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Behavioral/Cognitive

Size and Synchronization of Auditory Cortex Promotes Musical, Literacy, and Attentional Skills in Children

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Playing a musical instrument is associated with numerous neural processes that continuously modify the human brain and may facilitate characteristic auditory skills. In a longitudinal study, we investigated the auditory and neural plasticity of musical learning in 111 young children (aged 7–9 y) as a function of the intensity of instrumental practice and musical aptitude. Because of the frequent co-occurrence of central auditory processing disorders and attentional deficits, we also tested 21 children with attention deficit (hyperactivity) disorder [AD(H)D]. Magnetic resonance imaging and magnetoencephalography revealed enlarged Heschl's gyri and enhanced right–left hemispheric synchronization of the primary evoked response (P1) to harmonic complex sounds in children who spent more time practicing a musical instrument. The anatomical characteristics were positively correlated with frequency discrimination, reading, and spelling skills. Conversely, AD(H)D children showed reduced volumes of Heschl's gyri and enhanced volumes of the plana temporalia that were associated with a distinct bilateral P1 asynchrony. This may indicate a risk for central auditory processing disorders that are often associated with attentional and literacy problems. The longitudinal comparisons revealed a very high stability of auditory cortex morphology and gray matter volumes, suggesting that the combined anatomical and functional parameters are neural markers of musicality and attention deficits. Educational and clinical implications are considered.

Key words: auditory cortex; auditory evoked responses; magnetencephalography; morphometry; musical aptitude; musical learning; ADHD

Introduction

The brains of musicians are an excellent model for investigating the complexity and multimodality of auditory processing, the variability of individual hearing abilities, and the influence of dispositional and developmental factors on the maturation of neural and cognitive functions. Musical training improves discrimination of pitch (Micheyl et al., 2006; Seither-Preisler et al., 2007), timbre (Pantev et al., 2001), chords (Koelsch et al., 1999), rhythm (Rammsayer and Altenmueller, 2006), and melodies (Trainor et al., 1999). Moreover, musicians typically have highly developed auditory cortices (ACs; Schlaug et al., 1995; Schneider et al., 2002) with stronger functional activation (Besson and Faita, 1995; Pantev et al., 1998; Koelsch et al., 2002, 2005; Tervaniemi et al., 2006; White-Schwoch et al., 2013), enhanced top-down processing of auditory information (Zatorre and McGill, 2005; Zatorre et al., 2007; Scheich et al., 2011), and more efficient preattentive functions, particularly in response to the sounds of the trained instrument (Fujioka et al., 2006; Shahin et al., 2008; Chobert et al., 2014).

The gross morphology of the AC is associated with perceptual and cognitive skills, such as relative and absolute pitch ability (Schneider et al., 2005; Foster and Zatorre, 2010; Wengenroth et al. 2010, 2014) or speech learning (Golestani et al., 2007; Wong et al., 2008; Hartwigsen et al., 2010). Although there is evidence for a genetic influence on auditory and musical abilities (Oikkonen et al., 2014), it is unclear how a priori dispositions interact with environmental influences and in particular with musical training, which in turn has been shown to positively influence auditory brain functions (Jäncke et al., 2000; Muente et al., 2002; Sluming et al., 2007; Altenmüller, 2008; Chen et al., 2008; Jäncke, 2009; Wan and Schlaug, 2010; Strait and Kraus, 2014). Musically induced advantages have also been demonstrated in long-term studies (Hyde et al., 2009; Moreno et al., 2009; Chobert et al., 2014) and appear to be retained from childhood to adulthood (Skoe and Kraus, 2012).

From a clinical perspective, pathologies, such as stroke (Schneider et al., 2007; Grau-Sanchez et al., 2013), tinnitus (Schneider et al., 2009), Parkinson's disease (Nombela et al., 2013), and Alzheimer's disease (Janata, 2012), and learning disorders, such as dyslexia or attention problems (Kraus and Chan-

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Table 1. Description of participants

	Main group mean age at MTP1: 8.6 years ± 9 months				AD(H)D group mean age at MTP1: 8.9 years ± 8 months			
Total sample	$n = 111$ (54 males, 57 females)				$n = 21$ (all males)			
Longitudinal MRI sample	$n = 102$ (49 males, 53 females)				$n = 21$			
Longitudinal MEG sample	$n = 102$ (51 males, 51 females)				$n = 20$			
Type of musical training	Private + JeKi	Private only	JeKi only	None	Private + JeKi	Private only	JeKi only	None
Number of subjects	38	38	16	19	5	4	2	10
Age in months at MTP1	104.1 ± 8.5	101.8 ± 10.7	104.4 ± 8.5	97.8 ± 7.1	100.6 ± 4.7	108 ± 6.9	116 ± 5.6	103.9 ± 8.5
(years; months)	(8; 8)	(8; 6)	(8; 8)	(8; 2)	(8; 5)	(9; 0)	(9; 8)	(8; 8)
Musical starting age	85.5 ± 12.9	71.8 ± 14.7	95.3 ± 8.6		94.6 ± 4.7	90 ± 18.5	92 ± 5.7	
(years; months)	(7; 2)	(6; 0)	(7; 11)		(7; 11)	(7; 6)	(7; 8)	
Private I_{MP} at MTP1	1.9 ± 2.8	5.8 ± 5.6			0.35 ± 0.2	2.25 ± 2.6		
JeKi I_{MP} at MTP1	0.7 ± 1.3		0.4 ± 0.5		0.05 ± 0.1		1 ± 0	
(Total) I_{MP} at MTP1	2.6 ± 3.5	5.8 ± 5.6	0.4 ± 0.5		0.4 ± 0.3	2.25 ± 2.6	1 ± 0	
Private I_{MP} at MTP2	2.5 ± 3.0	8.3 ± 6.5			1.0 ± 0.8	4.5 ± 4.0		
JeKi I_{MP} at MTP2	1.7 ± 1.8		1.4 ± 0.8		0.6 ± 0.1		1.5 ± 0.01	
(Total) I_{MP} at MTP2	4.2 ± 4.2	8.3 ± 6.5	1.4 ± 0.8		1.6 ± 0.8	4.5 ± 4.0	1.5 ± 0.01	

Both the main group and the AD(H)D group included children with and without musical experience but in different proportions. The children were musically trained in extracurricular private lessons, the JeKi program offered at school, or both. I_{MPs} are separately listed for the JeKi-related and private training at MTP1 and MTP2. If not stated otherwise in the text, I_{MP} is the total accumulated practice (JeKi + private) at MTP2. All means and SDs are based on the total sample and not on the slightly reduced samples of the longitudinal MRI and MEG analyses.

drasekaran, 2010; Strait and Kraus, 2014), have been found to benefit from musical training. In AC, sensory bottom-up and attentional top-down processing are closely related to each other (Schadow et al., 2009; Scheich et al., 2011; Bailey, 2012). Hence, it is not surprising that central auditory processing disorders (CAPDs; Cacace and McFarland, 1998) appear in complex comorbidities of attention (Sergeant et al., 2003), language, and literacy problems (Dawes et al., 2009). These may be determined by genetic (Larsson et al., 2006), biochemical (Martel et al., 2009), or anatomical (Sowell et al., 2003) influences and have been ascribed to a delay in cortical maturation (Shaw et al., 2007; Konrad and Eickhoff, 2010). Therefore, the investigation of the young and adolescent brain may be a promising strategy for understanding the neural basis of CAPD and attention deficit (hyperactivity) disorder [AD(H)D]. Although in the normal population the prevalence of CAPD is 2–3% (Chermak and Musiek, 1997), it occurs in ~50% in subjects with AD(H)D (Riccio et al., 1994, 2005). This raises the question of whether perceptual problems cause attentional deficits or vice versa (Dawes et al., 2009). Although the variety of neurophysiological anomalies in AD(H)D (Sowell et al., 2003) is inconsistent with a purely auditory explanation (Woods et al., 2002), subtle hearing problems appear to be a contributing factor (Chermak et al., 1999; Bailey, 2012). Recent research has revealed that, apart from attentional problems, AD(H)D may involve a core deficit in auditory, visual, and motor timing (Falter and Noreika, 2011; Noreika et al., 2013), with timeframes ranging from milliseconds to minutes or even longer. The most consistent impairments are found in sensorimotor synchronization, duration discrimination, time-interval reproduction, and delay discounting. Moreover, there is growing evidence for an association between perceptual timing deficits and behavioral measures of impulsiveness and inattention (Noreika et al., 2013). Conversely, musical training has been shown to have a profound influence on auditory–motor timing skills in children (Reifinger, 2006; Slater et al., 2013). In the present study, we asked whether playing a musical instrument can enhance the neural efficiency of auditory information encoding in the developing brain—as reflected by auditory-evoked response latencies, amplitudes, and measures of neural synchronization—and thereby counteract auditory deficits in AD(H)D. We hypothesized that musically trained children might have larger Heschl's gyri (HGs) and faster auditory-evoked responses, which are advantageous for auditory, perceptual, and cognitive skills. Given the close interdependence between auditory and attentional functions, children with AD(H)D were expected to show the reversed pattern: reduced HG size and decreased neural efficiency. If temporal auditory encoding was affected, they might benefit from musical training.

