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The Effects of Gender on the Neural Substrates of Pitch Memory

Nadine Gaab¹, Julian Paul Keenan², and Gottfried Schlaug¹

Abstract

■ Imaging studies have indicated that males and females differ anatomically in brain regions thought to underlie language functions. Functional studies have corroborated this difference by showing gender differences in terms of language processing with females relying on less lateralized processing strategies than males. Gender differences in musical functions might show similar differences in functional asymmetries, although no detailed study has been performed. The current study employed a pitch memory task while acquiring functional magnetic resonance images to investigate possible differences in hemispheric processing between males and females. Gender differences were found in the time course of activation (during the first four imaging time points after the end of the auditory stimulus—

“perceptual phase”—and the subsequent three imaging time points after the end of the auditory stimulus—“memory phase”) in both anterior and posterior perisylvian regions. Male subjects had greater lateralized activations (left > right) in anterior and posterior perisylvian regions during the “perceptual” as well as during the “memory” phase. There was a trend for males to have more cerebellar activation than females. Females showed more prominently posterior cingulate/retrosplenial cortex activation compared to males. Although activation patterns differed, there was no difference in the behavioral performance between both genders. These data indicate that similar to language studies, males rely more on left lateralized hemispheric processing even for basic pitch tasks. ■

INTRODUCTION

Anatomic differences have been reported between the genders in regions that are classically associated with language processing, with the majority of studies indicating that females may be less lateralized than males (Good et al., 2001; Amunts et al., 1999; Shapleske, Rossell, Woodruff, & David, 1999; Kulynych, Vldar, Jones, & Weinberger, 1994), although the significance and magnitude of these anatomic differences is disputed (Foundas, Faulhaber, Kulynych, Browning, & Weinberger, 1999; Jancke, Schlaug, Huang, & Steinmetz, 1994).

These anatomic differences may lead to divergences in cognitive processing between the genders, such that females may employ a less lateralized processing than males (Coney, 2002; Voyer, 1996; McGlone, 1980). This idea has been examined in terms of actual brain/behavior relationships between the genders. While some functional brain mapping studies and behavioral studies have indicated that there are laterality differences (Coney, 2002; Walla, Hufnagl, Lindinger, Deecke, & Lang, 2001; Boucher & Bryden, 1997; Shaywitz et al., 1995), there is also conflicting evidence as well (Speck et al., 2000; Frost et al., 1999; Kertesz & Benke, 1989) indicating that both

genders activate similar brain regions in language processing. Complicating the situation even further, there is one study indicating that females may be more lateralized than males (Obleser, Eulitz, Lahiri, & Elbert, 2001).

Several studies have indicated that there is sharing in the neural substrates between language and music (Besson & Schon, 2001; Maess, Koelsch, Gunter, & Friederici, 2001). Therefore, the observed anatomic asymmetry in auditory-related regions should have the same implication for language (Good et al., 2001; Foundas, Leonard, Gilmore, Fennell, & Heilman, 1994; Kulynych et al., 1994; Steinmetz, Volkman, Jancke, & Freund, 1991) as well as for music processing (Keenan, Thangaraj, Halpern, & Schlaug, 2001; Schlaug, Jancke, Huang, & Steinmetz, 1995). Furthermore, the lesser anatomic asymmetry of females (as indicated in some studies) indicates that gender might have an influence not only on language processing but also on music processing. However, in terms of the potential impact of gender on brain differences in the processing of musical information, there have been only a few behavioral studies (Hough, Daniel, Snow, O'Brien, & Hume, 1994) and no functional imaging study. This is surprising given the hypothesized importance of musical processing in terms of language development, human communication, brain development, and evolution (Besson & Schon, 2001; Gray et al., 2001), as well as the speculation

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that both musical and language processing occupy similar (Peretz et al., 2002; Besson & Schon, 2001; Maess et al., 2001) or distinct (McFarland & Fortin, 1982; Erdozmez & Morley, 1981) neural substrates. In terms of musical processing, functional and anatomic differences depend on a variety of variables among them handedness, musicianship, and exceptional abilities, such as absolute pitch (Keenan et al., 2001; Ohnishi et al., 2001; Patel & Balaban, 2001; Pantev, Roberts, Schulz, Engelien, & Ross, 2001; Zatorre, 1985, 1998; Zatorre, Perry, Beckett, Westbury, & Evans, 1998); the effects of gender on music processing is relatively unexplored compared to studies done on the interaction between gender and language processing.

