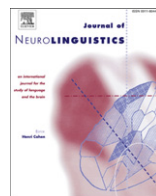




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# Reduced sensory oscillatory activity during rapid auditory processing as a correlate of language-learning impairment

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## ABSTRACT

Successful language acquisition has been hypothesized to involve the ability to integrate rapidly presented, brief acoustic cues in sensory cortex. A body of work has suggested that this ability is compromised in language-learning impairment (LLI). The present research aimed to examine sensory integration during rapid auditory processing by means of electrophysiological measures of oscillatory brain activity using data from a larger longitudinal study. Twenty-nine children with LLI and control participants with typical language development ( $n = 18$ ) listened to tone doublets presented at a temporal interval that is essential for accurate speech processing (70-ms interstimulus interval). The children performed a deviant (pitch change of second tone) detection task, or listened passively. The electroencephalogram was recorded from 64 electrodes. Data were source-projected to the auditory cortices and submitted to wavelet analysis, resulting in time-frequency representations of electrocortical activity. Results show significantly reduced amplitude and phase-locking of early (45–75 ms) oscillations in the gamma-band range (29–52 Hz), specifically in the LLI group, for the second stimulus of the tone doublet. This suggests altered temporal organization of sensory oscillatory activity in LLI when processing rapid sequences.

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## 1. Introduction

The auditory analysis of spoken language is an important aspect of language comprehension and communication. Research investigating the spatiotemporal properties of speech highlights the fact that crucial linguistic information within the auditory signal is coded by brief, rapid and successive spectrotemporal events, emerging as a result of consonantal articulation, in particular stop consonants. For instance, critical information for differentiating the stop consonant syllables [ba] and [pa] is conveyed by the voice onset time (VOT), which denotes the brief gap between the release burst by the articulators and the onset of laryngeal pulsing, or voicing: VOT for [ba] is shorter than for [pa], in American English about less than 25 ms, as compared to greater than 40 ms, respectively. Acoustic cues essential for the perception of other stop consonant-contrasts (e.g., [ba] versus [da]) are present in the trajectory of rapid frequency changes that precede the onset of the stationary spectral pattern characterizing the vowel. Such formant transitions typically occur within 40 ms (Borden & Harris, 1980; Kewley-Port, 1982; Phillips, 1999). As a consequence, some authors have argued that auditory processing of language requires exquisite temporal resolution, at high spectral accuracy over extended time periods (e.g., Hickok & Poeppel, 2007; Johnson, Nicol, Zecker, & Kraus, 2007; Telkemeyer et al., 2009; Zatorre, Belin, & Penhune, 2002). In particular, fast changes in the amplitude and frequency composition related to speech require rapid analysis on the level of bottom-up (sensory) processing, and then need to be identified and isolated from competing simultaneous sounds (e.g., environmental noise). This complex task is achieved in the healthy human auditory cortex with ease and in a seemingly effortless fashion. In this special issue on the neurocognitive precursors of difficulties in reading and arithmetic, we examine the electrophysiological correlates of such rapid sensory processing in children with and without language impairments. Specifically, the current report is concerned with sensory cortical oscillations evoked by fast-rate auditory events.

### 1.1. Rapid auditory processing

A well-known theoretical account that emphasizes the potential role of auditory temporal sensitivity in language development was initially proposed in Tallal and Piercy (1973a). Because the present research focuses on the sensory dynamics during auditory processing, this framework is presented below in some detail. It is important to note however that many other cognitive and physiological mechanisms affect language processing and thus have been shown to be involved in atypical language development (for reviews see Heim & Keil, 2004; Leonard, 1998; Peterson, McGrath, Smith, & Pennington, 2007). Here, we refer to the integration of two or more brief, successive acoustic cues that are rapidly presented to the central nervous system as rapid auditory processing (RAP). It was in the seventies of the last century, when Tallal and Piercy (1973a, 1973b, 1974, 1975) considered whether deficient RAP skills might constitute a basic impairment in developmental language disorders. The authors studied 6 to 9 year-old children diagnosed with specific language impairment (SLI), a condition characterized by a significant limitation in receptive and/or expressive language skills in the context of otherwise typical cognitive development. Even though the SLI children had normal hearing and sequencing abilities, difficulties arose specifically in those tasks that required discriminating and sequencing two rapidly occurring tones (within a temporal gap of less than 150 ms) or single tones having a short duration (75 or 125 ms). In contrast, age-mates with typical language development performed at above-chance levels, when two successive 75-ms tones were presented with a gap as brief as 8 ms (Tallal & Piercy, 1973a, 1973b). The auditory rate deficit in the “tens of milliseconds range” (Tallal, Miller, & Fitch, 1993) led the authors to focus on the phoneme level of speech given that specific acoustic cues occur within this time frame (see above). As expected, SLI children had problems differentiating the stop consonant–vowel syllables [ba] and [da], having formant transition durations of 43 ms. They succeeded, however, when this time period was artificially lengthened to 95 ms, stretched beyond the natural speed of speech (Tallal & Piercy, 1974, 1975).

Subsequent replication of the results across laboratories, tasks, and stimulus variations strengthened the hypothesis of a fundamental RAP dysfunction in SLI (for reviews and contradictory findings, see Heim & Benasich, 2006; Rosen, 2003; Tallal & Gaab, 2006). Tallal (2004) proposed that during sensitive periods of development, slower spectrotemporal processing in the auditory cortex may

disrupt acquisition and sharpening of precise phonological representations (i.e., unitary neural firing patterns), which provide the basis for higher level language learning, from semantics to syntax. In fact, a set of prospective studies using convergent methodologies emphasized the essential role of RAP skills for language outcome (for reviews, see Benasich & Leevvers, 2003; Heim & Benasich, 2006): Benasich and Tallal (1996) examined infants with an elevated risk of SLI by virtue of a family history of SLI (Choudhury & Benasich, 2003; Hayiou-Thomas, 2008; Tomblin, 1989). At age 7.5 months, these infants showed poorer discrimination of fast-rate tone doublets as compared to a control group with no known family history of SLI. Follow-up measures indicated that RAP thresholds are highly predictive of later language comprehension and production at 16, 24, and 36 months of age in all participants (Benasich & Tallal, 2002). On a neural level, 6 month-old infants at higher risk for SLI were found to exhibit a relatively delayed negative wave ( $N_{250}$ ) in the event-related potential (ERP) to rapid successive tones. The latency of the  $N_{250}$  component was inversely correlated with receptive and expressive language abilities at 24 months of age above and beyond family history of language disorders (Benasich et al., 2006). Further evidence can be gleaned from a prospective longitudinal study that investigated the maturation of auditory ERPs from 6 to 48 months in infants with a family history of SLI and controls without such familial risk (Choudhury & Benasich, 2010). Overall, the morphology of ERPs differed for fast- versus slow-rate stimuli and significant age-related changes were seen in both latency and amplitude. However, children with a family history of SLI differed in the rate of maturation of ERPs and only the response to stimuli that included a rapid temporal component (i.e., tone doublets with an interstimulus interval, ISI, of 70 ms) were predictive of later abilities. Specifically, only the  $N_{250}$  peak from the 70-ms ISI condition at 6 and 9 months reliably predicted language abilities at 3 and 4 years of age.

