Differentiating maturational and training influences on fMRI activation during music processing

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Abstract

Two major influences on how the brain processes music are maturational development and active musical training. Previous functional neuroimaging studies investigating music processing have typically focused on either categorical differences between "musicians versus nonmusicians" or "children versus adults." In the present study, we explored a cross-sectional data set (*n*=84) using multiple linear regression to isolate the performance-independent effects of age (5 to 33 years) and cumulative duration of musical training (0 to 21,000 practice hours) on fMRI activation similarities and differences between melodic discrimination (MD) and rhythmic discrimination (RD). Age-related effects common to MD and RD were present in three left hemisphere regions: temporofrontal junction, ventral premotor cortex, and the inferior part of the intraparietal sulcus, regions involved in active attending to auditory rhythms, sensorimotor integration, and working memory transformations of pitch and rhythmic patterns. By contrast, training-related effects common to MD and RD were localized to the posterior portion of the left superior temporal gyrus/ planum temporale, an area implicated in spectrotemporal pattern matching and auditory–motor coordinate transformations. A single cluster in right superior temporal gyrus showed significantly greater activation during MD than RD. This is the first fMRI which has distinguished maturational from training effects during music processing.

Keywords

Auditory discrimination; Developmental; Musical training

Introduction

The brains of musicians are considered an ideal lens through which functional and structural plasticity may be examined (for reviews, see Münte et al., 2002; Schlaug, 2001; Wan and Schlaug, 2010; Zatorre et al., 2007). During performance, a musician must rapidly integrate sensory cues (auditory, visual, proprioceptive) and motor commands (articulatory, respiratory, limb coordination) within his or her own person, as well as with other musicians

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engaging in the same activities. The learning of this rich and dynamic process is often begun at an early age and sustained over the course of many years. Thus, two important factors that influence brain function and structure in musicians are the duration/intensity of musical training (and the concomitant *explicit* learning of perceptual–musical skills), and normal maturational development (and the concomitant *implicit* learning of perceptual–musical skills).

Intensive training and practice on an instrument (including the voice) is nearly always a prerequisite for musicianship, and has been investigated extensively. Apart from differences in task (e.g., perception, working memory, or production), studies may also be distinguished by their statistical designs: specifically, how musician status was analyzed. Most cross-sectional functional magnetic resonance imaging (fMRI) investigations have used the categorical distinction (and subsequent statistical contrast) "musicians vs. nonmusicians," in both perception tasks (e.g., Gaab et al., 2003; Koelsch et al., 2005; Ohnishi et al., 2001) and production tasks (e.g., Bangert et al., 2006; Hund-Georgiadis and von Cramon, 1999; Meister et al., 2005). Artificial dichotomizations, however, result in well-known costs to statistical power (e.g., MacCallum et al., 2002), reducing the likelihood that true effects will be detected. Given the level of conservativeness with which statistical parametric maps are already thresholded (e.g., Lieberman and Cunningham, 2009), this additional loss of power is problematic. Nevertheless, only a handful of studies have parameterized some aspect of musical training—for example, years since commencement of training or intensity of musical practice—and used regression techniques to examine the association between that parameter and task-related functional activations (e.g., Kleber et al., 2010; Ohnishi et al., 2001).

Compared to the large fMRI literature exploring musical training effects, there have been few cross-sectional investigations exploring developmental aspects of brain activation during music processing. Early explorations of functional activation across the lifespan were hindered by methodological concerns, particularly the fidelity of normalizing the scans of children and adults to a common template (e.g., Gaillard et al., 2001). Subsequent empirical work, however, demonstrated that systematic changes in brain anatomy are below the effective resolution of fMRI once standard spatial smoothing algorithms have been applied (Burgund et al., 2002; Kang et al., 2003). With respect to brain anatomy, Burgund et al. (2002) measured the locations of 45 sulcus coordinates and 66 outer-boundary coordinates (in all three planes) in the brains of 20 children (aged 7–8) and 20 adults (aged 18–30) after all brains had been transformed to the same adult-derived template. A difference score between children and adults was then computed at each coordinate. Of these total 111 difference scores, only 5 were greater than 4 mm, and none was greater than 7 mm. With respect to fMRI activations, Kang et al. (2003) examined eight reliable activations elicited by a visuomotor task, and reported highly consistent results between children and adults with respect to activation time courses and the mean and variability of activation foci locations. A number of subsequent investigations have cited these empirical findings in choosing to use regression designs and a common normalization template to explore differences in fMRI activation across wide age ranges; for example, during visual working memory (Ofen et al., 2007 [ages 8–24]), word reading (Turkeltaub et al., 2003 [ages 6–22]) or word generation (Brown et al., 2005 [ages 7–32]).

Only one previous cross-sectional study has investigated maturational differences in music processing. Koelsch et al. (2005) compared activations elicited during a harmonic discrimination task (regular versus irregular chord progressions) in children aged 9.5–11 and adults aged 20–36. Because children and adults were analyzed separately rather than in a single design, however, no direct contrasts between the age groups were performed, and thus

no inferences could be made about whether (and where) patterns of fMRI activation were associated, positively or negatively, with age.

In sum, no previous fMRI study has simultaneously explored the influence of maturational development and musical training on brain function. In the present study, we used multiple linear regression to analyze the contributions of age and training (while controlling for task performance; cf. Brown et al., 2005) on fMRI activation during a *same*/*different* two-choice musical phrase discrimination task.

As summarized in Table 1, two-choice discrimination tasks are common among fMRI investigations of music processing, and elicit wide, bilateral activations across the cortex (frontal, temporal, and parietal lobes), the anterior insula, and the cerebellum. This wide pattern of activation is favorable for the present design, as it yields the potential to explore differences associated with both age and training throughout the brain. Specifically, we will explore whether any of the regions identified in Table 1 show activation that correlates with age and training (as well as task performance), using behavioral and imaging data from 84 subjects participating in a large study on the effects of music training across the lifespan. Previous in-depth reports on this data set have focused on behavioral (Forgeard et al., 2008; Norton et al., 2005) and morphological (Hyde et al., 2009; Schlaug, 2001; Schlaug et al., 2009) changes associated with musical training in young subjects. Understanding how age and training influences patterns of fMRI activation in a cross-sectional sample may inform future longitudinal work exploring maturation- and training-mediated changes in auditory processing (for reviews, see Besson et al., 2007; Jäncke, 2009; Kraus and Chandrasekaran, 2010).