In this study, we examined whether pitch processing would show similar hemispheric gender differences as has been reported for language processing. In particular, we were interested to examine whether we would find anterior (e.g., frontal opercular) and posterior (e.g., superior temporal gyrus) perisylvian differences between males and females. By employing a sparse temporal functional magnetic resonance imaging (fMRI) technique (Hall et al., 1999, 2000; Edmister, Talavage, Ledden, & Weisskopf, 1999; Bandettini, Jesmanowicz, Van Kylen, Birn, & Hyde, 1998) with a jitterlike acquisition, we were able to obtain an auditory activation pattern without interferences from the MR scanner noise.

RESULTS

During the early “perceptual” phase of our task (ITP 0–3 sec after the end of the auditory stimulus), the overall group analysis for the contrast pitch memory versus motor control revealed bilateral (more left than right) superior temporal gyrus (including primary and secondary auditory areas) as well as bilateral supramarginal gyrus, bilateral superior parietal lobe (right more than left), bilateral dorsolateral posterior frontal, and bilateral cerebellar (more left than right) activations (Figure 1A). In this early imaging phase (“perceptual” phase), males differed from females (Figure 1C and E, Figure 2A and B) by activating predominantly the left superior temporal gyrus (Talairach coordinates: $-55.3, -24.6, 3.6$) ($p < .05$, adjusted) in addition to a small activation of the right superior temporal gyrus (Talairach coordinates: $53.7, -11.1, -2.8$) (Figure 2A). Adjusting the significance threshold ($p < .001$, uncorrected) to examine further our prespecified hypothesis, additional differences in the anterior and posterior superior temporal gyrus and the left frontal opercular region were found (Figure 2B). The only other difference that emerged at that statistical threshold was a greater right cerebellar activation (lobules V and VI) in males compared to females. These activations were deemed significant and adjusted for multiple comparisons if a small volume correction using a sphere with a radius of 25 mm, centered on the local maximum, was applied that included the inferior frontal

gyrus, the superior temporal gyrus, and the cerebellum. At this lower threshold, an additional greater activation of the left posterior dorsolateral frontal cortex in males compared to females emerged as well.

During the later imaging time points (“memory” phase) of our task (ITP 4–6 sec after the end of the auditory stimulation), the overall group analysis for the contrast pitch memory versus motor control task showed activations of secondary posterior auditory areas bilaterally, superior parietal lobe (right more than left), temporal pole as well as cerebellar regions (lobules V and VI) bilaterally. In addition, there was activation of the posterior dorsolateral frontal cortex as well as the inferior frontal gyrus on the left (Figure 1B).