The RAP hypothesis has been expanded to explain the reading and spelling difficulties seen in developmental dyslexia. The reasoning was twofold: first, poor phonological skills, such as the awareness or sensitivity that *seat* and *beat* rhyme, are hallmarks of both SLI and dyslexia (for reviews, see Fitch & Tallal, 2003; Grigorenko, 2007; Heim & Benasich, 2006; Pennington & Bishop, 2009). Second, children with SLI are at a high risk for reading and other academic failure (Rissman, Curtiss, & Tallal, 1990). Longitudinal research has shown that approximately 50% of children classified as SLI subsequently or concurrently also meet the criteria for developmental dyslexia (Stark et al., 1984; Tomblin, Zhang, Buckwalter, & Catts, 2000). Conversely many, but by no means all, dyslexic individuals show oral language deficits (Byrne, 1981; Joannis, Manis, Keating, & Seidenberg, 2000).

Dysfunctional phonological representations due to a RAP deficit may thus not only lead to oral language delays in early childhood, but also to subsequent literacy deficits due to poor phonographic to orthographic mapping (Fitch & Tallal, 2003; Tallal et al., 1993). For instance, magnetoencephalography studies have reported atypical organization of the right auditory cortex in dyslexic children, adolescents, and adults, as revealed by a lack of hemispheric asymmetry of the sources underlying the obligatory evoked response to syllables that required rapid temporal processing (Heim, Eulitz, & Elbert, 2003a, 2003b). Breier et al. (2001) found that impaired perception of a phonemic contrast based on VOT (see above) and a non-speech analog were associated with poor phonological and decoding skills in dyslexic children. Finally, such deficits seem to be ameliorated by intensive training of auditory rate processing and are accompanied by significant changes in metabolic brain activity (Gaab, Gabrieli, Deutsch, Tallal, & Temple, 2007; Temple et al., 2003).

Several studies have failed to replicate the findings of a RAP deficit observed in SLI and dyslexia (for reviews, see Bishop, 2007; Bishop & Snowling, 2004). Relevant to the present study, electrophysiological measures, specifically the so-called mismatch negativity component of the auditory ERP, have not converged to show disrupted sensory processing in these conditions (Bishop, 2007). Such conflicting results might well be related to characteristics of the sample, such as age, or to the degree of task difficulty, among others. From an early age, tasks of rate processing are subject to a pronounced developmental trajectory, and are associated with the increasing ability to detect rapidly changing cues in the auditory environment (Benasich & Leevvers, 2003; Fox, Anderson, Reid, Smith, & Bishop, 2010). Accordingly, adults with a history of reading impairment may not show deficits in relatively simple tasks such as gap detection (Hautus, Setchell, Waldie, & Kirk, 2003). The same may be true for older children with SLI (Bishop, Carlyon, Deeks, & Bishop, 1999). Often such individuals have had many years of therapy and remediation and likely have developed (more or less

effective) alternative processing strategies. Such an explanation is supported by research reporting that more demanding acoustic tasks involving rapid, sequential, and brief stimuli continue to elicit higher thresholds in dyslexic adults (Hari & Kiesilä, 1996). McArthur and Bishop (2004) also reported divergence of ERP and behavioral data in adolescents with SLI. While diagnosed participants and peers with typically developing language did not differ on an auditory temporal resolution task, most of the SLI cases showed aberrant electrocortical responses to the same tonal stimuli presented in the behavioral paradigm. Thus, electrophysiological methods appear a promising avenue for investigating the course of neural timing during RAP. In particular, measures that allow direct assessment of the temporal and spatial parameters of cortical responses are needed.

### 1.2. Auditory processing and oscillatory brain activity in the gamma-frequency range

The present research utilizes data from an ongoing longitudinal study investigating auditory processing skills in children with language-learning impairment and their peers with typical language development using an ERP oddball paradigm. We focused on the early oscillatory activity generated in the auditory cortex of children when listening to rapidly presented complex tone doublets. The analysis of oscillatory activity allows researchers to extract the time-varying amplitude of the electrocortical signal reflecting the amount of energy in a given frequency range of neural activity (Tallon-Baudry & Bertrand, 1999). In addition, quantitative analyses of phase-locking across trials are possible. This approach provides estimates of the temporal stability of oscillatory responses across experimental trials, thus representing a measure of reliability of the oscillatory waveform over repetitions of a stimulus. By virtue of combining amplitude and phase-locking indices, information about sensory processing is available beyond the overall neural mass activity, as is the case in ERP/evoked potential studies, and extends to the temporal alignment of signals across many trials.

We particularly focused on early oscillatory responses in the gamma range, which tend to be time-locked and phase-locked to transient auditory stimuli and are typically seen at about 50 ms following stimulus onset, at frequencies around 40 Hz (Pantev et al., 1991). These responses are generally referred to as “evoked” gamma in order to emphasize their time-locked nature (Pantev, 1995). Evoked auditory gamma activity has been demonstrated to index learning and experience in the auditory system. For instance, Heim and Keil (2006) reported an increase in gamma activity for auditory stimuli that were previously trained to be associated with an aversive event.

In terms of auditory processing of language-relevant information, the power of the early (here: 40–60 ms) evoked gamma response discriminates language and non-language sounds (Palva et al., 2002). In addition to power measures, several electrophysiological studies have focused on inter-site coherence of beta and gamma oscillations, a measure of spectral similarity across electrodes (Doesburg, Emberson, Rahi, Cameron, & Ward, 2008). Pertinent to the present study, lower cross-scalp coherence in the gamma range was observed in adults with poor reading as compared with those with normal reading skills in a study that required tone-pair discrimination (Nagarajan et al., 1999). The coherence difference was visible most clearly in conditions that involved rapid (100 and 200 ms ISIs) tone sequences.

### 1.3. The research problem

The goal of the current study was to examine the auditory cortical dynamics in children with and without developmental language impairment, when they perceived fast-rate stimulus sequences. Using temporally sensitive wavelet analyses enabled us to examine the amplitude and phase consistency of two sensory responses occurring in rapid succession, evoked by pairs of brief tones presented with short (70-ms) ISIs. Aided by regional source modeling and source sensitivity mapping, we ensured the spatial sensitivity of the analyzed signal to auditory cortex. This resulted in measures of the amount and temporal organization of neural mass activity in human auditory cortex during RAP. Using the measures under consideration, we examined auditory cortical processing in children aged 6–9 years with a diagnosis of language-learning impairment (LLI). Children with typical language development (TLD) served as controls. Given the close behavioral similarities (e.g., basic auditory impairment, poor phonological skills) between SLI and dyslexia the term LLI has

become increasingly popular among researchers to encompass children with oral language and/or literacy difficulties (Tallal, 2001). Empirical findings that SLI often co-occurs with more general learning problems have further strengthened the view of a broader condition as suggested by the LLI concept (for reviews, see Fitch & Tallal, 2003; Grigorenko, 2007; Tallal & Benasich, 2002).

#### 1.4. Hypotheses

Given the evidence for a sensory timing deficit in LLI as reviewed above, we expected to see an overall reduction in early-evoked gamma amplitudes in the LLI group. Because the processing difficulties of LLI children specifically emerge for rapid auditory sequences, such a group difference should be most pronounced for the second of two rapidly presented stimuli. This prediction is consistent with the findings of Nagarajan et al. (1999), suggesting overall reduced gamma power in LLI during RAP. The present methodology allows us to also determine the precise temporal locus of any group differences. In terms of phase-locking, we expected the hypothesized RAP deficit in LLI to result in attenuated stability of fast oscillations across trials, again reflecting the inability of auditory cortex to produce temporally well-defined patterns when processing rapid stimulus sequences.