Methods

Subjects

Behavioral and imaging data were obtained from 84 individuals participating in a large study on the effects of music training on brain structure and function: 28 adults (aged 21–33) and 28 children (aged 9–11) participating in a cross-sectional arm, and 28 children (aged 5–7) participating in a longitudinal arm. Handedness was classified in adults per the Annett handedness questionnaire (Annett, 1970), and the same questionnaire was adapted for children as described in Norton et al. (2005). All subjects were classified as consistently right-handed. For the 42 subjects with musical training, the primary instrument (tallied for 5-to-7 s/9-to-11 s/Adults) was from the keyboard (12/4/8), string (1/8/6), or woodwind (1/2/0) family. All subjects (as well as the parents of the children) gave informed, written consent prior to taking part in the study, which was approved by the Internal Review Board of Beth Israel Deaconess Medical Center.

In each of the three age groups (5-to-7, 9-to-11, Adult), half of the subjects (*n*=14) had received musical training, and half (*n*=14) had not. No subject reported having absolute pitch. Demographic data from these six cells are presented in Table 1.

Musical stimuli and tasks

The scanner task comprised a *same/different* melodic discrimination (MD) or rhythmic discrimination (RD) judgment of pairs of five-note musical phrases (Fig. 1) via a button press with the index finger of the left ("same") or right ("different") hand. All phrases were recorded using a marimba-like sound (Cubase Universal Sound Module no. 13) to minimize any potential experience bias with a practiced instrument. These stimuli and paradigm have been used successfully in a previous study with young children (Overy et al., 2004). A single run was three minutes in duration and consisted of 12 trials: eight phrase pairs (either MD or RD) and four silence (motor control) trials (S), during which subjects heard no

auditory stimulus, but made a bimanual button press after an auditory cue. Within each run, 3 *same* and 5 *different* phrase pairs were presented. All subjects completed four runs (2 MD and 2 RD, in alternation). Subjects were familiarized with the discrimination task during a behavioral testing session prior to scanning.

In designing the study, the primary aim with respect to the scanner task was to make it feasible for children to perform. For this reason, we chose not to manipulate melodic or rhythmic parameters (e.g., Schönwiesner et al., 2005; Zatorre and Belin, 2001), and did not include a separate "listen only" baseline condition (e.g., Zatorre et al., 1994).

Regressor specification

Three regressors were used in all analyses. Two were task-independent (*Age* and *Training*), and one was task-dependent (*Performance*). We did not model the age at onset of training in our regression because the range of onset ages in our sample was substantially smaller than in previous investigations which did model age at onset. *Age* was quantified in years. *Training* was quantified as the "cumulative dose" of instrumental instruction and practice hours since the onset of musical training (including private lesson and ensemble time), as in previous studies (e.g., Bengtsson et al., 2005b; Kleber et al., 2010). Training hours were derived via retrospective questionnaires given to the adult subjects and the parents of children from the cross-sectional arm (9-to-11 year olds); and via weekly practice journals kept by parents of children in the longitudinal arm (5-to-7 year olds).

To guard against mistakenly attributing performance-mediated patterns of activation to either of our task-independent factors (cf. Brown et al., 2005), *Performance* was quantified as the sensitivity index d' Z(hit rate) – Z(false alarm rate), with appropriate correction for rates equal to 0 or 1 (Macmillan and Creelman, 2005, chap. 2). A unique d' was calculated for each subject across all four runs (2 MD and 2 RD) and used as the regressor in all analyses. (There was no significant difference in d' between MD and RD, as will be discussed in the Results.)

As both *Age* and *Training* were positively skewed, they were natural log transformed: ln(*value*+1). Under this transformation, the variance inflation factor for all regressors was acceptable (*Age*: 2.01; *Training*: 1.34; *Performance*: 2.40), indicating a valid regression model without multicollinearity (Kutner et al., 2004).

Image acquisition

Functional images were acquired via a sparse sampling design (e.g., Gaab et al., 2003, 2006) on a 3T General Electric magnetic resonance imaging scanner using a gradient-echo EPI-sequence with an echo time of 25 ms and a 64×64 mm matrix. Using a mid-sagittal scout image, 26 slices were acquired over 1.75 s with a voxel size of 3.8×3.8×4 mm. Scanning repetition time (TR) was kept constant at 15 s; stimuli were jittered between three time points such that the onset of the first axial slice occurred 1.25, 2.25, or 3.25 s after the end of the second phrase in each pair. The data from these three time points were combined during statistical analysis to allow for individual differences in hemodynamic response time across brain regions.

Image processing, first-level analysis, and contrast specification

All first-level image processing steps (movement correction, normalization to the MNI EPI template, smoothing with an isotropic 8 mm FWHM kernel, and resampling to 2 mm cubic voxels) were performed using the SPM5 software suite (www.fil.ion.ucl.ac.uk/spm/).

First-level analysis used a finite-impulse response basis function (window length=1 s, order=1) with scaling set to global normalization. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 200 s. Temporal autocorrelation was modeled as a first-order autoregressive [AR(1)] process. A box-car function was applied with an epoch length of 1 to the fMRI time series (12 acquisitions within each run: 8 MD or RD, 4 S), and no temporal derivatives were applied.

In designing the first-level contrasts, several interrelated issues were at play. Because we did not parametrically manipulate melodic or rhythmic properties and did not have a "listen only" baseline condition, we anticipated (and wished to accurately capture) similar patterns of activation during MD and RD. However, if such differences were present, they too should be accurately captured. To satisfy all these requirements, a set of three contrasts was constructed for each subject.