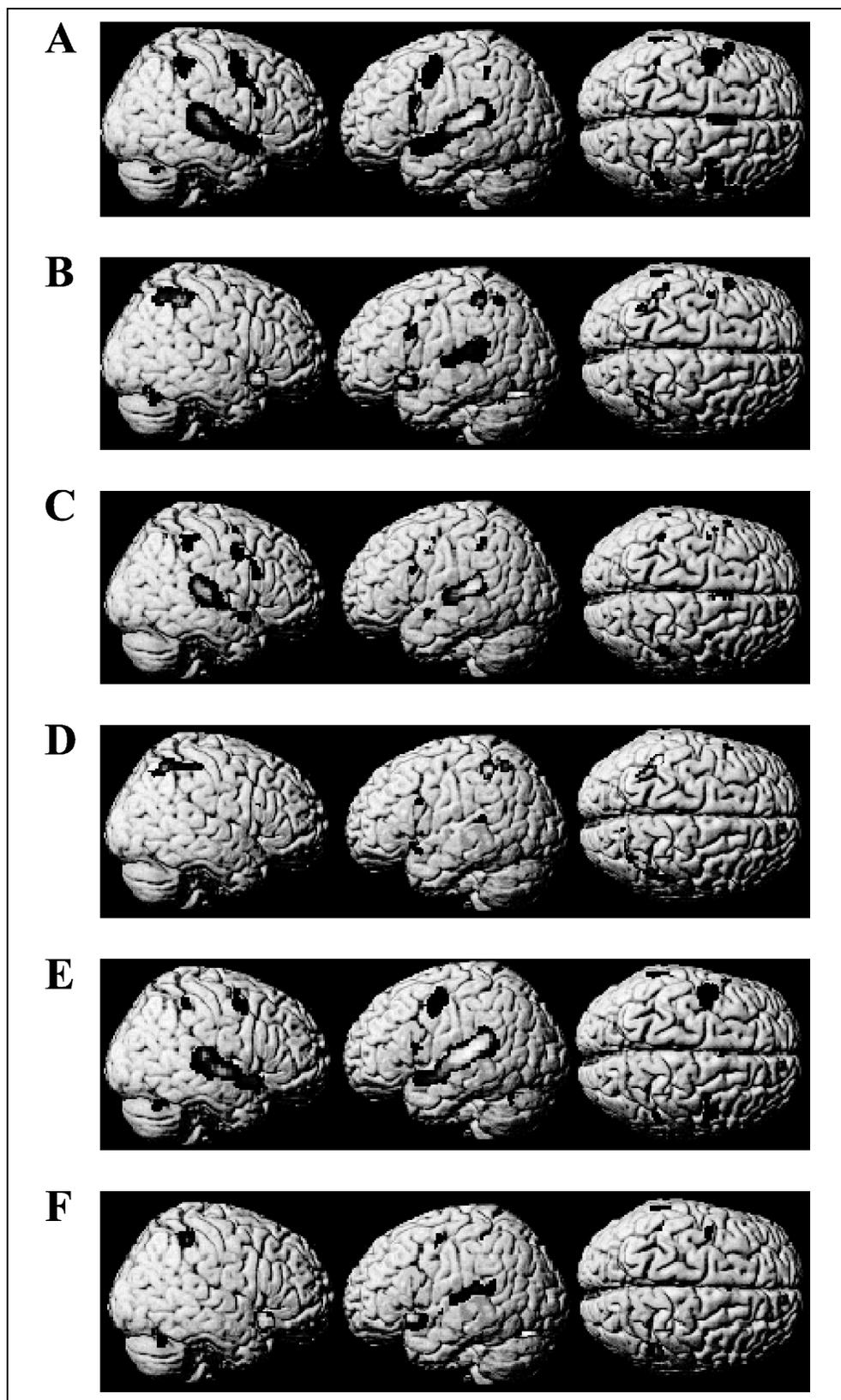
During these later imaging time points (ITP 4–6 sec), males did not exhibit any strong significant differences from females (Figure 1D and F). However, when the significance threshold was lowered ($p < .001$, uncorrected), differences were found in the right cerebellum again.

Females did not show any significant activation differences compared to males in the early, “perceptual” phase (ITP 0–3 sec) of the pitch memory task. During the “memory” phase (ITP 4–6 sec), females differed from males by showing activation of the posterior cingulate/retrosplenial region ($p < .05$, adjusted) (Figure 3). Females in comparison to males did not demonstrate significant activation in either left or right inferior frontal or superior temporal brain regions at any of the imaging time points (Figure 3).

DISCUSSION

These data confirm a number of theories regarding cognitive processing differences between the genders. Specifically, in our pitch memory task, males showed more lateralized temporal lobe activation during the early, “perceptual” phase compared to females, indicating that females are more symmetric and males more asymmetric in their activation pattern. This was further supported by finding more left hemisphere activation in the frontal opercular and posterior perisylvian activation in males compared to females when the strong statistical threshold was lowered. These activations were significant when a small volume correction was applied. The most pronounced and statistically strongest differences were seen in the left superior posterior temporal gyrus, a region commonly referred to as planum temporale. Anatomic differences have been reported between the genders in this region with the majority of studies indicating that females may be less lateralized (Good et al., 2001; Shapleske et al., 1999; Kulynych et al., 1994). Our data add functional significance to this anatomic trend using a pitch memory experiment. An MEG study examining early cortical responses to pure tones found a similar left hemisphere advantage in males compared to females, although native language modulated the degree of laterality in this study (Salmelin et al., 1999).

