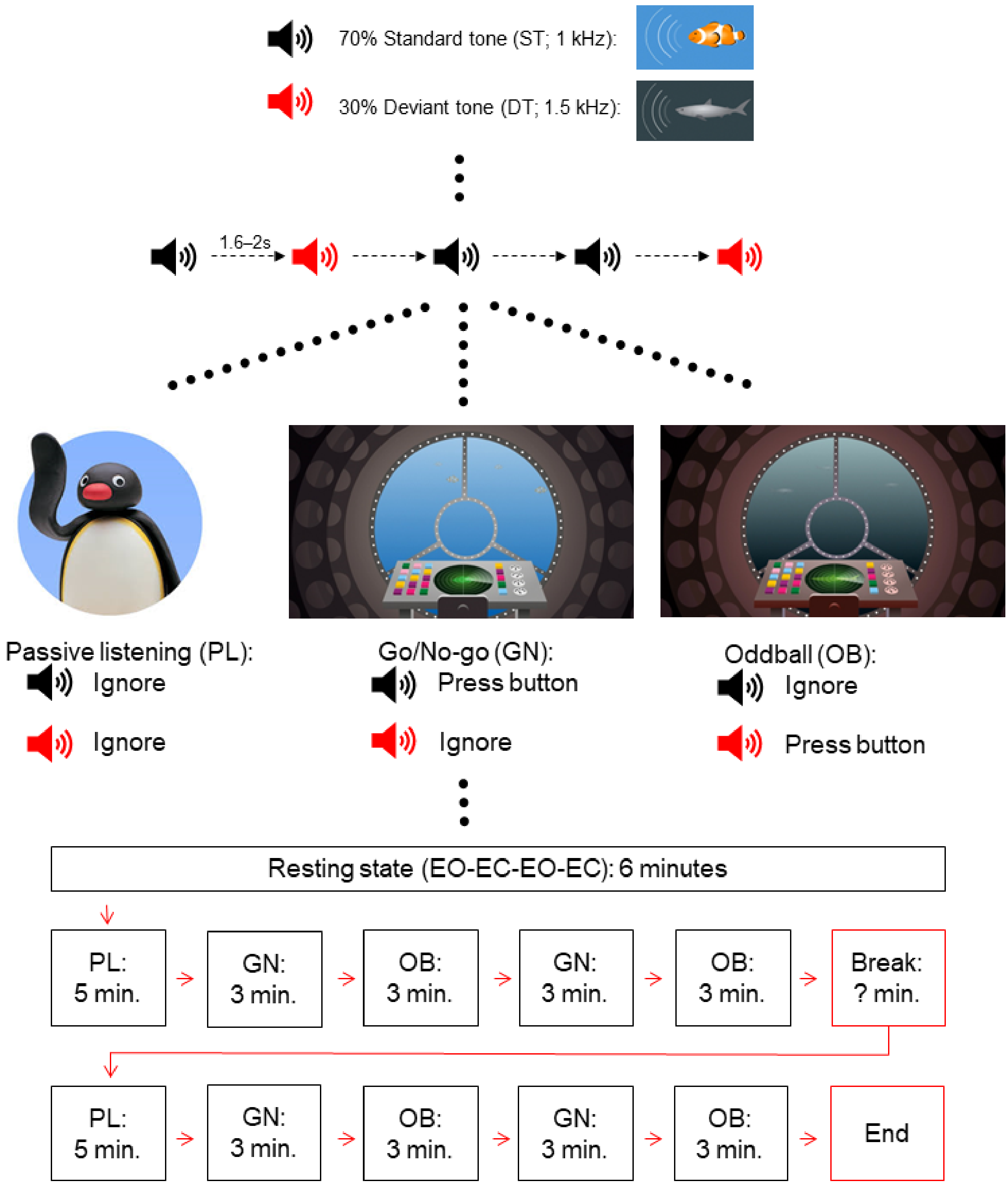
2.3 Stimuli, tasks & procedures

Participants in Study I completed a passive listening task where the stimulus consisted of a 1-kHz tone with a 50-ms duration (15-ms rise/fall time), which was presented monaurally alternating between the left and right ear. The inter-stimulus interval (ISI) varied randomly between 0.8 and 1.2s. Stimuli were controlled by the Presentation program (Neurobehavioral Systems Inc., San Francisco, CA, USA) running on a PC and delivered to the subject through plastic tubes and earpieces. The children were asked to ignore the tones, and they watched a silent cartoon during the whole recording.

In Studies II and III, participants completed variations of a simple auditory oddball paradigm (for a schematic overview of the procedure, see Figure 2). Auditory stimuli consisted of a 70-ms (10–ms rise/fall time) tone with a frequency of either 1.0 kHz (standard tone (ST); 70%) or 1.5 kHz (deviant tone (DT); 30%) at 65 dB SPL and were created with the Audacity software® (version

2.3.3) (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 indicate ST (GN), and press the button to indicate DT (OB). The number of stimuli was different in the PL task compared to the GN and OB: 150 stimuli per block vs. 90 stimuli per block, respectively (Figure 2). 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 2). 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 (version 3.2) (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 high-fidelity sound system.

Studies II and III were conducted in a child-friendly environment in which the participants were asked to help science by studying the clownfish population. We measured resting-state activity with 2x1.5 minutes of eyes open (EO) and eyes closed (EC) prior to the tasks. 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 looked 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 (Fig. 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 STs. Participants were also instructed to look in the middle of the window (Fig. 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 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 and 63 ST), were completed alternately before the break. During the break, we offered participants a snack and drink and the 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 2.



	#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 2 Experimental design and procedure of studies II & III.

2.4 M/EEG and MRI data acquisition

In Study I, the child and one accompanying adult were seated in a magnetically shielded room and instructed to avoid excessive head movements. The auditory cortical responses were recorded using a 306-channel whole-head system (Vectorview™, Elekta Neuromag Oy, Helsinki, Finland). This system measures magnetic field strength at 102 locations over the scalp, with two orthogonally oriented planar gradiometers and one magnetometer at each location. Prior to the measurement, four head-position indicator (HPI) coils were attached to the participant's scalp. HPI coils were digitized with a 3-D digitizer to determine their location in relation to three anatomical landmarks: the preauricular points and the nasion. At the start of the measurement, the HPI coil's location with respect to the MEG helmet was measured. Finally, eye blinks and movements were monitored by placing electro-oculogram (EOG) electrodes directly below and above the right eye and on the outer canthi of each eye.

In Studies II and III The brain responses were recorded using a 306-channel MEG system and the integrated EEG system (Elekta Neuromag® TRIUXTM, 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 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 (the 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 of 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 = 90°, matrix size = 256 × 256, slice thickness = 1.2 mm, sagittal orientation.

2.5 M/EEG and MRI data analysis

In Study I, the MEG signals were bandpass filtered at 0.1–200 Hz and sampled at 600 Hz. The raw data were processed using the spatio-temporal signal space separation method (Taulu & Simola, 2006). Offline, responses were averaged between -0.2 and 0.8 s after stimulus onset. Epochs contaminated by vertical or horizontal eye movements were rejected. To minimize the effect of heartbeat artifacts, the MEG signals were offline averaged with respect to the heart signal, and principal component analysis was used over this average to project out the resulting magnetic field component (Uusitalo & Ilmoniemi, 1997). Finally, the data were manually checked to exclude epochs with major artifacts. On average, 107 artifact-free averages were collected in the TD group and 111 in the SLI group.

The active source areas were modeled from the averaged data using equivalent current dipoles (ECD; Hämäläinen et al., 1993). Averages were filtered with a 40 Hz lowpass filter and baseline corrected (-0.2 to 0 s). Xfit software was used to estimate the localization of the current sources (Elekta, Oy, Helsinki, Finland). In each subject, the same 20 planar sensor pairs were selected in each hemisphere that best covered the dipolar field pattern. To identify the cortical response around 250 ms after auditory stimulation, ECDs were accepted when (i) they were within the time window of interest (175–325 ms), (ii) they had a goodness-of-fit value of >80%, and (iii) they had an inferior-posterior direction. Figure 3 depicts the activity of interest and the typical field distribution and dipole orientation (inferior-posterior). These criteria were based on the pattern of activation that is most reliably repeatable for this specific time window. ECD locations and orientations were fixed, while their amplitudes were allowed to vary. In each subject, the magnetic field patterns were visually inspected to identify local dipolar fields in each stimulus condition (i.e., ear and hemisphere). From the four resulting ECDs, one was chosen in each hemisphere to best fit the data under all conditions. As individual MR images of the subjects were not available, a spherical volume conductor model was used, with the default center defined as the origin (0, 0, 40). Dipole moment amplitudes were defined as the average of the peak (175ms–325ms). Data points around the peak were included if they exceeded two standard deviations above the mean activation of the whole epoch.

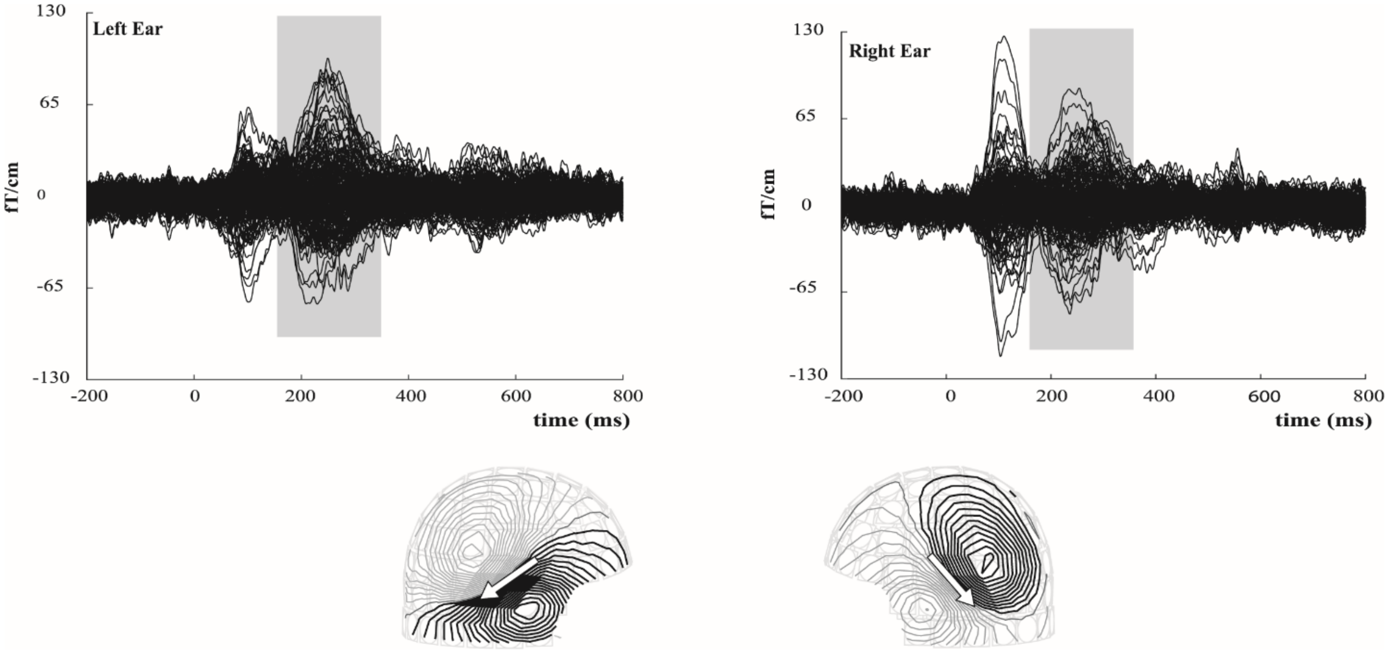


FIGURE 3 Butterfly plot of signals recorded by gradiometer sensors to left and right ear stimulation of one participant (top). ECD's were selected in the time-window of interest (window). The bottom figure shows the typical field distribution and dipole orientation (arrows).

In Studies II and III, MEG data were first processed with the temporal signal space separation (tSSS) and movement compensation options, implemented in the MaxFilterTM program (version 3.0; MEGIN Oy, Helsinki, Finland), to suppress external interference and compensate for head movements (Taulu & 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 0.16; Gramfort et al., 2014; Gramfort et al., 2013). Continuous M/EEG recordings were low-pass filtered with a finite-impulse-response filter at 40 Hz, the EEG data were 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 0 s) offset. Epochs were rejected for incorrect responses and large MEG signals (> 4 pT/cm for gradiometers and > 5 pT for magnetometers). Independent component analysis (ICA) was applied to suppress ocular and cardiac artifacts separately for MEG and EEG (Hyvärinen & Oja, 2000). Next, autoreject, an automatic data-driven algorithm, was used on the EEG data to repair or exclude bad epochs. We followed the 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., 1999a; Fischl et al., 1999b). 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. The conductivity values used for the intracranial tissue (brain, CSF), skull, and scalp were set to 0.33, 0.0132, and 0.33 S/m for children (Studies II and III) and 0.3, 0.006, and 0.3 for adults (Study III). The noise covariance matrix was calculated from the individual epochs 200-ms pre-stimulus baseline, using a cross-validation method implemented in MNE. 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 & Gramfort, 2015).

The source currents were examined using a cortically-constrained, depth-weighted ($p = 0.8$) L2 minimum norm estimate (Hämäläinen & 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 ROI label 30 (transverse temporal gyrus) as defined by the Desikan-Killiany Atlas

(Desikan et al., 2006). Amplitude values of the prolonged activity were calculated as an average over the 200–325 ms time window after stimulus presentation, which was determined by visual inspection of the grand averages. For the N250, only negative averages were included in the statistical analysis, as we assumed positive values would reflect cortical activity unrelated to our response of interest.

2.6 Statistical analysis

The data from Study I were analyzed using R (R Core Team, 2013) and the packages lme4 and pbkrtest (Bates et al., 2015; Halekoh & Højsgaard, 2014). The amplitude values of each factor: ear (2) and hemi (2) were extracted for each participant in each group (2), resulting in four amplitude values for each participant. We assessed the effect of impaired language development on auditory evoked source activity with a linear mixed model or, more specifically, a random intercept model (Brown & Prescott, 2015; Hox, 2017). In the estimation of the best model for the covariance structure (compound symmetry), we used a backward method with the maximum likelihood (ML) approach. The significance test to be used was the chi^2-test based on the likelihood ratio test (LRT) backward selection heuristic of two nested models to compare the models. In the diagnostics part of the model, we first confirmed the normality of residuals to be valid using a qq-plot and a scatter plot for groups. We also used a qq-plot to determine the normality of random intercepts. Using the final model, we defined contrasts for separate sets of regression coefficients. For testing if the contrast is zero, we used the Kenward-Roger (KR) approximation for the F-test by Halekoh and Højsgaard (2014). We obtained the numerator d = 1 from the KRmodcomp contrast calculations. For simplicity, the F statistic is the squared t statistic, and contrasts are reported using t-statistics, dfs, and p-values. In the first and most inclusive model, we had all variables (group, ear, and hemi), their pairwise interactions, and a three-way interaction.

In study II, we analyzed the child's auditory response at 250 ms (N250m) and the effects of age, sex, hemisphere, task (active/passive), and behavioral performance with a forward multiple linear regression model. 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 the square root of error %) from tasks completed inside the scanner, and the stop-signal reaction time (SSRT). Partial correlations (controlling for age) were calculated for behavioral performance measures and the 2×2 (hemi x task) auditory brain responses. Subsequently, 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. We reported our original p-values for all comparisons that we made but used an alpha of $< .01$ to limit the false positives. All statistical analyses were performed using SPSS Statistics 25.

In Study III, we compared the earlier (pre 250 ms) auditory responses of children and adults (same as in Study II). Based on Study II, we concentrated the analysis on the passive vs Go/No-go comparison (deviant tones). Auditory responses (P1-N1-P2) were analyzed separately; models contained one of the brain responses (P1, N1, or P2) as a dependent variable at a time. Two within-subject independent variables (hemisphere (left, right) and task (passive, no-go)) and one between-subject variable (group; children vs. adults) were included in the model. Models were estimated by using multigroup analysis with the Mplus statistical package (version 8.4) and a full information maximum likelihood (FIML) estimation method with robust standard errors (MLR). All available data were used in the analyses, and missing data were assumed to be missing at random (MAR) (Muthén & Muthén, 2012). Interactions and main effects were estimated by using additional parameters in the model.

3 RESULTS

3.1 Study I: Left hemisphere enhancement of auditory activation in language impaired children

Figure 4 shows the location of the selected dipoles (x, y coordinates in the axial plane) of each individual and the grand average location of the two groups. Figure 5 depicts the resulting grand average waveforms. There were no significant differences between the groups on any of the (x, y, z) coordinates ($p \geq 0.28$)

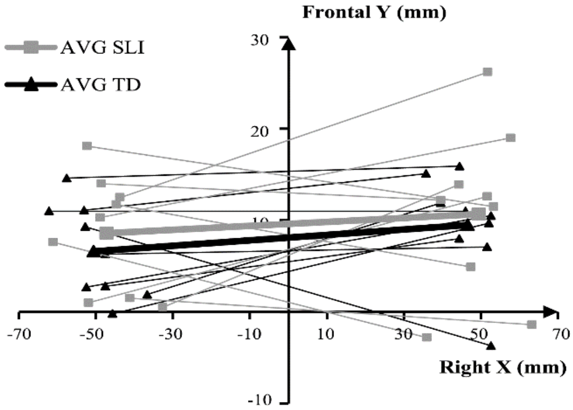


FIGURE 4 Dipole x and y coordinates in axial plane of each participant (thin lines) in SLI (grey) and TD group (black) as well as their averages (thick lines).

