Partially Overlapping Brain Networks for Singing and Cello Playing

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1 Abstract

This research uses an MR-Compatible cello to compare functional brain activation during singing and cello playing within the same individuals to determine the extent to which arbitrary auditory-motor associations, like those required to play the cello, co-opt functional brain networks that evolved for singing. Musical instrument playing and singing both require highly specific associations between sounds and movements. Because these are both used to produce musical sounds, it is often assumed in the literature that their neural underpinnings are highly similar. However, singing is an evolutionarily old human trait, and the auditory-motor associations used for singing are also used for speech and nonspeech vocalizations. This sets it apart from the arbitrary auditory-motor associations required to play musical instruments. The pitch distribution of the cello is uniquely similar to that of the human voice, but cello playing is completely independent of the vocal apparatus, and can therefore be used to dissociate the auditory-vocal network from that of the auditory-motor network. While in the MR-Scanner, 11 expert cellists listened to and subsequently produced individual tones either by singing or cello playing. All participants were able to sing and play the target tones in tune (<50C deviation from target). We found that brain activity during cello playing directly overlaps with brain activity during singing in many areas within the auditory-vocal network. These areas include dorsal motor and premotor areas, SMA and Pre-SMA, STG, ACC, aINS, IPS(R), and Cerebellum but, notably, exclude the PAG and Basal Ganglia (Putamen). Second, that activity within the overlapping areas is positively correlated with, and therefore likely contributing to, both singing and playing in tune as shown by correlations with performance measures. Third, that activity in auditory areas is functionally connected with activity in dorsal motor and pre-motor areas, and that the connectivity between them is positively correlated with good performance. This functional connectivity suggests that the brain areas are working together to contribute to task performance and not just coincidently active. Last, our findings showed that cello playing may directly co-opt vocal areas (including larynx area of motor cortex), especially if training begins before age 7.

2 Introduction

Playing musical instruments and singing both result in musical pitch patterns by integrating auditory perception with fine-motor control. Thus, an interesting question is whether the neural systems that control these two types of musical expression are similar. Auditory-motor integration for singing relies on neural systems for vocalization, where there is a relatively direct link between a motor action and the pitch produced. This evolutionarily old auditory-vocal system comprises auditory, motor and pre-motor regions in the dorsal stream, the cerebellum, basal ganglia and brainstem structures. Fig. 1 (B. A. Kleber and J. M. Zarate 2014). However, the auditory-vocal system is used for both speech and non-speech sounds as well as for singing. Furthermore, the vocal motor system follows a developmental sequence and does not require explicit training, at least for production of simple songs, which children produce by imitation, as with speech (Tourville, Reilly, and Guenther 2008; Zatorre, Chen, and Penhune 2007), which do require explicit training, and often thousands of hours of practice. Nonetheless, musical instrument playing has been shown to rely on many of the same structures in neuroimaging studies (Zatorre, Chen, and Penhune 2007). However, no previous studies have directly compared the brain networks engaged by singing and instrument playing. This comparison would allow us to assess whether learned auditory-motor associations involved in playing an instrument build on existing brain networks that are in place for vocal production, or whether they engage different or additional systems.

Current models of auditory-motor integration for music and speech comprise a feed-forward and a feed-back component (B. A. Kleber and J. M. Zarate 2014; Zatorre, Chen, and Penhune 2007; Tourville and Guenther 2011; S. Brown, Martinez, et al. 2004). The feed-forward component encompasses brain areas that are responsible for motor planning and motor execution. These include primary motor, dorsal pre-motor, and supplementary motor cortices (M1, dPMC, SMA), brainstem nuclei including the periaqueductal grey (PAG), and the cerebellum. The feedback component encompasses brain areas that process sensory feedback and compare it to the expected output. Notably these include the primary and periprimary auditory cortices within the superior temporal gyrus (STG) including Heschl's gyrus, the planum temporale, and planum polare (HG, PT, PP), as well as the superior temporal sulcus (STS). These also include the anterior insula (aINS), anterior cingulate cortex (ACC), and intraparietal sulcus (IPS). These models were informed by research on speech and non-speech vocalizations, singing, and musical instrument playing. The earliest work done on the neural correlates of vocalizations was done in non-human primates. This work showed that stimulation of the PAG induces vocalizations, and that lesioning this region leads to muteness (Jurgens 1976; Dujardin and Uwe Jürgens 2005). Work in non-human primates has also shown that the SMA/pre-SMA and ACC are important for initiating voluntary vocalizations. (Gooler and O'Neill 1987; Kirzinger and U. Jürgens 1982). This same work helped to identify a larynx specific region of primary motor cortex in non-human primates (for review see: (Jurgens 1976). Several studies have since characterized a larynx-specific area of M1 in humans (S. Brown, Ngan, and Liotti 2008; Grabski et al. 2012) and replicated the finding that vocalization tasks recruit the PAG, ACC, and Pre-SMA/SMA in humans (Schulz et al. 2005) for review see: (B. A. Kleber and J. M. Zarate 2014).

Building on findings from the early animal models of vocalization control, research on singing has been instrumental in characterizing the auditory-vocal network (Perry et al. 1999; S. Brown, Martinez, et al. 2004; J. Zarate and Zatorre 2005; B. Kleber et al. 2007; Larson et al. 2008). Some studies have specifically investigated the feed-forward components of the auditory-vocal network by masking sensory feedback during singing, or asking participants to ignore perturbed auditory feedback (Boris Kleber et al. 2013; J. M. Zarate and Zatorre 2008). These studies have highlighted the role of the aINS,

showing that it is more active during singing when sensory feedback is masked or perturbed. Other studies have focused on the effects of perturbed auditory feedback, and found that the ACC and and IPS are specifically involved in compensating for these perturbations (J. M. Zarate and Zatorre 2008).

These studies also highlight the effects of musical expertise. Areas within the basal ganglia (putamen) were more active for experts than for non-experts (J. M. Zarate and Zatorre 2008), while the aINS was less active for experts than for non-experts (Boris Kleber et al. 2013). However, the network of areas recruited is extremely stable throughout the singing literature and even shows some degree of overlap with the areas recruited for speaking in both auditory and motor regions (Hickok et al. 2003; Ozdemir, Norton, and Schlaug 2006). Differences between these two systems, like the relative right lateralization of auditory cortex for singing compared to speech, are thought to be related to the increased dependence on pitch processing during singing (Ozdemir, Norton, and Schlaug 2006). It therefore would seem likely that musical instrument playing, which is also highly dependent on pitch processing, would show a high degree of overlap with the brain areas recruited of singing.