Figure 1. Group mean activation maps for the entire group as well as for the male and female subgroups. Imaging time points: entire group (A) 0–3 and (B) 4–6 sec; female subgroup (C) 0–3 and (D) 4–6 sec; male subgroup (E) 0–3 and (F) 4–6.



Based on previous studies on a variety of cognitive tasks (Voyer, 1996; McGlone, 1980; Johnson & Kozma, 1977), including musical performance (Davidson, Schwartz, Pugash, & Bromfield, 1976) as well as anatomic

examinations of the corpus callosum (Highley et al., 1999; Oka et al., 1999; Steinmetz, Staiger, Schlaug, Huang, & Jancke, 1995; Johnson, Farnworth, Pinkston, Bigler, & Blatter, 1994; Holloway & de Lacoste, 1986;

Figure 2. (A) Significantly activated brain regions for the contrast “males > females” are presented for the early “perceptual” phase of the pitch memory task ($p < .05$, corrected for multiple comparisons; t values > 4.5). No significant difference was seen for the contrast “females > males” in these early imaging time points. (B) Additionally activated brain regions for the contrast “males > females” during the “perceptual” imaging time points using an uncorrected threshold ($p < .001$, significant after small volume correction; t values > 3.10). There was activation of the left frontal operculum ($-48, 16.1, 0.4$) in addition to a more extended activation of the superior temporal gyrus and posterior perisylvian region ($-57.1, -47.9, 11.2$). During the “perceptual” as well as during the “memory” phase, there was additional activation of the right cerebellum ($20.3, -57.6, -22.6$).