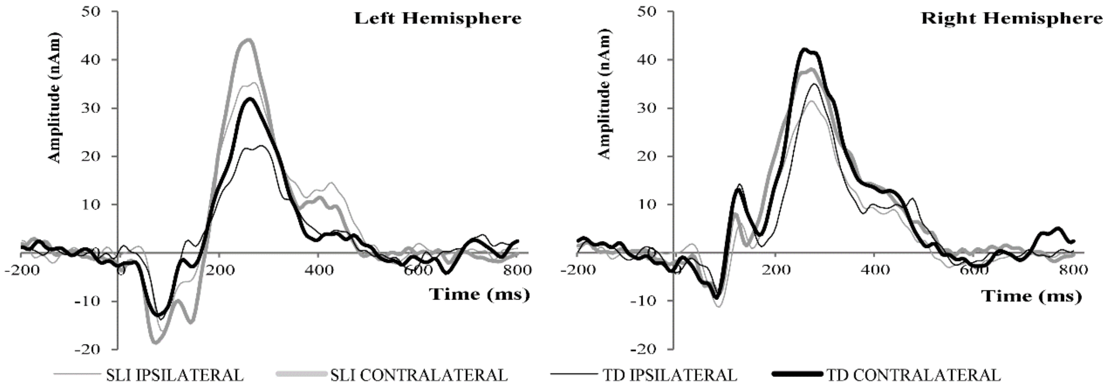


FIGURE 5 Grand average time-course of activation of the dipolar sources in the left and right hemisphere plotted separately for contralateral (thick lines) and ipsilateral (thin lines) responses for SLI (grey) and TD (black) group.

In this study, we found a significant interaction between group x hemisphere (t(50) = 2.648, p = 0.011 (Table 1); SLI was associated with stronger dipole moment amplitudes at ~**250ms** in the left hemisphere exclusively, as the estimated difference (ED) between groups (ED = −12.74, SE = 5.52) was significant in this hemisphere for both the ipsi- and contralateral stimulation condition, t(24.70) = 2.306, p = 0.03. In contrast, the difference between groups in the right hemisphere was negligible (ED = 0.45, SE = 5.52, t(24.70) = 0.082, p = 0.935). Consequently, the SLI group showed no significant difference in strength of dipole moment amplitude between the left- and right hemisphere (ED = −4.84, SE = 3.52, t(50) = −1.374, p = 0.176). In contrast, typical developing children show a significant cortical asymmetry pattern with stronger amplitudes in the right compared to the left hemisphere (ED = 8.35, SE = 3.52, t(50) = 2.370, p = 0.022) (Figure 6).

The SLI group further showed a significant positive correlation between phonological processing scores and N250m amplitude in the left hemisphere τb = 0.774, p = 0.006, but not in the right hemisphere τb = 0.278, p = 0.321. No such correlation was found in the TD group: p > .05. In the SLI group, those with higher N250m amplitudes in the left hemisphere performed better on the phonological processing task (Figure 7).

TABLE 1 Fixed effects of the model: estimate (standard error(s.e.)), degrees of freedom, t-value, and p-value.

	Est. Value (s.e.)	DF	t-value	p-value
(Intercept)	33.12 (4.28)	50	7.730	0.000
Group[a]	-0.45 (5.52)	16	-0.082	0.936
Ear[a]	8.34 (3.52)	50	2.368	0.022
Hemi[a]	-1.49 (4.31)	50	-0.346	0.731
Group x Hemi	13.19 (4.98)	50	2.647	0.011
Ear x Hemi	-13.71 (4.98)	50	-2.752	0.008

[a] Baseline for group: TD, for ear: Right and for hemi: Right.

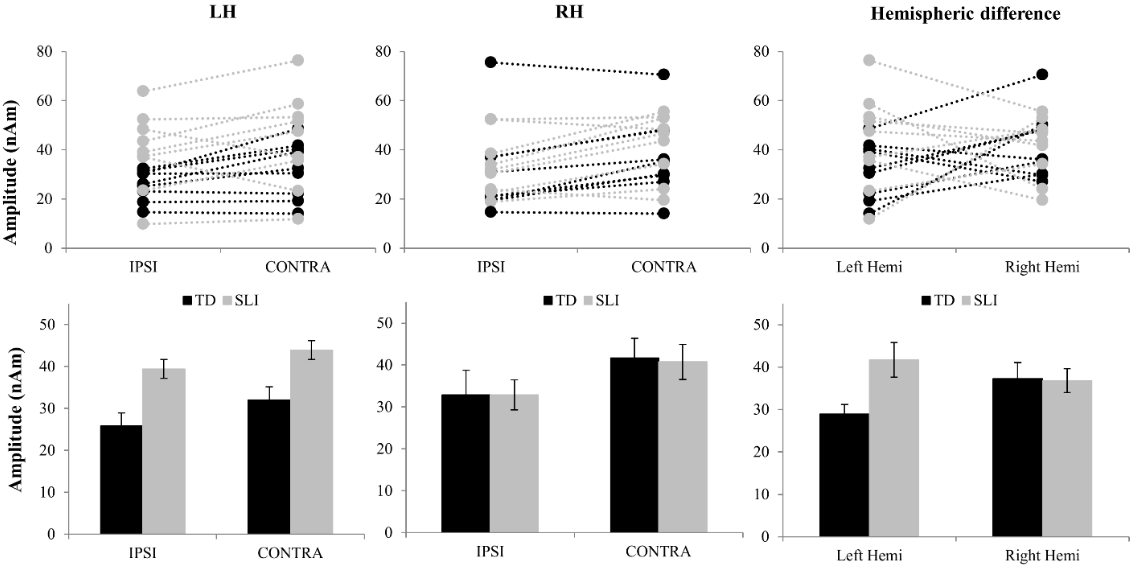


FIGURE 6 Individual (top) and averaged (bottom) strength of activation in the left hemisphere (LH; left) and right hemisphere (RH; middle) in response to ipsi- and contralateral auditory stimulation of children with SLI (grey) and typical language development (black). Hemispheric differences (right) are plotted as the difference in activation strength to contralateral stimulation (i.e., right ear for left hemisphere and vice versa). Whiskers in the bottom figures represent the standard error of the mean (SEM).

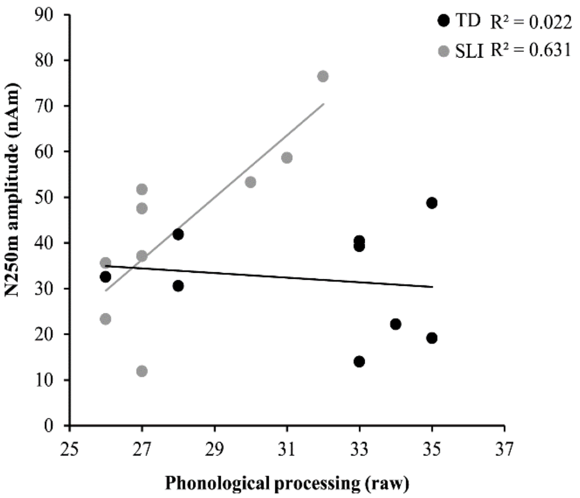


FIGURE 7 Scatterplot representing the correlation between phonological processing (raw score) and N250m amplitude in the left hemisphere, to contralateral stimulation, for the SLI (grey) and TD (black) group.

3.2 Study II: Activity level in left auditory cortex predicts behavioral performance in inhibition tasks in children

We found no significant effect of age on the N250 in the left ($p = .023$) and right hemisphere ($p = .612$). Furthermore, task (passive vs. no-go) had no significant effect on auditory response amplitude, $p > .05$ (Figure 9; Table 2). In the passive vs. no-go (deviant tones) comparison, Study II provided evidence for the behavioral relevance of the child-specific auditory activation at ~250ms. Left hemispheric auditory activity at ~250ms predicted behavioral performance on inhibition tasks. First, the multiple linear regression model (Table 2) showed that intra-individual variability of reaction times (ICV) was a significant predictor of the auditory brain response in children, together with hemisphere, age, and SSRT. More specifically, in the PL task, a stronger left hemisphere response amplitude was related to decreased ICV ($r = .479$, 95%CI = [.195 – .661], $p = .000$) SSRT ($r = .331$, 95%CI = [.113 – .543], $p = .02$) and ERR ($r = .314$, 95%CI = [-.026 – .553], $p = 0.028$). However, only the relationship between L PL and ICV was significant at our alpha level ($p < .01$). 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], $p = 0.041$) (Figure 8). However, only the relationship between L GN and ICV was significant at our alpha level ($p < .01$). Moreover, when behavioral responses were used as the dependent variable, linear regressions revealed that the auditory response in the left hemisphere (to the no-go tone) was a significant predictor of intra-individual variability of reaction time (p < .001) (Table 3) and explained 21% of the variance in the ICV.

The passive vs. OB (standard tone) comparison showed no significant associations between behavioral measures and the brain responses, except for a positive correlation between SSRT and auditory activation in the left hemisphere in the OB task; stronger activation in the left hemisphere during the OB task was related to smaller SSRTs (r = 0.355, 95% CI = [0.142 – 0.560], p = 0.008).

TABLE 2 Forward selection multiple linear regression analysis using hemisphere, task, age, sex, and behavioral performance as predictors of the brain responses at ~250ms.

	B	*SE B*	**Standardized beta**	**ΔR2**	**Significance F change**
Step 1				.06	.000
Constant	-21.73	1.93			
Hemisphere	4.82	1.22	0.246		
Step 2				.03	.003
Constant	-29.96	3.37			
Hemisphere	4.82	1.2	0.246		
GN_ICV	20.62	6.96	0.18		
Step 3				.02	.015
Constant	-41.88	5.89			
Hemisphere	4.82	1.19	0.246		
GN_ICV	23.88	7.02	0.211		
Age	1.04	0.43	0.152		
Step 4				.04	.002
Constant	-51.91	6.61			
Hemisphere	4.82	1.17	0.246		
GN_ICV	16.42	7.29	0.145		
Age	1.55	0.45	0.226		
SSRT	38.03	12.11	0.216		

Note: B = Unstandardized beta, SE B = standard error for the unstandardized beta, ΔR2 = R2 change. GN_ICV = Go/No-go intraindividual coefficient of variability. Excluded variables: reaction-time, response accuracy, sex, and task (p > .05)

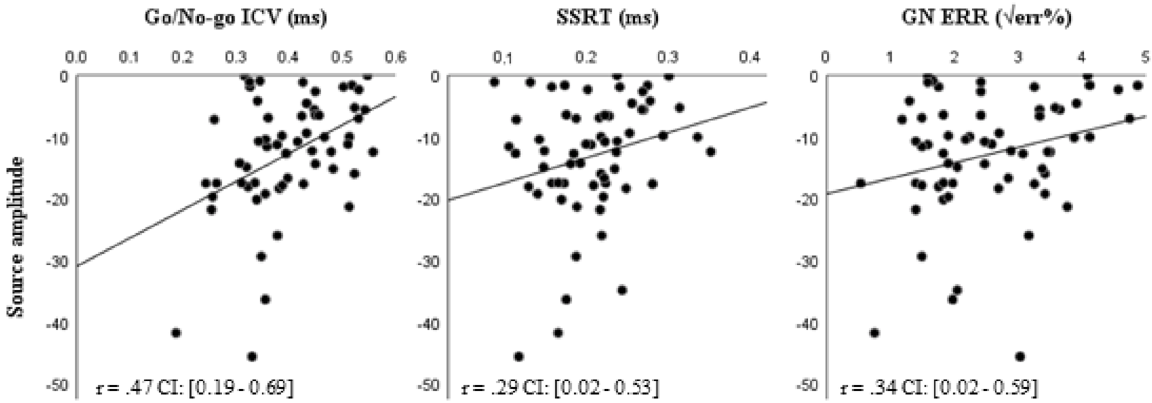


FIGURE 8 Scatterplots of the responses at ~250ms to the No-go tone and intraindividual coefficient of variability (ICV; left), stop-signal reaction time (SSRT; middle) and response accuracy (right).

TABLE 3 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 (NG) tone as the predictors.

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

Note: ICV = intra-individual coefficient of variability, ERR = response accuracy, SSRT = stop signal reaction time. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < .001$ significance of R2 change.

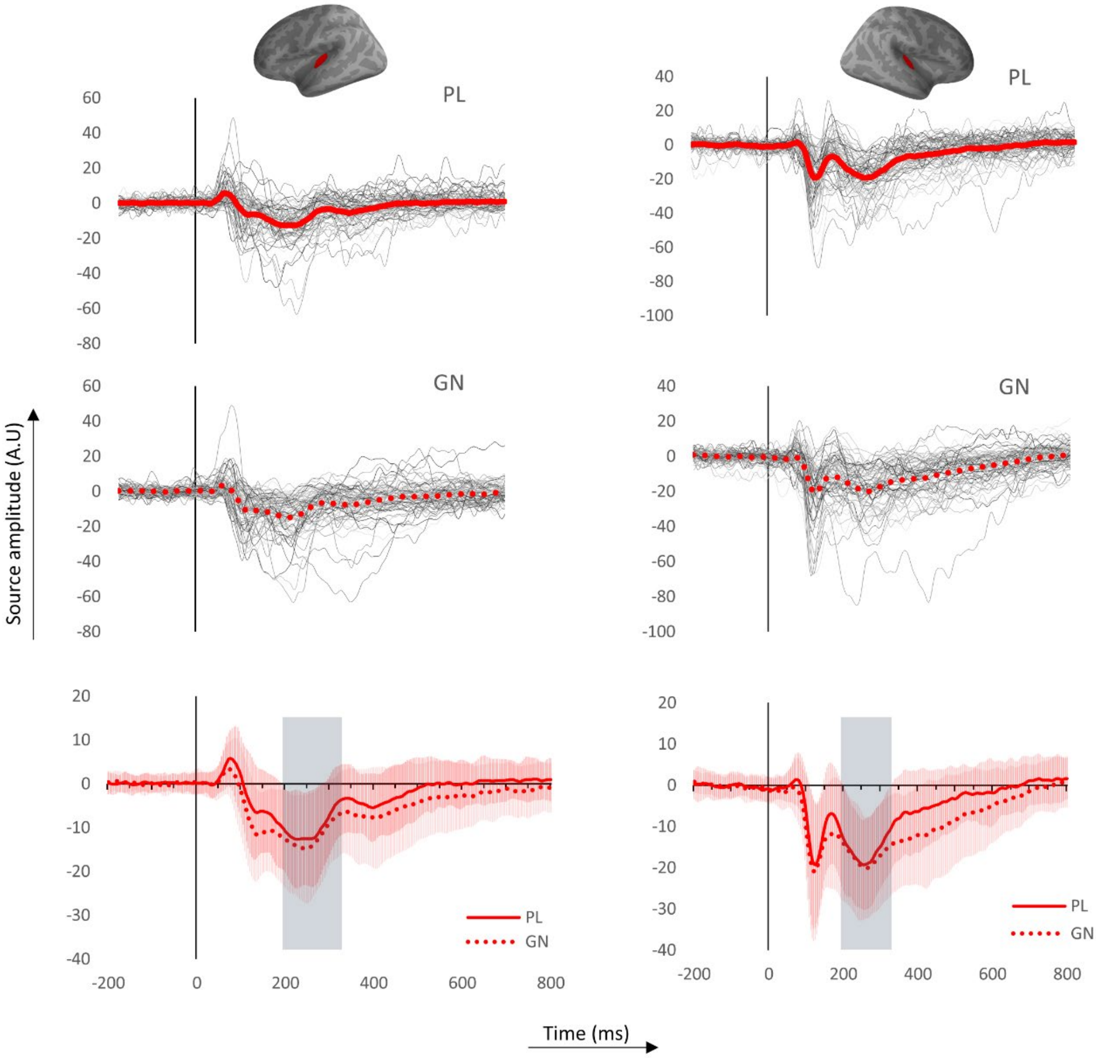


FIGURE 9 Source waveforms in the left and right transverse temporal gyrus for the PL (top) and GN (middle) deviant tones. Top and middle graphs show individual waveforms (gray) and the grand average waveform (red). Bottom graph shows the grand average waveforms of the PL (solid line) and GN (dotted line) and their standard deviation (red shaded area). Child-activity pattern starting at ~200 ms highlighted in gray shaded area.

3.3 Study III: Divergent associations between auditory activation and inhibition task performance in children and adults

Study III showed a qualitative difference between children and adults. Children rely on auditory areas to process the information during a Go/No-go task, with a prolonged peak activation pattern in the auditory cortex lasting well after stimulus presentation (~400ms). This study replicated earlier reports that the activity at ~250ms in the auditory cortex is specific to the child brain (Figures 10 and 11). In contrast, the adult activation pattern in the auditory cortex abates after ~200ms. Source localization of adult No-Go processing reveals that after the ~200ms peak activation, it is no longer in temporal areas but reflects predominantly activation in medial regions of the cerebral cortex (e.g., cingulate and prefrontal areas; figure 11). The marked qualitative differences in the activity pattern in this time window (200-400ms) between children and adults make statistical comparisons futile.

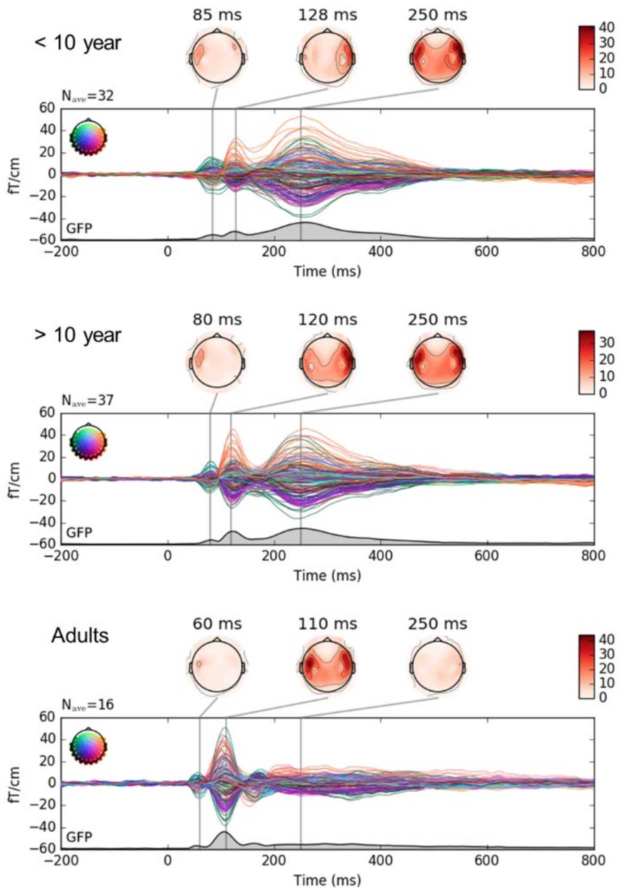


FIGURE 10 Developmental (age) differences in auditory brain responses to the passive listening (PL) standard tone (ST) as measured by the MEG gradiometers. Groups divided for illustration purposes between children younger than 10 (top), older than 10 (middle) and adults (bottom).