Functional imaging research on musical instrument performance has also helped inform our understanding of the auditory-motor integration system. Studies on piano and keyboard playing (Bangert et al. 2006; Baumann et al. 2007; R. M. Brown and Palmer 2012; Haslinger et al. 2004; Parsons et al. 2005), simulated violin performance (Martin Lotze et al. 1999; M Lotze et al. 2003), and simulated guitar playing (Vogt, Higuchi, and Roberts 2007; Buccino et al. 2004; Higuchi et al. 2012) show activation in many of the same core auditory and motor regions as are seen in the auditory-vocal network, but notably does not include the brainstem . However, as noted above, no direct comparison has been performed between vocal and instrumental pitch production. To directly compare singing and instrument playing we need to use an instrument that has a continuous (as opposed to discrete) pitch mapping like the voice, but whose control is completely independent of the vocal apparatus. Instruments in the violin family fit both criteria. fMRI research on violin playing has relied on imagined performance or finger tapping as a proxy for real performance because a violin could not be played in the scanner (M Lotze et al. 2003). Consequently, this research lacked the auditory feedback necessary to directly compare singing to playing. Other fMRI research on musical instrument playing has focused on the keyboard (Chen, Rae, and Watkins 2012; R. M. Brown and Palmer 2012). However, the keyboard differs from the voice in two key ways. First, the keyboard is a discrete pitch instrument, in which the pitch of each note is mapped to a key in a one-to-one manner, and cannot be changed once a key has been pressed. In contrast, the human voice is a continuous pitch instrument which can produce any pitch within a range, not just discrete values, and can change this pitch on an ongoing basis (notably, in response to a feedback perturbation) (Burnett et al. 1998). This continuous nature of pitch is paralleled in fretless string instruments from the violin family. Second, in keyboard playing, pitch and timing are controlled by the same movement, a key press. In singing, pitch and timing are often decoupled; pitch is controlled by the tension of the vocal cords while timing is controlled primarily by the diaphragm. This distinction is paralleled by the asynchronous movements of the left and right hands required to play instruments from the violin family, which control pitch value and timing of sound onsets and offsets, respectively.

In the present study we directly test the hypothesis that singing and cello playing recruit an overlapping network of brain regions in auditory, motor, and auditory-motor integration regions. Specifically, we are interested in the auditory-vocal network Fig. 1. To accomplish our goal, we have developed an MR compatible cello device where sound feedback is delivered directly to the player during scanning (A. Hollinger and M. Wanderley 2013; A. D. Hollinger and M. M. Wanderley 2015) Fig. 2. This cello uses

optical sensors embedded in the fingerboard and bridge to capture finger position and string vibration, respectively. The optical sensor on the bridge of the cello provides realtime, analog sound feedback. The MR cello lacks a resonant body, but the length of the fingerboard and strings, and, by extension, the locations of where fingers would be placed to produce specific notes are the same as those found on a standard full-size cello. We also constructed a miniaturized bow to fully leverage the continuous pitch nature of the cello. By comparing the neural correlates of singing to those of cello playing directly in the same individuals, we can determine the extent to which musical instrument playing makes use of functional brain networks that have evolved for singing. We expect that cello playing and singing will recruit largely overlapping areas in premotor and supplementary motor areas, auditory cortices, and the cerebellum. We also expect that activation in primary motor cortex will be specific to the hand and larynx areas, respectively. Additionally, because playing in tune requires auditory-motor integration, we expect to see activation in areas that are thought to be responsible for perceptual monitoring and error correction (IPS, ACC, aINS and thalamus). We also expect to see functional connectivity between these regions during both singing and cello playing, reflecting the network properties of these regions acting in concert to accomplish the task.

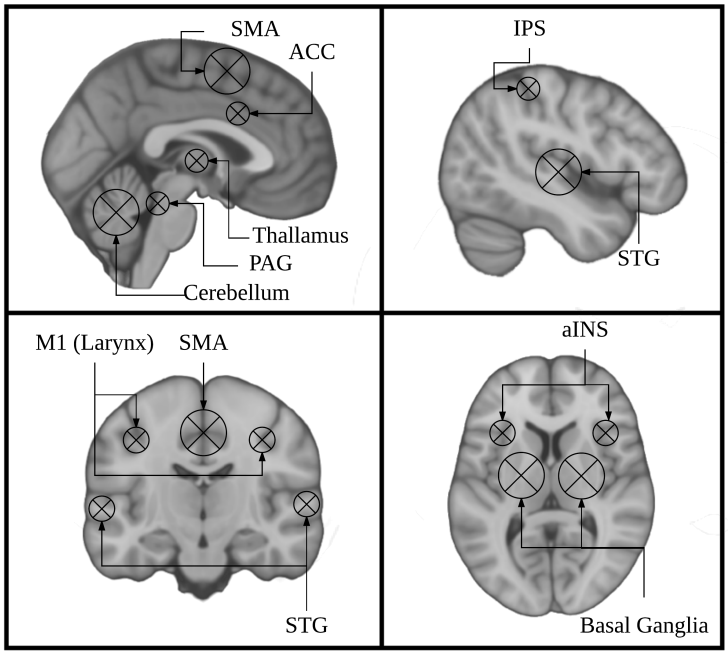

Fig 1. key regions identified using singing as a model instrument provide a framework for interpreting findings from research on musical instrument playing.

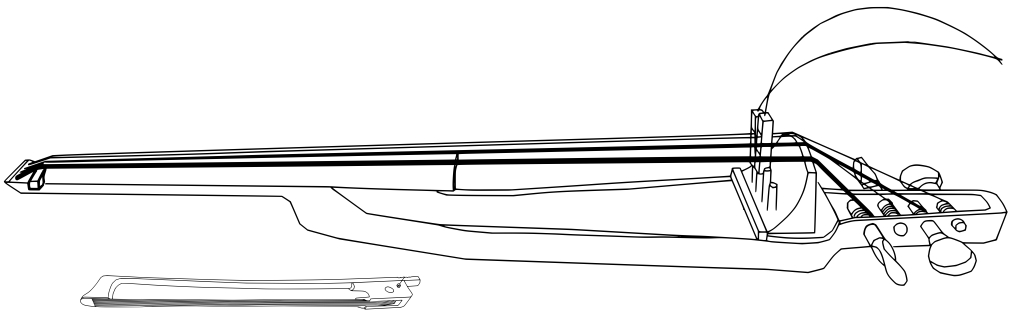

Fig 2. MR-Compatible Cello and bow developed for use inside the MR Scanner.

3 Materials and Methods

3.1 Subjects

A total of 12 expert cellists (6 Female) were recruited from the Montreal community. All participants were right handed, had normal hearing, did not report any neurological disorders, and had no contraindications for the MRI environment (mean age = 21.4, mean years experience = 13.9, mean starting age = 7.4, mean practice hours per week = 24.8). All participants gave informed consent to participate in the study in accordance with the Montreal Neurological Institute Research Ethics Board and the McConnell Brain Imaging Centre. Eleven participants were included in the final analysis, one participant was excluded from the analysis due to an equipment failure.

3.2 Experimental paradigm

3.3 Stimuli and task conditions

Participants were asked to listen to and subsequently produce target tones both singing and on an MR-Compatible cello. There were three experimental conditions: Sing/Play, Listen, and Rest. For all three conditions, we presented auditory target tones that were two seconds long. Presented tones were either E3, $F^{\#}3$, $G^{\#}3$ for cello, and E3, $F^{\#}3$, $G^{\#}3$ or E4, $F^{\#}4$, $G^{\#}4$ for singing depending on participant's vocal range. Tones were recorded by either a female vocalist, male vocalist, or on a cello. Tone presentation was followed by a pre-recorded auditory instruction to either Listen, Sing/Play, or Rest.