Materials and Methods

Subjects and procedure. One hundred eleven children without developmental disorders (main group; mean ± SD age at the outset of the study, 8.6 years ± 9 months; sex, 54 males and 57 females) and 21 children with AD(H)D (mean ± SD age, 8.9 years ± 8 months; sex, 21 males) participated in the study (Table 1). All AD(H)D children had been diagnosed by a pediatrician or a child psychologist. The written diagnoses were based on the children's case histories (including typical behavioral patterns at home, in kindergarten, and at school) and direct behavioral observations in controlled playing and/or testing situations. Only children with a diagnosis according to the International Classification of Diseases, 10th Revision (ICD-10) classifications F98.8 (attention deficit disorder; ADD) or F90 (ADHD) were included. Children with known neurological problems or other developmental disorders, such as dyslexia or dyscalculia, were excluded from the study. To quantify and compare the strength of attention, hyperactivity, and impulsivity problems, the parents of all 132 participants were asked to fill out the German standardized questionnaire DCL-HKS (Diagnostic Checklist for Hyperkinetic Disorders; for parents), which is part of the DISYPS-KJ (Diagnostic System for Psychiatric Disorders in Children and Adolescents; Doepfner and Lehmkuhl, 2000) and conforms to the ICD-10 and Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Editions criteria. The DCL-HKS separately assesses the three dimensions "attentional problems," "hyperactivity," and "impulsivity" and combines them to evaluate overall severity of AD(H)D, allowing a comparison with age-related norms. A percentile rank of 90 or higher is considered as an indication of AD(H)D (Doepfner and Lehmkuhl, 2000). In our study, 91% of children who were clinically diagnosed as AD(H)D were also identified as AD(H)D by DCL-HKS, but only 14% of the main group exceeded the age-related norm ($\chi^2 = 52.4$, df = 1, $p = 5.4 \times 10^{-13}$). Thus, there was a high level of agreement between DISYPS-based classifications and the pediatricians' diagnoses.

There were two measurement time points (MTP) at an interval of 13 months. At each MTP, there was a structural magnetic resonance imaging (MRI) and a functional magnetoencephalographic (MEG) session, as well as auditory and psychological tests to explore the elementary perceptual sensitivity (frequency discrimination), musical aptitude, and auditory-related cognitive functions (reading and writing skills). Although all AD(H)D children participated at both MTPs, five children in the main group were no longer available at MTP2. Moreover, for seven children [six of the main group and one of the AD(H)D group], the MRI or MEG data were not of sufficient quality for additional processing at either MTP1 or MTP2. These children were only included in cross-sectional correlational analyses if the respective data were available; they were excluded from the longitudinal comparisons (Table 1).

Musical education and group assignment. 68% ($n = 76$) of the main group and 43% (n=9) of the AD(H)D group received extracurricular music lessons but to a different extent. Approximately half of the children [main group, n=54; AD(H)D group, $n = 7$] were participating in the German musical education program "JeKi" [Jedem Kind ein Instrument (An Instrument for Every Child); www.jedemkind.de/englisch/research.php]. The program was (and still is, as of 2014) running in the state (Bundesland) of Nordrhein-Westfalen and in the city of Hamburg. It aims to offer all primary school children the opportunity to learn an instrument of their own choice at school. Of the 71 children who did not participate in JeKi, 29 had had no instrumental lessons at all. The remaining 42 non-JeKi children were having regular extracurricular music lessons (Table 1).

A detailed questionnaire for parents was used to estimate the total amount of music practice during the entire life of each child, preceding each of two MTPs. A cumulative musical practice index, I_{MP}, was calculated by combining parents' statements of the number of years of formal music education and the amount of time spent practicing where:

$$I_{\mathrm{MP}} = \sum_p y_p h_p + \sum_j y_j h_j,$$

y_p is the duration of private practice in years, h_p is the frequency of private practice in hours per week, y_j is the duration of JeKi practice in years, and h_j is the frequency of JeKi practice in hours per week.

I_{MP} refers only to the time spent practicing at home; lessons are not included. If not stated otherwise, I_{MP} represents the summed private and JeKi-related practicing intensities. Duration and frequency of practice are equally weighted; this simplification appears to be justified because, to our knowledge, no study has explicitly compared the effectiveness of the two aspects. If a child played more than one instrument, the corresponding practicing times were added. Because only the practicing time at home is considered, I_{MP} may also be regarded as a measure of a child's motivation to invest time in musical activities, which may be interpreted as a sign of musicality. The validity of this assumption was confirmed by the close correlation between the I_{MP} and the score achieved at the musical aptitude test Intermediate Measures of Music Audiation (IMMA; Gordon, 1986), performed at MTP2 (main group, $r = 0.62$, $p = 1.1 \times 10^{-9}$; all children, $r = 0.6$, $p = 9.6 \times 10^{-11}$; Fig. 1*C*). Because many children were just at the outset of formal musical education at MTP1, it appeared to be more favorable to assign the participants to musical expertise groups according to the I_{MP} at MTP2, when interindividual differences were more pronounced. The distribution of I_{MP} was relatively broad and bimodal and exhibited a saddle point at 2.5 (Fig. 1*A*). The saddle point was used as a cutoff to separate the main group into low practicers (LPs; $I_{\mathrm{MP}} \leq 2.5$; $n = 52$) and high practicers (HPs; $I_{\mathrm{MP}} > 2.5$; $n = 59$). The mean I_{MP} at MTP2 was 0.9 for LPs, 8.1 for HPs, and 1.4 for AD(H)D children (Fig. 1*B*). The JeKi participants had a mean I_{MP} of 3.5, approximately half of which was accounted for by the JeKi program (JeKi-related I_{MP}, 1.6). HPs achieved substantially higher musicality scores at the IMMA test than LPs ($t_{(59.5)} = -7.2$, $p = 8.8 \times 10^{-10}$) and AD(H)D children ($t_{(23.3)} = -7$, $p = 3.4 \times 10^{-7}$). The latter two groups did not differ in this respect. There were no significant age differences between LPs, HPs, and AD(H)D children.

The children's socioeconomic background was determined by a comprehensive questionnaire for parents. A principal components analysis revealed three relevant social dimensions: (1) education environment (including the mother's and father's highest professional degree and the number of books at home); (2) parental support (including the amount of parent–child communication, the frequency of common participation in cultural events, and the parents' personal interest in children's activities); and (3) resources and leisure activities (including courses in sports, arts, etc., and children's resources, such as their own room, personal computer, etc.). Parental income loaded as well on factors 1 and 3. The individual scores on each dimension were determined and compared across groups. AD(H)D children did not differ significantly in any dimension from LPs but achieved lower scores on factor 3 than HPs ($t_{(78)} = -3.0$, $p = 0.003$). Moreover, LPs were characterized by slightly lower scores on factors 1 ($t_{(83.7)} = -2.6$, $p = 0.011$) and 3 ($t_{(95.7)} = -2.6$, $p = 0.012$) than HPs.

LPs had significantly higher DCL-HKS scores in the DISYPS than HPs (Mann–Whitney U test, $U = 1034$, $z = 2.7$, $p = 0.006$). This suggests that musical expertise is associated with favorable attentional skills and a lower risk for AD(H)D.

Morphometry. AC anatomy was investigated by structural MRI. The individual surface of AC was 3D reconstructed from the MRI slices,

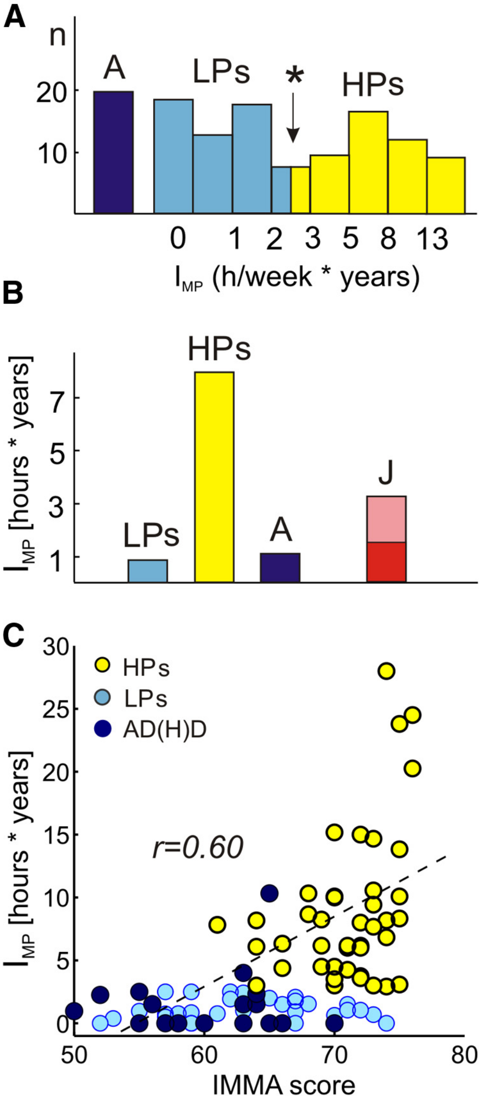

Figure 1. Intensity of musical activity. ***A***, Distribution of I_{MP} for AD(H)D children (A) and for LPs and HPs. The latter were defined by a cutoff value at the saddle point (asterisk at $I_{\mathrm{MP}} = 2.5$). ***B***, Left, I_{MP} group means (LP, HP, A); right, I_{MP} of JeKi participants (J): on average, half of the practicing time was devoted to the JeKi program (dark red part) and the other half to extracurricular musical lessons (bright red part). ***C***, Correlation of IMMA score and I_{MP} at the second MTP.