## 2. Methods

### 2.1. Study participants

In the current study, a total of 47 children between the ages of 6 and 9 years (average age 8.04 years) constituted the study sample. Eighteen participants (9 girls) with TLD comprised the control group and 29 participants (9 girls), formally diagnosed as language impaired, the LLI group. The LLI children were ascertained from private speech and language services in the metropolitan New York area and throughout New Jersey. Participants had to meet the following LLI criteria:

- (1) Language skills based on administered standardized measures: (a) Overall standard Core Language score or at least two overall standard language Index scores (Receptive Language, Expressive Language, Language Content, Language Structure) of the Clinical Evaluation of Language Fundamentals – Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003) less than or equal to 85 ( $\geq 1$  SD below the mean of 100); or (b) At least three standard subtest scores of the CELF-4 less than or equal to 8 ( $\leq 25$ th percentile) with a history of language therapy or intervention within the last six months; or (c) Criteria #b plus standard reading scores of three Woodcock Reading Mastery Tests – Revised (WRMT-R; Woodcock, 1987), namely Word Identification, Word Attack, and Passage Comprehension less than or equal to 85.

Criteria #1b and #1c allowed children into the study having significant disparities in various language functions, with very low performance in some skills and average performance in others. Using overall language scores (CELF-4 Core or Index scores) alone would obscure such weaknesses because multiple subtests are used to generate composite scores and can “average out” to a standard score in the normal range.

- (2) Nonverbal intelligence score as indicated by the performance IQ of the Wechsler Abbreviated Scale of Intelligence (WASI; The Psychological Corporation, 1999) of at least 85 and not lower than the overall language score (CELF-4 Core Language).
- (3) No history of hearing impairment, neurological disorder (e.g., epilepsy, brain injury), dyspraxia, oral facial disorder, autism, and psychiatric disorder (e.g., attention deficit/hyperactivity disorder, obsessive compulsive disorder) as determined by parental report.
- (4) Monolingual speakers of English.

Control participants with TLD were matched by chronological age (see Table 1) and fulfilled Criteria #2–#4. Oral language skills had to fall within the normal range (standard score  $> 85$ ) as assessed by the

**Table 1**

Basic demographic characteristics by participant group (typical language developers, TLD versus language-learning impaired, LLI).

	TLD ( <i>n</i> = 18)	LLI ( <i>n</i> = 29)	<i>t</i> -value	<i>p</i> -value
Age (years)	8.02 (0.99)	8.05 (1.02)	−0.08	<0.936
Birth weight (grams) <sup>a</sup>	3438.81 (532.94)	3385.32 (765.89)	0.26	<0.798
Gestational age (weeks) <sup>a</sup>	39.61 (0.92)	39.11 (2.78)	0.74	<0.463
Familial SES <sup>b</sup>	56.33 (7.05)	52.31 (10.33)	1.45	<0.154
Maternal age (years)	38.44 (4.25)	40.93 (4.33)	−1.93	<0.070
Maternal education level <sup>c</sup>	6.22 (0.65)	5.86 (0.92)	1.46	<0.153

Note. Means (standard deviations) are shown; all *p*-values are 2-tailed and non-significant.

<sup>a</sup> Information unknown in one LLI participant.

<sup>b</sup> Familial socioeconomic status (SES) is based on the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975). A mean score of 56.33 falls within the social stratum of major professional (55–66), while 52.31 corresponds to the minor professional category (40–54).

<sup>c</sup> Maternal education level ranging from 1 to 7 according to the Hollingshead criteria. A value of 5 represents partial college, while 6 indicates college/university graduation.

CELF-4. In addition, the children must have had unremarkable pre- and perinatal circumstances, been born full-term and of normal birth weight, and have no known family history of LLI.

The TLD participants were recruited through local New Jersey schools. Children and siblings of children involved in a prospective longitudinal study at the Infancy Studies Laboratory at Rutgers University were invited to participate as well; these children were originally ascertained from pediatric practices in Northern New Jersey.

Basic demographic information is listed in Table 1, indicating that the LLI and TLD groups did not significantly differ in terms of birth weight, gestational age, socioeconomic status, maternal age, and maternal education level. The majority of all participants were right-handers as assessed with a child-appropriate adaptation of the handedness questionnaire established by Coren (see the [Neuroscience for Kids web site](#)). Non-right-handedness was similar across groups, with 6% in TLD, and 14% in LLI,  $p < 0.400$ .

Table 2 shows that both groups satisfied inclusion criteria related to language and cognitive status. Consistent with their difficulties, LLI children had, on average, significantly lower scores in oral language (CELF-4) and reading (WRMT-R) measures. While all participants demonstrated at least normal nonverbal intelligence, the LLI group was significantly outperformed by the TLD on WASI Performance scale. Paired samples *t*-tests between CELF-4 (Core, Receptive, and Expressive) and WASI Performance IQ variables revealed that the LLI children had lower language scores than would be

**Table 2**

Standardized language and cognitive scores by participant group (typical language developers, TLD versus language-learning impaired, LLI).

	TLD ( <i>n</i> = 18)	LLI ( <i>n</i> = 29)	<i>t</i> -value	<i>p</i> -value
CELF-4				
Core language	111.28 (12.42)	81.48 (11.73)	8.28	<0.001
Receptive language	111.61 (11.36)	85.14 (10.47)	8.16	<0.001
Expressive language	111.28 (10.92)	82.69 (13.05)	7.76	<0.001
WRMT-R				
Word identification	109.89 (14.87)	86.76 (13.39)	5.52	<0.001
Word attack	103.67 (16.98)	84.03 (16.08)	3.98	<0.001
Passage comprehension	107.11 (11.10)	83.52 (12.57)	6.53	<0.001
WASI performance IQ <sup>a</sup>	110.17 (14.96)	100.03 (12.94)	2.46	<0.018

Note. Means (standard deviations) are shown; all *p*-values are 2-tailed and significant.

Abbreviations. CELF-4 = Clinical Evaluation of Language Fundamentals – Fourth Edition; WRMT-R = Woodcock Reading Mastery Tests – Revised; WASI = Wechsler Abbreviated Scale of Intelligence.

<sup>a</sup> In two TLD children the Abstract Visual Reasoning cluster of The Stanford-Binet Intelligence Scale, fourth edition (Thorndike, Hagen, & Sattler, 1986) was used as a WASI Performance IQ equivalent.



expected given their nonverbal cognitive ability,  $t_s(28) = -4.91$  to  $-6.34$ ,  $p_s < 0.001$ , which is a diagnostic feature of specific language impairment (American Psychiatric Association, 2000; Bishop, 1997). As expected, this was not true for the TLD group,  $t_s(17) = 0.29$  to  $0.46$ ,  $p_s < 0.653$  to  $0.773$ .

## 2.2. Materials and procedure

All study procedures were conducted at the Infancy Studies Laboratory, Rutgers University and were approved by the local Institutional Review Board. Written informed consent was obtained from the parents of the child participants; children provided verbal assent. Each child participated in two sessions on separate days: the first session involved standardized assessment of language, reading, and nonverbal cognitive skills as detailed in Section 2.1, and lasted 1.5–2 h. In the second session, RAP skills were explored by means of electroencephalography (EEG) during a visit lasting approximately 1–1.5 h.<sup>1</sup> At the end of each session, children received a small toy or game for participation; the parents were compensated for their time.