Participants underwent a familiarization session followed by an fMRI session. For both the familiarization session and the fMRI session, a microphone was suspended approximately 2 inches from their mouth, the MRI compatible cello device was placed along their torso using a specialized support, and headphones were provided (Sensimetrics S14 fMRI insert headphones, Dayton Audio DTA-1 amplifier). The microphone and cello were connected to a Mackie 802VLZ4, 8-channel mixer and to a midi controlled TCHelicon VoiceOne pitch shifter which was used to prevent the audio feedback from reaching the headphones on certain trials. Pink noise was played through the headphones to reduce bone conduction so that audio was being delivered exclusively through the headphones. All volume levels were adjusted on a per subject basis, but on average pink noise was presented at 78.3 dB SPL A and auditory targets were presented at approximately 15.6 dB above the noise floor. The experiment was run using custom scripts written in python. All vocalizations and cello sounds were digitally recorded using a Sound Devices 744T digital recorder Fig. 4.

A sparse sampling paradigm was used for the fMRI session (Belin et al. 1999), where a long delay in TR was used to allow tasks to be carried out in the relatively

silent period between functional volume acquisitions, thus minimizing acoustical interference and also avoiding movement-related artifacts since the scanning takes place after the motor production for each trial Fig. 5.

3.4 Procedure

To allow participants to adjust to the fMRI-compatible cello and the constraints of playing it in the scanner, each person underwent a 45 minute familiarization session no more than one week prior to their session in the MR-scanner. During the familiarization session each participant was asked to lie on a foam mat inside a structure that simulated the space constraints of the MRI environment. All participants were asked to perform a series of scales, which contained all of the target notes that would be presented during the experiment and a reduced duration (10-minute version) of the experimental task.

On performance trials, participants were instructed to sing or play back the target tone for 4seconds. For singing trials, participants were instructed to sing with closed lips in order to reduce breathing artifacts in the recorded signal and movement artifacts in the fMRI signal. For cello playing trials they were instructed to use as few bows as possible to reduce movement artifacts (apx 1second per bow). Between trials participants were instructed to keep their hands on the cello and to move as little as possible. During familiarization, participants went through 2 reduced-length experimental runs (one cello, one singing), with all conditions included in each run). Three participants underwent a second familiarization session due to equipment problems during their first scheduled session.

Within one week of the familiarization session, participants were tested in the Siemens Trio 3T magnetic resonance (MR) scanner at the Brain Imaging Center of the Montreal Neurological Institute. Each participant was fitted with MR-compatible headphones. The MR-compatible microphone was attached to the mirror support system. The MR-compatible cello was laid across the torso using a special MR-compatible stand. Sound levels were adjusted on a per participant basis so that, during trials with masked auditory feedback, participants could not hear their voice or the sound of the cello above the pink noise.

During the fMRI session, participants performed two cello playing runs and two singing runs. Run order was counterbalanced across participants. During each of these runs, trial order was pseudo-randomized. Following the presentation of each target tone, participants were instructed to sing or play the cello, or to listen. On rest trials no auditory target was presented. On some of the performance trials, auditory feedback was fully masked. The no audio condition and listen condition served as controls for the auditory and motor aspects of the performance trials.

3.5 MRI acquisition

A high resolution T1-weighted anatomical scan (voxel=1mm^3) was collected between runs 2 and 3. During the 4 functional runs, one whole-head frame of 28 contiguous T2*-weighted images were acquired (Slice order = Interleaved, TE=85ms, TR=10s, Delay in TR = 7.7s, 64x64 matrix, voxel size = 4mm^3). All tasks were performed during the 7.7s silent period between functional volume acquisitions. As such, the tasks were done in silence. Timing of the auditory stimulus presentation was varied randomly by up to 500ms to increase the likelihood of obtaining the peak of the haemodynamic response for each task. Within each run, each condition was presented 10 times for a total of 20 acquisitions per condition for singing and 20 acquisitions per condition for cello playing. A high resolution whole brain T1-weighted anatomical scan (voxel=1mm^3) was collected between runs 2 and 3.

3.6 Behavioral analyses

Individual trials of singing and cello playing were analyzed with pitch information extracted from audio signals. Each trial's audio was first segmented from the MR-compatible microphone recording by hand using Audacity software. The trials were then processed using a custom analysis pipeline implemented in Python, with a GUI for visualizing and optimizing analysis parameters.

The ambient noise in the scanner room had a peak resonance of 160Hz that interfered with the extraction of fundamental target pitches, so harmonics 3-10 of the cello and singing tones were used for pitch extraction. To reject room noise and to isolate harmonics of interest, the raw microphone signal was high-pass filtered with a cutoff at 367Hz and low-pass filtered with a cutoff at 4216Hz. Pitch estimation was then performed using the YinFFT algorithm provided in the Python module Aubio (Brossier 2007), producing a time-series of pitch estimations (detected harmonic, in Hz) and confidence ratings (between 0 and 1). Estimates were adjusted to their representative fundamental pitches before selecting stable pitch regions for further analysis. Stable pitch regions were defined as: segments of at least 150ms in which the rate of change of the pitch did not exceed 100Hz/sec (or apx. 0.07Hz per 32-sample pitch estimation window at the sampling rate of 44100Hz). Of these regions, only those that maintained a confidence rating of at least 0.7 were included. Trials were rejected if no regions were found to meet the stability and confidence criteria (see Fig. 3). In total, 92.4% of trials were retained. Rejected trials were excluded from the fMRI analysis.

Pitch accuracy was calculated on a per-trial basis as the deviation between the produced and target pitches, expressed in cents using equation 1. An overall accuracy score for each participant was then determined by calculating their mean pitch accuracy across all trials. Finally, scores were analyzed using a two way (instrument by target) ANOVA implemented in R (R Development Core Team 2008).

$$cents = 1200 * \log_2(\frac{Freq_{produced}}{Freq_{target}}) \tag{1}$$

3.7 fMRI Analyses

fMRI data were analysed using the FSL5.0 FEAT toolbox (Jenkinson et al. 2012). Brain extraction was carried out using BET2. Functional volumes were aligned to the high resolution anatomical and then to MNI152 standard space using FLIRT linear registration with 12DOF. Motion parameters were estimated using MCFLIRT and. fMRI time course was temporally filtered to remove drifts greater than 300ms. To boost the signal to noise ratio, images were spatially smoothed with an 8mm FWHM kernel. FLAME-1 mixed effects modeling was used to fit the GLM to the fMRI signal.

Significance was determined using an FSL cluster probability threshold of $p < 0.05$ with a voxel-wise significance level of z=3.3 ($p < 0.01$). The cluster probability threshold serves as a correction for multiple comparisons. Four contrasts were carried out: Singing vs Rest, Cello playing vs Rest, Cello Playing vs Singing, and Singing vs Cello Playing. Additionally, task performance (on a per-subject basis) was regressed against the BOLD signal for each of these contrasts. Statistical conjunctions were carried out using the conjunction script created by the Warwick University Department of Statistics, which also made use of the FSL tools (Nichols et al. 2005). This script carries out a voxel-wise thresholding of $p < 0.05$ in both conditions of interest, and then carries out a cluster correction of $p < 0.05$.