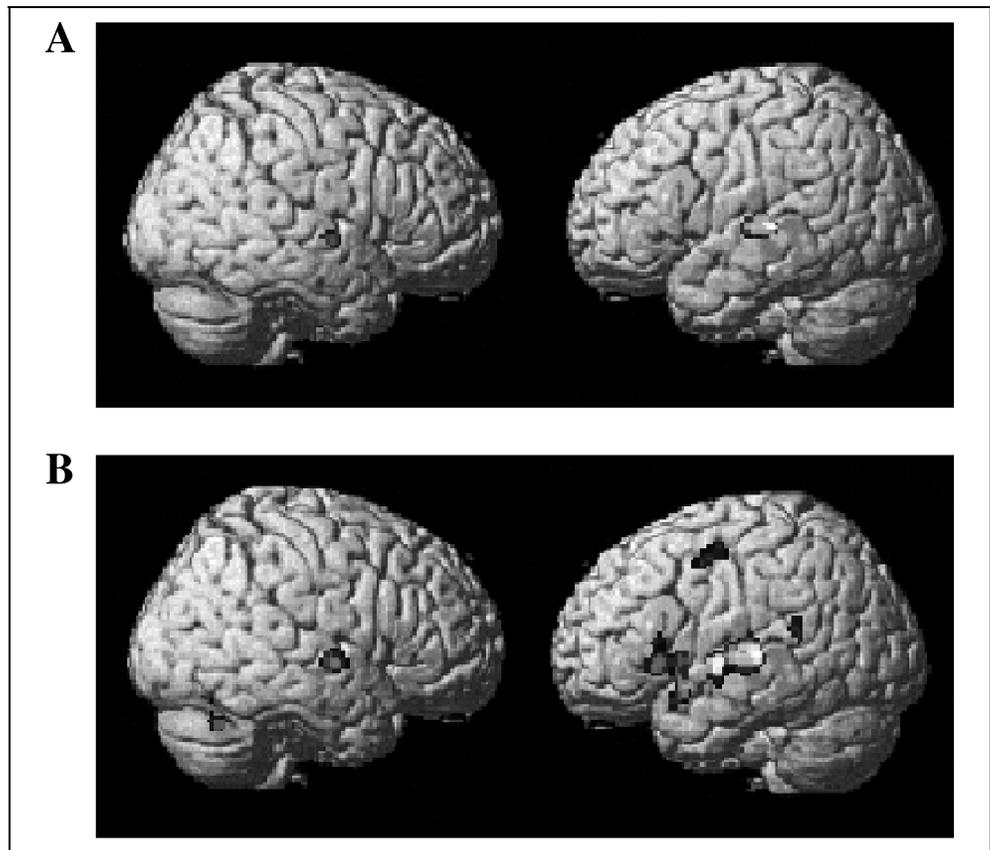
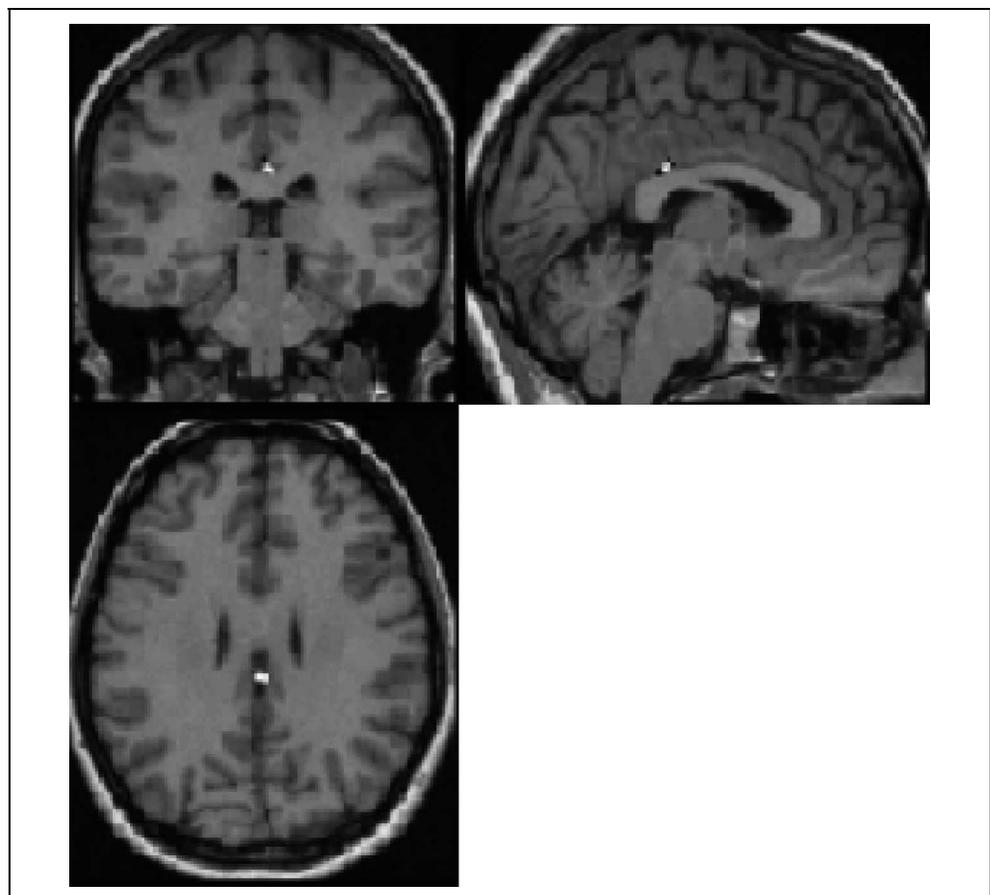


Figure 3. The contrast “females > males” showed no significant activations for the first imaging time points (“perceptual” phase), but a significant difference during the later imaging time points (“memory” phase) in the posterior cingulate/retrosplenial region ($1, -34.4, 20.7$). Activations are significant at $p < .05$, corrected for multiple comparisons (t values > 4.5).



DeLacoste-Utamsing & Holloway, 1982), it has been speculated that females might have a less lateralized strategy in processing auditory information due to their higher interhemispheric connectivity based on their relative callosal size differences (Preis, Jancke, Schmitz-Hillebrecht, & Steinmetz, 1999; Steinmetz, 1996; Filipek, Richelme, Kennedy, & Caviness, 1994; Jancke et al., 1994).