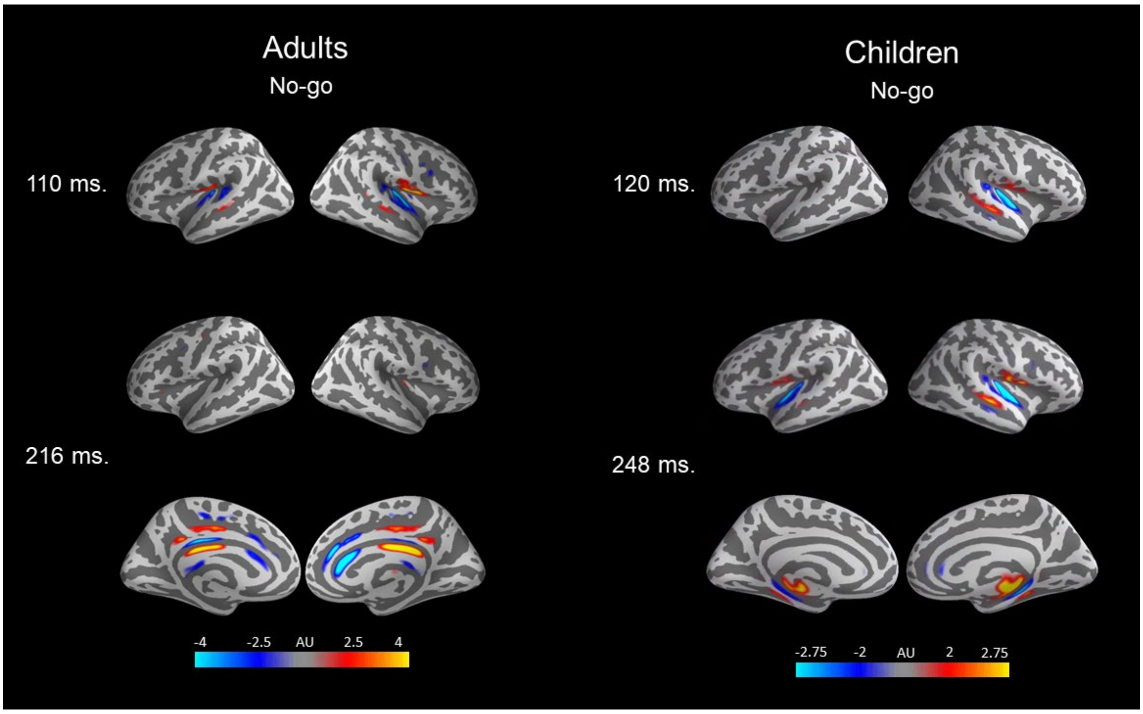


FIGURE 11 Grand average 3D visualization of the No-go (deviant tone) M/EEG combined source estimates for all children (right) and adults (left). 3D-plots presented for the two most prominent time-windows of activation in children (120ms and 248ms) and adults (110ms and 216ms).

No consistent effects of the task on the earlier auditory responses (P1-N1-P2) were found. Only in the P1 did we find evidence of an effect of task in both groups (adults and children) and hemispheres. The P1m was stronger in the passive listening condition compared to the no-go condition ($p < .001$).

Study III found divergent brain-behavior associations between adults and children. Auditory cortical responses (P1-N1-P2) in adults typically show a negative relationship with inhibition performance consistency. In children, we found no or weakly positive associations between the brain-behavior associations. More specifically, in adults, P1, N1, and P2 amplitudes were all related to ICV and, to a lesser extent, response accuracy (Table 4).

TABLE 4 Partial (correcting for age in children only) correlation between the P1-N1-P2-N250 amplitudes of the passive listening (PL) and Go/No-go (GN) tasks in the left (L) and right (R) hemisphere and behavioral measures. Significant correlations marked in bold.

Auditory response	**Child**			**Adult**		
	ICV	**ICV**	**SSRT**	**ICV**	**RA**	**SSRT**
L, PL, P1	-.052	.019	-.010	.117	-.024	-.116
R, PL, P1	.146	.180	-.072	.308	.164	-.047
L, GN, P1	-.034	-.005	-.105	**0.689****	.284	.270
R, GN, P1	.206	.189	-.020	-.022	-.162	-.191
L, PL, N1	**.302***	.249	.145	**-.701****	**-.670****	-.394
R, PL, N1	.082	.101	.092	.067	-.148	.062
L, GN, N1	.222	.231	.087	**-.612***	**-.793*****	-.448
R, GN, N1	.102	.107	.108	-.062	-.290	.017
L, PL, P2	-.122	-.189	-.051	**.647****	.434	.315
R, PL, P2	-.084	-.002	**-.278***	.053	.197	.157
L, GN, P2	-.045	-.131	-.107	**.538***	**.535***	**.550***
R, GN, P2	-.128	-.048	**-.331****	.000	.162	-.090
L, PL, N250[a]	**0.479*****	**0.314***	**0.331***	-	-	-
R, PL, N250[a]	-0.033	0.037	0.162	-	-	-
L, GN, N250[a]	**0.467*****	**0.343***	**0.292***	-	-	-
R, GN, N250[a]	0.077	0.036	0.231	-	-	-

[a] note: N250m data was reported in Study II, P1-N1-P2 in study III. ICV = intra-individual coefficient of variability, RA = response accuracy, SSRT = stop signal reaction time. *$p < 0.05$, **$p < .01$, ***$p < 0.001$.

4 DISCUSSION

This dissertation aimed to elucidate the functional significance of (developing) auditory processing in children. To this end, I investigated the complete sequence of brain responses to auditory stimuli (i.e., P1-N1-P2-N2(50)) in children and adults. I was especially interested in the behavioral relevance of the N250, a child-specific activation pattern in the auditory cortex. In this discussion, I first briefly state the main conclusion(s) based on the individual studies that (i) studied the significance of the N250 for atypical language development, (ii) N250 age differences and their relation to attention and response inhibition performance measures in children, and (iii) differences in auditory processing in adults and children in the context of inhibition tasks. Subsequently, in the general discussion, I will integrate my findings with the current literature on (the development of) auditory processing and its relevance for attention, inhibition, and language skills.

4.1 Study I: Left hemisphere enhancement of auditory activation in language impaired children

In Study I, we examined variation in the auditory N250m response in children with typical and atypical language development. We found stronger N250m dipole moments in children with specific language impairment compared to typically developing children in the left hemisphere. No differences were found in the right hemisphere. Additionally, dipole moment strength in the left hemisphere related positively to phonological score in the SLI group but not the typical developing group. The findings show the importance of a maturing auditory cortex in the left hemisphere for appropriate language development and suggest that atypically developing children rely on neural sources in the left hemisphere as a possible compensatory mechanism for delayed maturation of language processing.

Our findings are in line with earlier studies that highlighted the importance of auditory activation for language development. First, the N250m is specific to the developing brain (Čeponienė et al., 2002; Ponton et al., 2000) and stronger or more sustained activation in this time window, especially in the left hemisphere, is indicative of less developed language skills. Indeed, decreased N250m is used as an indicator of language and auditory development as it has been related to better language skills in typical developing children (Hämäläinen et al., 2013; Lohvansuu et al., 2014; Parviainen et al., 2011).

4.2 Study II: Activity level in the left auditory cortex predicts behavioral performance in inhibition tasks in children

In study II, we assessed age differences in the child-specific N250 response and investigated the effects of attention and inhibition task demands on its amplitude. Furthermore, to investigate its relevance for inhibition or attention task performance, the strength of the N250m was related to performance measures.

We found no effect of age on the strength of activation, which suggests that the N250 decreases non-linearly with age. This is in line with studies that investigated a wider age range and reported an initial increase in activation strength until the age of eleven and a subsequent decrease in amplitude (Ponton et al., 2000; Ponton et al., 2002). In addition, we showed that the N250 is unaffected by task demands (attention or inhibition), but the strength of activation in the left hemisphere was positively associated with inhibitory performance consistency, a measure of cognitive control. It suggests that children engage the basic auditory circuitry in the left hemisphere to support cognitive control processes.

4.3 Study III: Divergent associations between auditory activation and inhibition task performance in children and adults

Study III compared the auditory processing of children and adults in the context of a response inhibition task (Go/No-go). We found marked differences in the spatiotemporal characteristics of auditory activation between adults and children. Namely, 200-300 ms after auditory stimulation, children show continued, prolonged activation in the auditory cortex, even in the context of a Go/No-go task. In contrast, adult activity in the auditory cortex at ~200ms abates in favor of frontomedial regions of the cerebral cortex that are known to be associated with adult cognitive control processes. This is indicative of a qualitative difference between adults and children, which is important because traditional EEG-ERP analysis will have limited ability to reveal this difference and may also erroneously transfer spatial differences into amplitude effects. It also substantiates the claim that the N250m is specific to the child's brain and indeed a "hallmark of the child's obligatory response" (Sussman et al., 2008).

Additionally, children and adults show divergent brain-behavior associations between auditory activation and inhibition task performance. The early (i.e., P1-N1-P2) responses in children show no, or positive, brain-behavior correlations. In comparison, adults show negative associations between their auditory cortical responses and inhibitory performance. Taken together, the qualitative difference and the divergent brain-behavior associations suggest adults and children employ functionally distinct cortical resources for performance consistency in auditory-based cognitive control tasks.

4.4 Functional significance of the child auditory response for language and cognitive control processing

The auditory system has often been viewed as merely a relay station for auditory information accessible to auditory-related skills such as language and communication. More recently, the importance of the auditory system for broader, sensorimotor, and cognitive aspects of goal-directed behavior has been hypothesized (Kraus & White-Schwoch, 2015). In this dissertation, I provide evidence for the relevance of auditory processing for language, attention, and/or cognitive control skills, and, although in a remarkable different way, this appears true in both adults and children.

Judged by the behavioral relevance of language and inhibition tasks, children (partly) rely on auditory cortical resources around ~250ms after auditory stimulation to successfully perform these tasks. This child-specific activation pattern seems exceptionally flexible, as is evidenced by our two somewhat paradoxical pieces of evidence. First, this activation pattern is stronger in children with a delayed maturational profile (Study I), but within clinical groups, the strength of activation relates to better performance on language-related tasks (Lohvansuu et al., 2014; Study I). Second, in typical developing children, cognitive control processes rely on activation in the auditory cortex for performance consistency (Study II). It seems that this activation pattern is both an indicator of development and a functional, adaptable mechanism in the child's arsenal. In contrast, adults rely on earlier auditory responses for performance consistency in inhibition tasks and in a functionally distinct way. They typically do not show a dominant activation pattern in the auditory cortex in the ~250ms time window (Study III). Furthermore, adults' brain-behavior correlations between auditory activation and inhibitory performance are opposite those of typical developing children; while stronger auditory activation (in the left hemisphere) benefits inhibitory performance in children, it impedes it in adults (Table 4). It is worth noting that the relevant child's brain-behavior relationships are most consistently related to the N250, whereas the adult's (and inverse direction) relationships are related to the early auditory components (i.e., P1-N1-

P2).Thus, there is one notable discrepancy in brain-behavior associations between the earlier (P1-N1-P2) and later auditory activation patterns in children and a second discrepancy in P1-N1-P2 brain-behavior relationships between adults (negative correlation) and children (no correlation or a weakly positive correlation).

This was also noted by earlier studies that called the N250 "the additional process" (Johnstone et al., 1996) related to discriminative processing and argued the age-related reduction reflects the child's increased ability to control attentional focus. Our data demonstrates the uniqueness of this exogenous response pattern in children, as it is unaffected by task demands but still behaviorally relevant (Study II). The fact that the earlier auditory responses in children did not consistently show similar brain-behavior relationships, supports this hypothesis. Another possibility, however, is that the P1-N1-P2 are also behaviorally relevant for better task performance, but the functional significance of these auditory responses in adults and children might be diametrically opposed (i.e., a negative and positive relationship, respectively). Brain-behavior relationships might "flip" during development, complicating the detection of correlations in the early auditory responses of children. Nevertheless, it suggests that not only does the sequence of brain responses to auditory stimuli change with development, namely a more pronounced N1 and, in general, a gradual temporal dissociation of the earlier responses (P1-N1-P2) and an attenuation of the N2 (Albrecht et al., 2000; Čeponienė et al., 2002; Ponton et al., 2000; Sussman et al., 2008; Takeshita et al., 2002; Wunderlich and Cone-Wesson, 2006); their function in relation to inhibitory performance measures also changes.

The fading of the child's auditory N250 response during development seems logical considering the adult cognitive control processing literature. Indeed, auditory cortical activity is absent during passive conditions in this time window (Study III; Parviainen et al., 2006). Instead, during active (attention/inhibition) tasks, adults show a prominent activation peak in medial prefrontal areas (e.g., cingulate cortex) during this time-window (Study III), which is strongly associated with inhibitory and cognitive control processes (Botvinick et al., 2004; Chambers et al., 2009; Falkenstein et al., 1999; Huster et al., 2010; Nieuwenhuis et al., 2003; Smith et al., 2007). Thus, timing-wise, the child auditory N250 overlaps with known inhibitory control processes in adults. Arguably, the cortical resources that support cognitive control shift from sensory related areas (e.g., auditory cortex) in children to top-down, frontoparietal network areas in adults.

Together, the results in this dissertation suggest a developmentally specific emphasis on sensorimotor associations in children during (auditory) cognitive control tasks. Earlier evidence in adults showed that cognitive control is supported by a broad frontoparietal network including, but not limited to, the right inferior frontal gyrus, the pre-supplemental motor area (preSMA), and cingulate areas (Weiss & Luciana, 2022), which are also reported to contribute to the adult N2 in active tasks (Huster et al., 2010). Furthermore, fMRI studies showed that increased activation of the anterior cingulate gyrus (ACG) is related to superior cognitive control in adults (Bellgrove et al., 2004; van Belle et al., 2015). Intriguingly, one fMRI study showed that, while younger participants (between seven and fifteen years old) showed no association between (dorsal) ACG activity and cognitive control, in older participants (between fifteen and twenty-four years old), increased dorsal ACG activity was associated with superior cognitive control processing (van Belle et al., 2015). Instead, in children aged between eight and twelve years, superior cognitive control was associated with stronger activation in the rostral supplementary motor area (pre-SMA). In our study, children rely strongly on auditory activation during no-go trials, and it relates to performance consistency in cognitive control tasks (Study II). Taken together, it demonstrates a stronger emphasis on sensorimotor associations in children in contrast to the typical frontoparietal network that supports cognitive control in adults (Weiss & Luciana, 2022). Thus, the child brain is not merely a "miniature" adult brain, but the mechanisms that govern inhibitory performance in children are likely functionally distinct from those in adults. The maturational changes in the auditory responses coincide with improvements in inhibitory performance during childhood and adolescence, but this transition is likely aided by child-unique mechanisms.

It is likely the child-unique activation pattern supports inhibitory performance in auditory-based tasks through attentional or motor processes rather than being a core cognitive control processing feature in children for two reasons. First, this region is not typically associated with cognitive control or, indeed, response inhibition. Given that this concerns activity in the auditory cortex, it is unlikely it plays a role in inhibition tasks that do not use auditory stimuli. Second, the activation pattern in the child auditory cortex is likely part of the automatic circuit-level processing chain in children (Parviainen et al., 2019), as it is elicited in both active and passive conditions. Indeed, task requirements do not seem to affect the auditory responses.

The hypothesis that children rely more strongly on sensorimotor associations compared to adults is also supported by the finding that mostly the left hemisphere (contralateral to the hand used in the tasks) shows the brain-behavior associations. According to the adult literature, the right inferior frontal gyrus (rIFG) enables response inhibition prepared by the pre-supplemental motor area (Aron et al., 2004; Aron, 2007; Chambers et al., 2009; Puiu et al., 2020; Weiss & Luciana, 2022). Developmental changes include an increase in engagement of the fronto-parietal network with less activation in the bilateral inferior frontal gyrus and anterior and posterior cingulate gyrus (Stevens et al., 2007). Thus, these regions may be less specialized for successful response inhibition during childhood, when sensory processes may guide goal-directed behavior more strongly compared to adulthood. However, the exact role of the different hemispheres is still unclear and is a principal factor in the possible explanations of the behavioral relevance of the auditory responses in adults and children.

4.5 Hemispheric differences in language processing and response inhibition

The notable constant throughout the results discussed in this dissertation is the left hemisphere. Children with delayed language development only show increased activation in the left auditory cortex; the child-specific activation pattern at ~250ms in typical developing children only shows significant behavioral relevance in the left hemisphere, and similarly, adult auditory responses in the left hemisphere show associations with behavioral performance in inhibition tasks. An important question is why the left hemisphere appears to be uniquely relevant during different tasks (language and inhibition) and across groups (adults and (a)typically developing children). I argue there are two possible, not mutually exclusive, explanations: handedness and the (different) developmental trajectories of the auditory cortices, with possible relevance for auditory, language and inhibitory control processes.

Studies investigating auditory and language processing together have emphasized the importance of the left hemisphere. Indeed, activation strength of the N250 in the left auditory cortex is arguably a marker of language development, as stronger activity has been related to poorer performance in typical developing children (Hämäläinen et al., 2013; Parviainen et al., 2011;), and children with atypical language development show stronger responses compared to typical developing children (Study I). Our data is in line with previous studies showing that, while typical developing children prefer (i.e., have stronger responses in) the right hemisphere (Orekhova et al., 2013; Yoshimura et al., 2014), increased left hemisphere activity and, consequently, atypical auditory lateralization is possibly a key component of dyslexia (Johnson et al., 2013). Concurrently, auditory and language lateralization and hemispheric asymmetry in language disorders are hotly debated and complicated subjects (Bishop, 2013; de Guibert et al., 2011; Whitehouse & Bishop, 2008; Wilson & Bishop, 2018). In Study I, we found a lateralization effect in typical developing children (generally stronger responses in the right hemisphere). This is in line with studies investigating pure tone-processing in typical developing children (Orekhova et al., 2013; Parviainen et al., 2019) and adults (Howard & Poeppel, 2009; Jin et al., 2008; Pantev et al., 1998; Salmelin et al., 1999). In contrast, atypically developing children showed increased left hemisphere N250 amplitudes, resulting in an opposite (non-significant) asymmetry pattern compared to typically developing children (Study I).