Functional Connectivity analyses were carried out using the FSL5.0 FEAT toolbox. A seed region in auditory cortex was identified by masking the conjunction of singing

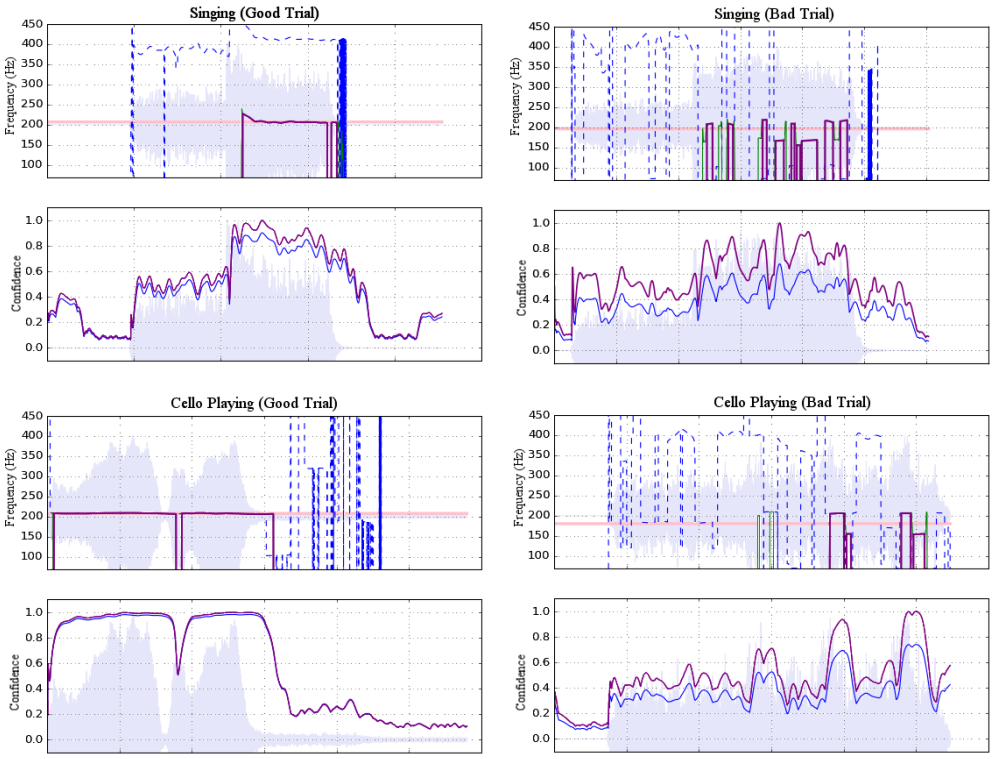

Fig 3. Examples of accepted (left) and rejected (right) trials for both singing (top) and cello playing (bottom). Each example shows a plot of pitch estimations above a plot of confidence ratings. For the former, dashed blue lines represent raw pitch estimation whereas solid purple lines represent potentially stable pitch estimates adjusted to the fundamental. For the latter, raw confidence ratings are shown in blue and normalized confidence ratings are shown in purple.

and cello playing from the functional data with an anatomically defined mask of Heschl's Gyrus (Harvard Structural Brain Atlas). Seed regions in primary motor cortex (M1) were identified by masking singing and cello playing with an anatomically defined mask of post-central gyrus (Harvard Structural Brain Atlas). An additional seed region was identified using a functionally defined mask of larynx area in M1 from Kleber et al. The activation time course in each of these regions was extracted and correlated with the whole-brain time course for each task of interest, which was estimated using the GLM. Correlated voxels were thresholded as described above. Regions that showed a correlated time course were then linearly regressed with task performance to determine whether those areas were contributing directly to good intonation.

4 Results

4.1 Task Performance

We first carried out a behavioural analysis to confirm that our participants, expert cello players, could sing 3 target tones and also play them on the MR-Compatible cello with at least quarter tone accuracy (50 Cents). By performing a two way anova (instrument by target tone), we found that participants could produce each of the three target tones within the specified accuracy both when singing (mean deviation from target= -8.9

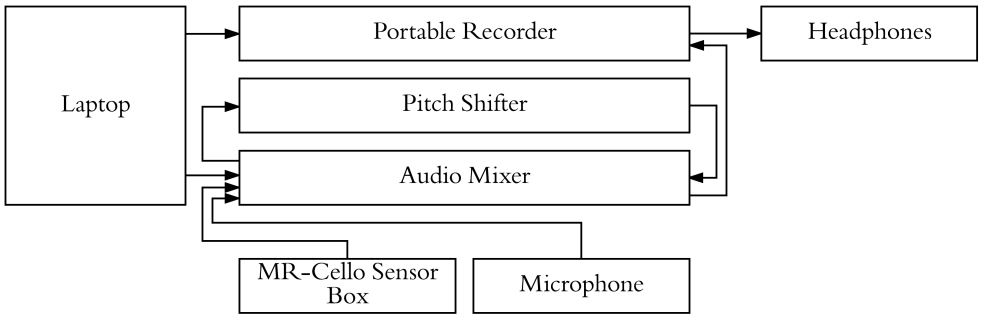

Fig 4. Experimental setup used to present stimuli, cello audio, and singing audio through headphones. Pitch shifter allowed for audio feedback from cello/singing to be blocked on specific trials while still presenting audio stimuli.

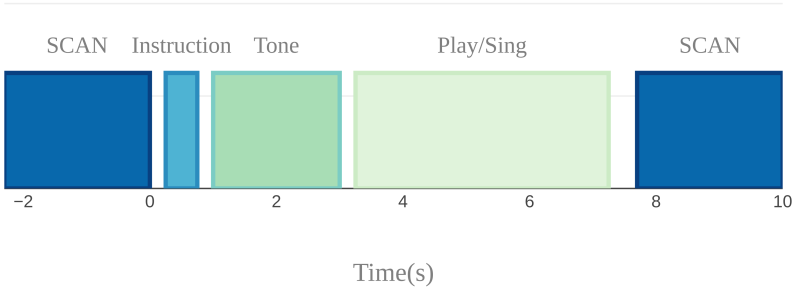

Fig 5. Sparse sampling design used to avoid auditory and motion artifacts. Auditory target presentation, instruction presentation, and singing and cello playing were done in the silent 7.7s period between scans

Cents, stdev = 58.9 Cents) and when playing the cello (mean = -7.79 Cents, stdev = 85.39 Cents) Fig. 6. There was no significant effect of instrument ($p<0.65$,$F = 0.21$), but there was a significant effect of tone ($p<7.14 \times 10^{-4}$, $F = 11.54$) and a significant tone by instrument interaction ($p<4.21 \times 10^{-8}$, $F = 30.65$). Post-hoc tests showed that, when playing the cello, participants tended to be flat on the highest tone (mean = -39 Cents) and that, in singing, they tended to be flat on the lowest note (mean = -15 Cents). The undershoot on the highest note for cello playing was likely because the note was the most difficult to reach within the confines of the scanner. The undershoot on the lowest note for singing, while significant, is within an eighth tone of the target pitch which is well below the quarter tone threshold for considering a note in tune. There was no within-subject correlation between performance on the cello and performance on the singing trials.