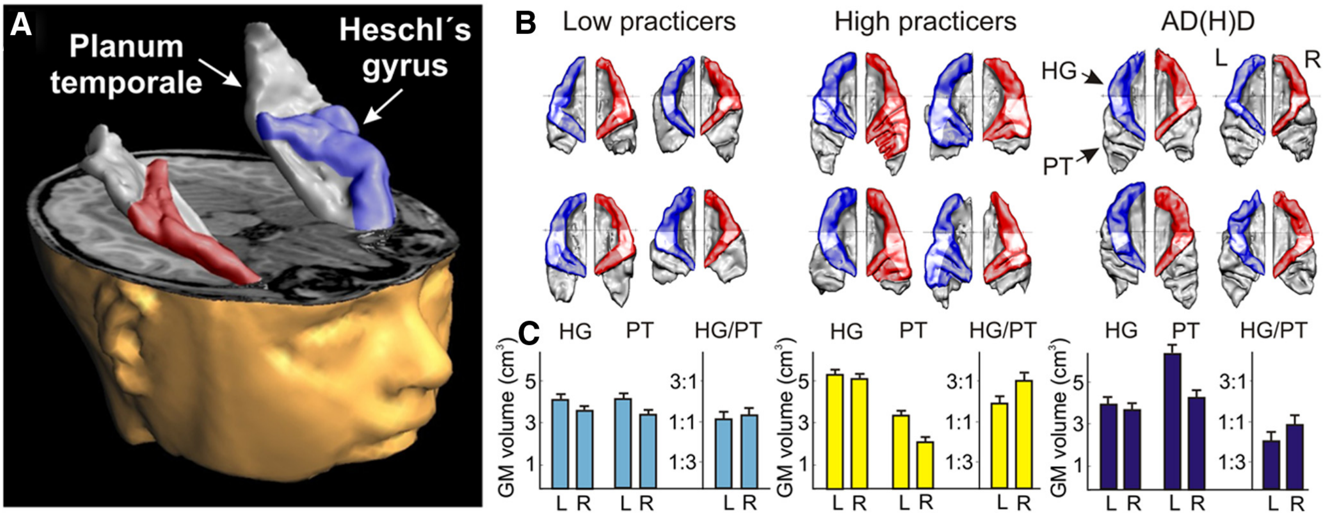

Figure 2. Individual morphology and relative gray matter volume of HG and PT. ***A***, 3D reconstruction of an individual AC. HGs and its duplications are colored in blue (left hemisphere) and red (right hemisphere). ***B***, A top view of 12 exemplary individual ACs reveals the characteristic large variability in size, gyrification, and hemispheric asymmetry of HG and PT. ***C***, Bar graphs showing the gray matter (GM) volumes of HG, PT, and HG/PT ratio in both hemispheres for the three groups. L, Left; R, right.

uncovering the complex shape of the HG, including primary auditory areas and the posteriorly located planum temporale (PT; Fig. 2*A*). In the literature, HG boundaries are defined in two different ways: (1) the region of primary AC within the HG; and (2) the complete HG, including HG duplications. Traditionally, the primary AC has been localized on the first transverse HG convolution (Steinmetz et al., 1989; Rademacher et al., 1993; Penhune et al., 1996, 2003). However, some cytoarchitectonic and functional imaging studies have shown that the primary AC is not necessarily confined to the first anterior HG but may partially occupy HG duplications (Rademacher et al., 2001; Da Costa et al., 2013; Herdener et al., 2013). HG morphology varies considerably across individuals. It ranges from a simple single gyrus to a variety of duplicated or even triplicated gyri, including either partial duplications (lateral, common stem, or medial) and/or complete posterior duplications (Schneider et al., 2005, 2009; Wengenroth et al., 2010, 2014; Marie et al., 2013). Recent fMRI studies have provided evidence for an anatomical–functional relationship, such that the activation of HG and its duplications follows the different morphological variants (Warrier et al., 2009; Da Costa et al., 2013; Wengenroth et al., 2014). The first complete Heschl's sulcus has been considered as the posterior border of HG (Leonard et al., 1998; Schneider et al., 2005) that separates the functional–anatomical entity of HG, including both primary core and secondary belt areas, from PT and furthermore divides AC into two parts: (1) an anterior auditory stream, including HG and anterior superior temporal gyrus (aSTG); and (2) a posterior stream, including PT. The $y = 0$ line was defined in all cases as an anterior borderline that separates HG from aSTG.

The 3D gray matter surface reconstructions of AC were calculated from T1-weighted structural MRI data (TrioTim, 3 Tesla; Siemens) after segmentation by using Brain Voyager software (Brain Innovation). All brain images were corrected for inhomogeneity and rotated in the direction of the anteroposterior commissural line but were not normalized to account for potential age-related changes between the two MTPs in the follow-up design. However, no such changes were observed for any of the tested groups. Using standard definitions of anatomical AC landmarks, the sagittal MRI slices of the individual ACs were segmented along the Sylvian fissure to obtain PT and HG (Schneider et al., 2005, 2009). The inclusion range of image gray values was calculated in a box around left and right AC. For gray matter surface reconstruction and morphometry, the "gray value inclusion range" was defined individually from the intensity histogram for each left and right AC by identifying the following: (1) the third-amplitude side lobe of the gray matter peak distribution toward CSF; (2) the saddle point between the gray and white matter peak. All gray value voxels inside this inclusion range were marked and used for 3D reconstruction and morphometry. The non-automated parts of this structural analysis, in particular the identification of landmarks from the individual 3D surface reconstructions of AC, were obtained by observers who were blind to subject, group, and hemisphere.

Magnetoencephalography. The function of AC was investigated by MEG recordings in response to acoustic stimuli. Using a Neuromag-122 whole-head MEG system, auditory-evoked fields were recorded in response to seven different sampled instrumental sounds (trumpet, flute, bass clarinet, piano, guitar, timpani, and plucked violin) and four synthetically generated harmonic complex sounds with a duration of 500 ms and a stimulus onset asynchrony randomized between 700 and 1000 ms. Each of the 11 stimuli was presented 100 times in pseudorandomized order. The children were instructed to listen to the sounds passively. They watched a silent video to keep them quiet and to reduce the probability of artifacts. This strategy was particularly important (and successful) for children with AD(H)D. The 100 repetitions of each stimulus increased the signal-to-noise ratio to enable robust source modeling as a basis for the additional analysis of the time course, latencies, and amplitudes of the auditory-evoked fields. The procedure had been tested and optimized in pilot studies before the study. The duration of the measurement session was ∼15 min. Cortical responses were averaged using the BESA program (BESA GmbH, Graefelfing, Germany) and collapsed into an individual grand average for source analysis (1100 averages). After artifact rejection (∼10%), the total amount of averaged epochs was reduced to ∼1000 trials. The source activity of the primary evoked response (P1) was separated from the later secondary negative N1 response complex, peaking at 200–270 ms after stimulus onset in our tested children, by spatiotemporal source modeling, using one equivalent dipole in each hemisphere. Signal strength was calculated relative to a 100 ms prestimulus baseline. For P1, the fitting intervals were individually adjusted according to the time interval around the respective peak, as defined by its half-side lobes (the time points at which the amplitude of the peak is halved). The P1 fitting results of our model were robust in all cases. Because the subsequent N1 response is still weak in primary school children (Ponton et al., 2002), it could not be observed in all subjects. Furthermore, at that age, the N1 peak latency is usually delayed (∼200–270 ms) compared with adults (∼100 ms; Fig. 3*B*). Therefore, in later analyses, we only included the more robust P1 amplitudes and latencies and the absolute peak latency difference ($\mathrm{P1}_{\mathrm{right} - \mathrm{left}}$), an indicator of the functional synchronization between right and left AC.

Auditory tests. For psychoacoustic testing, the "Dinosaur" threshold estimation program (Sutcliffe and Bishop, 2005; modified version: Huss et al., 2011) was used. In a two-alternative forced-choice paradigm, two pure tones were presented at an intensity of 65 dB SPL, each with durations of 200 ms and separated by an interstimulus interval of 500 ms. One

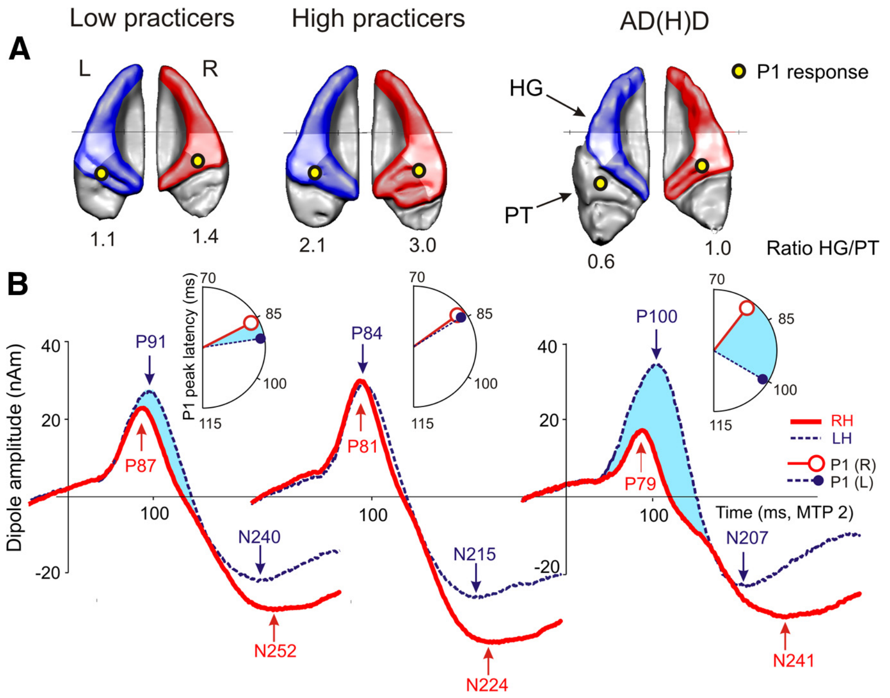

Figure 3. Localization, time course, and bilateral asynchrony of auditory-evoked P1 source activity in response to the sounds of various musical instruments and artificial tones. ***A***, The primary P1 responses (yellow circles) are projected onto the group-averaged surface meshes; P1 sources localized robustly on HG, except for AD(H)D children in the left hemisphere. Mean gray matter ratios HG/PT are indicated by numbers. L, Left; R, right. ***B***, Time courses of the averaged source waveforms for the right (red curve; RH) and left (blue curve; LH) hemisphere. Indicated P1 and N1 latencies refer to peak level. Mean latency differences between the two hemispheres are displayed in a clockwise manner. HPs demonstrate a remarkable left–right synchronization of the primary P1. Conversely, LPs show a slight bilateral P1 asynchrony; for AD(H)D children, the asynchrony is more pronounced (blue shaded area).