An interesting aspect of our results are that males had more cerebellar activations compared to females with regard to this pitch memory task. Over the last years, the cerebellum has been found to play a role in multiple musical perceptual tasks (Satoh, Takeda, Nagata, Hatazawa, & Kuzuhara, 2001; Riecker, Ackermann, Wildgruber, Dogil, & Grodd, 2000; Griffiths, Johnsrude, Dean, & Green, 1999; Hugdahl et al., 1999; Perry et al., 1999), as well as rhythmic processing (Penhune, Zatorre, & Evans, 1998). However, the role of gender in musical processing in the cerebellum has remained unexplored. Males having a greater right cerebellar activation (possibly connected to a greater left lateralized activation in the perisylvian region not seen in females) indicates a greater lateralized processing strategy. Recent anatomic data from our group (Schlaug, 2001) also indicate possible structural gender interactions in the cerebellum with male musicians significantly differing in cerebellar volume compared to male nonmusicians, whereas no such structural difference was seen comparing female musicians with female nonmusicians.

The stronger activation of the left frontal operculum (Broca's region) in males compared to females is intriguing considering some of the recent findings that implicate this region in music processing (Maess et al., 2001) in addition to its role in language processing. While there may be gender differences in the structure of Broca's regions (Amunts et al., 1999), not all functional studies using various language paradigms agree on gender differences in either anterior or posterior perisylvian regions. Frost et al. (1999), testing 50 males and females, found a left lateralized activation in a language comprehension task without any significant gender differences. This differs from a study by Shaywitz et al. (1995) in which a leftward lateralization in the inferior frontal region was found in a phonological task in males while the female activation pattern was more diffuse involving both left and right inferior frontal gyri. In terms of music processing, Broca's region has been implicated in rhythmic processing (Platel et al., 1997) as well as the analysis of music harmony (Maess et al., 2001; including Broca's right homologue). The current data may indicate that gender differences may influence musical processing in terms of Broca's region. The relation between these gender differences and the underlying anatomy is not known.

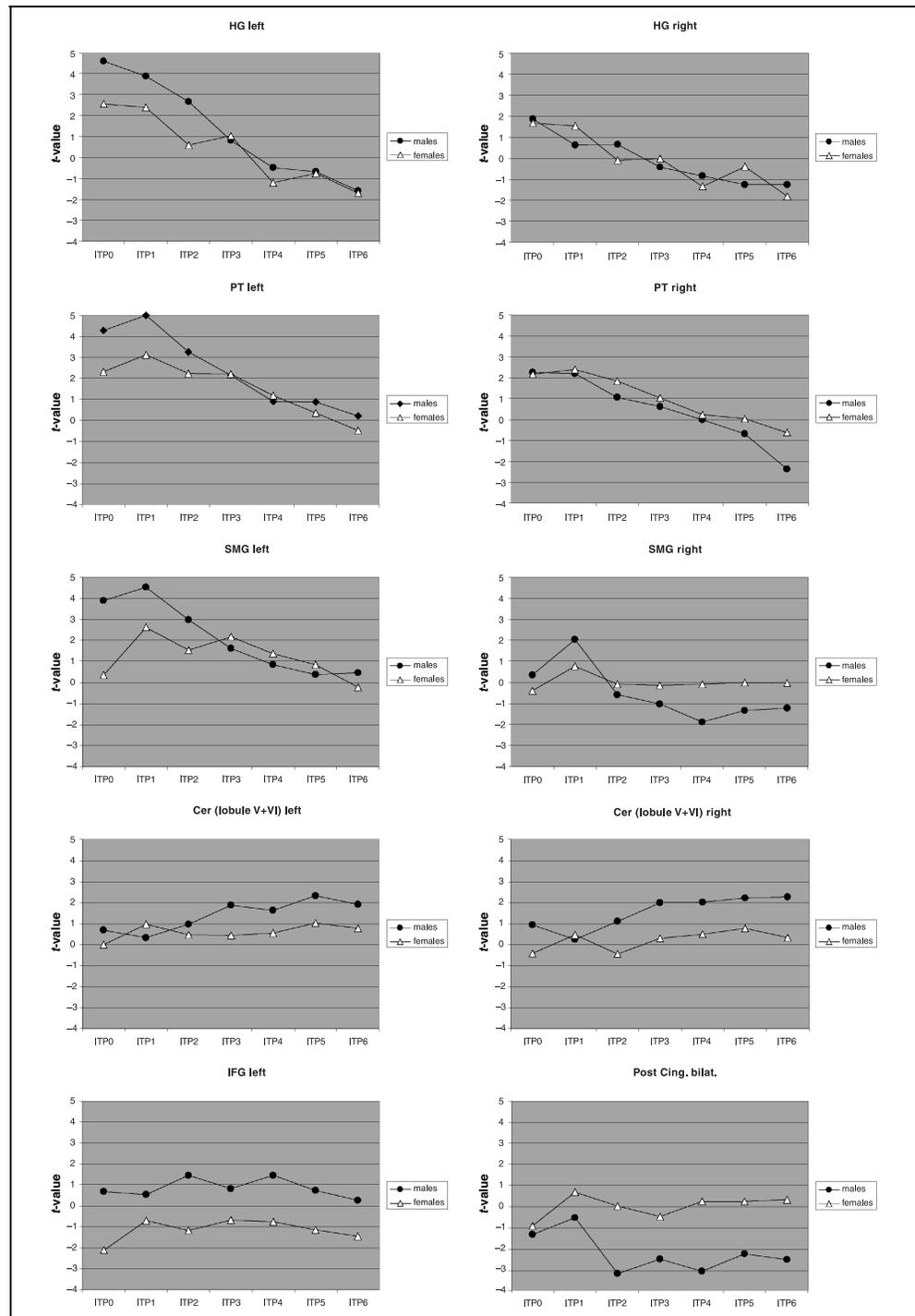
At the lower statistical threshold, we also observed an activation within the left dorsolateral frontal lobe. Although, we did not have any *a priori* hypothesis for