4.2 fMRI Findings

4.2.1 Similarities between singing and cello playing

To test the hypothesis that singing and cello playing activate a shared set of brain areas, we first identified the respective networks by performing two contrasts: Singing vs rest and Cello playing vs Rest. The Singing vs rest contrast was used to test the hypothesis that the singing task would activate the auditory-vocal network identified in previous literature (B. A. Kleber and J. M. Zarate 2014). We found that, consistent with the

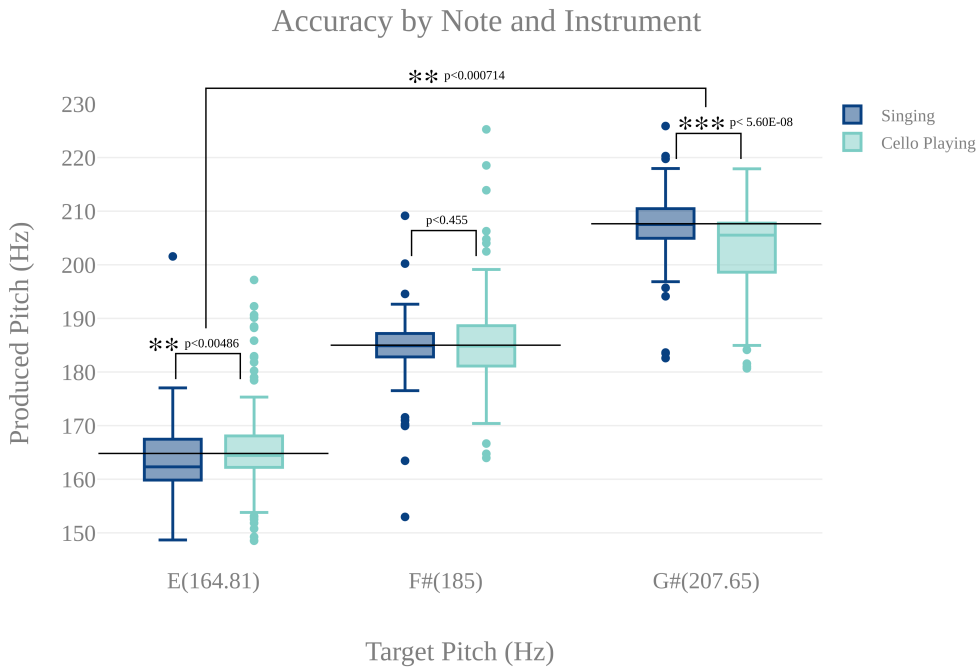

Fig 6. Accuracy by note for singing(dark blue) and cello playing(light blue). There is a highly significant main effect of note, but no main effect of instrument. There is a significant note by instrument interaction showing that singers were slightly flat on the lowest note and cellist were slightly flat on the highest. However, mean produced tones were within a quarter tone accuracy(50cents)

areas reported in the literature, singing activated Pre and Post central gyrus (R > L), SMA extending to ACC (bilateral), IPS (R), the length of the STG extending to supramarginal gyrus, STS, aINS (bilateral), cerebellum VI, VIIa, and CrusI-II (bilateral), thalamus extending into caudate (bilateral), the globus pallidus (bilateral), putamen (bilateral), and PAG, and the pons. In addition to areas within the auditory-vocal network, we also saw activity in middle frontal gyrus (right) Fig. **??**. This contrast did not show larynx-specific activation in M1; however, we found that larynx activation was present at an uncorrected threshold of $p<0.05$. To confirm this finding with a more focused though statistically stringent approach, we performed a fixed-effects analysis consistent with what has been done in previous studies of larynx function. This analysis showed significant activation in larynx area of both right and left M1 ($\text{zstat}_{\text{right}} = 5.3$, $\text{zstat}_{\text{left}} = 4.4$), in locations consistent with that reported by Brown et al in M1 for phonation ($\text{d}_{\text{right}} = 9.38\text{mm}$, $\text{d}_{\text{left}} = 9.16\text{mm}$) (S. Brown, Ngan, and Liotti 2008) Eqn.2.

$$\text{d}(p,q) = \sqrt{(p_1 - q_1)^2 + (p_2 - q_2)^2 + (p_3 - q_3)^2} \tag{2}$$

For cello playing vs rest, many of the same auditory-vocal areas were active compared to singing Fig. 9. Again, activity clusters are seen throughout the pre- and post-central gyri (bilateral), SMA extending into ACC, and IPS. Activity also extends the length of the STG and superiorly into the supramarginal gyrus. Clusters are also seen in middle frontal gyrus (right), and in the anterior insula (bilateral). In the cerebellum, activation extends through VI, VIIIa, VIIIb, VIIb, CrusI-II, Vermis CrusII,

and Vermis VI. Clusters of activity are also seen in thalamus (bilateral) extending into caudate (right), and in the globus pallidus (right).

To specifically test the hypothesis that singing and cello playing both engage some of the same components of the auditory-vocal network, we carried out a statistical conjunction of the cello vs rest and singing vs rest conditions (Nichols et al. 2005). The conjunction showed overlapping activation throughout the auditory-vocal network. However, no overlap was seen in Putamen, or Brainstem. In the cerebellum, overlapping activity was seen in VI, CrusI-II, VIIIa, and VIIIb Fig. 9

Task accuracy was then linearly regressed against both singing vs rest and cello playing vs rest to determine which of the active areas were correlated with, and therefore likely to be contributing to, task accuracy. In both cases, areas that were active for the task were positively correlated with task performance (no negative correlations were observed). Specifically, for singing, all regions of the auditory-vocal network were more active as participants performed better. For cello playing, pre- and post-central gyri, STG extending into the supramarginal gyrus, aINS, cerebellum, and thalamus were more active in participants that performed better. Fig. 9

We further hypothesized that singing and cello playing would show overlap in areas whose activity contributed to higher accuracy. To test this hypothesis, we carried out a statistical conjunction of the singing vs rest and cello vs rest regressions by task performance. This conjunction showed overlap in SMA extending into ACC, IPS, middle frontal gyrus (right), STG, supramarginal gyrus, the aINS, and thalamus extending to caudate. In the cerebellum, there was overlapping activation in VIIb, VIIIa, VIIIb, and VI Fig. 9

The previous analyses found that singing and cello playing activate a shared set of brain regions, and that activity in many of these regions is positively correlated with task accuracy. Building on these findings, we decided to test the hypothesis that areas within this set are functionally connected in both singing and cello playing Fig. 10. To accomplish this goal we performed a functional connectivity analysis using the activity in Heschl's gyrus (bilateral, from Harvard Brain Structural Atlas) as a seed region and correlating activity within this seed with activity in the rest of the brain on a voxelwise basis. For singing, we saw correlated activity in auditory cortices of the STG (bilateral) both within and around the seed area, supramarginal gyrus (bilateral), pre-central gyrus (right), inferior frontal gyrus (bilateral), and in VIIIa of the cerebellum (left). For cello playing, we saw correlated activation within the seed region and also in posterior STG extending into the supramarginal gyrus, pre- and post-central gyrus, and VIIIa, VIIIb, VIIb, VI (left), and Vermis VI of the cerebellum. The conjunction of singing and cello playing functional connectivity analyses showed shared connectivity in Heschl's gyrus, pre-central gyrus, and VIIIa of the cerebellum (left) Fig. 10

Functional connectivity in both singing and cello playing using the same seed region was then linearly regressed with task performance to determine the correlation between connectivity and pitch accuracy. In singing, higher functional connectivity was positively correlated with performance in the supramarginal gyrus, and in cerebellar VIIa (left) and VIIb (right). In cello playing, higher functional connectivity was positively correlated with performance in pre- and post-central gyrus, the supramarginal gyrus, and cerebellar VIIIa and VI (bilateral) Fig. 10