of the tones was a fixed standard with a frequency of 500 Hz, and the other tone had variable frequency. The maximum pitch difference between the stimuli was two semitones. Children were introduced to two cartoon birds. They were told that each bird would make a sound and the child had to decide which bird's sound was higher. Feedback was given online throughout the course of the experiment. A staircase procedure was used to adapt stimulus difficulty to the participant's previous answer. Therefore, the number of trials completed by individual participants varied slightly (maximum number of trials, 40). The threshold score (just noticeable frequency difference) was based on the point of 75% correct responses for the last four reversals.

At MTP2, the musical aptitude test IMMA by Gordon (1986) was also presented. The test measures the ability to internalize musical structures and to detect tonal or rhythmic modifications in sequentially presented patterns. The children listened to 40 pairs of tone sequences and 40 pairs of rhythms and made a same/different judgment by circling a pair of same or different faces on the answer sheet. The subtest scores were combined to generate a composite music aptitude score with a maximum of 80 correct answers. Because of the high correlation between the tonal and rhythm subtest ($r = 0.81$, $p = 13.5 \times 10^{-21}$), the individual composite scores were used for additional data analysis.

Cognitive tests. At MTP1, the children's nonverbal IQ was tested with the Culture Fair Intelligence Test (CFT1) of Cattell et al. (1997). The CFT1 consists of five subtests (substitutions, mazes, classifications, similarities, and matrices) and assesses the children's general fluid intelligence. At MTP2, i.e., 13 months later, the revised version of the CFT20 (CFT20-R; Weiß, 2008) for slightly older children was used. The CFT20-R comprises the four subtests substitutions, classifications, matrices, and reasoning.

Reading and spelling skills were determined at both MTPs. Reading fluency was determined by the German speed test Salzburger Lesescreening (SLS 1–4; Mayringer and Wimmer, 2003). The test contains 70 statements (e.g., "Bananas are blue"). The children had 3 min to successively read as many statements as possible and to decide whether they were true or false. A reading quotient was determined, referring to the age norms and scaled like the IQ (mean ± SD, 100 ± 15).

Spelling skills were assessed by the German test Hamburger Schreibprobe (HSP 1–9; May, 2002). Words and sentences were dictated by the experimenter. The children's task was to write them next to the corresponding pictures. The test took ~20 min. The HSP provided measures for the following: (1) three spelling strategies (alphabetic: phonological correctness; orthographic: consideration of learned rules; morphematic: correct usage of smallest grammatical units in language, such as word roots, affixes, etc.); and (2) the number of correctly spelled difficult word spots ("grapheme hits"). *T* values were determined to compare performance with age-related norms.

All experimental procedures were approved by the relevant local research ethics committee.

Statistical analyses. For the correlational analyses between structural, functional, and behavioral measures, we used Pearson's coefficients if, according to the Kolmogorov–Smirnov test, both tested variables were normally distributed. Otherwise, the nonparametric Spearman's ρ was used. Because the interindividual variability in musical expertise increased with age, correlations at MTP2 are more informative with regard to potential musical training effects. Hence, if not stated otherwise, indicated correlations refer to MTP2.

When testing for effects related to reading and literacy, only the main group (LPs and HPs) was considered to avoid biasing by the fact that most AD(H)D children showed slight impairments in these domains and did not play a musical instrument.

For the analysis of potential differences in gray matter volumes and their changes over time, a four-way repeated-measures ANOVA was calculated for the independent variables group [HPs, LPs, AD(H)D], hemisphere (right, left), AC region (HG, PT), and MTP (1, 2). Neurofunctional MEG effects were separately analyzed in three-way ANOVAs (group, hemisphere, MTP) for the dependent variables P1 latency and P1 amplitude. Moreover, a two-way ANOVA (group, MTP) was performed for the dependent variable bilateral P1 asynchrony (|right–left|), which indicates the extent of interhemispheric latency differences. To provide a common overview of group differences and developmental changes seen in the MRI (Table 2) and MEG parameters (Table 3), additional ANOVAs were calculated separately for each hemisphere and cortical region (MRI only). The considered dependent variables were gray matter volume, gray matter ratio (HG/PT), P1 amplitude, P1 latency, bilateral P1 asynchrony, and P1 latency reduction (MTP2 − MTP1). In case of a significant main effect group and homogeneous error variances (as indicated by Levene's test), *post hoc* comparisons between LPs, HPs, and AD(H)D children were performed with Scheffé's test (including a Bonferroni's correction for multiple comparisons). Otherwise, Tamhane's test was used. In case of significant interactions, the mean values of interest were compared with the Tukey's HSD test.

Two discriminant analyses were then performed to investigate how well different neural parameters segregate (1) LPs versus HPs and (2) the main versus AD(H)D group. The predictor variables were HG volume right, HG volume left, PT volume right, PT volume left, and bilateral P1 asynchrony. In addition, a linear multiple regression model was calculated (see Results).

All statistical analyses were performed with the software package IBM SPSS Statistics version 21.0.0.0.

Table 2. ANOVA results for the MRI-based morphology of AC

	MTP	LPs ($n = 50$; 29 males, 21 females)	HPs ($n = 52$; 20 males, 32 females)	AD(H)D ($n = 21$; all males)	Significance of MTP	Significance of group	*Post hoc* comparisons for group	Significance of group for boys only
HG (R) volume (mm ^{3})	1 2	3685 ± 156 3692 ± 152	5173 ± 153 5188 ± 149	3727 ± 241 3726 ± 234	n.s.	$F_{(2,120)} = 28.2$; $p = 8.9 \times 10^{-11}$; partial $\eta^2 = 0.32$	LP versus HP, $p = 1.3 \times 10^{-9}$; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 4.8 \times 10^{-6}$	$F_{(2,67)} = 11.3$; $p = 6.1 \times 10^{-5}$; partial $\eta^2 = 0.25$
HG (L) volume (mm ^{3})	1 2	4193 ± 190 4193 ± 193	5377 ± 186 5409 ± 190	3998 ± 293 3937 ± 298	n.s.	$F_{(2,120)} = 13.5$; $p = 5 \times 10^{-6}$; partial $\eta^2 = 0.18$	LP versus HP, $p = 1.2 \times 10^{-4}$; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 5.3 \times 10^{-5}$	$F_{(2,67)} = 9.2$; $p = 2.9 \times 10^{-4}$; partial $\eta^2 = 0.22$
PT (R) volume (mm ^{3})	1 2	3453 ± 181 3488 ± 171	2203 ± 177 2163 ± 168	4359 ± 279 4344 ± 265	n.s.	$F_{(2,120)} = 27.3$; $p = 2 \times 10^{-10}$; partial $\eta^2 = 0.31$	LP versus HP, $p = 4 \times 10^{-6}$; LP versus AD(H)D, $p = 0.026$; HP versus AD(H)D, $p = 3.5 \times 10^{-9}$	$F_{(2,67)} = 8.8$; $p = 4.1 \times 10^{-4}$; partial $\eta^2 = 0.21$
PT (L) volume (mm ^{3})	1 2	4188 ± 221 4207 ± 213	3475 ± 216 3429 ± 209	6304 ± 341 6445 ± 398	n.s.	$F_{(2,120)} = 27.5$; $p = 2 \times 10^{-10}$; partial $\eta^2 = 0.31$	LP versus HP, n.s.; LP versus AD(H)D, $p = 1.5 \times 10^{-6}$; HP versus AD(H)D, $p = 1.6 \times 10^{-10}$	$F_{(2,67)} = 10.5$; $p = 1 \times 10^{-4}$; partial $\eta^2 = 0.24$
HG/PT (R)	1 2	1.40 ± 0.18 1.37 ± 0.18	3.00 ± 1.18 3.00 ± 1.18	0.98 ± 0.28 0.96 ± 0.28	n.s.	$F_{(2,120)} = 30$; $p = 2.8 \times 10^{-11}$; partial $\eta^2 = 0.33$	LP versus HP, $p = 7.6 \times 10^{-8}$; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 5.3 \times 10^{-11}$	$F_{(2,67)} = 14.6$; $p = 5.5 \times 10^{-6}$; partial $\eta^2 = 0.3$
HG/PT (L)	1 2	1.15 ± 0.15 1.13 ± 0.15	2.05 ± 0.15 2.05 ± 0.15	0.68 ± 0.23 0.62 ± 0.23	n.s.	$F_{(2,120)} = 16.9$; $p = 3.3 \times 10^{-7}$; partial $\eta^2 = 0.22$	LP versus HP, $p = 3.3 \times 10^{-4}$; LP versus AD(H)D, $p = 2.4 \times 10^{-5}$; HP versus AD(H)D, $p = 2.4 \times 10^{-5}$	$F_{(2,67)} = 7.5$; $p = 0.001$; partial $\eta^2 = 0.18$

ANOVA group comparisons for MRI-based gray matter volumes of HG, PT, and HG/PT ratio in the right (R) and left (L) hemisphere for both MTPs. Morphometric values: mean ± SEM (cubic millimeters). To test whether the unequal gender distributions in the three groups [all AD(H)D children were male] may be responsible for some of the observed effects, the right column shows the corresponding results for boys only.