### 2.2.1. Electrophysiological assessment

Stimuli in the RAP paradigm were complex tones with a fundamental frequency of 100 or 300 Hz with 15 harmonics (6 dB roll-off per octave). Each tone was 70 ms in duration (rise and fall times of 5 ms). The tones were presented in pairs with varying ISIs of 300, 70, or 10 ms using a blocked design; we exclusively considered the 70-ms ISI pairs in this study. Due to the length of the session, participants received only two of the three ISI blocks: either 300 and 70 ms blocks or 70 and 10 ms blocks. Thus, all children were exposed to the 70-ms ISI tone doublets. We focused our analyses on the 70-ms ISI block for two reasons. First, this choice has the advantage of high statistical power and greater signal-to-noise ratio, as compared to the blocks containing other ISIs, and that had smaller sample sizes. Second, to assess oscillatory activity in sensory cortex, we used Morlet wavelets (see Section 2.2.2.), which cannot resolve the responses to paired tones when they are separated by only 10 ms. As compared to the 70-ms ISI condition, the 300-ms presentation rate was also problematic as this ISI leads to longer analytic epochs, which may be differentially affected by slow shifts in the oscillatory activity between the two stimuli. Consequently, comparisons across different ISIs and thus segments with different lengths are invalid.

The 70-ms ISI also falls within the “tens of milliseconds range” (Tallal et al., 1993) that is critical for discrimination of rapid formant transitions (maximum ca. 80 ms) and VOTs (discrimination range ca. 25–70 ms, phonetic boundary ca. 30 ms) inherent to stop consonants (Borden & Harris, 1980; Kewley-Port, 1982; Phillips, 1999). In their seminal work, Tallal and Piercy (1973a, 1973b, 1974, 1975) found that LLI children displayed low temporal sensitivity to both nonverbal and verbal acoustic changes, presented in the tens of milliseconds range. Specifically, these children required a gap of  $\geq 305$  ms in order to accurately sequence two successive 75-ms tones, and were able to discriminate the stop-consonant syllables [ba] and [da] when the formant transitions were synthetically extended to 95 ms, but not at 43 ms, i.e., near the natural speed of speech. Further, a series of studies examining RAP skills in infants suggests that the ability to resolve a 70-ms ISI predicts language outcome at later ages regardless of family history for LLI (e.g., Benasich et al., 2006; Benasich & Tallal, 2002; Benasich, Thomas, Choudhury, & Leppänen, 2002; Choudhury & Benasich, 2010).

Tone pairs were delivered with an intensity of 75 dB free field via speakers to the left and right of the child. Each ISI block comprised 833 tone pairs (tone pairs = trials), which occurred in a typical oddball paradigm. The standard tone doublet was 100–100 Hz (low–low), and the deviant a low-high pair (100–300 Hz). The deviant doublet was presented with 20% probability (166 trials) among the repetitive standard stimuli; a pseudo-random mode ensured that at least 3 and no more than 10 standards occurred between each deviant. The intertrial interval (onset to onset) was fixed at 700 ms. Four regularly placed pauses within a block allowed participants to take a short break. There were also brief pauses between ISI blocks, which typically lasted about 30 s.

<sup>1</sup> Following EEG testing, children worked on a behavioral RAP discrimination task, which was a modified version of the Auditory Repetition Test designed by Tallal and Piercy (1973a, 1973b). These results are not reported here.

Children were seated in a comfortable chair and listened to the tone doublets under two conditions: passive and active. The two different block conditions allowed us to assess the consistency of the early evoked gamma response across time and under different instructions. In the passive condition, participants watched a silent video and were asked to ignore the sounds. During the pauses, the experimenter spoke to the children (to ask about fatigue, comfort, etc.) and posed questions about the movie to insure they were attending to it. Each child was motivated to respond correctly in order to earn stickers (placed on a cut-out shape) needed to “buy” a prize at the end of the session (all participants got a prize at the end of the session regardless of the number of stickers they received).

In the active condition, participants were to press a button located on a response pad as quickly as possible when they heard the deviant (target) tone pair. A total of 33 practice trials ensured that each child understood the task correctly. Feedback was only provided at this time. While the passive condition always preceded the active condition<sup>2</sup>, ISI block presentation order was counterbalanced among participants. Including both conditions allowed us to consider the reliability of sensory effects irrespective of instruction, at a higher signal-to-noise ratio, based on a greater number of trials.

During both conditions, the EEG was recorded from 64 sensors using an Electrical Geodesics™ (EGI, OR, USA) system with a sampling frequency of 250 Hz referenced to the vertex (recording site Cz). Impedances were maintained below 50 kΩ, as recommended for the EGI high input-impedance amplifiers. Horizontal and vertical electro-oculogram (EOG) was determined from electrodes above, below, and lateral to the eyes. All channels were pre-processed online by means of 0.1 Hz high-pass and 100 Hz low-pass filtering.

Channels with bad signal quality throughout the entire recording session (on average 6%) were interpolated offline, using a spline interpolation method (Perrin, Pernier, Bertrand, & Echallier, 1989). Correction for ocular artifacts was performed on the raw data by applying the algorithm implemented in commercial BESA software (Version 5.1, see Berg & Scherg, 1994). For both conditions, stimulus-locked epochs were then extracted from 400 ms prior to the onset of the first tone of a doublet until 800 ms after the onset of the first tone. Single trial epochs were inspected for artifact contamination using the interactive artifact module of BESA. This tool defines individual rejection criteria based on the distribution of epochs in terms of mean amplitude and gradient (first temporal derivative) values. For artifact rejection and all subsequent analyses, data were arithmetically re-referenced to average reference. Epochs that were contaminated with artifacts after eye correction were rejected, a total of 19% for standard stimuli. Thus, a mean of 539 trials were retained per ISI block across all children, with slightly fewer trials retained in the LLI group (mean = 518 trials). This difference was not significant when compared in a non-paired *t*-test,  $t(46) = -1.31$ ,  $p < 0.197$ . The deviant's probability of occurrence resulted in reduced signal-to-noise ratio, as compared to the number of standard trials. Since the present study focused on early mandatory auditory processing, we included only the standard tone pairs in all analyses presented below. Artifact-free epochs pertaining to standards were then submitted to the source estimation and spectral analysis steps described below (see Section 2.2.2.).

#### 2.2.2. Data analysis: oscillatory brain activity

To assess early oscillatory activity in sensory cortex, we projected the artifact-free EEG segments to nine discrete regional sources placed in a 4-shell ellipsoidal head model using BESA (Scherg & Von Cramon, 1986). Regional sources as employed here do not provide precise neuroanatomical localization, but represent the multi-electrode event-related potential data in an anatomically meaningful low-dimensional space, which overcomes some of the problems associated with using voltage maps (Scherg, Ille, Bornfleth, & Berg, 2002). As a key advantage, the interpretation of source current amplitude enhancement as an increase in brain electric activity is possible, whereas in voltage maps, the polarity of deflections often poses problems in interpretation (e.g., dependency of the reference electrode). Regional sources in BESA are sensitive to current changes irrespective of their orientation in

<sup>2</sup> The passive and active conditions were interleaved with a 4-min resting EEG (no auditory stimuli presented), which is not considered in the present study.



space, and therefore captured electrocortical activity originating from a wider range of areas. This is achieved by representing three orthogonal orientations, the magnitude (modulus) of which constitutes the source strength at a given location (see Sabatinelli, Lang, Keil, & Bradley, 2007). When adopting this technique, it is important to ensure that activity is not misrepresented in another cortical area, far from the true underlying source. Here, we used source sensitivity maps to allow our model (see below) as a whole to provide spatial specificity, such that the modeled sources are primarily sensitive to local activity. This can be achieved by using a sufficient number of model sources, evenly distributed across the cortex.