gender-related functional differences in this region, activation in the region has been described when musicians with and without absolute pitch had to make an explicit judgment whether an interval was a minor or major third or when AP musicians passively listened to the same tone pairs (Zatorre et al., 1998). It was thought that this region was activated when a verbal label was associated with a pitch or an interval identification. In our study, males activated this region more than females. Future studies will have to determine the role of this region in gender interactions with a variety of auditory tasks.

We observed a bihemispheric pattern of activation that was more left-lateralized in males compared to females. The bihemispheric activation across the entire group as well as the left-more-than-right lateralization in activation in males is different compared to some other studies finding a more rightward activation pattern in a mixed gender group (Zatorre, Evans, & Meyer, 1994) using a similar task but different control conditions. The issue of right-more-than-left and left-more-than-right activations in pitch tasks or more general in musical tasks is unsolved. There is almost an equal number of articles reporting a left lateralization of the activation pattern than there are articles reporting a right lateralization of the activation pattern (Clarke et al., 2000; Celsis et al., 1999; Salmelin et al., 1999; Griffiths et al., 1997; Platel et al., 1997; Zatorre et al., 1994). Across all studies, a bihemispheric activation pattern is most commonly found. This is our finding as well (Figure 1A–F), although gender seems to affect the lateralization of activation similar to what is reported in language studies. We cannot completely rule out that our subjects used some sort of verbal code to solve the pitch memory task, although none of them reported doing this and none of our subjects had absolute pitch. It is also unlikely that the visual prompt shown at the end of the auditory stimulation could have caused the more left-than-right activation in the male subgroup, since the inherent cerebrovascular delay in response to a visually presented verbal command would have caused a left temporal lobe activation at our last imaging time points, but this was not seen.

Although the distinction between a “perceptual” phase (early imaging time points) and a “memory” phase is arbitrary, the activation maps (Figures 1 and 2) as well as the regional data (Figure 4) support a distinction into two phases. Zatorre et al. (1994) argued that a distinction between a more perceptual analysis mechanism involving primarily temporal cortex (including primary auditory cortex) and an auditory working memory mechanism involving complex temporo-frontal interactions can be made in pitch memory tasks. Our decision to distinguish between a more perceptually weighted initial phase and a more memory-weighted later phase is based on these observations. As can be seen in Figure 1 as well as in the more detailed region-of-interest analysis

Figure 4. Regional group mean t values for all imaging time points (ITP) for selected regions of interest (HG = Heschl's gyrus; PT = planum temporale; SMG = supramarginal gyrus; Cer = cerebellum; IFG = inferior frontal gyrus; Post Cing = posterior cingulate/retrosplenial gyrus. Low or negative t values in some regions might be explained by using average t scores of the entire anatomically defined region. Nevertheless, gender differences are evident in most of these selected regions.