4.2.2 Differences between singing and cello playing

In order to characterize the differences in brain activity between singing and cello playing, two contrasts were first carried out: singing vs cello playing and cello playing vs singing Fig. 9. For singing vs cello playing, no significant clusters of activation were observed after correcting for multiple comparisons. However, the PAG and Putamen were active in the Singing-Rest contrast, and not in Cello Playing-Rest, or the

conjunction of Cello-Rest and Singing-Rest. Additionally, at an uncorrected threshold of z=1.8 differences can be seen in larynx area of motor cortex. In order to directly test the hypothesis that the larynx area of motor cortex was more active for singing than for cello playing, which was one of our predictions, we performed a region of interest analysis of post central gyrus using the mask of laryngial motor area described above. This analysis showed more activation for singing than for cello playing in larynx area. We further tested this hypothesis by performing a 2factor Anova (Instrument by Region of Interest) with spherical ROI in hand motor regions (bilateral) and larynx area of motor cortex (bilateral). This analysis showed significant effects of both Instrument and ROI, as well as a significant Instrument x ROI interaction driven by a highly significant difference between cello playing and singing in hand motor regions Table. 1. However, no significant difference was observed in larynx area ($p < 0.13$, F=2.45) Fig. 8. To understand why the contrast of singing vs cello playing showed sub-threshold differences in larynx area but the anova did not, we decided to consider potential covariates. Based on previous research showing that early trained musicians show advantages in pitch tasks, we hypothesized that early trained musicians may use larynx area of motor cortex to a greater extent than late trained musicians. To test this, we included starting age as a covariate. While starting age itself did not significantly correlate with larynx activation in either singing($r = -0.31$, $p < 0.34$) or cello playing($r = -0.41$, $p < 0.26$), the contrast of singing vs. cello playing in larynx area was significant when accounting for the effect of starting age ($p < 0.0091$, F=8.3) Fig. 7. Additionally, when data were divided into early and late starting groups (as in (Penhune 2011), cellists that beginning musical training before age 7 (n=5) showed significantly more activation in larynx area during cello playing than did those that started age 7 and up (n=6) ($p<0.01$, F=10.26) Fig. 7.

	p	**F**
$Instrument$	8.28×10^{-5}	19.68
ROI	2.42×10^{-2}	5.53
$Instrument * ROI$	1.03×10^{-6}	34.47
$InstrumentInHand(bilateral)$	1.71×10^{-5}	33.6

Table 1. Two way anova showed a main effect of Instrument and ROI, and a significant Instrument x ROI interaction driven by a highly significant difference in Hand area (bilateral)

For cello playing vs singing, there was more activation in STG extending to the SMG, pre- and post-central gyri, and in the posterior insula. In the cerebellum, cello playing showed more activation than singing in I-IV, in VI and in VIIIb (bilateral). In pre- and post-central gyri as well as in the cerebellum, the activation peaks were centered on areas associated with hands/arms (Yousry et al. 1997).

No significant differences in functional connectivity were observed when directly contrasting singing and cello playing.

Discussion

4.3 Findings

Four conclusions may be reached from this research study. First, that brain activity during cello playing directly overlaps with brain activity during singing in many areas within the auditory-vocal network. These areas include dorsal motor and premotor areas, SMA and Pre-SMA, STG, ACC, aINS, IPS(R), and Cerebellum but, notably, exclude the PAG and Basal Ganglia (Putamen). Second, that activity within the

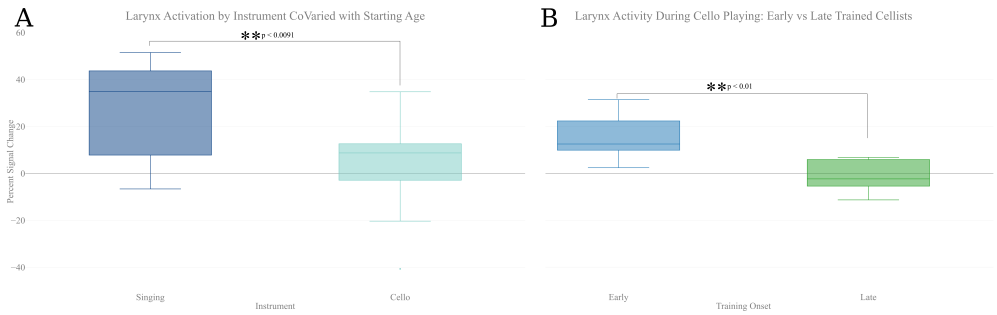

Fig 7. A: Mean cope values in larynx area of motor cortex for singing (blue) and cello playing (turquoise). When starting age is included as a covariate, Anova shows a significantly more activity in larynx area during singing than cello playing. B: Mean cope values in larynx area of motor cortex during cello playing for Early trained (blue) and Late trained (green) cellists. Cellist that started training before age 7 show significantly more activity in larynx during cello playing than do those that started age 7 and later

overlapping areas is positively correlated with, and therefore likely contributing to, both singing and playing in tune as shown by correlations with performance measures. Third, that activity in auditory areas is functionally connected with activity in dorsal motor and pre-motor areas, and that the connectivity between them is positively correlated with good performance. This functional connectivity suggests that the brain areas are working together to contribute to task performance and not just coincidently active. Last, our findings showed that cello playing may directly co-opt vocal areas (including larynx area of motor cortex), especially if training begins before age 7.

4.4 Questions Answered

4.4.1 Neural Correlates of Learned, Arbitrary Associations

This study provides evidence that relatively new auditory-motor integration tasks like stringed instrument playing make use of the auditory-vocal network, which is thought to be an evolutionarily old system Fig. 9. The interpretation that cello playing makes use of neural mechanisms that evolved for singing is consistent with the theory of Neuronal Recycling proposed by Dehaene et al (Dehaene and Cohen 2007). This theory proposes that cultural tasks (like arithmetic) are too new to be the product of evolution and that, as a result, they have to make use of cognitive mechanisms that are in place for more basic tasks (like direction processing). We propose that our findings are an example of the same concept but in the auditory-motor domain. The auditory-vocal network used for singing develops without explicit training, much like spatial processing in the visual domain. After explicit instruction, cello playing brain activity patterns overlap with singing throughout the auditory-vocal network much like arithmetic with neural mechanisms for spatial processing. Potentially the best point of evidence supporting this interpretation is our finding that cello playing might even activate larynx area of motor cortex despite cello playing not relying on the larynx. We cannot rule out the possibility that cellists were humming subvocally during the cello playing task. However, if subvocal humming was responsible for the larynx activation observed during cello playing, it seems likely that other vocalization specific areas would also be recruited, which is not the case. No significant activation was observed in basal ganglia or brainstem areas that, in singing, are active even during imagined singing (B. Kleber et al. 2007).