The first two contrasts directly captured relative differences in activation between MD and RD: *MD>RD* (i.e., [*MD>S*]>[*RD>S*]); and *RD>MD* (i.e., [*RD>S*]>[*MD>S*]). To capture relative *similarities* in activation between MD and RD, the third contrast used of the "minimum statistic" (Nichols et al., 2005) at the first level (Rudert and Lohmann, 2008): *MD∧RD* (i.e., min([*MD>S*],[*RD>S*])). The minimum statistic map simply takes the more negative parameter estimate (β-value) between the two constituent maps. Statistically, it is both more accurate and more conservative than the *average* of the two conditions (as would be calculated in a repeated-measures or flexible factorial design). For example, a given voxel with a high β-value in *MD>S* a null β-value in *RD>S* will take the null value rather than the (possibly supra-threshold) average value. Thus, a positive β-value in *MD∧RD* indicates *at least* some activation across both task conditions. Defined in this way, all contrasts may be analyzed and thresholded identically at the second level, described below.

Second-level analysis

Second-level (random-effects) analyses using the Multiple Regression module in SPM5 were performed separately on the three first-level contrasts from all subjects, with *Age*, *Training*, and *Performance* as (mean-centered) regressors. For each contrast, five SPM *t*-maps were generated: four "partial correlation SPMs" (that is, separate voxel-wise positive and negative correlations with *Age*, *Training*, and *Performance*), and one "average subject SPM" interpreted as the expected response for a subject of average age, training, and performance after removing error associated with these three linear effects (Nichols, 2008).

Anatomical regions of interest

Given the already ambitious scope of this aim, we restrict our analyses to regions strongly associated with task-induced *increases* in activation (i.e., Table 1), rather than task-induced *decreases* in activation (i.e., within the default mode network; Buckner et al., 2008; Raichle et al., 2001). A single anatomical mask was created *a priori* as the union of bilateral masks from the Automated Anatomical Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) and queried using the WFU Pick Atlas (Maldjian et al., 2003). The full mask covered six broad regions: (1) superior temporal gyrus (plus pole), middle temporal gyrus (plus pole), Heschl's gyrus, and temporal (Rolandic) operculum; (2) opercular, orbital, and triangular inferior frontal gyrus; (3) precentral gyrus and supplementary motor area; (4) superior parietal lobule and inferior parietal lobule/supramarginal gyrus; (5) insula; and (6) cerebellum (lobules I–X, crus I, crus II). This image was used to define a small volume correction ("small" being relative in this case, as the mask retained 46,776 voxels of the total 156,984 in-brain voxels), which was then thresholded at voxel-level p=.001 and cluster-level p=.05 (FWE corrected). (SPM8 was used to correctly visualize significant activations within the anatomical mask in Figs. 3 and 4).

Scatter plots

Finally, to confirm that any observed linear correlations were not spuriously driven by subjects at either end of the spectrum, MarsBaR v0.43 (http://marsbar.sourceforge.net/) was used to extract each subject's mean β-value from each significant cluster. To aid interpretation, *simple* correlation scatter plots were created.

Results

Behavioral data

Task performance (d') was expected to increase both with age and with level of musical training. To test this, a 3 (*Age* group)×2 (*Training* group)×2 (*Task*: MD vs. RD) analysis of variance (ANOVA) was performed. As seen in Fig. 2, a significant main effect was present for *Age* ($p<.0001$, $\eta^2=.453$) and *Training* ($p<.0001$, $\eta^2=.054$), but not *Task* ($p=.259$, $\eta^2=.002$). (η^2 is the proportion of total variance in the ANOVA uniquely explained by a given effect; Keppel and Wickens, 2004). The *Age×Training* interaction was not significant ($p=.525$, $\eta^2=.006$), nor was this interaction further modulated by *Task* ($p=.930$, $\eta^2<.001$). Furthermore, MD and RD d' values were highly correlated across the sample ($r=.697$, $p<.0001$). This analysis reveals that *Age* and *Training* had statistically independent influences on d' (together explaining 50% of the total variance); indeed, even small amounts of training in the 5-to-7 year old group were reflected in increased d'. The overall similarity of performance in the MD and RD conditions motivated our decision to use the same d' regressor across all multiple regression SPMs, as noted in the Section 2.3.

Imaging data

Average subject effects—First, we examined the *MD∧RD* average subject SPMs. Fig. 3a presents surface renderings and sections for supra-threshold activations, and Table 3 presents the associated SPM statistics. The statistically average subject in our paradigm (age=$[e^{2.57} – 1]$=12.07 years; cumulative training dose=$[e^{3.15} – 1]$=22.35 hours; d'=1.90; cf. Nichols, 2008) exhibited activation in bilateral superior temporal gyrus (STG), middle temporal gyrus (MTG), and presupplementary motor area (Pre-SMA; cf. Johansen-Berg et al., 2004), consistent with previous musical discrimination paradigms in adult subjects (cf. Table 1).

Second, we examined the *MD>RD* and *RD>MD* average subject SPMs. At $p_{voxel} < .001$, there were here were no significant clusters in either contrast. This null result is consistent with our prediction that the present stimuli and paradigm would elicit largely similar patterns of activation during MD and RD. As a further illustration of this point, Fig. 3b presents a "voxel-wise scatter plot" of all 156,984 *t*-values in the *MD>S* and *RD>S* average subject SPMs (estimated at the second level using the same three-factor multiple regression design). The strong voxel-wise correlation ($r=.900$) further reflects the overall similarity between MD and RD at the group level.

However, we hypothesized that *MD>RD* might reveal *some* activation in right STG, based on a previous report using these same stimuli (Overy et al., 2004). Applying a new small volume correction consisting solely of the AAL masks for right STG plus its pole (3082 in-brain voxels), a single cluster emerged at $p_{voxel} < .001$ (Fig. 3c; 157 voxels; peak at {64, −10, −4}; $p_{cluster} =.007$). (At $p_{voxel} < .001$, there were no supra-threshold voxels in right MTG or its pole.)

These average subject effects, however, were not the focus of the present study. Statistically, activation in an average subject SPM is statistically independent from activation in a partial correlation SPM, as the two utilize distinct calculations for their *t*-values (i.e., a one-sample

t-test versus a regression slope *t*-test). Thus, the activations (or lack thereof) in Fig. 3 should not be seen as definitive. Rather, Fig. 3 serves simply as a manipulation check prior to exploring the primary question of interest: how *Age*, *Training*, or *Performance* might modulate patterns of fMRI activation during musical discrimination.