Table 3. ANOVA results for the MEG-based auditory-evoked P1 response

	MTP	LPs ($n = 49$; 29 males, 20 females)	HPs ($n = 53$; 22 males, 31 females)	AD(H)D ($n = 20$; all males)	Significance of MTP	Significance of group	*Post hoc* comparisons of group	Significance of group for boys only
P1 (R) amplitude (nAm)	1 2	24.4 ± 1.5 31.2 ± 1.6	34.6 ± 1.4 34.5 ± 1.5	19 ± 2.3 29.1 ± 2.5	n.s.	$F_{(2,119)} = 28.6$; $p = 7.3 \times 10^{-11}$; partial $\eta^2 = 0.32$	LP versus HP, $p = 0.0003$; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 7.8 \times 10^{-6}$	$F_{(2,119)} = 17.1$; $p = 9.8 \times 10^{-7}$; partial $\eta^2 = 0.33$
P1 (L) amplitude (nAm)	1 2	25.6 ± 1.4 32.6 ± 1.6	36.9 ± 1.3 36.8 ± 1.6	19.4 ± 2.2 28.6 ± 2.5	n.s.	$F_{(2,119)} = 3.6$; $p = 0.032$; partial $\eta^2 = 0.06$	LP versus HP, n.s.; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 0.05$	n.s.
P1 (R) latency (ms)	1 2	91 ± 2 87 ± 1	89 ± 2 81 ± 1	82 ± 2 79 ± 2	$F_{(1,119)} = 126.2$; $p = 2.1 \times 10^{-20}$; partial $\eta^2 = 0.52$	$F_{(2,119)} = 4.6$; $p = 0.012$; partial $\eta^2 = 0.07$	LP versus HP, n.s.; LP versus AD(H)D, $p = 0.016$; HP versus AD(H)D, n.s.	$F_{(2,119)} = 4.1$; $p = 0.02$; partial $\eta^2 = 0.11$
P1 (L) latency (ms)	1 2	96 ± 2 91 ± 2	92 ± 2 84 ± 2	103 ± 3 100 ± 3	$F_{(1,119)} = 81.2$; $p = 1 \times 10^{-13}$; partial $\eta^2 = 0.41$	$F_{(2,119)} = 10.2$; $p = 8 \times 10^{-5}$; partial $\eta^2 = 0.15$	LP versus HP, $p = 0.04$; LP versus AD(H)D, $p = 0.05$; HP versus AD(H)D, $p = 1.3 \times 10^{-4}$	$F_{(2,119)} = 5.7$; $p = 0.005$; partial $\eta^2 = 0.14$
P1 (R) latency reduction (ms)	1–2	4.8 ± 0.7	8.5 ± 0.7	3.0 ± 1.1		$F_{(2,119)} = 12.2$; $p = 1.6 \times 10^{-5}$; partial $\eta^2 = 0.17$	LP versus HP, $p = 8.6 \times 10^{-4}$; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 2.1 \times 10^{-4}$	$F_{(2,119)} = 4.2$; $p = 0.019$; partial $\eta^2 = 0.11$
P1 (L) latency reduction (ms)	1–2	4.9 ± 0.9	8.1 ± 0.8	3.4 ± 1.4		$F_{(2,119)} = 5.9$; $p = 0.004$; partial $\eta^2 = 0.09$	LP versus HP, $p = 0.031$; LP versus AD(H)D, n.s.; HP versus AD(H)D, $p = 0.014$	n.s.
Bilateral P1 asynchrony |R–L| (ms)	1 2	7.4 ± 0.9 6.9 ± 1.0	4.4 ± 0.9 3.9 ± 1.0	22.9 ± 1.4 22.2 ± 1.6	n.s.	$F_{(2,119)} = 61.5$; $p = 4.6 \times 10^{-19}$; partial $\eta^2 = 0.51$	LP versus HP, $p = 0.016$; LP versus AD(H)D, $p = 8.4 \times 10^{-6}$; HP versus AD(H)D, $p = 6.4 \times 10^{-7}$	$F_{(2,119)} = 31.7$; $p = 1.9 \times 10^{-10}$; partial $\eta^2 = 0.48$

ANOVA group comparisons for MEG-based auditory-evoked P1. Right (R) and left (L) hemispheric amplitudes, latencies, and bilateral asynchronies at both MTPs and P1 latency reduction over time. P1 amplitude (nanoamperemeter; nAm) and latency (ms): Peak value and time point of the primary response arising from HG; Bilateral P1 asynchrony: P1 latency difference |R-L|; mean ± SEM. To test whether the unequal gender distributions in the three groups [all AD(H)D children were male] may be responsible for some of the observed effects, the right column shows the corresponding results for boys only.

Results

Neuroanatomical correlates of auditory ability and dysfunction

There was substantial inter-individual variability in the size of HG and PT and the number of HG duplications in both hemispheres (Fig. 2*B*). As evident from Table 2 and the bar graphs in Figure 2*C*, HPs had larger HGs (5287 mm ^{2}) than LPs (3941 mm ^{2}) and AD(H)D children (3847 mm ^{2}). The effect was observed for both hemispheres but was more pronounced on the right side. Conversely, PTs were considerably larger in AD(H)D children (5363 mm ^{2}) than in LPs (3834 mm ^{2}) and HPs (2817 mm ^{2}). As shown in Table 2, the PT enlargement in AD(H)D children was significant for both hemispheres, albeit more pronounced on the left side. Hence, there was a clear volumetric predominance of HG over PT in HPs, with a mean HG/PT ratio that was approximately twice that of musically inexperienced children (2.5 in HPs vs 1.2 in LPs; Fig. 3*A*, Table 2). Conversely, AD(H)D children showed a low HG/PT ratio, especially on the left side (mean, 0.6). Figure 4*F* shows that the left HG/PT ratio was negatively correlated with the DISYPS-based DCL-HKS index of AD(H)D symptom strength ($r = -0.44$, $p = 3.2 \times 10^{-7}$). The HG/PT ratio of the right hemisphere was strongly correlated with I_{MP}