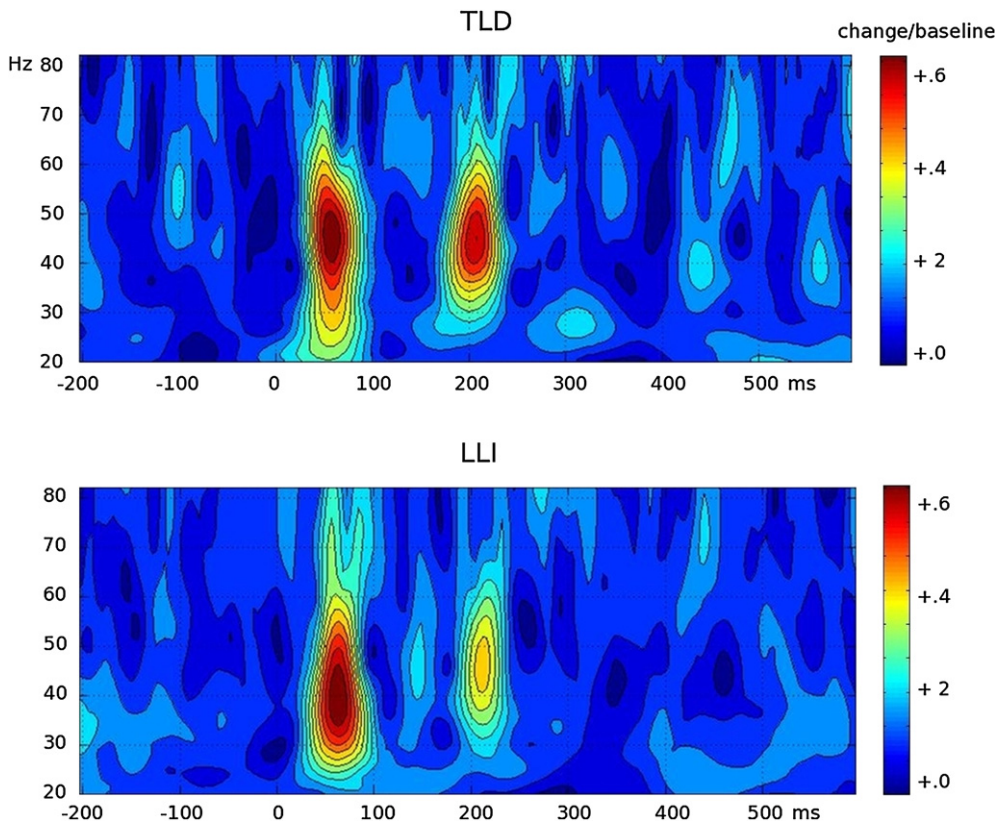
Our model included (i) two lateral sources at locations corresponding to the left and right Heschl's gyrus, thus capturing auditory cortex (i.e., the sources of interest), and (ii) 10 bilateral sources in left and right occipital, inferior temporal, parietal, central, and frontal areas (i.e., the control sources), for a total of 12 regional sources. Locations were selected to be spatially equidistant and to minimize the overlap of the sensitivity of the sources to currents from distant regions, using sensitivity maps in BESA. This model was applied to each participant's artifact-free EEG segments, resulting in a time course of source strength at each regional source, for three orthogonal orientations of the source. In a first interactive step, it was ensured that the two sources in auditory cortex capture energy in the 50–100 ms segment after the onset of each standard stimulus, and that the control sources in non-auditory regions did not. All participants included in the final sample met this criterion. Then, we exported the single-trial source-projected data representing bilateral auditory cortex activity, discarding the activity at the control loci. The three source orientations at each of the two auditory cortex locations were kept separately and submitted to wavelet analysis.

Time-frequency representations of the signal were established using convolution of the signal with complex Morlet wavelet as described in detail elsewhere (Tallon-Baudry & Bertrand, 1999; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). Morlet wavelets are easily and rapidly computed and afford near-optimum time resolution while retaining satisfactory frequency resolution in the frequency range of interest. They are thus superior to Fourier-based methods or spectrograms. Furthermore, Morlet wavelets were employed in previous studies of auditory gamma responses (Knief, Schulte, Bertrand, & Pantev, 2000) and thus facilitate cross-study comparison. In our study, complex Morlet wavelets were generated in the time domain for different analysis frequencies  $f_0$ , ranging from 20 to 80 Hz in steps of 0.833 Hz. The parameter  $\sigma_f$  specifies the width of the wavelet in the frequency domain, and varies with the analysis frequency  $f_0$  and the user-selected ratio  $m$ , with  $m = f_0/\sigma_f = 7$ . The parameter  $m$  is a constant value across all wavelets of a family, representing the ratio of a given analysis frequency and its bandwidth. Thus each individual wavelet will have different length and bandwidth, depending on its analytic frequency, leading to varying time-frequency resolution across the spectrum. This constant was selected to achieve good time and frequency resolution in the frequency range of interest. Time and frequency resolution for oscillations below 20 Hz is sub-optimum with the wavelet family employed here (Kronland-Martinet, Morlet, & Grossmann, 1987), and thus these frequencies are not reported in this study. Wavelets were normalized to have equal amounts of energy and were then applied to the source-space projected signal at two auditory locations (left and right Heschl's gyrus) with three time series each, representing orthogonal source orientations. For each artifact-free epoch, time-varying energy in a given frequency band was obtained as the squared absolute value of the convolution of the cosine-square-tapered source signal with the wavelet. This was done separately for the three orientations of the regional source at each of the two locations. Single trial time-by-frequency (TF) matrices were averaged in order to obtain the evolutionary spectrum for each source location, orientation, and experimental condition. After averaging, the model source orientations at each source location were combined as the Euclidean distance. An epoch from 280 to 100 ms prior to stimulus onset was used as an estimate of general noise. The mean of this baseline epoch was divided from TF matrices for each frequency and time point for each source location, respectively.

In addition to time-varying spectral amplitude, we also analyzed the intertrial phase-locking of the neural oscillations measured with the wavelet family. To this end, the normalized, complex representations of the TF matrices were averaged according to the algorithm described e.g., in Tallon-Baudry and Bertrand (1999). This procedure results in a measure of phase stability across trials, for each time point and frequency, referred to as the phase-locking index (PLI; see Keil, Stolarova, Moratti, & Ray, 2007, for an application in conjunction with source estimation). The PLI is bounded between 0 and

1; 0 indicating random distribution of phase across trials and 1 indicating perfect identity of the phase across trials, at a given time and frequency.