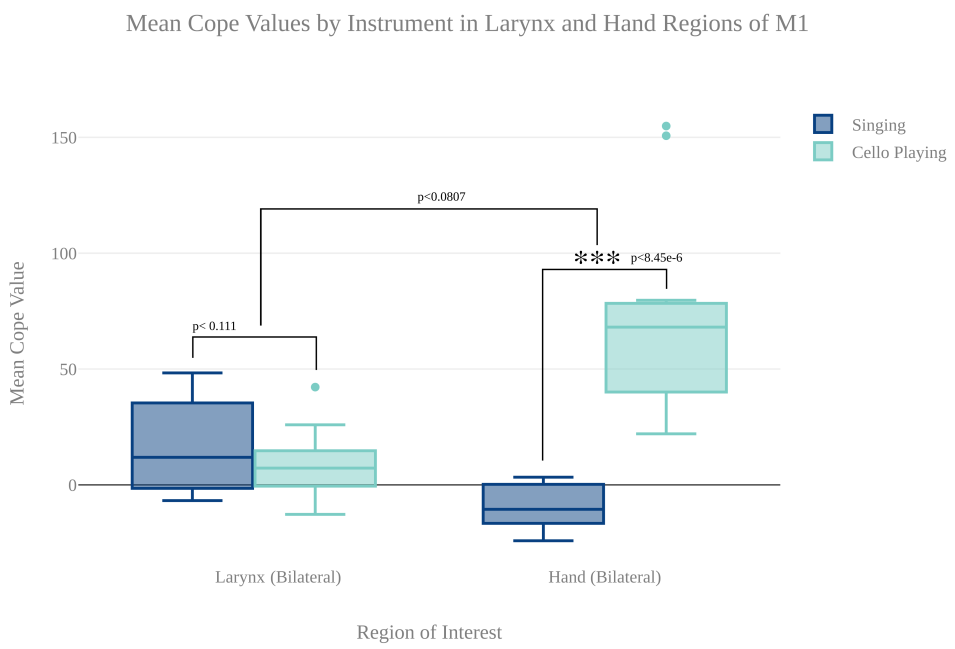

Fig 8. Mean cope values in larynx and hand area of motor cortex for singing (blue) and cello playing (turquoise). Anova showed no significant effect of instrument or brain area, but did show a significant instrument by region interaction.

4.4.2 The Role of the ACC and aINS

Some brain areas, like the ACC and aINS, are reported to be active both in studies of musical instrument performance and singing, but are given different interpretations according to the task. In studies of piano performance, the activity of the ACC is thought to reflect coordination of hand movements (Parsons et al. 2005) while in studies of singing the ACC is thought to be specifically involved in inducing vocalizations (B. Kleber et al. 2007) as has previous work done in animal models (Uwe Jürgens 2002). Similarly, the aINS is thought to integrate somatic information from the body to support bi-manual coordination in piano playing (Parsons et al. 2005) and to coordinate the vocal musculature during singing (B. Kleber et al. 2007) together with other interoceptive inputs (Boris Kleber et al. 2013). In our study, we found that activity in the aINS and ACC was directly overlapping during cello playing and singing. Consequently, we propose that the role of the aINS and ACC is to coordinate the movements of whichever motor effectors are required in order to produce pitched sounds, and that their activity is not specific to any one motor system.

4.4.3 The Role of the Brainstem

One of most prominent differences observed between singing and cello playing was the lack of brainstem activity, including in the PAG, for cello playing relative to rest. The PAG is one of the key regions identified through singing research as instrumental to producing vocalizations (B. A. Kleber and J. M. Zarate 2014), a finding which we replicated in the present study. However, the lack of activation in cello playing suggests a limit to the previously discussed interpretation that cello playing makes use of existing mechanisms in place for singing. While it may be the case that regions like the ACC

and aINS, or even the larynx area of motor cortex, can be re-purposed to coordinate activity of motor systems other than those required to produce vocalizations, lower level physiological systems like the brainstem are likely exclusive to vocal control and respiration. Early animal work on the PAG found that it was the first point at which stimulation produced "normal sounding" vocalizations (Jurgens and Pratt 1979), and later work found that different types of electrical activity in the PAG directly correlated with adduction and abduction of the the laryngial and respiratory musculature during vocalizations in non-human primates (Larson 1991). While systems that coordinate breathing may come into play for more complex instrumental performance aspects like phrasing which are tightly coupled to respiration, these systems are unlikely to be directly involved in the hand/arm movements required to produce single notes. Without recording muscle activity of the larynx during cello playing, we cannot rule out the possibility that cello playing causes larynx activity. However, we can say conclusively that playing the cello does not incidentally produce vocalization and, consequently, that the descending signals from the brainstem to the musculature are specific to each instrument.

4.4.4 The Role of the Putamen

Another difference observed between singing and cello playing was the lack of putamen activation in cello playing, though both cello playing and singing activated the GP. The finding that cello playing and singing both recruit the GP is consistent with previous work in both keyboard playing (eg. (Parsons et al. 2005)) and singing (eg. (J. M. Zarate and Zatorre 2008)). However, research in singing has also shown that recruitment of the putamen is specifically linked to expertise, with expert singers recruiting the putamen to a greater extent than novice singers when compensating for, or ignoring, introduced pitch perturbations (J. M. Zarate and Zatorre 2008). In this study, neither experts nor novices recruited the putamen when simply singing single notes without an introduced manipulation. The interpretation given to this finding in Zarate 2008 is that the putamen is likely involved in correcting for perceived errors in auditory feedback, and that singing single tones was simple enough that no real error correction was needed. They also note that lesions of the putamen have been linked to dysarthria (Uwe Jürgens 2002). In our research, no feedback manipulation was introduced either during cello playing or singing. As such, it could be the case that participants were correcting for incorrect intonation during singing and not cello playing. However, both singing and cello playing show a higher degree of pitch variability at the start of trials, compared to the end. This suggests that corrections to produced pitch were being carried out in both cases. Following from this, it could be the case that the putamen was not recruited for cello playing during our experiment because the function of the putamen is unique to the vocal domain. However, this would be in conflict with findings regarding the putamen's role in other types of sensorimotor adaptation (eg. (Seidler, Noll, and Chintalapati 2006)) and auditory-motor integration tasks like tapping to the beat (Kung et al. 2012). More likely, it is the case that, similar to the aINS and ACC, the putmen servers a more domain general role in auditory-motor integration, and was not shown to be active for cello playing due to a lack of statistical power. We predict that the putamen will be recruited for both cello playing and singing in future studies involving tasks that more directly probe for auditory-motor integration.