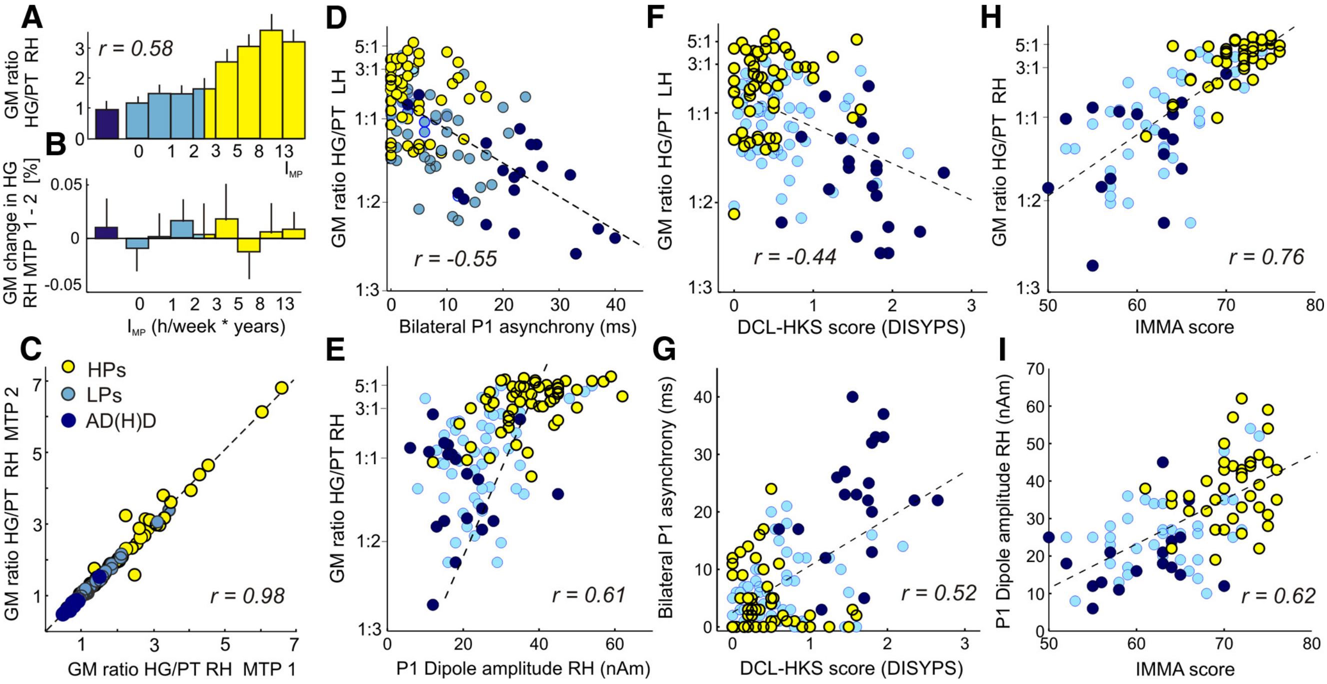

Figure 4. Anatomical and functional markers of musicality and AD(H)D. ***A***, Correlation of right hemispheric gray matter (GM) ratio of HG/PT and musical practicing index. ***B***, Percentage of GM changes in HG between the first and second MRI MTP as a function of musical practice. ***C***, Correlation between the HG/PT ratios at both MTPs. ***D***, Correlation of functional and anatomical asymmetries. The P1 synchrony between the right and left hemisphere increases significantly with the GM ratio HG/PT, indicating that the strong asynchrony observed in AD(H)D children is related to a relative dominance of the PT. ***E***, Correlation between P1 dipole amplitude and HG/PT ratio in the right hemisphere. ***F–I***, Correlations of AD(H)D symptom strength (DCL-HKS score in DISYPS) and IMMA score with structural and functional parameters, respectively. Because of the slightly skewed distribution of "GM ratio HG/PT LH," this variable was inversely transformed (1/value) for the correlational analysis in ***D*** and ***F***. LH, Left hemisphere; RH, right hemisphere.

(main group only, $r = 0.58$, $p = 3 \times 10^{-12}$; all children, Fig. 4*A*) and the musicality score achieved at the IMMA (main group only, $r = 0.69$, $p = 1.1 \times 10^{-13}$; all children, Fig. 4*H*). The correlations with I_{MP} were already evident at the first MTP when musical experience was still low in most subjects ($r = 0.57$, $p = 3 \times 10^{-12}$). Even for the JeKi participants, the time invested in practicing the JeKi instrument at home was related to right HG volumes [$r = 0.28$, $p = 0.048$; AD(H)D children excluded].

There was an interaction of region × hemisphere ($F_{(1,120)} = 19.28$; $p = 2.5 \times 10^{-5}$; partial $\eta^2 = 0.14$): PTs were larger on the left (4675 mm^2) than on the right side (3335 mm^2; $p \leq 0.01$). For HG, this asymmetry was smaller and not significant. Correspondingly, the HG/PT ratio was higher for the right than for the left hemisphere ($F_{(1,120)} = 0.0001$; partial $\eta^2 = 0.12$).

We also compared the gray matter volume of right HG at MTP1 with the time that was subsequently invested into instrumental practice (I_{MP} between the two MTPs). The extent of musical practice before the study (I_{MP} at MTP1) was partialled out to control for differences in early musical training. Nevertheless, there was a robust correlation between right HG gray matter volume and the musical practicing behavior from MTP1 to MTP2 ($r = 0.45$, $p = 3 \times 10^{-6}$). This precludes the possibility that the observed relation between neuroanatomy and the actual practicing intensity was mediated by earlier training influences.

To estimate the relative importance of musical training versus musical aptitude for the right HG/PT ratio, a linear multiple regression model with I_{MP} and the IMMA score as predictors was calculated. The relative contributions to the model, which explained almost half of the observed anatomical variance ($R^2 = 0.42$), were $\beta = 0.83$ for the IMMA score versus $\beta = 0.17$ for the I_{MP}. This highlights the crucial importance of neuroanatomical dispositions for musical skills and suggests that musical training was not the cause of the observed interindividual variability in AC morphology.

Primary auditory-evoked responses

The volumetric predominance of HG in HPs and left PT in children with attention disorders was paralleled by corresponding functional findings. We performed MEG recordings in which the subjects were instructed to listen passively to the sounds of various musical instruments and artificial tones. The AC responses were modeled with one equivalent current dipole in each hemisphere (see Materials and Methods). As expected, responses were robustly localized in the right and left HG in the main group. However, for the AD(H)D children, the source was more posterior in the PT of the left hemisphere (Fig. 3*A*). Figure 3*B* depicts the averaged time course of the auditory response (source waveform) at MTP2 for LPs, HPs, and AD(H)D children, respectively. Typically, a first positive response complex, referred to as the P1, arises ~70–100 ms after tone onset. The N1 response, which was not present in all children at this age because of a late maturation of this component, showed a typical peak latency of 200–270 ms after tone onset. Table 3 displays the P1 peak amplitudes and latencies of the right and left hemisphere at both MTPs. Furthermore, the latency reduction from MTP1 to MTP2 and bilateral P1 asynchrony are indicated.

There were significant group differences, with HPs exhibiting larger P1 amplitudes ($F_{(2,119)} = 16.2$; $p = 6 \times 10^{-7}$; partial $\eta^2 = 0.21$) and shorter P1 latencies ($F_{(2,119)} = 3.4$; $p = 0.037$; partial $\eta^2 = 0.05$) than LPs and AD(H)D children. This pattern was also reflected by a robust correlation between the right hemispheric HG/PT ratio and P1 amplitude (main group only, $r = 0.65$, $p = 3.6 \times 10^{-13}$; all children, Fig. 4*E*). There were significant correlations between the IMMA musicality score and P1 amplitude ($r = 0.58$, $p = 8.5 \times 10^{-10}$) and latency ($r = -0.34$, $p = 0.001$), with the former effect being more pronounced for the right hemisphere (Fig. 4*I*).

AD(H)D children were characterized by an atypical lateralization pattern of accelerated right hemispheric (81 ms) and delayed left hemispheric responses (101 ms). This complements the atypical P1 source localizations observed in the AD(H)D group (Fig. 3*A*).

Moreover, there were significant main effects for hemisphere, with higher P1 amplitudes on the left side ($F_{(1,119)} = 32.5$; $p = 8.9 \times 10^{-8}$; partial $\eta^2 = 0.21$) and shorter P1 latencies on the right side ($F_{(1,119)} = 120$; $p = 9.8 \times 10^{-20}$; partial $\eta^2 = 0.5$).

Interhemispheric synchronization

Bilateral asynchrony ($|\mathrm{P1}_{\mathrm{right}\,-\,\mathrm{left}}|$) varied considerably among groups ($F_{(1,119)} = 61.5$; $p = 4.6 \times 10^{-19}$; partial $\eta^2 = 0.51$; Fig. 3*B*; Table 3). As evident from the superposition of the right- and left-hemispheric source waveforms, AD(H)D children showed a very high mean asynchrony of 22.5 ms, approximately three times higher than in LPs (7.1 ms; $p = 1.1 \times 10^{-13}$) and more than five times higher than in HPs (4.2 ms; $p = 3 \times 10^{-19}$). Figure 4*G* shows that bilateral asynchrony gradually increased with the DISYPS-based DCL-HKS index of AD(H)D symptom strength ($r = 0.52$, $p = 1 \times 10^{-9}$).

Bilateral asynchrony decreased significantly with increasing I_{MP} (main group, $r = -0.27$, $p = 0.006$), which provides evidence for a beneficial influence of musical practice on interhemispheric integration. Moreover, there was a negative correlation with the morphometric gray matter ratio HG/PT (main group, $r = -0.55$, $p = 2.2 \times 10^{-7}$; all children, Fig. 4*D*), which means that a relative HG dominance was associated with bilaterally more synchronous P1 responses.

Anatomical and functional maturation

For gray matter volume, there was no significant difference between the two MTPs, and there were no interactions for MTP × hemisphere or MTP × group. Table 2 displays the mean volumes of HG, PT, and HG/PT ratio for the right and left hemisphere at both MTPs with significance values for the respective group and longitudinal comparisons. The individual gray matter volumes of AC were extremely stable over time. For HG, the changes between the two MTPs were only 0.02% (Fig. 4*B*), resulting in a correlation of $r = 0.98$ (Fig. 4*C*).

For the functional MEG data, the correlation of the amplitudes, latencies, and bilateral asynchronies of the P1 was very high between the two MTPs (amplitude, $r = 0.79$, $p = 4.9 \times 10^{-27}$; latency, $r = 0.88$, $p = 9 \times 10^{-40}$; asynchrony, $r = 0.93$, $p = 3 \times 10^{-53}$), albeit lower than for the HG and PT gray matter volumes. Hence, the source waveforms were highly reproducible as individual neurofunctional fingerprints. As expected from previous findings (Ponton et al., 2002), the P1 showed a mean latency reduction of ~5 ms over the considered time interval of 13 months as a function of natural maturation (main effect of MTP, $F_{(1,119)} = 113.2$; $p = 5.5 \times 10^{-19}$; partial $\eta^2 = 0.49$). Moreover, there was a significant interaction for group × MTP ($F_{(2,119)} = 9.5$; $p = 1.4 \times 10^{-4}$; partial $\eta^2 = 0.14$). The mean latency reduction was relatively small in AD(H)D children (3 ms), somewhat higher in LPs (5 ms), and highest in HPs (8 ms; Table 3). This signifies a delayed maturation of AC in the AD(H)D group, which is contrasted by an exceptionally fast maturation in musically active children. Unlike P1 latency, P1 amplitude and bilateral asynchrony did not differ significantly between the two MTPs. Also, there were no hemispheric differences in the degree of P1 acceleration over time.