For both time-varying amplitude changes and time-varying PLI, we extracted the mean of a time-frequency window representing early (45–75 ms) oscillations in the lower gamma-band range (29.167–51.667 Hz), for the left and right regional source locations. This range was chosen to account for the inter-individual variability of the peak gamma response that was located between 30 and 50 Hz across participants, which is consistent with previous reports on this brain response (Pantev, 1995). Accordingly, two dependent variables (amplitude and PLI) for the standard tone doublet were evaluated by means of Analysis of Variance (ANOVA) crossing the between-subjects factor of Group (LLI, TLD), and the within-subjects factors Tone (first, second), Condition (passive, active), and Hemisphere (left, right). Differences were deemed significant when  $p < 0.05$ . Contrast analyses were used to follow up significant interaction effects. Because no irrelevant variables were included in the present analyses, we refrained from Bonferroni correction for multiple comparisons (Nakagawa, 2004). This should result in a compromise between maintaining statistical power and avoiding the risk of Type II error inflation.



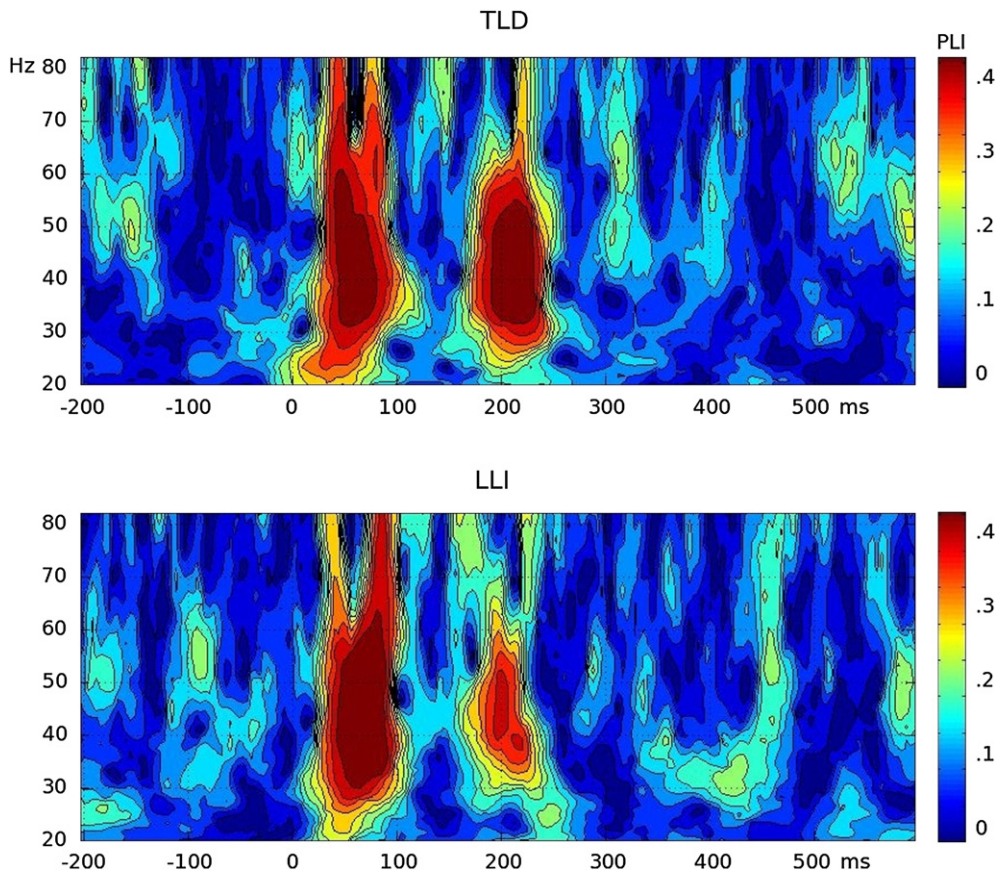
**Fig. 1.** Grand mean baseline-corrected time by frequency plots for the two groups in the experiment, 18 children with typical language development (TLD; top), and 29 language-learning impaired children (LLI; bottom). Values are averaged across the left and right hemispheres and were obtained by wavelet analyses of the single-trial source waveforms at two regional sources, one in each temporal lobe (see Section 2.2.2.). The plots show time running from left to right, frequency from bottom to top. The amount of spectral amplitude change at a given time and frequency is coded by color, with increase over the baseline level coded in increasingly warm (red) colors. A pre-stimulus segment was used as the baseline, and amplitude values indicate relative change after dividing the baseline mean (change/baseline). Note the two oscillatory responses to the tone doublet, each with an onset latency of approximately 45 ms, with respect to the onset of each tone in the pair. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### 3. Results

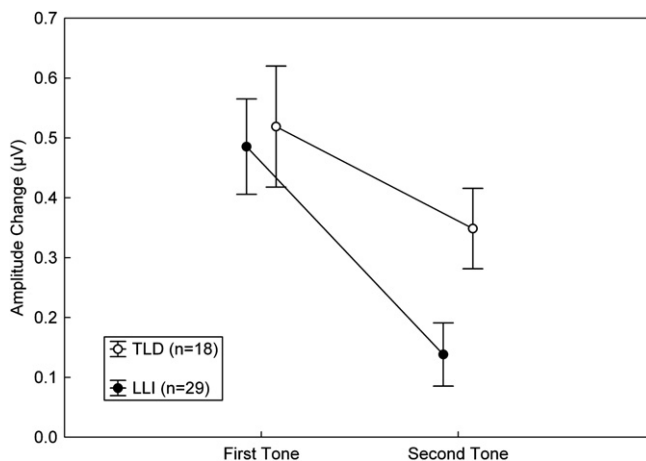
In the current study, we focused on electrocortical activity that was projected to regional source locations of bilateral auditory cortex and subsequently submitted to wavelet analysis (see Section 2.2.2.). We were particularly interested in early sensory high-frequency oscillations in the gamma-band range (centered around 40 Hz) occurring within 120 ms after stimulus onset as reported in adults (e.g., Pantev, 1995) and children (Yordanova et al., 2000, 2002).

As illustrated in the time-frequency representation of amplitude averaged across hemispheres and conditions (passive, active), the standard tone doublet elicited a reliable early evoked oscillatory response in the time segment between 45 and 75 ms and in a frequency band ranging from 29 to 52 Hz (see Fig. 1). When examining the time by frequency representation of intertrial phase-locking (see Fig. 2), two instances of heightened phase-locking coincided in time with the evoked gamma amplitude modulations in both the LLI and TLD group, further supporting the premise that these early responses are indeed the result of phase alignment across trials.