Age effects—Significant positive (but not negative) partial correlations with *Age* were present in *MD∧RD*, visualized in Fig. 4. Neither positive nor negative correlations with *Age* were present in the *MD>RD* or *RD>MD* partial correlation SPMs. Table 3 presents the associated statistics. Three distinct left hemisphere clusters were significant at $p_{voxel} < .001$: (1) temporofrontal junction (Fig. 4a; i.e., planum polare [BA 38; 51% of the cluster within this AAL mask], orbital IFG [BA 47; 31%], and anterior insula [BA 13; 18%]); (2) premotor cortex (lateral BA 6; 77%) extending into opercular (BA 44; 12%) and triangular (BA 45; 11%) inferior frontal gyrus; and (3) intraparietal sulcus (with 70% and 30% in inferior and superior parietal lobules, respectively). No clusters were significant in the right hemisphere.

Training effect—A positive partial correlation with *Training* was present in *MD∧RD* (shown in Fig. 5), but not in *MD>RD* or *RD>MD*. A single cluster was significant in left posterior STG (BA 22p), with a peak located within the probabilistic limits of the planum temporale defined by Westbury et al. (1999) after conversion to Talairach space using GingerALE (www.brainmap.org/ale). (The entire cluster is inferior to the probabilistic limits of inferior parietal cortex defined by the Anatomy toolbox.) This cluster possessed no spatial overlap with clusters in the positive *Age* correlation. No significant negative correlations with *Training* were present in the *MD∧RD*, *MD>RD*, and *RD>MD* partial correlation SPMs.

Performance effects—No significant positive or negative partial correlations with *Performance* were present in the partial correlation SPMs for *MD∧RD*, *MD>RD*, or *RD>MD* at either $p_{voxel} < .001$ or $p_{voxel} < .005$: the largest observed cluster had 2 voxels ($p_{cluster} = .978$) and 24 voxels ($p_{cluster} = .999$) at these respective thresholds.

Discussion

The present study used multiple linear regression to statistically isolate the contributions of maturational development (quantified as chronological age) and musical training (quantified as cumulative hours) to fMRI activation associated with performing melodic discrimination (MD) and rhythmic discrimination (RD) tasks. MD/RD was deemed a useful task with which to investigate maturational and training-mediated differences during music processing, for two reasons. First, MD/RD tasks have been frequently explored in both healthy individuals (cf. Table 1) and neuropsychological patients (e.g., Milner, 1962; Samson and Zatorre, 1988). Second, MD/RD elicits wide activation across the brain (cf. Table 2), yielding the potential for significant correlations with the regressors of interest. A major statistical advantage of our design is the increase in power (or more accurately, the prevented loss of power) achieved by using continuous predictor variables (*Age*, *Training*, *Performance*) rather than artificially categorized variables ("musicians vs. nonmusicians"; "children vs. adults").

We intentionally designed our task to be successfully performed by both children and adults, and thus did not parametrically manipulate melodic or rhythmic properties in the stimuli (e.g., Schönwiesner et al., 2005; Zatorre and Belin, 2001). We thus expected largely similar patterns of activation during MD and RD conditions. This hypothesis received support via a direct comparison of *t*-values in the *MD>S* and *RD>S* average subject SPMs (Fig. 3b). Additionally, only one small cluster in right STG was significant in *MD>RD* after applying a very small volume correction. Furthermore, although *MD∧RD* revealed significant partial

correlations with the regressors of interest, *MD>RD* and *RD>MD* did not. For all these reasons, we focus the scope of our discussion towards exploring brain regions and cognitive processes common to both melodic and rhythmic discrimination, and how they are modulated by age and training.

Age-related effects

Strong positive partial correlations with age (Fig. 3; Table 3) were found in three spatially distinct left hemisphere regions: temporofrontal junction (TFJ; planum polare, orbital IFG, and anterior insula), ventral premotor cortex (vPMC), and intraparietal sulcus (IPS). Activation in each of these regions is frequent in two-choice musical discrimination paradigms (cf. Table 1), as well as other paradigms which require attention or working memory operations on rhythmic auditory stimuli (discussed below). Two detailed reviews (Janata and Grafton, 2003; Lewis and Miall, 2003) have independently highlighted the involvement of all three regions in attention and working memory, particularly with respect to stimulus sequencing, timing, and temporal tracking. Here, we will propose that the observed pattern of results reflects a maturational component to the recruitment of regions which together support (1) *dynamic attending* to an unfolding musical event in both pitch space and time (TFJ and vPMC) and (2) *working memory* operations in pitch space and time (IPS). (We here use "attending" to refer to a temporally-guided continuous mental action, so as to avoid confusion with "attentional set" or "attentional demands"; cf. Janata and Grafton, 2003; Jones and Boltz, 1989). We first review evidence that supports this idea before relating it to the observed maturation effects.

Left TFJ—Recent fMRI meta-analyses of orbital IFG (Vigneau et al., 2006), planum polare (Olson et al., 2007), and anterior insula (Mutschler et al., 2009) each discuss aspects of processing of complex auditory signals such as speech and music, implicating the TFJ as a region of higher-order auditory association cortex. One aspect of this processing machinery particularly relevant to the current paradigm is the temporal sequencing and tracking of auditory stimuli that evolve over time.

A number of previous auditory perception fMRI studies highlight the role of left TFJ in temporal sequencing and tracking would be consistent with this notion. For example, Levitin and Menon (2003) reported focal activation in left orbital IFG/anterior insula during passive listening to temporally coherent (versus temporally scrambled) excerpts of music. Noesselt et al. (2003) reported activation in left insula and left planum polare during a passive word listening task that increased with word presentation rate (i.e., a stimulus tempo effect). Grahn et al. (2011) reported increased activation in left anterior insula/orbital IFG during an auditory (versus a visual) tempo discrimination task, and attribute this modality difference as reflecting the enhanced sense of beat in the auditory modality (cf. Patel et al., 2005). Motor production studies also suggest a role for TFJ in sequencing and tracking.