Functional or structural differences between the hemispheres could help explain discrepancies between studies investigating hemispheric differences in auditory and language processing. First, while the left hemisphere typically processes speech, the right hemisphere is more dominant in nonspeech (e.g., pure-tone) processing. Extending this, the theory of asymmetric sampling in time (AST) asserts that temporal features, not necessarily stimulus type, determine cerebral asymmetries. This theory states that the left hemisphere samples fast-rate (e.g., phonemic) auditory information between ~12 and 50 Hz and the right hemisphere samples slow-rate (e.g., syllabic) auditory information between ~3 and 7 Hz (Goswami, 2011; Poeppel, 2003; Poeppel et al., 2008). Given the complexity of language-related processes, the functioning of both hemispheres (and possible interactions) is likely more dynamic than previously suggested. Anatomical differences between hemispheres, as well as the effect of atypical development, add to the complexity. Indeed, cortical folding of the auditory cortices reduces the M/EEG signals due to non-uniform orientations of the underlying neural currents (Shaw et al., 2013). These cancelation effects may be asymmetric, resulting in an amplitude bias to the right (or left). As I already mentioned, possible changes to the underlying neuroanatomy during (atypical) development could further bias the M/EEG signals. For example, a study into the neuroanatomical basis of developmental dyslexia found higher mean curvature and a greater folding index in the left hemisphere of the dyslexic group compared to controls (Płoński et al., 2016).

Like our findings in Study I, in Studies II and III we also reported the strongest auditory responses in the right hemisphere. However, the relevant brain-behavior associations between auditory activation and inhibitory control in adults and children were mostly with the left hemisphere. In children, the relevance of the left hemisphere should be considered in conjunction with its suggested slower maturation and stronger experience-driven plasticity compared to the right hemisphere (Paetau et al., 1995; Parviainen et al., 2019). Accordingly, genetic regulation of auditory cortical activation strength is more strongly linked to the right hemisphere compared to the left hemisphere (Renvall et al., 2012). In addition to auditory responses, activity in the prefrontal areas during cognitive control tasks also shows a developmental shift in laterality, with possible elevated importance of the left hemisphere during childhood (Zelazo et al., 2008). However, handedness could also explain the hemisphere-specific brain-behavior correlations between auditory activation and inhibitory control, as the participants were right-handed. In adults, plasticity or hemisphere-specific maturation effects are likely inconsequential. In my assessment, the most likely explanation for the findings in the left hemisphere is different for children and adults; children rely more strongly on child-unique processes combined with the flexibility of the left hemisphere to support language and cognitive control processes. In contrast, adults likely developed a superior way of processing auditory stimuli, and the negative correlation between auditory responses in the left hemisphere and inhibitory control performance measures could reflect that processing efficiency as the contralateral (i.e., right) inferior frontal gyrus enables response inhibition (paragraph 4.4). If this is true, the left hemisphere-specific effects in adults from Study III depend on the handedness of the participant, but the results in the child groups should not depend on handedness.

4.6 Strengths, limitations, and future directions

An important strength of this dissertation was the inclusion of combined M/EEG data acquisition and individual MRIs. Several confounding factors that influence magneto- and electrophysiological measures, as I mentioned in the introduction, have limited the interpretability of previous studies. First, EEG studies are limited in their spatial sensitivity, which is crucial to investigate hemispheric differences that play a key role in auditory-related cognitive tasks. Our findings emphasize the importance of including spatial information to understand the spatiotemporal characteristics of auditory responses and their relevance for cognitive processes.

A second important aspect highlights the strength of EEG compared to MEG, as the sensitivity of MEG decreases with increasing source depth and radial orientation. This is especially important in the context of the auditory go/no-go task because MEG has limited ability to detect sources in the prefrontal and cingulate areas. Although the data is not presented in this dissertation, while visually comparing the 3D plots of the no-go responses, we saw remarkable differences in these areas between the MEG only and the M+EEG data. The combination of M+EEG data proved critical in answering the research questions we were interested in.

Another strong advantage of this study was the visual environment created for the experiment (studies II and III). To keep the participants engaged in an otherwise long and monotonous task, Studio Dennis Parren made animation videos that were unrelated to the task but interesting to the participants. Listening to more than one thousand beeps can be arduous, especially for children, but embedding it in a game made the experience enjoyable to the participants. This is most clearly evidenced by our drop-out percentage: out of 78 children that participated, only one did not complete the tasks (1.3%). Additionally, we received a lot of positive feedback from the participants, who said it was fun to "play" (i.e., participate in the experiment). This allowed us to collect a lot of data from multiple auditory (oddball) tasks, resulting in the final strength: a comparison without common confounding factors such as motor activity, stimulus frequency, and probability in a relatively large sample of children.

While the large sample of children in Studies II and III is an important strength of this dissertation, the number of children in Study I and adults in Study III are considerably smaller. We maximized power by employing a linear mixed model (LMM), which has distinct advantages in terms of false positives and statistical power in studies with small sample sizes. Nevertheless, the correlations should be interpreted with care. It is likely our reported correlation coefficients for the adult group in Study III and the SLI group in Study I do not represent the true value in their respective populations, as correlations typically stabilize at larger sample sizes.

Two important considerations should still be addressed. First, in studies II and III, we investigated the behavioral significance of auditory cortex activation in children and adults, arguing for its functional significance in cognitive control processes. However, most (or the strongest) relationships were between auditory activation and individual response time variability (ICV) in an auditory Go/No-go task. It is still unclear how broadly this relationship can be interpreted under the general domain of cognitive control processes. Second, we extracted the auditory responses from the primary auditory cortex (transverse temporal gyrus). However, as the latency of the auditory responses increases, the signal propagates throughout the lateral temporal cortex. Thus, the generator areas of the auditory evoked responses change (e.g., increase in involved areas) with time after sound onset, but the evoked responses were uniformly gathered from the primary auditory cortex only.

As the studies included in this dissertation used a cross-sectional design, they were not well suited to determining the causality of the investigated effects. Nevertheless, in combination with previous studies, we argue a compelling case could be made about the directionality of our results. Indeed, we argued that the N250 underlies a compensatory mechanism in children with atypical language development, and as such, it is more likely a consequence (delayed maturation) of atypical language development than a cause. In addition, we hypothesized that the strength of the auditory responses in the ~250ms time window in children benefits cognitive control processes (i.e., causes better performance) until a more efficient auditory processing network is established. In this view, the improved efficiency in adults manifests as opposite (i.e., negative) brain-behavior associations between auditory evoked responses and cognitive control processes.

These hypotheses should be investigated more thoroughly. Most importantly, the present paradigm comparing passive and active oddball tasks should be employed in a longitudinal design to determine causality. Alternatively, non-invasive brain stimulation studies could reveal a possible causal effect of the child-specific auditory response on response inhibition and language processes. It is advisable to also include magnetic resonance spectroscopy (MRS) to measure the biochemical changes in the brain. The maturation of GABAergic and glutamatergic neurotransmission crucially contributes to the functional maturation of the cortex (La Magueresse & Monyer, 2013) and it is likely they play an important role in the development of auditory and inhibitory processes (Du et al., 2016; Sanes & Kotak, 2011; Silveri et al., 2013). Finally, future studies should include sufficient left- and right-handed participants to determine whether the reported effects in the present studies depend on handedness or are specific to the left hemisphere.

In conclusion, the studies included in this dissertation show that auditory cortex activation in children is associated with language processing and response inhibition. Overall, engagement of the basic auditory circuitry, especially in the left hemisphere, is associated with improved performance in children but is associated with poorer inhibitory control in adults. Most notably, a child-specific activation pattern at ~250 ms after auditory stimulation is both an indicator of auditory and language development as well as functionally relevant to the child's brain. As auditory processing becomes more efficient, this activation pattern becomes obsolete. These maturational changes are accompanied by improvements in language and inhibition task performance, but this is likely aided by child-unique mechanisms.

YHTEENVETO (SUMMARY)

Kuuloaivokuoren aktivaation toiminnallinen merkitys lapsen kognitiivisille taidoille

Kuuloon perustuvan tiedon käsittely kriittisissä kehityksen vaiheissa on ratkaisevassa roolissa keskeisten taitojen, kuten lukemisen, kirjoittamisen ja kielen oppimisen, kannalta. Viimeaikaisen tutkimuksen pohjalta on ilmennyt, että myös yleisemmät kognitiiviset taidot, kuten toiminnanohjaus, tarkkaavaisuus ja reaktioinhibitio, ovat riippuvaisia kuuloaivokuoren kehityksestä. Kuuloaivokuoren kehitys perustuu jokapäiväisiin äänikokemuksiin. Auditiiviset kokemukset (esim. lukeminen, musiikki, kielellinen vuorovaikutus) muovaavat aivojen reaktioita tuleviin kuuloärsykkeisiin, ja yhdessä ne ohjaavat suoriutumistamme kuulonvaraisissa tehtävissä. Lisäksi aivojen kehitykselliset muutokset ohjaavat kuulojärjestelmän rakenteellista muodostumista sekä kuuloaivokuoren alueiden mahdollista toiminnallista uudelleenjärjestäytymistä. Yhdessä nämä tekijät ohjaavat tapaa sitoutua tavoitteelliseen toimintaan. Ottaen huomioon kuulotiedon käsittelyn kehityksen merkityksen kognitiivisille taidoille, tiedämme yllättävän vähän siitä, miten lapsen aivojen kuulotiedon käsittely liittyy kognitiivisiin toimintoihin ja miten tämä eroaa aikuisen aivoista.

Tämän väitöskirjan tavoitteena on selvittää kuulotiedon käsittelyn merkitystä lapsen aivoissa. Selvitimme, miten eri-ikäisten lasten ja aikuisten aivot reagoivat kuuloärsykkeisiin eri tilanteissa (passiivinen kuuntelu tai vastausta vaativat tehtävä) ja miten nämä aivojen reaktiot ovat yhteydessä kielen kehitykseen (tutkimus I) ja käyttäytymisen säätelyyn ja inhibitioon (tutkimus II ja III). Keskityimme aivovasteeseen, joka nähdään erityisesti lasten aivoissa, ja joka tyypillisesti puuttuu aikuisilta. Magnetoenkefalografia (MEG) ja elektroenkefalografia (EEG) ovat aivojen kuvantamistekniikoita, joilla voidaan rekisteröidä aivojen sähköistä toimintaa (EEG) ja niiden magneettikenttiä (MEG). Tutkimuksessa I vertasimme yksinkertaisten äänien herättämiä aivovasteita viivästyneestä kielenkehityksestä kärsivien lasten ja tyypillisesti kehittyvien lasten välillä ja tutkimme, miten aivovasteet liittyivät kielellisiin taitoihin. Tutkimuksissa II ja III osallistujat pelasivat peliä, jossa heidän oli käytettävä kaikuluotainta havaitakseen joko kalan (ääni 1) tai hain (ääni 2). Osallistujien tehtävänä oli joko jättää kaikki äänet huomiotta tai painettava nappia jommankumman äänimerkin kohdalla. Tutkimuksessa II selvitimme lasten aivovasteita näissä eri tilanteissa (passiivinen tehtävä tai tehtävä painaa nappia) ja aivovasteiden ominaisuuksien yhteyttä tehtävässä suoriutumiseen. Tutkimuksessa III vertasimme lasten ja aikuisten kuuloaivovasteita.

Havaitsimme, että lapsilla, joiden kielellinen kehitys oli viivästynyt, oli voimakkaammat aivovasteet vasemmassa aivopuoliskossa verrattuna tyypillisesti kehittyviin lapsiin. Viivästyneen kielenkehityksen omaavilla lapsilla voimakkaammat vasteet olivat yhteydessä parempaan suoriutumiseen kielen käsittelyn tehtävissä. Tämä korostaa vasemman kuuloaivokuoren kypsymisen merkitystä kielen kehitykselle. Tulokset viittaavat kuitenkin myös siihen, että kuuloaivokuoren voimakkaampi aktivaatio voi kompensoida viivästynyttä kielenkehitystä. Tutkimuksessa II havaitsimme, että vaikka tehtäväkonteksti ei vaikuta lasten aivovasteisiin, lapset, joilla on vahvemmat vasteet vasemmassa aivopuoliskossa, pystyvät paremmin ehkäisemään jo aloitettua toimintaansa. Tämä viittaa siihen, että lapset käyttävät vasemman aivopuoliskon kuuloaivokuoren resursseja kontrolloidakseen käyttäytymistään kuuloon perustuvissa kognitiivisissa tehtävissä. Havaitsimme myös olennaisia eroja aikuisten ja lasten kuuloaivokuoren toiminnassa. Erityisesti lapsilla havaittiin pitkittynyt kuuloaivokuoren aktivoituminen verrattuna aikuisiin, joilla aktiivisuus siirtyi etuaivojen alueille, joiden tiedetään olevan olennaisia ongelmanratkaisutaidoille, itsesäätelylle ja tavoitteelliselle käyttäytymiselle. Näin ollen käyttäytymisen säätelyn taustalla olevat hermostolliset mekanismit ovat erilaisia aikuisilla ja lapsilla: kun lapset nojaavat vahvemmin aistitoimintaan käyttäytymisensä ohjaamiseksi, aikuiset käyttävät "korkeamman tason" kognitiivisiin taitoihin liittyviä alueita. Sitä, että lapsen aivoissa korostuu aistien käsittely, osoittaa myös kuulovasteiden ja kognitiivisten tehtävien suoritustason välinen yhteys. Lapsilla vasemman aivopuoliskon voimakkaammat kuuloaivovasteet ovat yhteydessä parempaan suoriutumiseen, kun taas aikuisilla suhde on päinvastainen: vasemman aivopuoliskon voimakkaammat kuuloaivovasteet ovat yhteydessä huonompaan suoriutumiseen.

Tässä väitöskirjassa esitetyt tulokset viittaavat siihen, että lapsen aivot eivät ole vain aikuisen aivot "pienoiskoossa", vaan aivomekanismit, joiden avulla lapset hallitsevat käyttäytymistään, ovat todennäköisesti toiminnallisesti erilaiset kuin aikuisilla. Lapsille tyypilliset kuuloaivovasteet pienenevät kehityksen myötä, kun aivot löytävät tehokkaampia tapoja käsitellä kuuloaistitietoa. Tämä tapahtuu samanaikaisesti, kun lapsen kyky hallita käyttäytymistään paranee. Siirtymistä lapsen ja aikuisen välisestä suorituksesta näissä tehtävissä auttavat kuitenkin lapselle ominaiset mekanismit; lapset näyttävät käyttävän aistitietoa käyttäytymisensä ohjaamiseen, kunnes aikuisen kaltaiset (prefrontaaliset) aivoverkostot ovat muodostuneet.

Näissä tutkimuksissa aivojen ja käyttäytymisen väliset yhteydet rajoittuivat vasempaan kuuloaivokuoreen. Tämä liittyy todennäköisesti siihen, että oikea aivopuolisko liittyy voimakkaammin geneettiseen säätelyyn, mikä tarkoittaa, että sen kehitys on mahdollisesti voimakkaammin geneettisten vaikutusten hallitsemaa. Vasemman aivopuoliskon kuulovasteiden tiedetäänkin kypsyvän hitaammin kuin oikean aivopuoliskon. Näin ollen vasen aivopuolisko saattaa olla herkempi kokemukseen perustuville muutoksille, jotka antavat lapsille tarvittavaa joustavuutta.

Yhteenvetona voidaan todeta, että tämän väitöskirjatyön tutkimukset osoittavat, että lasten kuuloaivokuoren aktivaatio on käyttäytymisen kannalta merkityksellistä sekä kielen käsittelyn että käyttäytymisen säätelyn kannalta. Kuuloaivokuoren toiminta, erityisesti vasemmassa aivopuoliskossa, auttaa suorituskykyä lapsilla, mutta on yhteydessä heikompaan käyttäytymisen säätelyyn aikuisilla. Erityisesti lapsilla nähtävä aivovaste on sekä indikaattori kuulotiedon käsittelyn ja kielen kehityksestä, että toiminnallisesti merkityksellinen lapsen aivoille. Kun kuulotiedon käsittely tehostuu, tämä aivovaste käy tarpeettomaksi.

Tämä voi tarkoittaa, että kielen ja käyttäytymisen säätelyn taitojen lisääntyminen nojaa mekanismeihin, jotka ovat ominaisia yksinomaan lasten aivoille.

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ORIGINAL PAPERS

I

LEFT HEMISPHERE ENHANCEMENT OF AUDITORY ACTIVATION IN LANGUAGE IMPAIRED CHILDREN

by

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Left hemisphere enhancement of auditory activation in language impaired children

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Specific language impairment (SLI) is a developmental disorder linked to deficient auditory processing. In this magnetoencephalography (MEG) study we investigated a specific prolonged auditory response (N250m) that has been reported predominantly in children and is associated with level of language skills. We recorded auditory responses evoked by sine-wave tones presented alternately to the right and left ear of 9–10-year-old children with SLI ($n = 10$) and children with typical language development ($n = 10$). Source analysis was used to isolate the N250m response in the left and right hemisphere. In children with language impairment left-hemisphere N250m responses were enhanced compared to those of controls, while no group difference was found in the right hemisphere. Consequently, language impaired children lacked the typical right-ward asymmetry that was found in control children. Furthermore, left but not right hemisphere N250m responses correlated positively with performance on a phonological processing task in the SLI group exclusively, possibly signifying a compensatory mechanism for delayed maturation of language processing. These results suggest that enhanced left-hemisphere auditory activation reflects a core neurophysiological manifestation of developmental language disorders, and emphasize the relevance of this developmentally specific activation pattern for competent language development.