Fig. 3 depicts the mean gamma amplitude as a function of tone position in the standard doublet for the two participant groups. Both groups showed significantly reduced responses to the second, as

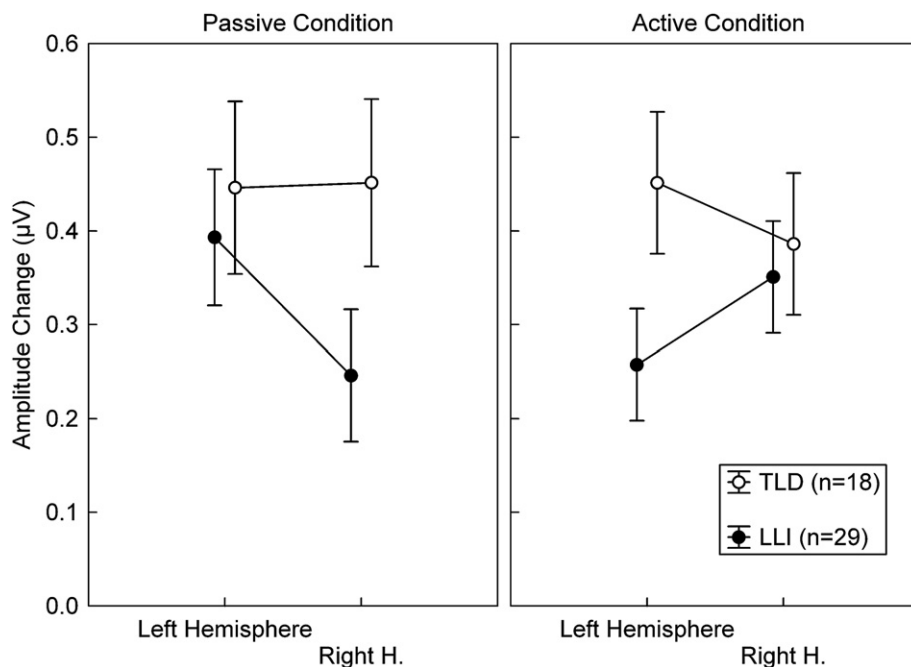


**Fig. 2.** Grand mean time by frequency representation of the phase-locking index (PLI) for the two groups in the experiment, 18 children with typical language development (TLD; top), and 29 language-learning impaired children (LLI; bottom). Values are averaged across the left and right hemispheres. Phase-locking indices reflect the amount of phase stability across trials for a given time and frequency. The plots show time running from left to right, frequency from bottom to top. The amount of spectral phase-locking across trials is coded by color, with greater numbers indicating greater phase-locking.



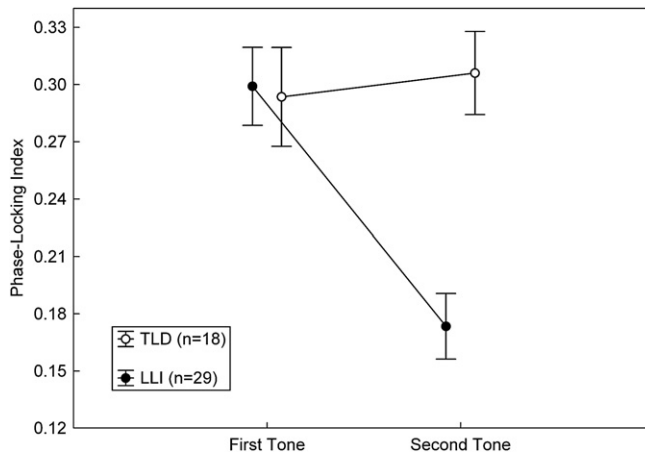
**Fig. 3.** Amplitude change of the early gamma response across stimulus positions in the tone doublet (first, second) for the two participant groups. Values represent means of 18 children with typical language development (TLD; open circles) and 29 language-learning impaired children (LLI; filled circles). Vertical bars indicate standard errors of mean.

compared to the first tone,  $F(1,45) = 50.30$ ,  $p < 0.001$ , with generally smaller amplitudes for the LLI children,  $F(1,45) = 9.01$ ,  $p < 0.01$ . Critical to the hypothesis of a RAP dysfunction in LLI, however, there was evidence for a significant Group by Tone interaction,  $F(1,45) = 5.87$ ,  $p < 0.05$ . Focused contrasts revealed that participants with LLI negatively digressed from their TLD peers in terms of the oscillatory response to the second,  $F(1,45) = 24.26$ ,  $p < 0.001$ , but not to the first of the two tones.



**Fig. 4.** Amplitude change of the early gamma response as a function of condition (passive, active) and hemisphere (left, right) for the two groups in the study. Values represent means of 18 children with typical language development (TLD; open circles) and 29 language-learning impaired children (LLI; filled circles). Vertical bars indicate standard errors of mean.





**Fig. 5.** Phase-locking index of the early gamma response across stimulus positions in the tone doublet (first, second) for the two experimental groups. Values represent means of 18 children with typical language development (TLD; open circles) and 29 language-learning impaired children (LLI; filled circles). Vertical bars indicate standard errors of mean.

In addition, mean amplitude systematically varied as a function of Group by Condition by Hemisphere,  $F(1,45) = 4.99$ ,  $p < 0.05$  (see Fig. 4). In the LLI group, this is reflective of a significantly larger left than right hemisphere response when passively listening to sounds,  $F(1,45) = 5.37$ ,  $p < 0.05$ , and stronger left-hemisphere engagement in the passive versus active condition,  $F(1,45) = 4.70$ ,  $p < 0.05$ . No such differential response was observed in participants with TLD.

As a second dependent variable, we examined the phase stability of early gamma oscillations across trials, the so-called PLI for each tone position in both study groups (see Fig. 5). Paralleling the mean amplitude, PLI significantly decreased for the second tone of the standard pair in both groups,  $F(1,45) = 40.12$ ,  $p < 0.001$ , but was generally less prominent for children with LLI,  $F(1,45) = 26.36$ ,  $p < 0.001$ . Consistent with the amplitude data and supportive of a RAP deficit in LLI, this parameter was also modulated by a Group  $\times$  Tone interaction,  $F(1,45) = 59.85$ ,  $p < 0.001$ . Contrast analyses revealed that the LLI children exhibited significantly reduced phase stability, compared to individuals with TLD, only for the second stimulus of the tone doublet,  $F(1,45) = 91.17$ ,  $p < 0.001$ . Finally, a significant main effect of Condition was found,  $F(1,45) = 4.82$ ,  $p < 0.05$ , indicating larger PLI values (difference on average 0.024) during passive listening than during active detection of target tone pairs.

Upon visual inspection, there was a small latency difference in the peaks of the grand mean evoked gamma responses as shown in Fig. 3. We conducted post-hoc analyses on latencies to guide potential future work and to determine whether such latency differences were reliable. Because the signal-to-noise ratio of the gamma responses varies considerably between individuals, a Jackknifing procedure was used (see Keil & Müller, 2010, for a similar approach). Jackknife-based statistics involve re-computation of the desired test statistic, leaving out one observation at a time from the sample set. New averaged waveforms are formed to replace each of the participants' individual waveforms or time-varying spectra, or other event, for each experimental condition. The latency of each event of interest can be scored as the point in time when a criterion is reached. Jackknifed statistics are then calculated and appropriate corrections are applied to account for the averaging (Miller, Patterson, & Ulrich, 1998). Using this approach with Jackknifed  $t$ -tests, peak latencies of both gamma responses were found to not differ between study groups (all Jackknifed  $t_s(46) < 1.39$ ,  $ps > 0.1$ ).

#### 4. Discussion

Electrocortical measures, specifically ERPs, have been proposed as an informative avenue to detecting whether auditory processing is altered in children with LLI (Bishop, 2007; Tallal & Gaab,

2006). In the current study, we capitalized on electrophysiological parameters of sensory oscillatory rhythms, which are not only indicative of neural activation at high temporal resolution, but are also capable of indexing the temporal organization of early auditory processing across stimulus trials.