Left vPMC—In addition to its well-known involvement in both rhythmic motor production tasks (both complex rhythms and simple isochronous rhythms; e.g., Bengtsson et al., 2005a; Jäncke et al., 2000), left vPMC is also active during non-motor tasks that require accurate attending in time. Schubotz and von Cramon (2002) reported bilateral vPMC activation that increased with the complexity of a pitch deviant detection task within isochronous sequences of 12 isochronous tones. Grahn and McAuley (2009) found correlations between individual differences in listeners' ability to "hear" an implied isochronous beat during a silence between two to-be-judged rhythms and activation in both left premotor cortex and left insula. Chen et al. (2008) reported bilateral vPMC activation while subjects passively listened to or anticipated subsequent synchronized tapping with auditory rhythms (as well as expected activation during actual tapping). Schulze et al. (2011) also reported left vPMC

activation during non-motor covert rehearsal of a previously presented sequence of pitches or syllables.

It is interesting to note that vPMC activation during music perception and production tasks frequently extends into opercular IFG/BA 44 (e.g., Chen et al., 2008; Jäncke et al., 2000; Schubotz and von Cramon, 2002; Schulze et al., 2011), as was also the case with our findings. This pattern of activation might suggest that an articulatory rehearsal component of working memory (cf. Baddeley, 2003; Hickok and Poeppel, 2007) is at work, as has been proposed previously (Schubotz and von Cramon, 2002; Schulze et al., 2011).

Taken together, these results suggest a role for vPMC in tracking a dynamic, temporally predictable sequence (cf. Schubotz and von Cramon, 2002), an activity that may be relevant to the motor system (cf. Chen et al., 2008) particularly when motor responses (e.g., go/no-go button presses, synchronization or continuation tapping, rhythm reproductions) are required, independent of a particular effector system (cf. Bengtsson et al., 2005a).

IPS—As reviewed in Foster and Zatorre (2010a), the IPS is a multisensory integration region, receiving input from visual, auditory, and tactile sensory cortices anatomical inputs from visual, auditory, and tactile sensory cortices. As such, IPS serves as an ideal location in which abstract transformations of sensory information (such as visual or auditory objects) are performed in working memory to prepare and guide future decisions or actions (for a discussion, see Grefkes and Fink, 2005). Within the auditory domain, previous studies have shown bilateral IPS activation during two-choice discrimination tasks in which a musical phrase must be compared to a pitch-shifted version (Foster and Zatorre, 2010a) or temporally reversed version (Zatorre et al., 2010).

It is clear from Table 1 that explicit transformations in working memory are not the only types of operations that elicit IPS activity. Consistent with the reviews of Janata and Grafton (2003) and Lewis and Miall (2003), IPS may also play a role in attending. For example, Coull and Nobre (1998) reported strong left IPS activation in a task which required attending to both spatial and temporal properties of a visual cue. Left IPS activation was also present in the "listen with anticipation to tap" condition (Chen et al., 2006) that also elicited vPMC activation.

Maturation and entrainment—We have suggested that the TFJ, vPMC, and IPS jointly support rhythmic attending and working memory operations on auditory sequences. In addition to the studies discussed above, support for this hypothesis can also be found from the developmental literature on the perception and production of temporal intervals. Specifically, as individuals move from childhood into adulthood, they show increased flexibility in synchronizing and attending to different levels within a metrical hierarchy (eighth-note level, quarter-note level, etc.; e.g., Drake et al., 2000; McAuley et al., 2006). The improved ability to entrain or "lock in" to a temporal sequence at multiple timescales facilitates *dynamic attending* via the phase locking of attentional (neural) oscillators at those different timescales (Jones, 2009; Large and Jones, 1999). The substantial age-related improvements in performance on the MD/RD task (Fig. 2) might thus be explained by improved entrainment to (and subsequent working memory operations on) the to-be-discriminated stimuli (all of which corresponded to a 4/4 metrical structure) at multiple timescales, driven by increased recruitment of the TFJ, vPMC, and IPS.

General maturational effects—The possibility that general physiologic factors related to maturation (rather than specific to music processing) contributed to age-related effects cannot be excluded. Changes to blood oxygenation hemodynamic response (e.g., Richter and Richter, 2003) and baseline blood flow (e.g., Biagi et al., 2007) could alter the

relationship between measured fMRI signal and neuronal activity. More fundamentally, higher synapse and neuronal density in children (e.g., Huttenlocher, 1979) may lead to an altered neuronal response during many tasks. However, the spatially distinct pattern of age-correlated differences (Figs. 4a and b) compared to the average subject response (Fig. 3a) suggests a maturational response specific to particular aspects of a network involved in music processing rather than a more generic maturational effect on fMRI responses.

Partial correlations with training

A single region was found to show a partial correlation with *Training* during both MD and RD: left posterior STG/planum temporale (PT; e.g., Shapleske et al., 1999). As reviewed by Griffiths and Warren (2002) and Warren et al. (2005), bilateral PT activation is found in response to a wide range of auditory stimuli (simple sound patterns, pitch sequences, objects in auditory space, environmental sounds, voices, and speech) and experimental paradigms (perception, auditory object spatial rotation, working memory, and covert rehearsal). One interpretation of these diverse findings is that PT serves as "computational engine" involved in sequencing spectrotemporal patterns and comparing them to stored templates (Griffiths and Warren, 2002), facilitating an auditory input/motor output coordinate transformation which may also involve ventral premotor cortex (Warren et al., 2005). Such processing machinery would certainly benefit the discrimination task used in our paradigm, and indeed, the *MD^RD* average subject activation (Fig. 3a) shows strong pSTG activation (as do other auditory discrimination paradigms; cf. Table 1). The present results suggest that left pSTG is selectively modulated by musical training.

This asymmetry in training-mediated pSTG activation dovetails nicely with previous findings. The PT has a well-known, leftward hemispheric asymmetry (Geschwind and Levitsky, 1968) that is associated with the hemispheric lateralization of language (e.g., Moffat et al., 1998; Steinmetz et al., 1991). This leftward asymmetry is further exaggerated in musicians with absolute pitch (e.g., Keenan et al., 2001; Schlaug et al., 1995), and performance on a pitch-naming test is positively correlated both with left PT volume (Zatorre et al., 1998) and left PT fMRI activation during passive listening to music (Ohnishi et al., 2001). Our results add to these findings, showing that left posterior pSTG activation during an active discrimination task (rather than passive listening) is modulated by the extent of musical training in *non*-AP possessors.