Although the maturing brain is pre-eminently suitable to acquire language, some children have difficulties in learning to fluently speak or understand their native tongue for no apparent reason. Approximately 5% of primary school children (6–11 years) are estimated to have specific language impairment (SLI, also known as developmental language disorder, DLD[1–3]). Cognitive impairments in SLI include deficits in speech perception[4], working memory and phonological short-term memory[5–7]. Its causes are still unknown, although it has been suggested it is a, heterogeneous, heritable neurodevelopmental disorder that can affect auditory processing[8]. Indeed, children with SLI have demonstrated altered processing of auditory information and atypical evoked brain responses to sounds[9–12].

The sequence of brain responses to passive auditory stimulation have originally been characterized using EEG scalp recordings as a waveform with positive and negative peaks with the nomenclature focused on the order of the peaks (P1-N1-P2-N2) or latency (e.g. N100, N250). The peaks that dominate the mature and the developing auditory evoked response differ substantially. In short, whereas the adult waveform is typically dominated by the short lived P1-N1-P2 responses, the child waveform is characterized by a peak around 100 ms (referred to as P1 in EEG and P1m in MEG recordings)[13,14] and one robust peak around 250 ms after stimulus presentation (N250/N250m or N2/N2m)[15–18]. In primary school children (~6–11 years), the emerging N1(m) overlaps in space and time with both the P1(m) and the N250(m). This complicates the isolation of the N250m and emphasizes the need to include source information to reliably separate and extract neurophysiological signatures that reflect distinct processes. When the underlying neural generators of these main components in the child waveform are modelled with equivalent current dipoles (ECDs), they reflect currents with an anterosuperior direction (P1(m)) and an inferior-posterior direction (N250(m) and N1(m))[14–16,19].

The developmental changes in the N250(m) suggest it is an important signature of (auditory) brain maturation. The N250(m) starts to gradually decrease in amplitude around a certain age (~10–11 years) until it is no

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longer or barely visible in the adult waveform[16–18,20]. This decrease has been attributed to cortical reorganization, as more efficient cortical networks are established during development[17,18]. Nevertheless, it has been less intensively studied, arguably because the N1(m) is the most dominant response in adults[21]. Similarly, the P1(m) in children received more attention, possibly because it is argued to be the most dominant response in children[22], especially during early years.

Even though the child N250(m) shows a similar source configuration as the adult N1, they most likely reflect functionally distinct processes[18,19,23]. For example, the N1 and N250 are differentially affected by inter stimulus intervals (ISIs) and thus have different refractory properties. Shortening the ISI attenuates the N1(m) while the N250(m) is enhanced or unaffected[18,24,25]. By changing the experimental design one can emphasize either component.

The buildup of N250m signal strength with shorter ISIs suggests it has a role in neural models of learning[25]. The idea that processing at this time-window reflects increased receptiveness to learn new items fits well with recent studies that have related prolonged or stronger activity in this time-window, particularly in the left hemisphere, to poorer performance on language related tasks[19,26]. This evidence suggests that left hemisphere auditory cortex activity around 250 ms plays a crucial role in processing language until more efficient cortical networks are established. Its potential role in language learning makes it especially interesting for SLI. However, to our knowledge there are no earlier studies focusing on the source activity in this time-window in children with SLI.

Earlier studies on auditory processing in SLI and dyslexia suggest deviances in P1-N1-P2 complex to simple speech and non-speech sounds[9–12,27–31], but the results are mixed. The few studies focusing on N250 in dyslexia reported either enhanced activation in dyslexics[26,31] or no difference to controls[32,33].

Hemispheric differences are likely to clarify discrepancies between studies and may provide pivotal information for understanding atypical language development. Typically developing children generally show a hemispheric preference for auditory brain responses[13,14,34], and it has been proposed that atypical auditory lateralization is the core underlying neural deficit of dyslexia[34]. Studies using EEG are, however, limited in their spatial sensitivity and less sensitive to hemispheric differences, possibly leading to a failure to consistently show a role for hemisphere-specific changes in (language) development. MEG can readily distinguish between sources in the auditory cortices of the left and right hemisphere and can utilize the components' source information to separate functionally distinct processes that mature differently[35]. Indeed, a longitudinal MEG study of auditory evoked responses and language development in typically developing children reported a positive correlation between an increase in P1m amplitude in the left hemisphere and linguistic tests[14]. Nevertheless, the functional significance of having atypical auditory cortical responses for language development has not been established.

The aim of the present experiment was to map typical and atypical N250m responses and to study its functional significance for auditory language skills by correlating the N250m to behavioral performances. Using MEG, we compared the auditory evoked dipole source activity in the N250m time window (~250 ms post-stimulation) of children with SLI and with typical language development in response to passively listening to sine-wave tones presented alternately to the right and left ear. The use of alternating tones allowed us to look at ipsi- and contralateral stimulation and to investigate possible differences between the two hemispheres in more detail. Based on the previous literature we hypothesized stronger neural activation approximately 250 ms after auditory stimulation in the left auditory cortex of children with impaired language development compared to typically developing children. We had no hypotheses pertaining to the behavioral performances, which were used to analyze post-hoc correlations.

Materials and Methods

Subjects.

The original source of the data reported here is a larger study by Helenius and colleagues, but only the behavioral results reported in Table 1 overlap with the original study[36]. Eleven children with SLI (mean age 9 years 8 months; age range from 106 to 127 months) and ten typical developing (TD) children (mean age 9 years 6 months; age range from 110 to 118 months) participated in that study. One child did not complete this particular passive listening task, resulting in a group of ten children with SLI (3 females) and ten TD children (3 females).

All participants were contacted through a larger study aiming to highlight the etiology, linguistic development and prognosis of SLI in the City of Vantaa, Finland[37,38]. The children in the SLI group had been diagnosed at the Helsinki University Central Hospital prior to school entry. All subjects were native Finnish speakers; one SLI child had a bilingual background. An informed consent was obtained from all subjects and/or their legal guardians, in agreement with the prior approval of the Helsinki and Uusimaa Ethics Committee at the Helsinki University Hospital. The experiments were approved by the Helsinki and Uusimaa Ethics committee and the methods were carried out in accordance with guidelines and regulations. The present study reports on the passive listening task not reported in the earlier articles. The behavioral results have been published before[36,37].

Behavioral testing and analysis.

All subjects were tested on a concise neuropsychological test battery tapping non-linguistic reasoning[39] (Block design), vocabulary[39], verbal short-term memory and reading related skills (Table 1). In the block design test, the subject is required to copy a pattern from a figure using colored blocks, in order to assess their ability to understand complex visual information. Verbal short-term memory was tested using the digit span forward subtest[39] and the sentence repetition tests[40] and phonological encoding/decoding with the pseudoword repetition test (NEPSY). In these tests, the subjects have to repeat a sequence of numbers, pseudowords or complete sentences. A measure of oral reading speed was obtained from silent reading of sentences[41] and reading aloud a narrative passage (the number of words read in 1 min). The sentence reading test (ALLU)[41] consists of 20 trials composed of a picture that matches one of the four written sentences. The task is to identify as many correct picture-sentence pairs as possible in 2 min and the total score is the number of correctly identified sentences. Naming speed was estimated as the time to name color squares, digits[42] (RAN) or color squares, letters and digits in a 5 × 10 matrix[43] (RAS). Phonemic awareness was assessed using the phonological

	TD Children	SLI children	p Value
Vocabulary[a]	11.2 (2.5)	8.5 (3.4)	ns, $p = 0.062$
Block design[a]	11.1 (1.9)	11 (3.2)	ns, $p = 0.932$
Digit span[b]	7.0 (1.2)	5.9 (1.1)	ns, $p = 0.051$
Pseudoword repetition[c]	11.5 (1.2)	7.7 (4.0)	$p = 0.015$
Sentence repetition[c]	10.0 (2.8)	5.7 (4.1)	$p = 0.013$
Phonological processing[c]	11.4 (2.3)	7.9 (2.5)	$p = 0.004$
Sentence reading[d]	13.2 (3.1)	11.1 (4.2)	ns, $p = 0.221$
Reading speed (min)	83.1 (35.5)	66.3 (30.4)	ns, $p = 0.270$
Naming speed (ms)[e]	46.6 (9.8)	47.5 (7.8)	ns, $p = 0.822$

Table 1. Cognitive profiles of the typically developing (TD) and language impaired (SLI) children. [a]WISC-III standard score [b]WISC-III raw score[39], [c]NEPSY standard score[40], [d]ALLU[41], [e]RAS[43], standard deviations in parentheses, p values from t-tests (adapted from Helenius and collegagues[36] with permission).

processing subtest of NEPSY[40]. The main purpose of the behavioral testing was to provide cognitive profiles for both groups (Table 1), not to diagnose SLI, as the SLI subjects had been diagnosed earlier. However, in order to study the functional significance of the auditory response, scores were also used to analyze post-hoc correlations between the behavioral tests that showed differences between groups ($p < 0.10$, Table 1) and the neural responses of interest (i.e. N250m). To do this, we used Kendall's tau non-parametric correlation because it is more appropriate for small data sets and/or when participants have the same scores, as in the current study[44]. We controlled the false discovery rate by using the Benjamini-Hochberg procedure[45]. Hannus and colleagues[37] provide interpretation of the different cognitive profiles in an earlier paper. In short, we expect the different p-values of the tests to reflect their sensitivity and specificity to diagnose SLI in Finnish children.

Stimuli and MEG recordings.

The stimulus was created using Sound Edit (Macromedia, San Francisco, CA, USA) and consisted of a monaural 50-ms (15-ms rise/fall time) 1-kHz sine wave tone, 65 dB HL. Stimuli were presented alternately to the left and right ear in order to probe ipsi- and contralateral auditory pathways in each hemisphere. Inter-stimulus interval (ISI) varied randomly between 0.8- and 1.2-s.

During the measurement, the child and one accompanying adult were seated in a magnetically shielded room and instructed to avoid excessive head movements. Stimuli were controlled with the Presentation program (Neurobehavioral Systems Inc., San Francisco, CA, USA) running on a PC and delivered to the subject through plastic tubes and earpieces. The children were asked to ignore the tones and they watched a silent cartoon during the whole recording.

The auditory cortical responses were recorded using a 306-channel whole-head system (Vectorview™, Elekta Neuromag Oy, Helsinki, Finland). This system measures magnetic field strength at 102 locations over the scalp; two orthogonally oriented planar gradiometers and one magnetometer at each location. Prior to the measurement, four head-position indicator (HPI) coils were attached to the participant's scalp. HPI coils were digitized with a 3-D digitizer in order to determine their location in relation to three anatomical landmarks; preauricular points and nasion. At the start of the measurement, HPI coils locations with respect to the MEG helmet were measured. Finally, eye blinks and movements were monitored by placing electro-oculogram (EOG) electrodes directly below and above the right eye and on the outer canthi of each eye.

MEG analysis.

The MEG signals were bandpass filtered at 0.1–200 Hz and sampled at 600 Hz. The raw data were processed using the spatio-temporal signal space separation method[46]. Offline, responses were averaged from −0.2 to 0.8 s relative to stimulus onset. Epochs contaminated by vertical or horizontal eye movements were rejected. To minimize the effect of heartbeat artifacts the MEG signals were offline averaged with respect to the heart signal and principal component analysis was used over this average to project out the resulting magnetic field component[47]. Finally, the data were manually checked to exclude epochs with major artifacts. On average 107 artifact-free averages were collected in the TD group and 111 in the SLI group.

The active source areas were modelled from the averaged data using equivalent current dipoles[48] (ECD). Averages were filtered with a 40 Hz lowpass filter and baseline corrected (−0.2 to 0 s). Xfit software was used to estimate the localization of the current sources (Elekta, Oy, Helsinki, Finland). In each subject, the same 20 planar sensor pairs were selected in each hemisphere that best covered the dipolar field pattern. To identify the cortical response around 250 ms after auditory stimulation, ECDs were accepted when (i) in the time window of interest (175–325 ms), (ii) they had a goodness-of-fit value of $>80\%$ and (iii) they had a predominantly inferior-posterior direction. These criteria were based on the pattern of activation that is most reliably repeatable for this specific time-window. ECD locations and orientations were fixed, while their amplitudes were allowed to vary. In each subject, the magnetic field patterns were visually inspected to identify local dipolar fields in each stimulus condition (i.e. ear and hemisphere). From the resulting four ECDs one was selected in each hemisphere that best fit the data in all conditions. As individual MR images of the subjects were not available, a spherical volume conductor model was used with the default center defined as the origin (0, 0, 40). Dipole moment amplitudes were defined as the average of the peak (175ms–325ms). Data points around the peak were included as long as they exceeded two standard deviations above the mean activation of the whole epoch.

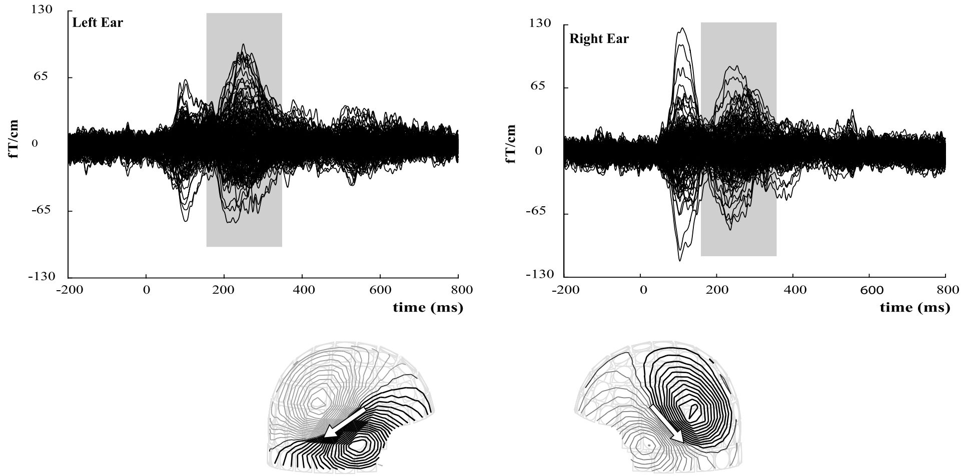

Figure 1. Butterfly plot of signals recorded by gradiometer sensors to left and right ear stimulation of one participant (top). ECD's were selected in the time-window of interest (window). The bottom figure shows the typical field distribution and dipole orientation (arrows).

Statistical model and analysis. The data were analyzed using R[49] and the packages *lme4* and *pbkrtest*[50,51]. The amplitude values of each factor: ear (2) and hemi (2) were extracted for each participant in each group (2), resulting in four amplitude values for each participant.

In order to assess the effect of impaired language development on auditory evoked source activity we used a linear mixed model (LMM) or, more specifically, a random intercept model[44,52,53]. A random intercept model is, in our case, more suitable than ANOVAs because it resolves the non-independence of multiple responses from the same subject by assuming a different baseline value for each subject (i.e. random intercept). In addition, it has more opportunities to control for possible problems that may arise due to our small sample size (i.e. power and type 1 error rate). LMM has fewer assumptions compared to ANOVAs[54], violations of which affect the type 1 error rate and power of ANOVA F tests[55].

In the estimation of the best model for the covariance structure (compound symmetry), we used a backward method with the maximum likelihood (ML) approach. The significance test to be used was the chi^2-test based on the likelihood ratio test (LRT) backward selection heuristic of two nested models to compare the models. For small sample sizes, this approach was reported to be more conservative compared to the Akaike information criterion (AIC), maintaining the type 1 error rate of a maximum model[56], while increasing the power substantially[57]. The final model is a collection of fixed and random effects. Here, we calculated it with the restricted maximum likelihood (REML) approach to reduce the bias of the estimators of variances of the random intercept and the residual. The REML is less affected by a small sample size and has consistently shown lower type 1 error rates[58,59].

In the diagnostics part of the model, we first confirmed the normality of residuals to be valid using a qq-plot and a scatter plot for groups. Furthermore, we established the normality of random intercepts utilizing a qq-plot. Using the final model, we defined contrasts for separate sets of regression coefficients. For testing if the contrast is zero, we used the Kenward-Roger (KR) approximation for F-test by Halekoh and Højsgaard[51], as this method produced acceptable type 1 error rates even for smaller samples[59,60]. In the contrast calculations from KRmodcomp, we obtained the numerator $d = 1$. Then, F statistics is the squared t statistics, and for simplicity, contrasts are reported by using t-statistics, dfs and p-values.

Results

Source analysis. In 90% of the participants (18/20) we were able to select at least one dipole in each hemisphere in the time-window of interest. In the other two (one in SLI group and one in TD group) we were unable to find dipoles meeting our criteria and thus they were excluded from further analysis. In Fig. 1, the gradiometer butterfly plots of the auditory evoked fields of one participant are shown; the time window used for source localization is marked by a window. The corresponding field distributions and dipole orientations are depicted on the bottom of Fig. 1.

Figure 2 shows the location of the selected dipoles (x, y coordinates in axial plane) of each individual and the grand average location of the two groups. Figure 3 depicts the resulting grand average waveforms. There were no significant differences between the groups on any of the (x, y, z) coordinates ($p \geq 0.28$).

Modelling. In the first most inclusive model we had all variables (group, ear, and hemi), their pairwise interactions and a three-way interaction. Using a cut-off of $\alpha = 0.05$, we dropped first the three-wise interaction group*ear*hemi, chi$^2(1) = 0.085$, $p = 0.78$, and second the pairwise interaction group*ear, chi$^2(1) = 0.006$, $p = 0.94$. Furthermore, the equality of variance in SLI and TD group was checked and could be assumed, chi$^2(1) = 1.263$, $p > 0.26$. The final random intercept model was calculated using the restricted maximum

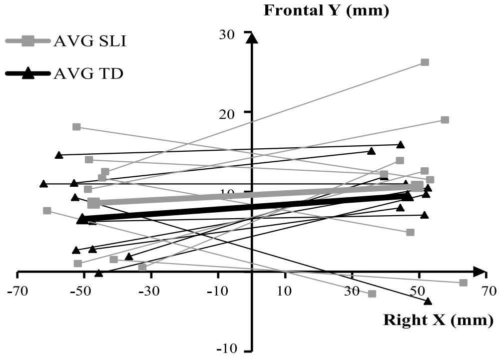

Figure 2. Dipole x and y coordinates in axial plane of each participant (thin lines) in SLI (grey) and TD group (black) as well as their averages (thick lines).