Possible influences of gender

To test the possibility that the unequal gender distributions in the three groups [all AD(H)D children were male] may have been responsible for some of the observed effects, the ANOVAs indicated in Tables 2 and 3 were repeated for boys only [21 AD(H)D children, 30 LPs, 24 HPs]. For the MRI-based analyses all main effects of group and for the MEG-based analyses, most main effects of group were still significant (see right columns of Tables 2 and 3). An inspection of the effect sizes (partial η^2), which unlike *p* values do not depend on the sample size and may be compared across different analyses, indicates that these are similar for the mixed group and the male subgroup. This excludes the possibility that the effects seen in the original analyses are attributable to a gender bias.

Neuroanatomical and functional markers of musicality and AD(H)D

To test how well different neurological parameters discriminate between LPs and HPs (first analysis) and children without developmental disorders and with AD(H)D (second analysis), we performed discriminant analyses that combined the four MRI-based predictors gray matter volumes of right and left HG and PT and the MEG-based predictor bilateral P1 asynchrony. In the first analysis, the established discriminant function allowed for a correct assignment of 78% of cases to the groups of LPs and HPs (Wilks' $\lambda = 0.58$, $\chi^2 = 51.8$, df = 5, $p = 5.8 \times 10^{-10}$). Gray matter volume of right HG was the most important segregating factor, with HPs showing substantially larger volumes than LPs. In the second analysis, the discriminant function correctly assigned 91% of cases to the groups of AD(H)D children and children without attention deficit disorder (Wilks' $\lambda = 0.51$, $\chi^2 = 79$, df = 5, $p = 1 \times 10^{-13}$). Bilateral asynchrony of the P1 response and enlarged gray matter volume of left PT (which is associated with a more posterior localization of the left P1 in PT; Fig. 3*A*) yielded the most important contributions to the auditory cortex-related etiology of AD(H)D.

Auditory and cognitive skills

Frequency discrimination was measured with the Dinosaur Test (Sutcliffe and Bishop, 2005; modified version: Huss et al., 2011). The children's frequency difference limens ranged from 0.05 to 1.9 semitones and correlated with I_{MP} ($r = -0.35$, $p = 4.7 \times 10^{-5}$), the IMMA musicality score ($r = -0.5$, $p = 2.8 \times 10^{-7}$), and HG gray matter volume, especially in the right hemisphere (right, $r = -0.34$, $p = -0.0001$; left, $r = -0.23$, $p = -0.009$). To clarify whether the morphology of right HG explains differences in pitch perception regardless of musical training, partial correlations were computed, in which the influence of I_{MP} was controlled. The correlation was still significant ($r = -0.22$, $p = 0.015$). Conversely, when neuroanatomical dispositions (right and left HG volumes) were partialled out, the correlation remained significant as well ($r = -0.26$, $p = 0.004$). This shows that AC morphology and musical training both have an influence on the accuracy of auditory perception.

Intelligence, as measured with the CFIT [MTP1: CFT1 (Cattell et al., 1997); MTP2: CFT20-R (Weiß, 2008)], did not significantly differ between LPs, HPs, and AD(H)D children (MTP1, $F_{(2,128)} = 0.48$, n.s.; MTP2, $F_{(2,122)} = 0.42$, n.s.).

The children's literacy skills, which were measured by the German tests SLS (Mayringer and Wimmer, 2003) and HSP (May,

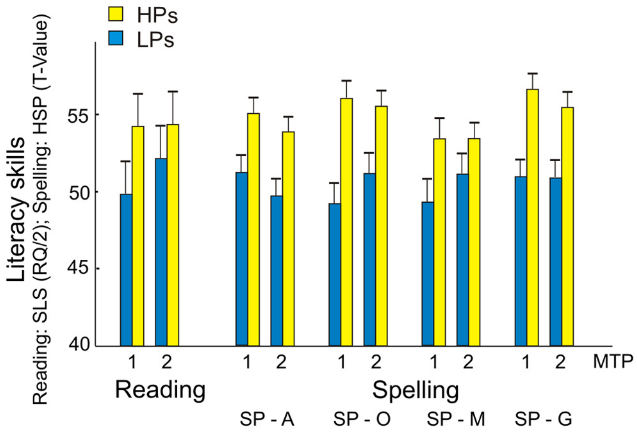

Figure 5. Reading and literacy skills. Differences between LPs (yellow) and HPs (blue) with regard to five indicators of literacy at the first (1) and second (2) MTP. A value of 50 corresponds to the mean of the age-related norm. Reading skills refer to the reading quotient (RQ/2) obtained by the German test SLS. Spelling skills refer to the *T* values for three spelling strategies (SP-A, alphabetic; SP-O, orthographic; SP-M, morphematic) and the number of correctly spelled difficult word spots (SP-G, grapheme hits) for the German test HSP. Error bars indicate SEM.

2002), were related to musical activities. In the following, only the results of the main group are considered to avoid biasing by the poorer frequency discrimination scores, lower reading and spelling skills, and lower I_{MP} of the AD(H)D children. In principle, cognitive advantages related to musical training may be indirectly mediated by a more supportive social background. To consider this possibility, the individual scores on the three socioeconomic dimensions education environment, parental support, and resources and leisure activities were arithmetically eliminated in partial correlation analyses. At MTP1, four indicators of reading and spelling abilities were positively correlated with I_{MP} (reading quotient, $r = 0.21, p = 0.037$; orthographic strategy, $r = 0.37, p = 1.8 \times 10^{-4}$; morphematic strategy, $r = 0.27, p = 0.01$; grapheme hits, $r = 0.33, p = 8.6 \times 10^{-4}$). At MTP2, there was a positive correlation for three indicators of literacy (orthographic strategy, $r = 0.27, p = 0.007$; morphematic strategy, $r = 0.35, p = 3.5 \times 10^{-4}$; grapheme hits, $r = 0.37, p = 1.8 \times 10^{-4}$; Bonferroni's-adjusted α level for multiple correlations, $p \leq 0.01$). The adjustment for socioeconomic status shows that the observed correlations between musical training and literacy were not an indirect consequence of social support. The corresponding group differences between LPs and HPs are indicated in Fig. 5; a value of 50 in the figure corresponds to the mean age-related norms of the literacy tests SLS and HSP. The performance of LPs was typical for their age, whereas HPs exceeded expectations on all indicators of literacy.

With regard to neuroanatomy, there were significant positive correlations between the gray matter volume of right HG and each of the five performance measures of reading and spelling ($p < 0.05$). To test whether the gross morphology of AC was causing differences in literacy skills, partial correlations were computed, in which the influence of musical training (I_{MP}) was eliminated. In this case, none of the correlations between the anatomical and literacy measures remained significant.

Discussion

In our study, structural MRI and functional MEG were applied to 132 elementary school children. There were remarkable individual and group-specific differences in gross morphological size, neural efficiency, and bilateral synchronization of AC. These combined anatomical and functional parameters turned out to be reliable neural markers of musicality, perceptual skills, and attention deficits. The longitudinal comparisons revealed a high stability of AC morphology but with systematic plastic changes at the functional level.

Individual differences in the gross morphology of AC

Children with musical training showed considerably larger HGs–particularly in the right hemisphere–than children without musical training. Conversely, AD(H)D children were characterized by exceptionally small HGs that were associated with enlarged PTs. Thus, the ratio HG/PT appears to be a key indicator of interindividual differences in AC morphology. However, the extent to which such differences are a result of experience-dependent, intrauterine, or genetic influences or a combination of these factors is a matter of debate in both cross-sectional (Golestani et al., 2011; Herholz and Zatorre, 2012; Ressel et al., 2012; Zatorre 2013; Oikkonen et al., 2014) and longitudinal (Hyde et al., 2009; Moreno et al., 2009; Besson et al., 2011; Penhune, 2011; Schellenberg, 2011; Chobert et al., 2014) studies. Prenatal investigations have shown that the HG is developed by week 31 of gestational age. In most cases, right HG develops 1 to 2 weeks earlier than the left (Chi et al., 1977). The morphology and asymmetry of the PT becomes visible at gestational week 30 and appears to remain fairly stable across fetuses, newborns, children, and adults (Preis et al., 1999). Studies with monozygotic and dizygotic twins have demonstrated that morphometric differences of AC are predominantly attributable to genetic factors; heritability is estimated at 80% for the left and 77% for right HG (Hulshoff Pol et al., 2006). The remaining variance may be accounted for by common environmental influences *in utero* and after birth and a combination of error and specific external influences not shared by the twins (Carmelli et al., 2002).

In our longitudinal study, the gray matter volume of relevant structures in AC was extremely stable over time, which suggests that the gross morphology of AC has primarily stabilized at the primary school age. Nevertheless, it is possible that other neuroanatomical parameters, such as cortical thickness or white matter connectivity, are still susceptible to auditory learning. The high interindividual variability in the size, shape, and lateralization of HG and PT observed in children (Fig. 2*B*) and adults (Schneider et al., 2002, 2005, 2009; Warrier et al., 2009) may be a result of a complex interaction between genetic factors and early auditory learning.

Furthermore, our data demonstrate that the gray matter volume, especially of the right HG, is directly related to both musical aptitude, as measured by the IMMA test (Gordon, 1986), and the intensity of musical practice at the outset of formal musical training. A regression analysis revealed that the right HG/PT ratio was predominantly explained by the aptitude measure (83%), whereas the practice measure played a subordinate role (17%). Furthermore, the amount of musical practice between MTP1 and MTP2 significantly depended on AC morphology, even after controlling for the time invested in musical activities before the study. This suggests that a large right HG signifies high musical potential, which increases a child's intrinsic motivation to learn and practice a musical instrument regardless of social influences.