Caveats

The results of any study must be viewed through the window framed jointly by its subjects, stimuli, paradigm, analysis, and inferential logic. With respect to our subjects (as is the case with any cross-sectional design based on a convenience sample), inferences can only be made about *differences* associated with a predictor variable, and not *changes* associated with a predictor variable. With respect to our stimuli, we did not systematically manipulate melodic or rhythmic properties in a parametric fashion, preventing a potentially more sensitive analysis (in both the conceptual and the statistical sense) of the differences in neural mechanism behind melodic versus rhythmic discrimination, as in Zatorre and Belin (2001). With respect to our paradigm, ours precluded us from isolating listening/attending processes from working memory/rehearsal processes, as in Schulze et al. (2011).

With respect to our analysis, although multiple regression has many advantages, inferences can only be made about factors included in the model. We modeled two task-independent variables (age and hours of training), but did not include another important factor (age of onset of training) due to a very limited range of values (4.00–8.46). The age at which musical training commenced influences structural (e.g., Schlaug et al., 1995) and functional (e.g., Ohnishi et al., 2001) differences within musicians' brains. The amount of training

itself also has pronounced effects on musicians' brain morphometry (e.g., Bengtsson et al., 2005b; Schlaug, 2001). Structural differences associated with either age or training can mediate observed patterns of fMRI activation (cf. Foster and Zatorre, 2010b). The lack of performance-related effects (quantified here as here, d') at the voxel level is also noteworthy; further analyses (perhaps exploring signal change within specific ROIs) may reveal more subtle effects of performance on activation patterns.

Finally, with respect to making inferences, we have constrained ourselves to discussing how age and training modulate *patterns of activation* in fMRI. This is an accurate statement, but is moot with respect to questions concerning developmental neuroanatomy and neurophysiology (cf. Brown et al., 2005; Poldrack, 2010).

Longitudinal implications

Although the present study was cross-sectional in nature, its results will inform subsequent analyses of the longitudinal arm of our investigation of the effects of training on music processing in children (e.g., 2009; Hyde et al., 2009; Schlaug et al., 2005). Other groups using a shorter-term longitudinal design (i.e., training over weeks or months rather than years) have already reported evidence of functional plasticity in children (e.g., Fujioka et al., 2006 [11–14 months]; Moreno and Besson, 2006 [8 weeks]; Moreno et al., 2009 [24 weeks]; 2011 [4 weeks]).

Conclusion

We interpret the distinct cortical regions associated with age and the duration musical training to be related to specific cognitive operations at work during a musical discrimination task. Age effects were localized to regions implicated in attending to and performing working memory operations on dynamic auditory stimuli; training effects were localized to a region known both for its role in spectrotemporal pattern matching and auditory–motor coordinate transformations. These findings improve our understanding of how maturational development and musical training shape brain function.

Acknowledgments

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Fig. 1.
Sample stimuli for the MD and RD task. Asterisks indicate a change in Phrase 2.
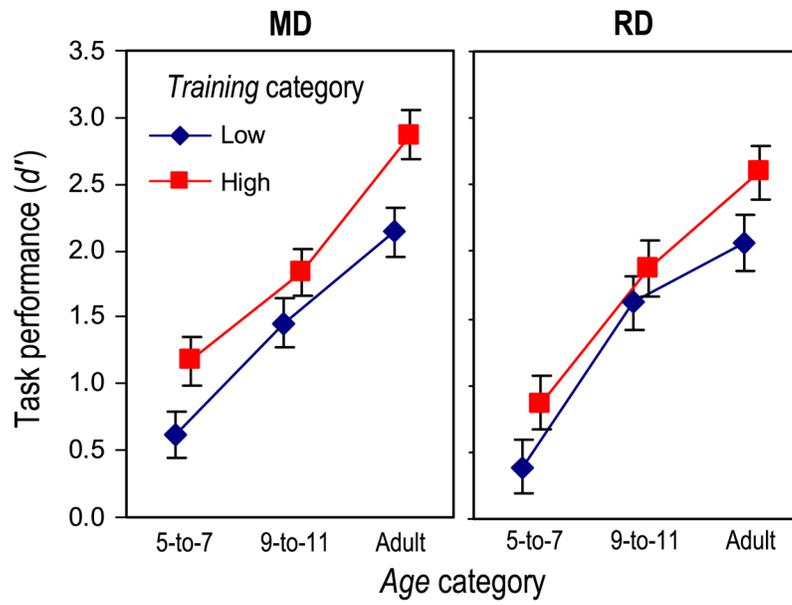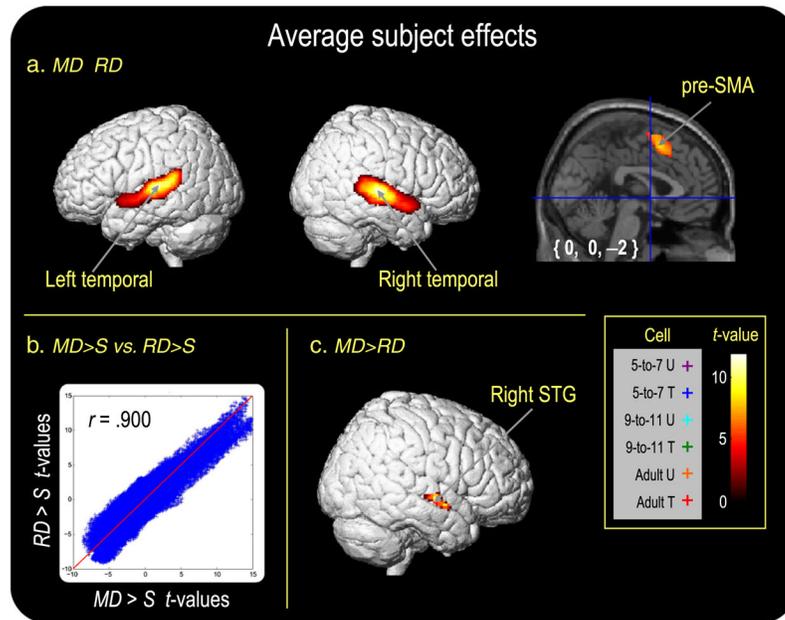
Fig. 2.
Task performance (d') as a function of *Age, Training*, and *Task* (MD vs. RD). *r*-values are partial correlations.