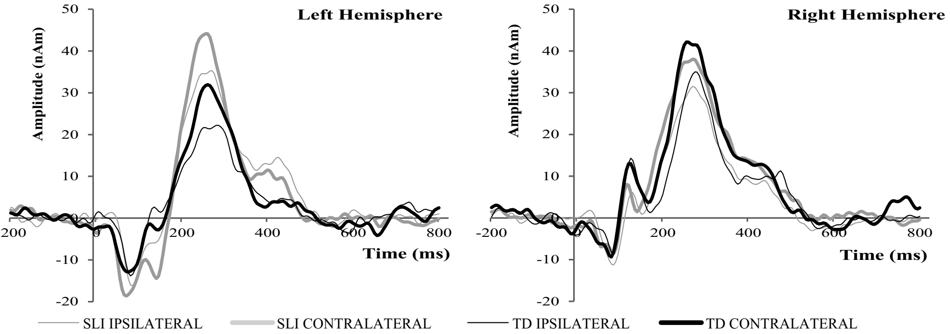

Figure 3. Grand average time-course of activation of the dipolar sources in the left and right hemisphere plotted separately for contralateral (thick lines) and ipsilateral (thin lines) responses for SLI (grey) and TD (black) group.

	Est. Value (s.e.)	DF	t-value	p-value
(Intercept)	33.12 (4.28)	50	7.730	0.000
Group[a]	−0.45 (5.52)	16	−0.082	0.936
Ear[a]	8.34 (3.52)	50	2.368	0.022
Hemi[a]	−1.49 (4.31)	50	−0.346	0.731
Group × Hemi	13.19 (4.98)	50	2.647	0.011
Ear × Hemi	−13.71 (4.98)	50	−2.752	0.008

Table 2. Fixed effects of the model: estimate (standard error(s.e.)), degrees of freedom, t-value and p-value. [a]Baseline for group: TD, for ear: Right and for hemi: Right.

	Lower	Est.	Upper
Intercept	5.64	9.03	14.44
Residual	8.69	10.57	12.86

Table 3. Approximate 95% confidence intervals for the standard deviation of random effects.

likelihood (Tables 2 and 3). In Table 2, the estimates, standard errors and their ratios (t-values) are shown. Estimates and confidence intervals of the random effects are shown in Table 3.

Effect of ipsilateral vs. contralateral stimulation. The mixed effects model revealed an interaction between ear and hemi, $t(50) = -2.752$, $p = 0.008$. Generally, contralateral stimulation showed greater amplitudes compared to ipsilateral stimulation. In the right hemisphere this estimated difference (ED) was clearer (ED = 8.34, SE = 3.52) and significant $t(50) = 2.367$, $p = 0.022$. In the left hemisphere this difference was smaller (ED = −5.37, SE = 3.52) and not significant $t(50) = 1.524$, $p = 0.134$. Figure 4 depicts the individual (top) and

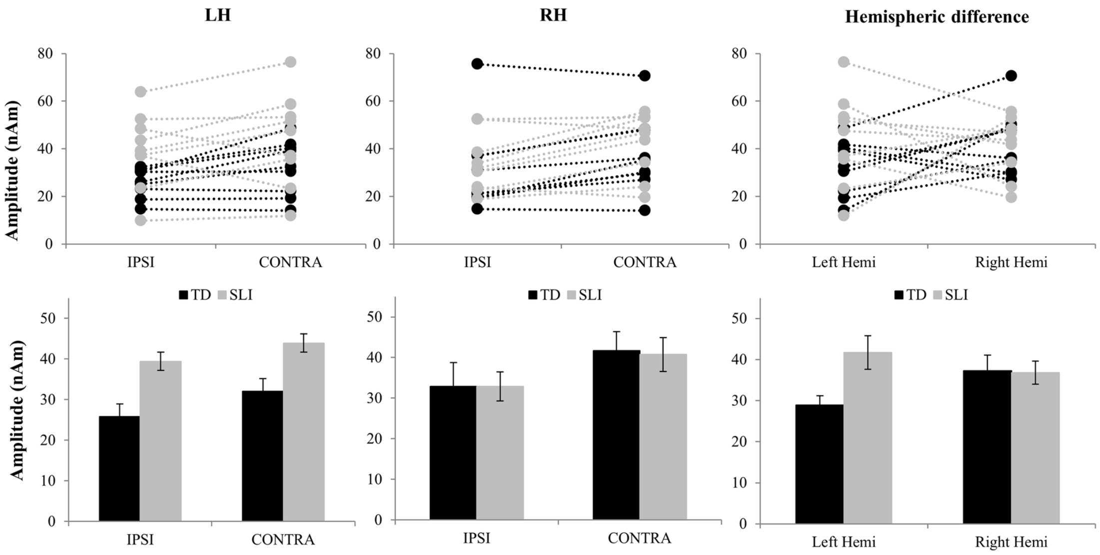

Figure 4. Individual (top) and averaged (bottom) strength of activation in the left hemisphere (LH; left) and right hemisphere (RH; middle) in response to ipsi- and contralateral auditory stimulation of children with SLI (grey) and typical language development (black). Hemispheric differences (right) are plotted as the difference in activation strength to contralateral stimulation (i.e. right ear for left hemisphere and vice versa). Whiskers in the bottom figures represent the standard error of the mean (SEM).

averaged (bottom) strength of activation resulting from ipsi- and contralateral stimulation in the left (left) and right (middle) hemisphere for both groups. The ipsi-contralateral effect did not seem to differ between groups since neither the three-way interaction (ear*hemi*group) nor the two-way interaction (ear*group) were significant ($chi^2(1) = 0.085$, $p = 0.771$ and $chi^2(1) = 0.006$, $p = 0.937$, respectively).

Group differences in the two hemispheres.

The mixed effects model revealed a significant interaction between group and hemisphere, $t(50) = 2.648$, $p = 0.011$ (Table 1). This effect was limited to the left hemisphere as the difference between groups (ED $= -12.74$, SE $= 5.52$) was significant in this hemisphere for both the ipsi- and contralateral stimulation, $t(24.70) = 2.306$, $p = 0.03$. In contrast, the difference between groups in the right hemisphere was negligible (ED $= 0.45$, SE $= 5.52$), $t(24.70) = 0.082$, $p = 0.935$. Figure 4 (left vs. middle) depicts the plots corresponding to this difference. Finally, TD children showed significantly higher amplitudes in the right compared to the left hemisphere (ED $= 8.35$, SE $= 3.52$, $t(50) = 2.370$, $p = 0.022$), indicating a cortical asymmetry in this group (Fig. 4; right). Children in the SLI group show the opposite pattern with stronger activation in the left hemisphere compared to the right hemisphere (ED $= -4.84$, SE $= 3.52$), but this difference was not significant $t(50) = -1.374$, $p = 0.176$.

Correlation between behavioral skills and brain responses.

Post-hoc correlations were performed between the amplitude of the N250m to contralateral stimulation and the behavioral measures for each group. Data were checked for outliers, and none were found (all individual values < 1.8 SD). In the TD group, no significant correlations were found. However, in the SLI group, we found a significant positive correlation between phonological processing scores and N250m amplitude in the left hemisphere $\tau_b = 0.774$, $p = 0.006$, but not the right hemisphere $\tau_b = 0.278$, $p = 0.321$. In the SLI group, those with higher N250m amplitudes in the left hemisphere performed better on the phonological processing task (Fig. 5). When corrected for the other behavioral tests that showed differences between groups (i.e. vocabulary, digit span, pseudoword repetition and sentence repetition), the corrected p-value was 0.03.

Discussion

In this study we assessed typical and atypical variation in the N250m response and examined its functional significance for language processing. As was hypothesized, auditory processing in the cortical time-window of the N250m was altered in children with impaired language development and this alteration was limited to the left hemisphere; N250m dipole moment in the left hemisphere was stronger in SLI children. In our view these findings illustrate the association between maturation of the auditory cortex in the left hemisphere and language development, with relevance for neurodevelopmental disorders.

Our results provide further support for the hypothesis that stronger or more sustained activation in the cortical timing of the N250(m)[31], especially in the left hemisphere[19,26], is indicative of less developed language skills. This cortical response is observed to be specific to the developing brain[16,17,19] and weaker neural activation in this time window has been related to better reading skills in typical developing children[19,26,31]. Indeed, the decrease in amplitude of the N250(m) (and increase in N1(m)) have been speculated to reflect more automatized auditory

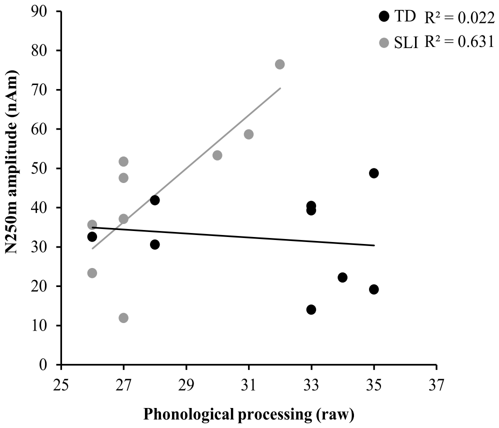

Figure 5. Scatterplot representing the correlation between phonological processing (raw score) and N250m amplitude in the left hemisphere, to contralateral stimulation, for the SLI (grey) and TD (black) group.

processing[19,61]. Paradoxically, in our clinical group, higher N250m amplitudes in the left hemisphere were related to better performance on a phonological processing task; a core deficit in SLI and a crucial component in learning to read[62,63]. Presumably, children with SLI rely more strongly on neural sources in the left hemisphere as a possible compensatory mechanism for delayed maturation of language processing. However, this correlation should be interpreted with care, as correlations typically only stabilize at considerably larger sample sizes[64]. Therefore, we do not expect the current correlation coefficient to accurately represent the true value in the SLI population and acknowledge that this might be an over-estimation of the effect size[65] or a type-1 error. Nevertheless, our claim is substantiated by an EEG study that identified an enhanced N250 response as a compensatory mechanism for phonological processing deficits in dyslexic children but not in typical developing children[31].

The simplest account of our data is an enhanced auditory brain response in the left hemisphere of children with SLI. Several studies have already observed the relationship between language skills and auditory evoked responses in left hemisphere[14,36,66] and some have focused on the N250(m)[19,26]. However, the source activity of the N250m has not been contrasted between children with typical and impaired language development. By using MEG ECD source modelling techniques, we were able to show hemisphere-specific alterations (i.e. increase in left hemisphere exclusively) in the auditory evoked responses of children with impaired language development. In our view, this illustrates the different role of the two hemispheres in developmental language disorders and emphasizes the need to include spatial information to properly distinguish between activation patterns possibly varying in time and between hemispheres. For estimating the detailed location of activation in the two hemispheres, information on individual brain anatomy should be used, which was not available in the present study. Importantly, group differences in source strength could not be explained by differences in dipole locations.

Although it is not possible to draw strong conclusions on hemispheric asymmetry based on our data, given the recent debate on the role of lateralization and asymmetry in developmental language disorders[67–70], we will discuss findings we think are relevant to this discussion. Furthermore, we will speculate on how the interaction between hemispheres could be affected by developmental language disorders.

We used monaural stimulation in order to probe ipsi- and contralateral pathways, allowing us to investigate hemispheric differences (left vs right), laterality effects (ipsi vs contra) and their interactions. The data showed a contralaterality effect in both groups; a greater amplitude in the hemisphere contralateral to the stimulated ear compared to the ipsilateral hemisphere. Typical developing children showed overall higher amplitudes in the right compared to the left hemisphere. Both results are in good agreement with previous literature on hemispheric asymmetry in pure tone processing and contralaterality effects in children[13,71] and adults[13,72–75]. In the present study however, children with impaired language development showed an opposite, but not statistically significant, asymmetry pattern, indicating a lack of typical asymmetry similar to what was found in dyslexic children[34].

Given that speech vs. nonspeech processing typically reflect opposite asymmetry patterns (i.e. leftward vs. rightward respectively), it is important to distinguish between studies looking at auditory and language lateralization. In addition to opposite asymmetry patterns of speech and nonspeech processing, the theory of asymmetric sampling in time (AST) proposes that cerebral asymmetries relate more to the temporal features of auditory information. In this view, the right hemisphere samples slow (syllabic) rate auditory input (~3–7 Hz) and the left hemisphere fast (phonemic) rate auditory input (~12–50 Hz)[76–78]. For certain language processes (e.g. phonological processing), both temporal features must be integrated. This dynamic nature of cerebral asymmetry needs to be considered when discussing asymmetries and hemispheric differences in relation to language and auditory processing, and make it likely interhemispheric connections play a crucial role.

In addition to functional hemispheric differences, anatomical hemispheric differences might also explain the differences between our two groups. Indeed, studies reporting white and grey matter structural differences in children with developmental language disorder are numerous[79–81]. However, of special interest for M/EEG studies is a report that demonstrated a more convoluted auditory cortex produces stronger cancelation effects resulting in lower measured EEG and MEG signal[82]. The authors argued that the left hemisphere is typically more convoluted resulting in the rightward bias in pure-tone processing. In the present study, the enhanced auditory responses in the left hemisphere of the SLI group could be explained by a less convoluted left auditory cortex, or more focal cortical activity in the left hemisphere compared to controls[82]. Importantly however, a recent study investigating the neuroanatomical basis of developmental dyslexia identified an atypical sulcal pattern with more convolutions in left hemispheric perisylvian regions compared to controls as a biomarker of dyslexia[83]. Assuming this result can be extrapolated to our subjects, one would expect lower amplitudes in the left hemisphere in the SLI group. Future studies combining neuroanatomical and functional (MEG) data are needed to clarify laterality of auditory and language processing in developmental language disorders.

Even though it appears inevitable that an abnormal neural activity pattern in the left hemisphere disrupts the cerebral asymmetry of language processes, the question remains whether interhemispheric auditory connections are affected or that it only reflects the primary dysfunction in the left hemisphere. Due to the nature of the present study and the complexity of the auditory system, we cannot conclusively say whether this is the case. Based on our results, it is tempting to conclude that auditory pathway interactions are unaffected by impaired language development, as differences in the right hemisphere were negligible. It should be noted however, that during monaural stimulation, there is no competition between both ears. Others have argued that the stronger the competition between the ears (e.g. in a dichotic listening task), the stronger the interactions between the auditory pathways[84].

To examine interaural interaction in developmental language disorders the 'frequency tagging' method can be used. With this method, auditory input to each ear is 'tagged' with amplitude modulations of different frequencies that can later be decoded from the cortical responses. This has proven a useful tool to evaluate the central auditory pathways in more detail[85]. Indeed, one study utilizing this method observed weaker ipsilateral suppression (a measure of interaural interaction) in dyslexics depending on the strength of ROBO1 expression (a known dyslexia gene)[86]. The authors demonstrated that the weaker this gene-expression in dyslexic individuals, the weaker the interhemispheric interaction. Interestingly, this gene is also suggested to be involved in neuronal migration underlying brain lateralization in healthy subjects with a specific function in supporting a short-term buffer for arbitrary phonological strings[87]. These results indicate that impaired language development is associated with weaker interaction between auditory pathways which may be especially detrimental for phonological processing.

Two issues regarding the increased N250m response amplitude and atypical hemispheric balance still require clarification. First, this study's design was not well suited to determine whether they are a cause, correlate or consequence of developmental language disorder. Similar to many comparable studies, not all our SLI children show an increased N250m and atypical hemispheric balance. Thus, atypical hemispheric balance (or indeed increased N250m) should not be seen as a critical cause of SLI. We suggest it is more likely a consequence, as we argue that the increased N250m can (partly) compensate for the language deficit. It is also possible the processing differences in the left hemisphere causes problems in language-related functions or that the auditory and language deficits are both markers of an underlying neurodevelopmental disorder[9].

Second, we are left with an apparent dichotomy where the N250m is suggested to be both indicative of poorer (in TD group) and superior (in SLI group) language skills. We do not consider it an impossibility that processing in this time-window is both an indicator of language or auditory development as well as a useful tool for the developing brain. The fact that this neural process is present in most children suggests it is beneficial for development, the fact that in adults it typically is not, suggests the brain develops a more efficient way of processing auditory stimuli. We surmise that neural processing in this time-window is exceptionally flexible, which should be a useful tool, and indeed a necessity, in the learning environment of the child brain.

This study's main limitation is its sample size. Small sample sized studies raised considerable debate[65,88–92] and we agree that they deserve additional scrutiny. We strived for maximal power by using methods that have specific advantages concerning type 1 error rates and statistical power with small sample size studies, namely; (i) a statistical model with fewer assumptions (LMM) (ii) model selection (LRT backward heuristic), (iii) model fit (REML), and (iv) evaluating significance (KR approximation). Furthermore, several authors have defended small-N designs, mainly for its inferential validity[88,90–93]. Nevertheless, we caution against taking our findings, especially the correlation, at face value.

To conclude, we provide evidence that neural activation at ~250 ms is functionally meaningful for the integrity of language skills and substantiate the claim that enhanced left-hemisphere auditory activation reflects a core neurophysiological manifestation of developmental language disorders. We found significantly stronger activation in the left hemisphere of the SLI group, as compared to controls, that unmistakably differed in language skills. We suggest this might reflect a compensatory mechanism for language processes. The effect was isolated to the language dominant left hemisphere and is thus in agreement with other studies associating altered neural responses in the left hemisphere to language skills and impaired language development.

Data Availability

The dataset analyzed during the current study are not publicly available due to legal restrictions but are available from the research group on reasonable request.

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Author Contributions

T.P. and P.H. designed the research and performed the experiments, S.B. analyzed the data and wrote the main manuscript, S.B. and S.K. did the statistical analysis. All authors reviewed the manuscript.