The size of right and left HG was also positively correlated with auditory and literacy skills, which is evidence for a close interdependency between AC morphology, perception, and cognition. According to partial correlations, accuracy of frequency discrimination was independently influenced by right HG volume and the extent of musical practice. Conversely, the exceptionally good performance in reading and spelling in HPs

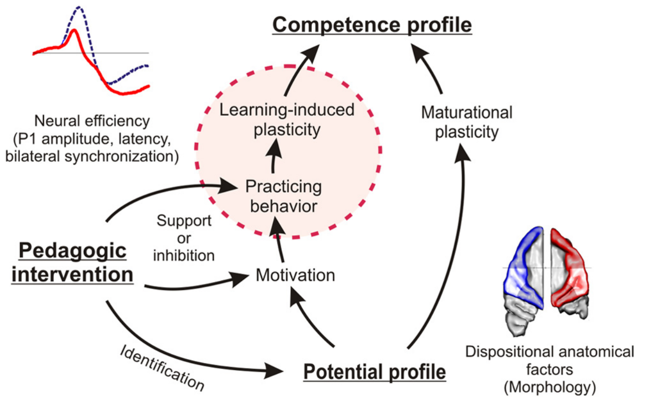

Figure 6. Neurocognitive model of competence development. The model describes the interaction between dispositional factors (potential profile, bottom), natural maturation (right vertical path), and training-induced plasticity (left vertical path). Pedagogic interventions (left) may affect learning-induced plasticity at different levels, thereby contributing to the manifestation of the individual competence profile (top). In the case of music processing, AC morphology (bottom right) and the source waveforms of the auditory-evoked fields (top left) represent dispositional and training-induced factors, respectively.

depended only on musical training, regardless of neuroanatomical dispositions and social background. This corroborates the existence of learning-induced transfer effects from the musical to the literacy domain and is consistent with previous longitudinal studies reporting positive musical transfer effects on general auditory skills (Banai and Ahissar, 2013; Putkinen et al., 2013), speech-related abilities (Ho et al., 2003; Magne et al., 2006; Forgeard et al., 2008; Moreno et al., 2009; Besson et al., 2011), and cognitive development (Trainor et al., 2009; Schellenberg, 2011; Corrigall et al., 2013).

At present, it is only possible to speculate why the gray matter volume of the left PT was substantially greater in AD(H)D children and why this measure was correlated to AD(H)D-relevant behavior, as measured by the DCL-HKS score of the DISYPS (Doepfner and Lehmkuhl, 2000). Apart from genetic influences, a delay in the neural pruning process may be a factor (Castellanos et al., 2002). From birth to puberty, the overall number of cortical neurons and synapses decreases as a consequence of maturational and use-dependent plasticity (Iglesias et al., 2005). A disturbance of this process in the form of diminished or delayed pruning may result in oversized anatomical structures and functionally inefficient neural networks. Consistently, Sowell et al. (2003) reported that children and adults with AD(H)D have more gray matter in large portions of the posterior temporal cortices bilaterally, which is associated with a reduced myelination and white matter connectivity in these regions.

Individual differences and plastic changes in the neural efficiency of AC

We found that the primary auditory-evoked responses of musically active children have a significantly higher amplitude, shorter latency (at least on the left side), and higher bilateral synchrony, which suggests enhanced neural efficiency of the underlying networks; this may either be attributable to a larger number of neurons or increased synchronization (Eggermont and Ponton, 2002). As expected (Ponton et al., 2002), the longitudinal comparison revealed maturational plasticity in all children, leading to decreasing P1 peak latencies with age. Short latencies signify a high degree of myelination of the transmitting nerve fibers and indicate a mature developmental state (Roberts et al., 2009). Our findings show that this natural development was accelerated in children with regular musical practice.

The size ratio of HG/PT and the bilateral asynchrony of the P1 response differentiated children with respect not only to musicality but also to the incidence of attention disorders. AD(H)D children showed an atypical volumetric predominance of PT over HG, especially on the left side, and an intriguing bilateral asynchrony of the P1 that was more than five times higher than in the musically experienced group. Moreover, the left P1 response was characterized by delayed latencies and a posteriorly shifted source location. This suggests that supratemporal lobe functions are crucially involved in attention deficits, complementing the influence of executive functions located in parietofrontal cortical networks (Sergeant et al., 2003; Larsson et al., 2006; Konrad and Eickhoff, 2010). We assume that the oversized and probably inefficient left PT, together with diminished white matter connectivity in the posterior temporal regions (Sowell et al., 2003), can explain the observed functional anomalies in our AD(H)D sample.

Poeppel (2003) proposed an asymmetric sampling in time (AST) model, which was later refined by Meyer et al. (2012). The model is based on the observation that the auditory association cortex is asymmetrically driven by temporal modulations in acoustic signals. While the left AC is basically involved in decoding rapidly changing acoustic segments (~40 Hz), the right AC supports the processing of suprasegmental, slowly changing acoustic cues (~4 Hz). The model postulates that the left hemispheric analysis of fine-grained acoustic information, which is important for the phonetic discrimination of voice onset times in speech (stop consonants b-p, d-t, g-k) and onset-based instrumental timbres in music, is a prerequisite for the subsequent slow right hemispheric pattern analysis of prosodic and rhythmic information. Consistently, the left PT is involved in the analysis of voice-onset times (Jäncke et al., 2002), whereas the right PT supports the processing of speech melody (Meyer et al., 2004) and speech rhythm (Geiser et al., 2008). Hence, a developmental deficit in the left PT would cause problems not only in the initial fast analysis but also in the subsequent slow analysis of the contralateral hemisphere, leading to difficulties in discriminating the onsets of syllables and perceiving rhythmic structures in speech and music. Both types of deficits are characteristic for children with CAPD and dyslexia (Hämäläinen et al., 2013; Leong and Goswami, 2014), which are frequently associated with AD(H)D (Sergeant et al., 2003). Recent studies have confirmed the significance of the AST model for dyslexia (Goswami, 2011; Lehongre et al., 2011; Kraus, 2012). It might be promising to test the validity of this approach for CAPD and AD(H)D. In particular, the model might account for the growing body of evidence that, beyond well known deficits in executive functions (Konrad and Eickhoff, 2010), auditory timing deficits are associated with AD(H)D (Falter and Noreika, 2011; Noreika et al., 2013). The strong interdependence between auditory and attentional functions is evidenced by the multimodal organization of AC with wide feedback loops to subcortical and prefrontal regions that also comprise attentional networks (Scheich et al., 2011). The striking bilateral asynchrony measured in our AD(H)D sample may reflect a disturbed division of labor in temporal signal analysis between left and right AC that originates from a developmental anomaly of the left PT and has negative consequences for attentional, linguistic, and literacy skills. Our findings suggest that the high correlation between CAPD and AD(H)D (Riccio et al., 1994, 2005) signifies common deficits in primary auditory processing

(Chermak et al., 1999) rather than in attentional top-down processing (Sagvolden et al., 2005).

Our data also indicate that musical training has the capacity to synchronize the activation of left and right AC and thereby to increase interhemispheric transfer. The inverse neurofunctional patterns seen in musically experienced and AD(H)D children suggest that musical activities may be beneficial not only for auditory (Kraus and Chandrasekaran, 2010) but also for attentional, linguistic, and literacy skills (Golestani et al., 2007; Wong et al., 2008; Hartwigsen et al., 2010). In particular, playing an instrument may counteract developmental delays by accelerating the functional maturation of AC and enhancing the synchronization of left and right hemisphere functions, for example, through intensified white matter connectivity (Zatorre et al., 2012). By combining the structural characteristics with the functional P1 asynchrony, it was possible to predict AD(H)D (as diagnosed by pediatricians and/or psychologists) with ~90% accuracy. Thus, our experimental approach may also be of clinical relevance.

Neurocognitive model for musical potential and competence

In general, our findings suggest that the gross morphology of AC has primarily stabilized at an age when intensive formal musical education normally starts. The high morphological variability between subjects may instead be attributed to early informal musical experiences, general auditory learning, intrauterine learning, or genetic influences. The gray matter volume of right HG appears to have a considerable influence on a child's motivation to learn and practice a musical instrument. This training, in turn, seems to intensify the neural efficiency of AC (enhanced and accelerated P1 responses with a high bilateral synchrony). Therefore, the influences of musical aptitude and musical training should not be seen as mutually exclusive but rather as mutually reinforcing. On this basis, we propose an extended neurocognitive model that describes development from a set of dispositional factors, specified as a potential profile, to a competence profile that represents the neurocognitive state accomplished so far (Fig. 6). There are two main paths that affect the speed and quality of development. On one hand, biological factors, such as genes, hormones, and transmitters, promote maturational plasticity with age and enable the development of perceptual and cognitive skills (Fig. 6, right path). On the other hand, advantageous predispositions (in the case of music, a large right HG) are likely to increase motivation to practice. This, in turn, may lead to training-induced neural plasticity (left path) and enhanced neural efficiency (in the case of music, boosted, accelerated, and highly synchronized P1 responses to auditory stimuli). Most studies on auditory plasticity have focused on the practice aspect (Fig. 6, red dashed circle) and have demonstrated considerable learning-induced changes (for review, see Strait and Kraus, 2014). Our data suggest that it may be also important to consider a child's latent potentials and intrinsic motivations (left side of the figure), because early identification, support, and pedagogic interventions are likely to promote brain development.

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