Fig. 3.

Thresholded activation in the average subject SPMs. (a) Activation common to both MD and RD (scatter plot inserts visualize the simple correlations between *Age* and the mean β-value from each active cluster). (b) A different scatter plot illustrating the similarity of voxel values between second-level *MD>S* and *RD>S* average subject SPMs. (c) Significantly increased activation in MD relative to RD. *Abbreviations:* pre-SMA: presupplementary motor area; STG: superior temporal gyrus. *r*-values are partial correlations with $p<.05$ (*) or $p<.001$ (***). The scatter plot was made using a custom-built data visualization toolbox (http://tools.robjellis.net).

Fig. 4.
Thresholded activation in the *MD∧RD* positive partial correlation with *Age*. Scatter plots visualize the simple correlations between *Age* and the mean β-value from each active cluster in temporofrontal junction (a), premotor cortex (b), and intraparietal sulcus (c). *r*-values are partial correlations with *p*<.001 (***).
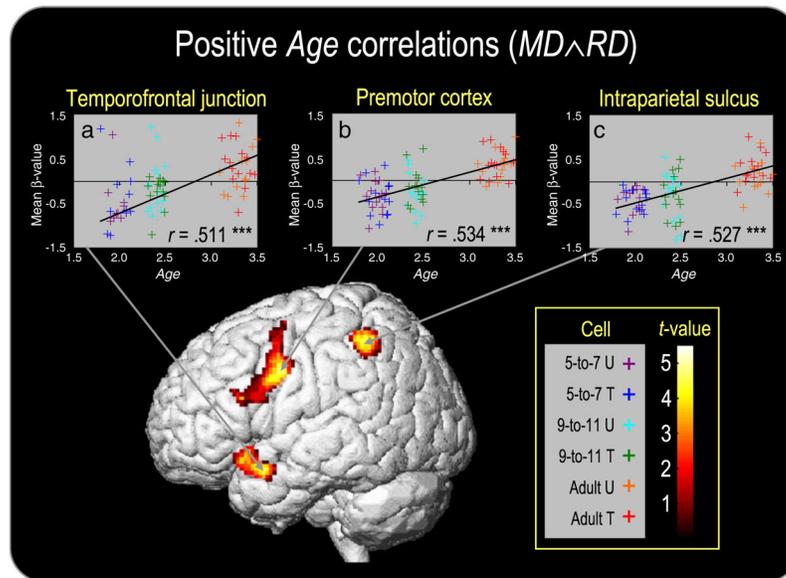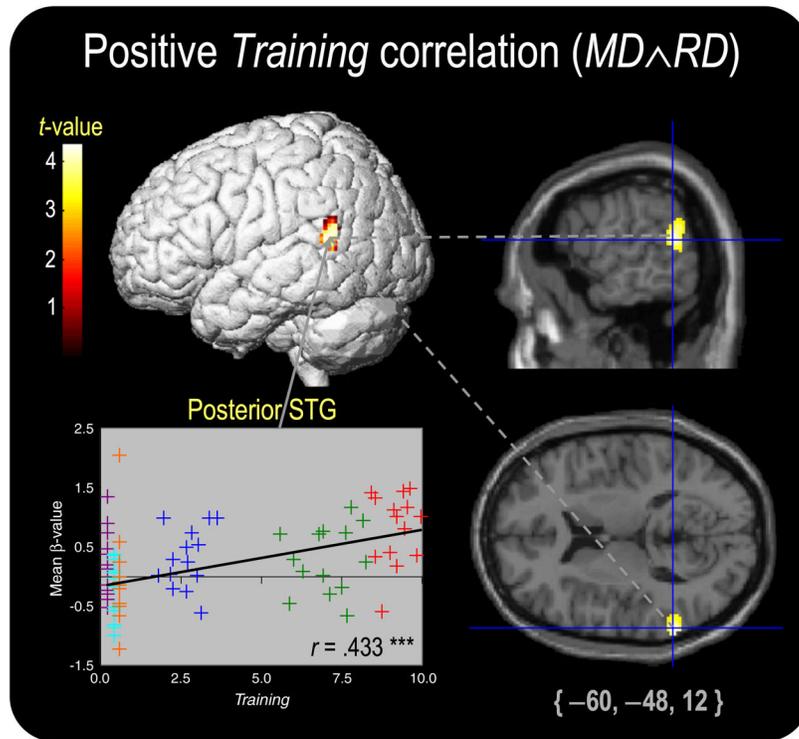
Fig. 5.
Thresholded activation in the *MD∧RD* positive partial correlation with *Training*. Scatter plots visualize the simple correlations between *Training* and the mean β-value from the active cluster. *r*-values are partial correlations with $p < .001$ (***).

Table 1

Regions of interest in the present study, derived from reported or clearly visualized significant fMRI activations in 13 two-choice musical discrimination tasks. Anatomical and/or Brodmann area (BA) labels are provided together, as different authors use different terminology.