Additional Information

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II

ACTIVITY LEVEL IN LEFT AUDITORY CORTEX PREDICTS BEHAVIORAL PERFORMANCE IN INHIBITION TASKS IN CHILDREN

by

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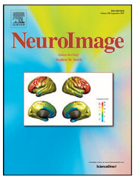

Activity level in left auditory cortex predicts behavioral performance in inhibition tasks in children

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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 in school-aged children (6-14y) to show that child 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 activation pattern was significantly correlated with the variability of behavioral response time. Since this activation pattern is typically 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 cortical resources for cognitive control from sensorimotor associations in the auditory cortex of children to top–down regulated control processes involving (pre)frontal and cingulate areas in adults.

1. Introduction

The development of basic auditory circuits in the brain, and consequently efficient and versatile auditory behavior, relies on everyday aural experiences (Gordon et al., 2003; Tierney et al., 2015). Auditory sensory processing during development not only enables human communication and language learning, but it also plays a role in cognitive and sensorimotor aspects of behavior (Kraus et al., 2012). Indeed, the effect of auditory experience extends, for example, into attention and cognitive control processes that rely on auditory processing (Kraus and White-Schwoch, 2015). Presumably, an interaction between auditory, sensorimotor and cognitive processing governs the resulting phenotype of goal directed behavior (Kraus and White-Schwoch, 2015). Given the evident importance of auditory sensory development for cognitive skills, we have surprisingly limited understanding of how the typical development of cortical auditory processing 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 prolonged activation pattern approximately 250ms after auditory stimulation, as it is typically reported in a wide age range of children but is clearly less pronounced 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 prolonged activation pattern at ~250 ms (N2m/N250m) (Paetau et al., 1995; Ponton et al., 2000; Čeponienė 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, prolonged, activity (Sussman et al., 2008) 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 (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 timeline of sensory activation. To go beyond the descrip-

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tive 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, activity in these time-windows show different refractory periods; whereas shortening the inter stimulus interval (ISI) attenuates the earlier response pattern, the later, prolonged activity is enhanced (or unaffected) (Takeshita et al., 2002; Karhu et al., 1997).

The later time-window (i.e., ~200-300ms) shows remarkable differences between adults and children. The auditory activation in children in this late time-window is evoked even by purely passive stimulation (van Bijnen et al., 2019; Parviainen et al., 2019; Albrecht et al., 2000; Takeshita et al., 2002; Johnstone et al., 1996), but under these circumstances it is typically absent in adults (Sussman et al., 2008; Ruhnau et al., 2011). Instead, adults consistently show an evoked response in this time-window only in active tasks, localized in the cingulate cortex and important for inhibition and cognitive control processes (Falkenstein et al., 1999; Nieuwenhuis et al., 2003; Huster et al., 2010). In other words, the passive nature of the child's auditory response would suggest it is related to obligatory, stimulus-dependent processes. However, timing-wise it overlaps with known cognitive processes in the adult brain, such as cognitive control and response inhibition.

The prolonged activation pattern in children 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) inhibition (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 in language tests (Parviainen et al. 2011; Hämäläinen et al., 2013). An empirical link between (the maturation of) this prolonged activity pattern and cognitive skills such as attention and inhibition has not been established.

Here, we utilized the excellent temporal accuracy of electrophysiological recordings and increased spatial sensitivity of combined MRI, MEG and EEG techniques to explore the behavioral significance of the child auditory activation at 250 ms. We used comparisons between three variations of a simple auditory oddball paradigm (Fig. 1); a passive oddball task, a "detection" oddball task (press button for deviant tone) and an "inhibition" or Go/No-go task (press button for standard tone). Based on earlier findings we expected the child auditory response to be present in both the active and passive (oddball & Go/No-go) tasks. We focused on (i) the effect of task on the amplitude of the auditory activation pattern in children and (ii) the relationship between this amplitude and behavioral performance measures of inhibition and/or attention (reaction time, response accuracy and intra-individual variability in reaction times).

We combined M/EEG recordings and individual MRIs 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 generally has a better spatial resolution compared to EEG, the sensitivity of MEG decreases with increasing source depth and radial orientation (Baillet, 2017; Gross, 2019).

2. Materials and Methods

2.1. Participants

Participants were Finnish speaking school-aged (6 years in Finland) children (6-14 years) recruited through schools and the National Registry of Finland. None of the participants had neurological disorders or were on medication affecting the central nervous system. In total, 78 children 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 Fig. 1), 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. 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). 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 activation pattern 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 in accordance with the Declaration of Helsinki. All participants received compensation for participation (movie ticket or gift card).

2.2. 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 kHz (standard tone(ST); 70%) or 1.5 kHz (deviant tone(DT); 30%) at 65 dB SPL and were created with the Audacity software® (version 2.3.3) (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 (Fig. 1).

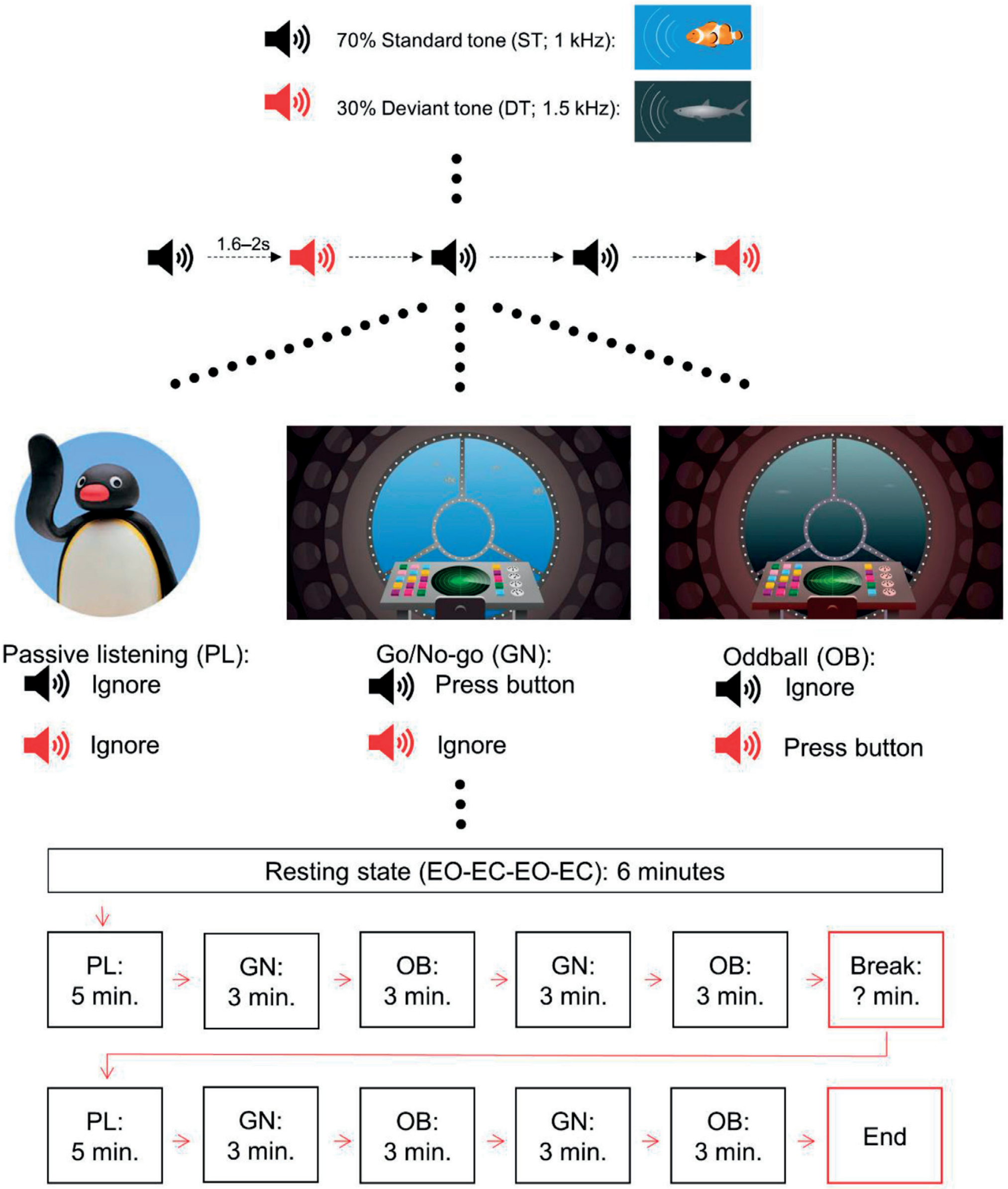
The stimuli were embedded in a game. We created a visual environment resembling a submarine, where the captain gave instructions to the participants "inside" the submarine (Fig. 1). Visual stimuli were created by Studio Dennis Parren (www.dennisparren.com) and were there for the sole purpose of engaging the participants. All stimuli were controlled by PsychoPy (version 3.2) (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 high-fidelity sound system.

2.3. 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 (Fig. 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 (Fig. 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



	#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

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

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 Fig. 1.

2.4. *M/EEG and MRI*

The brain responses were recorded using a 306-channel MEG system and the integrated EEG system (Elekta Neuromag® TRIUX^{TM}, 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 = 90°, matrix size = 256 × 256, slice thickness = 1.2 mm, sagittal orientation.

2.5. *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) 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 (SyS) 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.

2.6. *Data analysis*

MEG data were first processed with the temporal signal space separation (tSSS) and movement compensation options, implemented in the MaxFilter^{TM} 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 0.16) (Gramfort et al., 2014; Gramfort et al, 2013). Continuous M/EEG recordings were low-pass-filtered with a finite-impulse-response filter at 40 Hz, the EEG data were 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., 1999a; Fischl et al., 1999b). 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 0.33, 0.0132 and 0.33 S/m. 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 prolonged activity 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 Figs. 4 and 7). Only negative averages were included in the statistical analysis, as we assumed positive values would reflect cortical activity unrelated to our response of interest.

2.7. *Statistical analysis*

As shown in Fig. 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

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.

	Mean	SD	Range
Age (years)	10.17	1.44	6–14
M/EEG experiment			
GN RT (ms)	484.20	82.74	328–693
GN ICV	0.4	0.09	0.19–0.56
GN ERR ($\sqrt{\%}$)	2.54	1	0.53–4.87
OB RT (ms)	480.67	82.03	234–728
OB ICV	0.38	0.11	0.18–0.82
OB ERR ($\sqrt{\%}$)	1.78	0.85	0–3.87
Behavioral assessment			
SSRT (ms)	205.94	56.20	87–351
Digit span*	10.55	2.65	5–17
Symbol search*	12	2.58	5–18
Coding*	10.88	2.98	4–19
Block design*	11.61	2.97	4–17
Similarities*	10.39	2.63	2–16

* = standardized score.

(ST or DT), probability (30% or 70%) and motor response (None) were identical, and the number of trials close to equal.

A forward multiple linear regression analysis was performed to test for the effects of age, sex, hemisphere, task and behavioral performance. 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. Partial correlations (controlling for age) were calculated for behavioral performance measures and the 2 × 2 (hemi x task) auditory brain responses.

Subsequently, 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. We report our original p-values for all comparisons that we make, but use an alpha of < .01 to limit the false positives. In Bonferroni terms we thus (only) correct for five different statistical tests. We argue a more conservative correction might not be appropriate as our tests are not independent. Note that the regression models still select predictors based on an alpha of .05.

3. Results

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. We found no significant effect of age on the response in the left- and right hemisphere; the age distribution and age-brain associations are depicted in Fig. 2.

Both in the passive and the active tasks the children's strongest activation pattern in our time-window of interest was located in the auditory cortex (Fig. 3). We first present the Passive vs Go/No-go (deviant tones) comparison and subsequently the Passive vs Oddball comparison (standard tones).

3.1. Passive vs Go/No-go

3.1.1. Left hemisphere auditory activity at ~250ms predicts behavioral performance on inhibition tasks

The source waveforms for the PL and GN deviant tones are presented in Fig. 4. Fig. 5 shows the individual data points as well as the average (line) and standard deviation (bar) extracted from the neural responses in the transverse temporal gyrus for each condition.

The multiple linear regression model, as shown in Table 2 revealed that hemisphere, ICV, age and SSRT are significant predictors of the auditory brain responses. Sex, task, RT and response accuracy did not significantly contribute to the model.

To further investigate the behavioral relevance of the brain responses, and because age and behavioral performance measures are strongly correlated, we subsequently performed a bootstrapped (10.000 samples) partial correlation (controlled for age). This revealed significant positive correlations between amplitudes in the left hemisphere (irrespective of task) and the ICV on the Go/No-go task (Table 3). Stronger left-hemisphere activation was related to lower intra-individual variability (ICV) in reaction times.

More specifically, in the PL task, a stronger left-hemisphere response amplitude was related to decreased ICV ($r = .479$, 95%CI = [.195 – .661], $p = .000$) SSRT ($r = .331$, 95%CI = [.113 – .543], $p = .02$) and ERR ($r = .314$, 95%CI = [-.026 – .553], $p = 0.028$). But only the relationship between L PL and ICV was significant at our alpha ($p < .01$). 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], $p = 0.041$). But only the relationship between L GN and ICV was significant at our alpha ($p < .01$). Fig. 6 shows the corresponding scatterplots.

Finally, 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 task. As shown in Table 4, the amplitude of the auditory response in the left hemisphere (to the No-go tone) was a significant predictor of intra-individual variability of reaction time ($p < .001$).

3.2. Passive vs Oddball

3.2.1. Left hemisphere auditory activity at ~250ms predicts stop-signal reaction time

The source waveforms for the PL and OB standard tones are presented in Fig. 7. Fig. 8 shows the individual data points as well as the average (line) and standard deviation (bar) extracted from the neural responses in the transverse temporal gyrus for each condition.

The multiple linear regression model, as shown in Table 5 revealed that hemisphere, SSRT and age are significant predictors of the auditory brain responses. Sex, task, RT, ICV and response accuracy did not significantly contribute to the model.

To further investigate the behavioral relevance of the brain responses, and because age and behavioral performance measures are strongly correlated, we subsequently performed a bootstrapped (10.000 samples) partial correlation (controlled for age). This revealed significant positive correlations between amplitudes in left hemisphere during the OB task and SSRT (Table 6.). 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], $p = 0.008$).

As shown in Table 7, the linear regression model revealed that the strength of the auditory response in the oddball task was not a significant predictor of the SSRT ($p = 0.019$) at our alpha ($p > .01$).

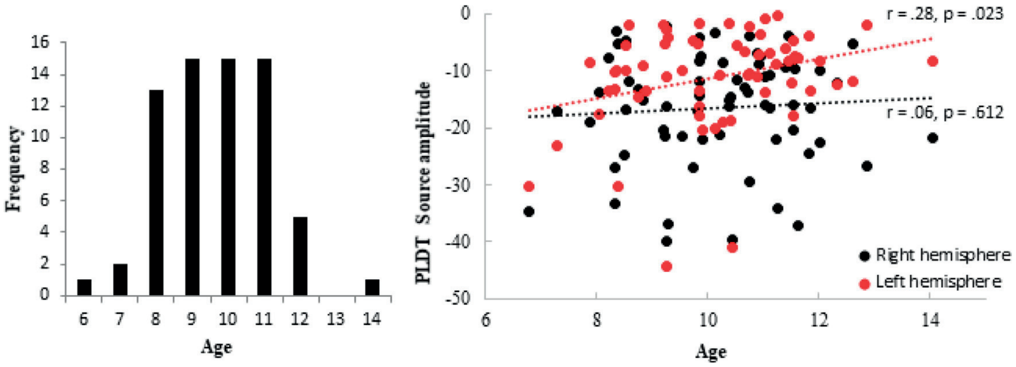


Fig. 2. Age distribution (left) and age brain associations (right) of the passive listening deviant tone (PLDT) in the left- and right-hemisphere.

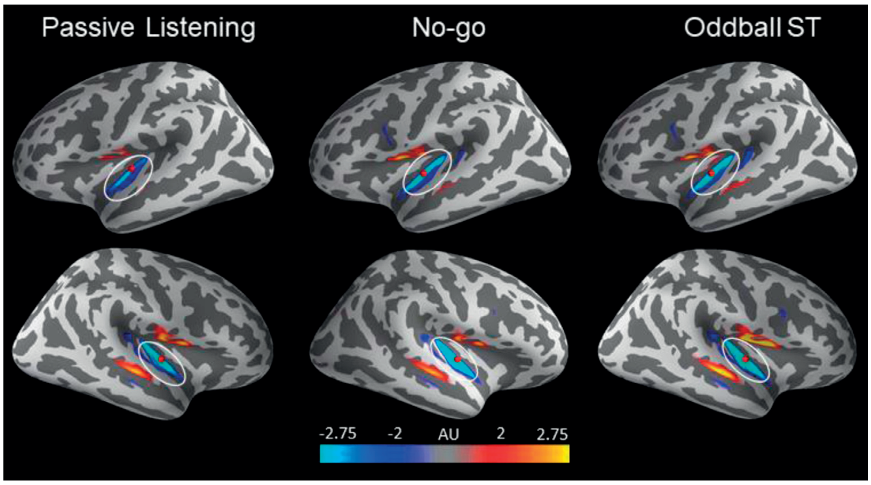


Fig. 3. Grand-average 3D visualization of the M/EEG combined estimates of the source distribution at 248ms post auditory stimulation in children. Superior temporal regions circled in white, red dot represents peak coordinate.

Table 2

Forward selection multiple linear regression analysis using hemisphere, task, age, sex and behavioral performance as predictors of the brain responses at ~250ms.

	B	*SE B*	Standardized beta	ΔR2	Significance F change
Step 1				.06	.000
Constant	-21.73	1.93			
Hemisphere	4.82	1.22	0.246		
Step 2				.03	.003
Constant	-29.96	3.37			
Hemisphere	4.82	1.2	0.246		
GN_ICV	20.62	6.96	0.18		
Step 3				.02	.015
Constant	-41.88	5.89			
Hemisphere	4.82	1.19	0.246		
GN_ICV	23.88	7.02	0.211		
Age	1.04	0.43	0.152		
Step 4				.04	.002
Constant	-51.91	6.61			
Hemisphere	4.82	1.17	0.246		
GN_ICV	16.42	7.29	0.145		
Age	1.55	0.45	0.226		
SSRT	38.03	12.11	0.216		

Note: B = Unstandardized beta, SE B = standard error for the unstandardized beta, ΔR2 = R2 change. GN_ICV = Go/No-go intraindividual coefficient of variability. Excluded variables: reaction-time, response accuracy, sex and task ($p > .05$).