The experiment described here investigated RAP in 6–9 year-olds (mean age 8 years) diagnosed with LLI and typically developing controls using oscillatory EEG activity in the gamma range. Children were exposed to paired complex tones presented at a rate (70-ms ISI) that is essential for accurate speech processing while they performed a deviant (pitch change of second tone) detection task, or while listening passively. Analyses targeted time-varying amplitude changes and phase consistency (i.e., PLI) of the early evoked gamma response in the different task conditions. Data were projected to a source-space representation including the bilateral auditory cortices. All participants demonstrated reliable gamma activity bursts in the time segment between 45 and 75 ms and in a frequency band ranging from 29 to 52 Hz, following both tone stimuli. Differences between LLI and TLD children were apparent across tasks, with significantly reduced amplitude and phase-locking of oscillatory rhythms for the second tone of the doublet in the LLI group. Importantly, no additional or unusual energy was measured in the 50-Hz band, which suggests that lower harmonics of the 100-Hz stimuli (standard tone doublets) did not contribute to the measured signal.

#### 4.1. Sensory neural mass activity: amplitude and phase

The implications of the present study are twofold: First, we found that early sensory cortical oscillations elicited by brief and rapidly presented auditory events discriminate LLI and TLD children. Neural mass activity in the gamma range was identical across groups for the first tone, but children with LLI showed substantially reduced spectral amplitude for the second of the two complex tones. Auditory evoked gamma-band oscillations in the 50-ms temporal range, as observed here, have been taken to reflect the engagement of auditory cortex in stimulus processing (Pantev, 1995). This cortical response is primarily modulated by physical properties (Pantev et al., 1991), but also by changes in the rhythmic and spectral structure of the auditory stimulus stream (Snyder & Large, 2005), suggesting that it is a potential index of sensory processing in the auditory domain. In our study, typically developing children were able to rapidly respond to both complex tones, presented at a 70-ms ISI, whereas LLI children showed diminished temporal resolution in that the second response was suppressed.

Second, to examine potential neurophysiological mechanisms underlying dysfunctional RAP, wavelet transformation of single trials was used to estimate the consistency of the cortical response timing across trials: Averaging of the complex normalized phase values over trials for each time/frequency point in the TF plane results in the PLI, an index of temporal stability of a given oscillation (Tallon-Baudry & Bertrand, 1999). The PLI data in our study mirrored the effects seen in the spectral power analysis. This result suggests altered temporal organization of cortical oscillations for the second of two stimuli, likely underlying the reduction in spectral amplitude. In other words, the latency of the cortical response to the second tone in LLI children was more variable than in controls with TLD, leading to suppression of the average oscillatory activity. Explanations for such a pattern include the fact that neural masses cannot be engaged in a well-synchronized and orderly fashion in children with LLI, when rapid processing is needed. This in turn may represent a marker of a temporal processing deficit in developmental language disorders as suggested in previous studies (Nagarajan et al., 1999).

Recent theoretical interpretations incorporate the idea that pre-stimulus oscillatory activity may be a pre-requisite for the rapid and flexible engagement of neural circuits in stimulus processing (Rajagovindan & Ding, 2010). In line with this notion, Benasich, Gou, Choudhury, and Harris (2008) studied power spectra of resting EEG in toddlers at an elevated risk of developing LLI due to a positive family history and a control cohort with no such history. Across groups, frontal gamma-band power was found to be robustly correlated with concurrent language and cognitive measures, with lower mean power density seen for at-risk children at ages 16 through 36 months. Because this age range is characterized by dramatic bursts in the linguistic and cognitive domain and also coincides with maturation of both language-related temporo-frontal regions and thalamo-cortical/cortico-thalamic circuits, it is suggested that children at increased risk for LLI may lag in the maturation of these cortical



regions and/or may recruit different brain areas in the process of establishing high-frequency oscillatory networks (Benasich et al., 2008).

Intriguingly, we observed a slight but significant PLI enhancement across groups for the passive, as compared to the active task. In this task, children responded to the presence of rare deviant tone pairs (i.e., the targets) with a button press. Although detailed analysis of these targets was not the focus of the present study (see Section 2.2.1.), reduced PLI values are reflective of a more random distribution of phase angles over trials during the active condition, thus reflecting a less orderly temporal organization of the oscillations (Lachaux, Rodriguez, Martinerie, & Varela, 1999). Diminished phase-locking may underlie slight amplitude reductions in the active condition that were also observed in the present study, particularly in the left hemisphere of LLI children. Generally, task effects on early sensory processing are consistent with the activity of re-entry processes, potentially modulating sensory activity in a top-down fashion (Keil et al., 2009). Previous studies examining effects of instructions and selective attention on auditory evoked gamma (Tiitinen et al., 1993) have reported an amplitude increase as a function of attention selection. We did not observe such facilitation effects of task on amplitude. Although outside the scope of the present analyses, the role of attention, anticipation, and task type for the modulation of sensory oscillatory activity is an interesting topic for future research, with implications for understanding the role of task demands and attentional allocation on cortical correlates of learning and plasticity (Keil et al., 2007).

Neurophysiological studies have shown that rapid elements of speech and non-speech signals tend to be lateralized to left-hemisphere auditory areas (e.g., Abrams, Nicol, Zecker, & Kraus, 2006; Belin et al., 1998; Zaehle, Wüstenberg, Meyer, & Jäncke, 2004), while slower acoustic cues preferentially involve the right hemisphere (Abrams, Nicol, Zecker, & Kraus, 2008; Boemio, Fromm, Braun, & Poeppel, 2005). Recently, children with poor reading skills were found to exhibit aberrant cerebral asymmetry to low-frequency temporal features in speech as indexed by evoked potentials (Abrams, Nicol, Zecker, & Kraus, 2009). The present study was not designed to address aspects of hemispheric asymmetries, and we observed neither hemispheric differences in the TLD group nor a left hemispheric disruption for rapid tone doublets in LLI children. It is conceivable that other cognitive variables, such as working memory capacity, may impact the auditory evoked gamma-band response as well, and that differences between children with LLI and TLD control participants may reflect such higher-order differences. Future research can directly address such hypotheses with suitable experimental paradigms.

In this context, it is important to consider some of the limitations of the current research report. We reduced the dimensionality of the solution space given by a high number of electrodes, using regional source modeling, which may be sensitive to noise differences between individuals and represent noise as part of the source activity (Scherg et al., 2002). In group studies, the risk of noise prevailing in the group with the phenotype of interest (here: LLI) is always to be considered. It seems unlikely, however, that overall noise effects should compromise the second of two tones alone, leading to a reduction in phase-locking for a specific time and frequency range, rather than affecting the entire time by frequency plane.

#### 4.2. Conclusions

In sum, our results suggest that individuals with LLI are impaired in their ability to integrate rapidly presented, brief acoustic events in sensory cortex. Specifically, LLI children exhibited lower gamma power and phase synchronization to the second of two fast rate tones. Synchronous oscillations in the gamma frequency range have been linked to a variety of cognitive and perceptual functions (e.g., Eulitz et al., 1996; Kaiser & Lutzenberger, 2003; Keil, Gruber, & Müller, 2001). A growing body of research suggests that neural synchrony plays an important role in the development of cortical networks (for a review, see Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010). In this vein, an intriguing link between activity-dependent self-organization of neuronal assemblies, RAP abilities, and language acquisition has been proposed (Tallal, 2004; Tallal & Gaab, 2006). Poor temporal resolution in the oscillatory engagement of these assemblies may hinder fine-grained sensory analysis of phonemes in the ongoing speech stream. Thus, one possible conclusion from the present data is that the Hebbian cell assemblies underlying phoneme representation in LLI may be deficient in their initiation and/or maintenance of synchronous activity.

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