	Brown and Martinez (2007)	Foster and Zatorre (2010)	Gaab et al. (2003)	Gaab et al. (2006)	Grahn et al. (2011)	Koelsch et al. (2005)	Koelsch et al. (2009)	Platel et al. (1997)	Rao et al. (2001)	Schulze et al. (2009)	Schulze et al. (2011)	Tillman et al. (2006)	Zatorre et al. (1994)
Judgment type	[1]	[1]	[2]	[2]	[3]	[4]	[1]	[5]	[2]	[2]	[7]	[6]	[2]
Temporal lobe													
STG / BA 22	◐	◐	◐	◐	◐	◐	◑	◐	◑	◐	◑	◖	◑
PT / pSTG / BA 22p	◐	◖	◐	◖	◐	◐	◐	◑	◑	◐	◑	◑	◑
STS	◖	◑	◑	◐	◑	◑	◑	◑	◑	◐	◑	◑	◑
MTG / BA 21	◐	◑	◑	◑	◗	◐	◑	◑	◖	◑	◑	◖	◗
Heschl's / BA 41, 42	◖	◐	◐	◖	◑	◑	◑	◑	◑	◐	◑	◑	◑
Planum polare / BA 38	◐	◑	◐	◑	◑	◑	◑	◖	◑	◖	◖	◖	◑
Frontal lobe													
IFG / BA 44	◐	◑	◖	◑	◐	◐	◑	◖	◐	◐	◖	◗	◑
IFG / BA 45	◐	◑	◑	◑	◖	◐	◖	◑	●	◗	◖	◗	◐
IFG / BA 47	◑	◑	◑	◑	◖	◐	◑	◑	◐	◑	◖	◑	◗
Premotor / lat.BA 6	◐	◑	◑	◑	◐	◐	◐	◗	◐	◗	◐	◑	◑
SMA / med. BA 6	◐	◑	◑	◐	◐	◑	◖	◑	◖	◖	◐	◑	◑
Parietal lobe													
IPL / Angular / BA 39	◑	◑	◑	◑	◑	◑	◑	◑	◑	◑	◑	◑	◑
IPL / Supramarginal / BA 40	◖	◑	◖	◖	◖	◖	◖	◖	◑	◐	◖	◖	◐
IPS	◑	◐	◑	◐	◑	◑	◐	◑	◐	◐	◖	◑	◑
SPL / BA 7	◑	◑	◐	◐	◐	◑	◑	◑	◐	◐	◖	◑	◗
Other													
Anterior insula	◐	◑	◐	◐	◐	◐	◐	◑	◐	◑	◖	◗	◐
Cerebellum	◖	◑	◐	◐	◗	◑	◑	◑	◑	◐	◐	◑	◑

Dark symbols (◖ and ◗) indicate significant left or right hemisphere activation, respectively; pale gray symbols indicate no significant activation. *Judgment type:* [1] *same/different* pairs of melodies or rhythms (Brown and Martinez, 2007; Foster and Zatorre, 2010a, 2010b; Koelsch et al., 2009); [2] *same/different* tones within a melody (Gaab et al., 2003, 2006; Rao et al., 2001; Schulze et al., 2009; Zatorre et al., 1994); [3] *speeding up/slowing down* rhythms (Grahn et al., 2011); [4] *regular/irregular* harmonic progressions (Koelsch et al., 2005); [5] *yes/no* change in pitch or change in rhythm in a sequence (Platel et al., 1997); [6] *timbre A/timbre B* of a target chord (Tillman et al., 2006); [7] similar to [2], but here referring to significantly greater activity during explicit rehearsal of pitches versus syllables (Schulze et al., 2011).

Abbreviations: IFG: inferior frontal gyrus; IPL: inferior parietal lobule; IPS: intraparietal sulcus; lat.: lateral; med.: medial; MTG: middle temporal gyrus; PT: planum temporale; SPL: superior parietal lobule; SMA: supplementary motor area; STG: superior temporal gyrus; pSTG: posterior STG.

Table 2

Demographics for the 84 subjects, grouped into six "cells" as a function of age and training.

Cell	Males/females	Mean (SD)/range			
		Age at scan (years)	Age of commencement (years)	Practice (years)	Cumulative dose (h)
5-to-7 U	7/7	6.23 (.56)/5.10–7.11	—	—	—
5-to-7 T	5/9	6.46 (.80)/5.04–7.38	6.03 (.77)/4.84–6.91	.38 (.17)/.16–.82	15.57 (8.86)/4.94–35.91
9-to-11 U	8/6	10.07 (.67)/9.10–11.16	—	—	—
9-to-11 T	5/9	10.28 (.73)/9.08–11.12	5.74 (1.35)/4.01–8.46	4.61 (1.61)/1.24–6.63	1535 (1144)/268–3792
Adult U	6/8	27.17 (3.50)/20.96–33.00	—	—	—
Adult T	8/6	25.87 (2.85)/21.51–31.33	5.21 (1.05)/4.00–8.00	19.07 (4.51)/10.00–26.00	10,888 (5053)/4473–20,849

T: trained; U: untrained. "Cumulative dose" is the total number of hours since the beginning of training; for details, see Section Regression specification.

Table 3

SPM statistics for all significant activations in the *MDARD* average subject SPMs and positive partial correlation SPMs for *Age* and *Training*. Where present, probabilistic labels ("Assigned to") are given for individual peaks, as defined by the SPM5 Anatomy toolbox (version 1.8; Eickhoff et al., 2005).

Effect	Extent (voxels)	p-value (cluster)	Peak location [a]	Assigned to	Peak t	MNI coordinates		
Avg. sub.	2178	<.0001	L. Sup. temporal	Te 1.0 [30%] [b]	11.92	−50	−26	4
			L. Mid. temporal	Te 3 [40%] [c]	10.55	−60	−32	8
			L. Sup. temporal	—	7.28	−54	0	−6
	2109	<.0001	R. Sup. temporal	Te 3 [40%] [c]	10.97	66	−22	8
			R. Sup. temporal	—	10.74	58	−20	2
			R. Sup. temporal	Te 1.0 [50%] [b]	9.87	60	−8	2
	507	.001	Pre-SMA [d]	Area 6 [50%] [d]	7.48	2	10	54
			Pre-SMA [d]	Area 6 [40%] [d]	6.26	2	6	64
Age	500	.001	L. Premotor [e]	Area 6 [70%]	5.15	−56	2	36
			L. Inf. frontal oper.	Area 44 [60%]	4.21	−58	14	24
	370	.006	L. Inf. frontal orb.	—	5.51	−40	18	−14
			L. Sup. temporal pole	—	4.06	−48	8	−18
	281	.014	L. Inf. parietal	hIP 2 [30%] [f]	5.04	−40	−48	52
			L. Inf. parietal	hIP 3 [50%] [f]	4.73	−34	−52	44
Training	248	.029	L. Sup. temporal	—	4.36	−60	−48	12

Abbreviations: Inf.: inferior; L.: left; Mid.: middle; oper.: opercular; orb.: orbital; Post.: posterior; R.: right; Pre-SMA: presupplementary motor area; Sup.: superior.

Notes:

[a] AAL locations implicitly refer to gyri;

[b] subregion of BA 41;

[c] subregion of BA 22;

[d] neither the AAL or the Anatomy toolbox differentiates pre-SMA from SMA-proper;

[e] the AAL does not differentiate BA 4 from BA 6;

[f] subregion of the intraparietal sulcus.