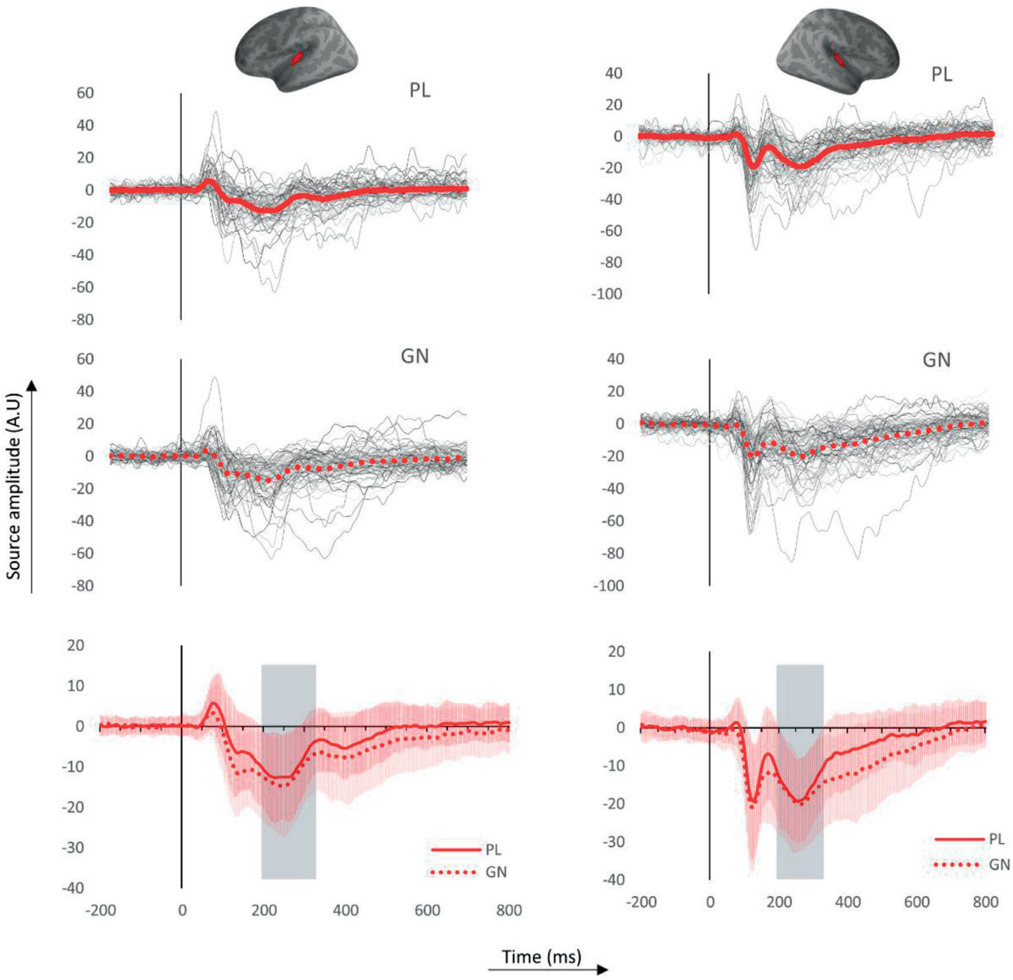


Fig. 4. Source waveforms in the left and right transverse temporal gyrus for the PL (top) and GN (middle) deviant tones. Top and middle graphs show individual waveforms (gray) and the grand average waveform (red). Bottom graph shows the grand average waveforms of the PL (solid line) and GN (dotted line) and their standard deviation (red shaded area). Child- activity pattern starting at ~200 ms highlighted in gray shaded area.

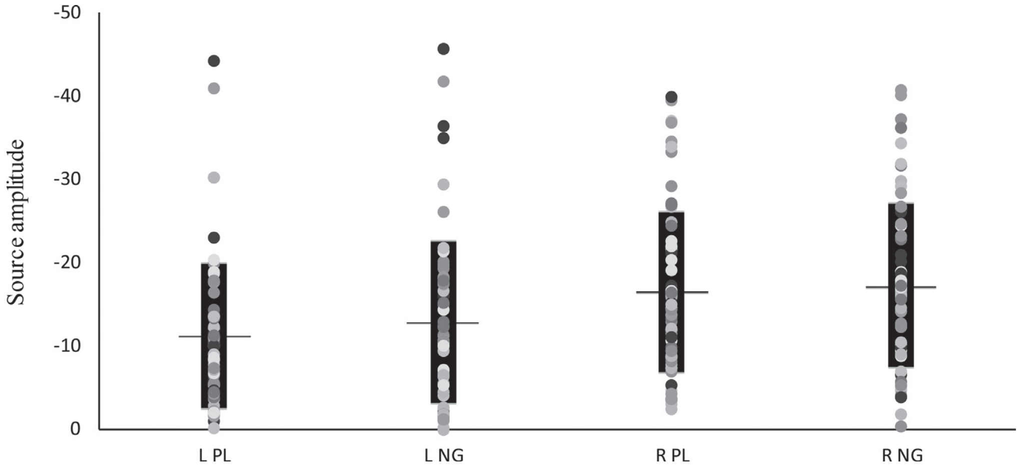


Fig. 5. Individual data points (dots), average (horizontal line) and standard deviation (black bar) for the conditions: passive listening (PL) deviant tone and No-go (NG) deviant tone in the left (L) and right (R) hemisphere.

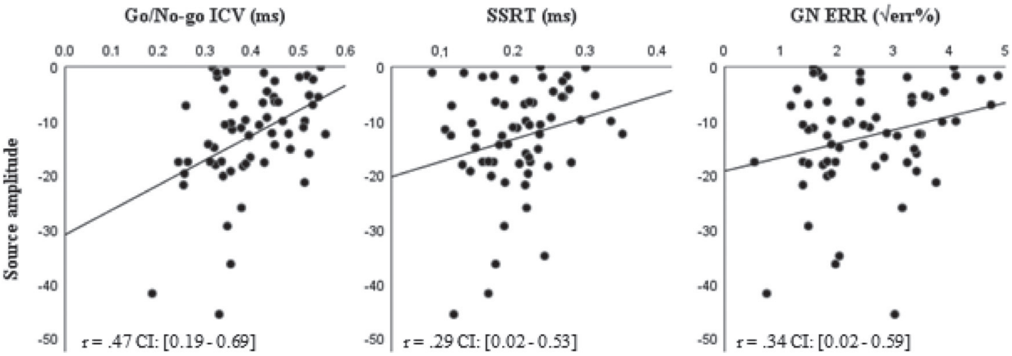


Fig. 6. Scatterplots of the responses at ~250ms to the No-go tone and the behavioral performance measures: intraindividual coefficient of variability (ICV; left), stop-signal reaction time (SSRT; middle), and response accuracy (right).

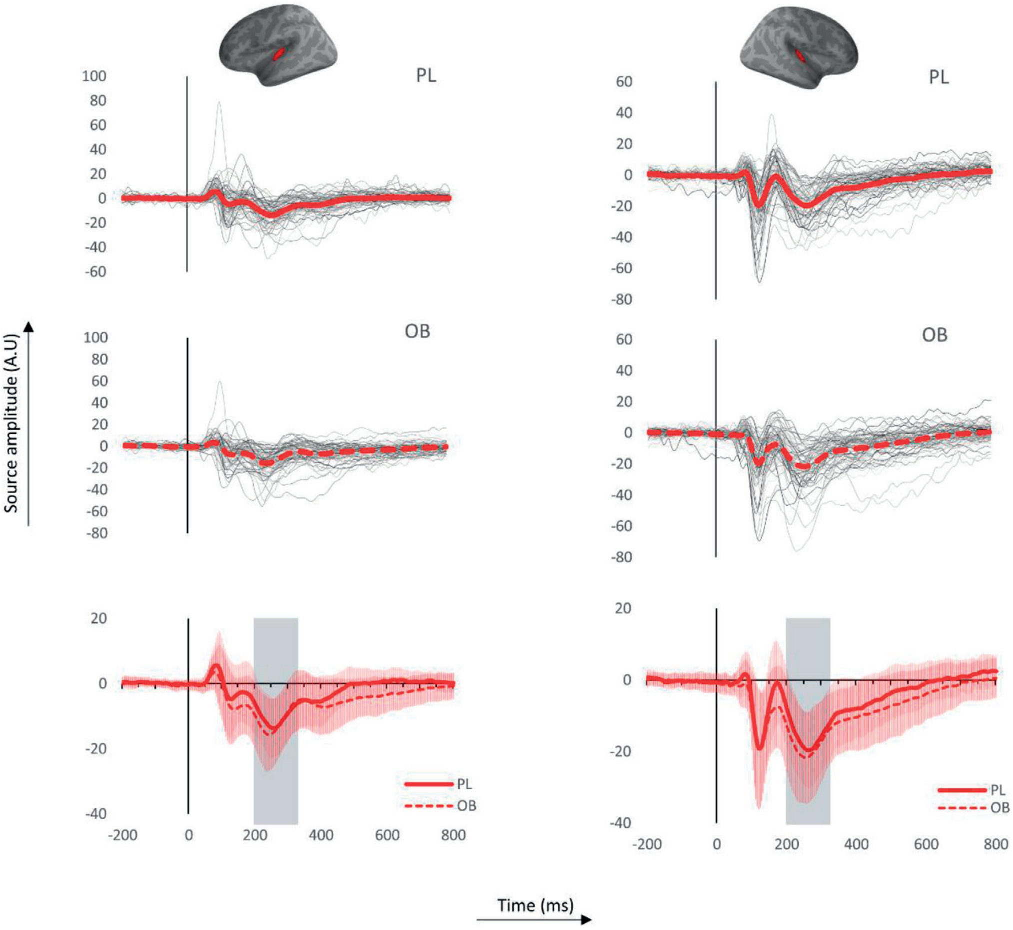


Fig. 7. Source waveforms in the left and right transverse temporal gyrus for the PL (top) and OB (middle) standard tones. Top and middle graphs show individual waveforms (gray) and the grand average waveform (red). Bottom graph shows the grand average waveforms of the PL (solid line) and OB (dotted line) and their standard deviation (red shaded area). Child activity pattern starting at ~200 ms highlighted in gray shaded area.

4. Discussion

We assessed the age differences and especially the functional significance of a robust activation pattern at ~250ms (N250m) in children. Age of the children did not seem to strongly affect the strength of activation in this time window. It suggests a non-linear decrease during development of this auditory activation pattern with age. Indeed, previous studies with a wider age range found an initial increase in activation strength until the age of eleven, after which a gradual decrease was reported (Ponton et al., 2000; Ponton et al., 2002), continuing well into adolescence (Sussman et al., 2008). Importantly, we showed that the strength of activation in children in the 250-ms time-window is unaf-

Table 3
Bootstrapped (10 000 samples) partial correlation (controlled for age) between the 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 ≤ 0.001.

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 (NG) tone as the predictors.

Performance measure	Step	Standardized Beta	Δ 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.

*** p < .001 significance of R2 change.

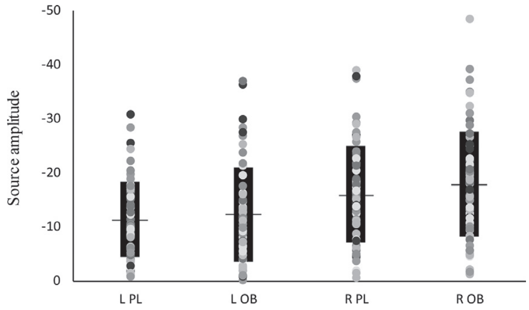


Fig. 8. Individual data points (dots), average (horizontal line) and standard deviation (black bar) for the conditions: passive listening (PL) standard tone and oddball (OB) standard tone in the left (L) and right (R) hemisphere.

Table 6
Bootstrapped (10 000 samples) partial correlation (controlled for age) between the brain responses in left (L) and right (R) hemisphere 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. PL = passive listening, OB = oddball. **p < 0.01.

fected by task demands, but in the left hemisphere it was associated with superior performance on inhibition tasks and measures of cognitive control. Our findings bring important novel understanding of the functional significance of the child auditory activation pattern for the developing skills in cognitive control. It seems that engagement of the basic auditory cortex circuitry in the left hemisphere supports cognitive control in children as measured by the ICV.

The strength of the prolonged activation in the left, but not right, hemisphere was most consistently associated with performance on inhibition tasks. Left-hemisphere response strength during No-go trials 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 prolonged activation 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

Table 5
Forward selection multiple linear regression analysis using hemisphere, task, age, sex and behavioral performance as predictors of the brain responses at ~250 ms.

	B	SE B	Standardized beta	ΔR2	Significance F change
Step 1				.08	.000
Constant	-22.1	1.73			
Hemisphere	5.12	1.1	0.29		
Step 2				.02	.014
Constant	-27.07	2.64			
Hemisphere	5.12	1.09	0.29		
SSRT	24.16	9.73	0.15		
Step 3				.03	.005
Constant	-41.31	5.66			
Hemisphere	5.12	1.07	0.29		
SSRT	36.04	10.47	0.22		
Age	1.16	0.41	0.18		

Note: B = Unstandardized beta, SE B = standard error for the unstandardized beta, ΔR2 = R2 change. SSRT = stop-signal reaction time. Excluded variables: reaction-time, response accuracy, ICV, sex and task (p > .05).

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.

behavioral importance of temporal processes is further supported by our and other studies' finding that ICV, while unrelated to reaction time, is a much better predictor of inhibitory success (r = .79) than traditional measures of reaction time (r = .22) (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 (in auditory tasks) 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 in children than what has previously been indicated in adults. Most notably, the No-go activation in the 200-325 ms. time-window exhibits clear differences between our data of children to what is typically reported in adult studies: whereas the adult major activation peak is typically localized in medial regions of the cerebral cortex (e.g., cingulate cortex) (Nieuwenhuis et al., 2003; Huster et al., 2010), in the current study, children's strongest activation pattern was in the auditory cortex (Fig. 3.). Importantly, there is a vast literature that emphasizes the importance of both the 200-300 time-window and the cingulate cortex for inhibitory and cognitive control processes in adults (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 those findings in the mature brain, our data show that children rely strongly on activation in the auditory cortex during the 200–300-ms time-window and although also evoked without task demands, it contributes to task performance in inhibition tasks.

This suggests that the activity pattern during auditory inhibition tasks (e.g., Go/No-go or SST) in children and adults are qualitatively different. Consequently, with possible divergent cortical origins of the signals, it is not informative to compare sensor-level amplitude measures between adults and children in this time-window. 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). Thus, 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 in a cognitive control task 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 children 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 the child response pattern are unclear and should be the subject of further investigation. Our results indicate engagement of the auditory sensory regions in the child brain, both in passive conditions and during task demands. This could indicate a developmentally specific emphasis on sensorimotor associations in children while successful performance on inhibition tasks in adults relies on cognitive control networks. In the present study, the strength of the prolonged activation in children showed a positive correlation with performance consistency, and thus seems to aid cognitive control in children. We hypothesize it reflects neural processes that allow for a flexible use of neural resources that (causally) improves performance on cognitive control tasks in children. However, future brain manipulation studies should ascertain a possible causal link of this brain-behavior relationship. A similar relationship has been suggested in non-human primates where a recent study identified prolonged activity in the auditory cortex to reflect sensorimotor representations important for behavioral inhibition (Huang et al., 2019).

It is noteworthy that even though the right hemisphere showed stronger responses, left hemisphere activity showed 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 suggested to mature slower than the right (Paetau et al., 1995; Parviainen et al., 2019), based on the later emergence of the earlier N100 response. In addition, auditory responses in the right-hemisphere have been more strongly linked with genetic regulation compared to the left-hemisphere (Renvall et al., 2012). Others have suggested a similar developmental shift in the functional lateralization of prefrontal areas during cognitive control tasks, also emphasizing the importance of the left-hemisphere during development (Zelazo, Carlson & Kesek, 2008), Finally, 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 few theoretical considerations of this study need to be addressed. First, most brain-behavior correlations did not hold for the passive vs oddball comparison. Arguably, the standard tones used in that comparison were behaviorally less relevant compared to the deviant tones in the Go/No-go. We hypothesize that task relevance of the auditory response is an important factor determining (the strength of) the brain-behavior relationship. This would suggest that the deviant tones are more relevant than the standard tones, perhaps because deviant tones required active inhibition in the context of a Go/No-go task.

Second, we focused our discussion on the ICV and argued it reflects cognitive control. It is, however, good to note that the actual relationship is shown between child neural activity in the (left) auditory cortex and individual response time variability in a Go/No-go task and stop-signal reaction times (SSRTs). How broadly this can be interpreted, both in terms of other auditory neural responses as well as cognitive processes under the general domain of cognitive control (e.g., selective attention, inhibition or conflict monitoring) is up to debate and should be subject of further investigation.

To conclude, we provide unique evidence that the child 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 correlation between activation strength and performance measures are limited to the left-hemisphere. We presume this reflects the general lateralization of function of the auditory cortices and experience-driven plasticity which is more strongly linked to the left-hemisphere.

Credit author statement

Sam van Bijnen: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing- Original Draft, Visualization, Project administration. **Lauri Parkkonen:** Methodology, Resources, Funding acquisition, Writing- Review & Editing. **Tiina Parviainen:** Conceptualization, Methodology, Resources, Writing- Review & Editing, Supervision, Funding acquisition.

Data availability statement

Raw data are not publicly available due to legal restrictions. Derived data supporting the findings of this study are available here: https://osf.io/rhb5z/.

Declarations of interest

None.

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III

DIVERGENT ASSOCIATIONS BETWEEN AUDITORY ACTIVATION AND INHIBITION TASK PERFORMANCE IN CHILDREN AND ADULTS

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