4.5 The association between auditory and motor regions

This study also provides direct evidence supporting the idea that cello playing not only recruits many of the same brain areas as singing, but that it makes use of the same network of brain regions. First, we found that good intonation is positively correlated

with functional brain activity within the areas that are recruited both for singing and cello playing Fig. 9. This shows that the same activity in both instruments plays a role in accomplishing the same behavioural goal. Second, we found that auditory (bilateral HG) and motor (dorsal pre-motor, SMA) regions within the areas common to singing and cello playing were functionally connected during both tasks, and that the degree of functional connectivity is positively correlated with good intonation Fig. 10. In other words, the same brain areas are working together to accomplish both singing and playing the cello in tune. This finding addresses the potential criticism that the brain areas observed in the GLM analyses are coincidently active but not necessarily interacting. The functional connectivity findings are also consistent with previous work showing that singing recruits a functionally connected network of brain areas (J. M. Zarate, Wood, and Zatorre 2010)

4.6 Questions Not Answered

Even when directly comparing singing and cello playing within the same individuals, some questions are still unanswered. For instance, we found increased activation in cello playing relative to singing in STG. There are two main ways that increased activation may be interpreted when activity falls within regions that are active for both tasks. The first is that increased activation is a sign of enhanced processing. The second that it is a sign of decreased cognitive efficiency. We propose that the years of explicit training required to play the cello results in enhanced processing during cello tasks relative to singing. This interpretation is consistent with previous work in singing, which has shown that expert singers recruit STG to a greater extent than do novices (J. M. Zarate and Zatorre 2008). Following from this, we would predict that if expert singers were compared to expert cellists there would be less of a difference in STG activity levels. A third possible interpretation is that the difference is the result of a confounding factor like intensity or another physical feature of the sound. While we cannot directly address this concern with our data, we could not find any research suggesting that certain timbres would preferentially result in increased or decreased global activity in STG nor do we think that differences in intensity were systematic enough to produce the observed effect.

Our research also cannot address the question of how these findings would generalize to discrete pitch instruments like the keyboard or guitar. These instruments do not allow for the online pitch adjustments that are integral to singing or playing continuous pitch instruments in tune. However, based on the fact that singing and cello playing show such a high degree of overlap in recruited brain areas despite being such physically different tasks, we would speculate that discrete pitch instruments would show a high degree of overlap as well. This prediction would also be consistent with the large body of research showing that many of the same brain areas are recruited during both piano playing (Parsons et al. 2005) and guitar playing (Vogt, Higuchi, and Roberts 2007) (for review: (Zatorre, Chen, and Penhune 2007)).

4.7 Future Directions

Using auditory feedback to meaningfully alter movements is one of the core features of auditory-motor integration. In the present study we did not specifically test how auditory feedback affected motor output. As such it is possible, though unlikely, that our participants were relying exclusively on the feed-forward component of the auditory-motor integration network and that auditory feedback was not being used to inform their movements. One of the classic ways of studying the neural correlates of auditory-motor integration is to use pitch perturbation paradigms, where participants are specifically instructed to compensate for introduced perturbations in auditory

feedback (Burnett et al. 1998; J. M. Zarate, Wood, and Zatorre 2010)). In so doing, researchers can directly observe which brain regions are involved in integrating auditory feedback with motor planning and execution. Using such paradigms in future experiments will allow us to observe how this auditory-motor integration occurs in cello playing and once again compare these findings with singing.

Another axis along which singing and cello playing might differ, even if the same brain areas are recruited, is the timing of the different processing steps. For instance, it could be the case that the auditory-motor integration network processes and responds to pitch perturbations more quickly during vocal tasks than cello playing due to the evolutionary significance of the voice. Directly comparing the latency of event related potentials during both singing and cello playing would allow us to address this question. In doing so, we would gain a more complete understanding of how new skills make use of existing mechanisms in the brain for accomplishing similar tasks.

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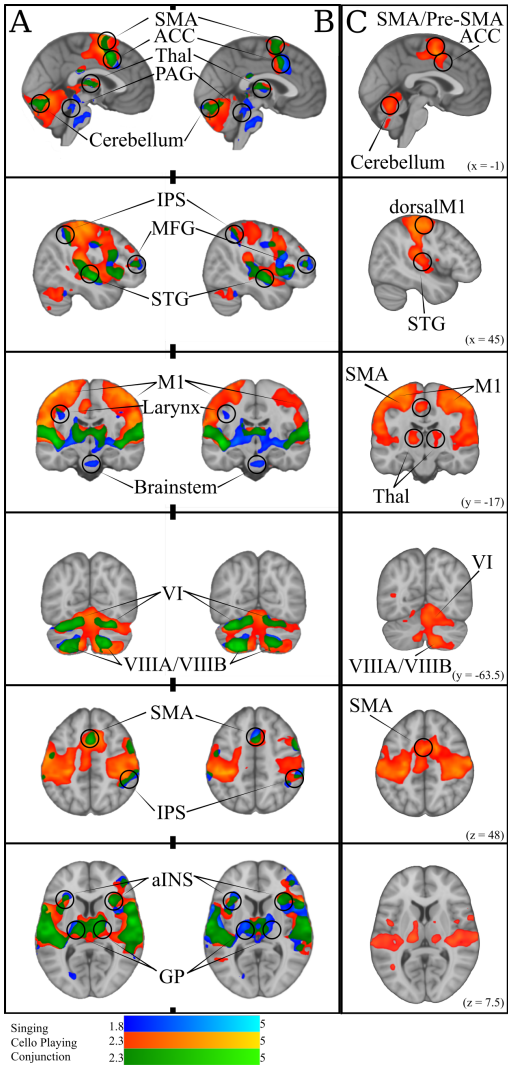

Fig 9. A: Simple Singing (blue), cello playing (orange), and conjunction (green). B: Simple singing (blue), cello playing (orange) and conjunction (green) regressed by task accuracy with better performance correlated with more activation. The conjunction of singing and cello playing shows overlapping activation in SMA, ACC, Thalamus, PAG, IPS, MFG, STG, MI (larynx area for singing), aINS, GP, and VI, and VIIIA/VIIIB of the cerebellum. All of these regions were positively correlated with better intonation. C: Cello playing > Singing throughout dorsal motor and premotor regions, SMA/Pre-SMA., posterior STG, Thalamus, and Cerebellum

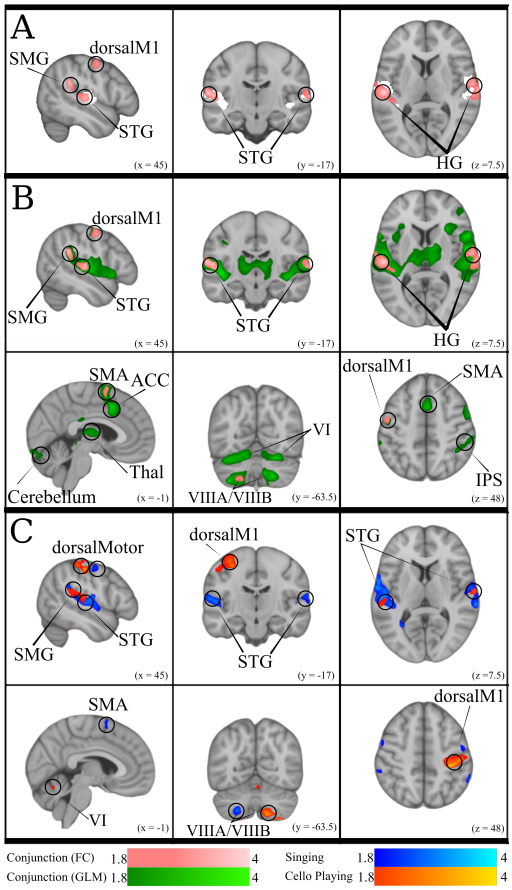

Fig 10. A: Conjunction of functional connectivity during Singing and Cello Playing (pink) overlayed on bilateral Heschle's Gyrus seed region (white). B: Conjunction of Functional Connectivity during Singing and Cello Playing (pink) overlayed on Conjunction of simple singing and cello playing (green). C: Functional connectivity for Cello Playing > Singing (orange) and Singing > Cello Playing (blue)