(Figure 4), the activation patterns for temporal and nontemporal regions differed between the early and late imaging time points. Initially, there was strong primary auditory cortex activation that was later followed by more prominent activation of secondary auditory areas as well as other frontal and parietal brain areas.

Females differed from males by having more bilateral activation of the posterior cingulate/retrosplenial cortex. This region has been implicated recently in memory tasks when the familiarity of faces or voices needed to be judged (Shah et al., 2001). Furthermore, the

retrosplenial cortex has been implicated in episodic memory retrieval and emotional salience (Valenstein et al., 1987). Therefore, the gender differences in brain activation may provide evidence for strategic processing differences for the memory component of our pitch memory task.

In summary, the processing of this pitch memory task revealed a more left than right lateralized processing during the early "receptive" phase in males compared to females. Activations were seen in regions with gender-related structural brain differences according to several

reports, such as the superior temporal gyrus, the frontal operculum, and the cerebellum, although the degree and the magnitude of these differences are still disputed among several studies. Females showed more activation than males in the posterior cingulate/retrosplenial region, possibly indicating a gender difference in the memory component of our task. Since both groups did not differ in their performance and since performance differences can therefore not explain the activation differences, our observed gender differences might indicate a difference in perception or strategy in solving the pitch memory task.

METHODS

Participants

Twenty right-handed volunteers (age range: 18–40; 10 females and 10 males) participated in the study after giving written informed consent according to institutional guidelines. Some of the subjects in this study were also part of a different analysis on the time course of the activation pattern and on the relationships between performance and activity changes (Gaab et al., submitted). None of the participants in this study had any specific musical training or were trained in playing a musical instrument. However, most of them had received some musical instruction, usually as part of their regular high school education. None of the participants had any history of neurologic or hearing impairment. All participants were strongly right handed according to a standard handedness questionnaire (Annett, 1992).

Experimental Task

All participants performed a pitch memory task contrasted with a motor control task. Subjects were instructed to listen to a sequence of six or seven individual sine wave tones lasting a total of 4.5 sec. Each tone had a duration of 300 msec with an attack and decay rate of 50 msec. Tones were separated by a 300-msec pause. All sine wave tones had frequencies between 330 and 622 Hz. Although our target and probe tones corresponded to fundamental frequencies, the distractor tones were microtones, and therefore the tone sequences do not correspond to western tonal melodies. The frequency difference between the first and the last or second to last tone was between 41 and 64 Hz. The frequency range from the lowest to the highest tone in all tone sequences was not more than 110 Hz. The differences between the distractor tones and the target/probe tones ranged from 2.8 to 76.3 Hz. The visual prompt after the tone sequence instructed subjects to compare either the last or the second to last tone with the first tone and make a decision whether these tones were “same” or “different” using a button press response. We chose to vary the number of tones and the comparison tone (second to last tone with first tone and

last tone with first tone) across sequences to increase the subject’s attention to the stimuli and to reduce the possibility that participants would not pay attention to the intervening tones. The overall sequence length was kept constant by varying slightly the pause between the last tone and the visual prompt (Figure 5). Participants were asked to keep their eyes open and fixate a cross in the middle of the screen. The control condition was a rest condition in which participants were asked to fixate a cross in the middle of the screen that was interrupted during each trial by a visual prompt (either “right” or “left”) asking for right or left button presses. The behavioral data were calculated as correct responses in percent of all responses. All participants were trained on the pitch memory task for approximately 10 min prior to the actual MR session using samples of the stimulation material. All participants performed above chance in the prescanning testing phase. There were no significant differences in the behavioral performance between both genders ($p > .05$).

fMRI Scanning

fMRI was performed on a Siemens Vision (Siemens, Erlangen, Germany) 1.5-T whole-body MRI system using a gradient-echo EPI sequence with an echo time (TE) of 50 msec and a 64×64 matrix. Using a midsagittal scout image, a total of 24 axial slices parallel to the bicommissural plane were acquired over 2.75 sec every 17 sec (voxel size was $4 \times 4 \times 6$ mm). Initiation of the first set of 24 slices was triggered by a TTL pulse from a PC, synchronized with stimulus presentation.

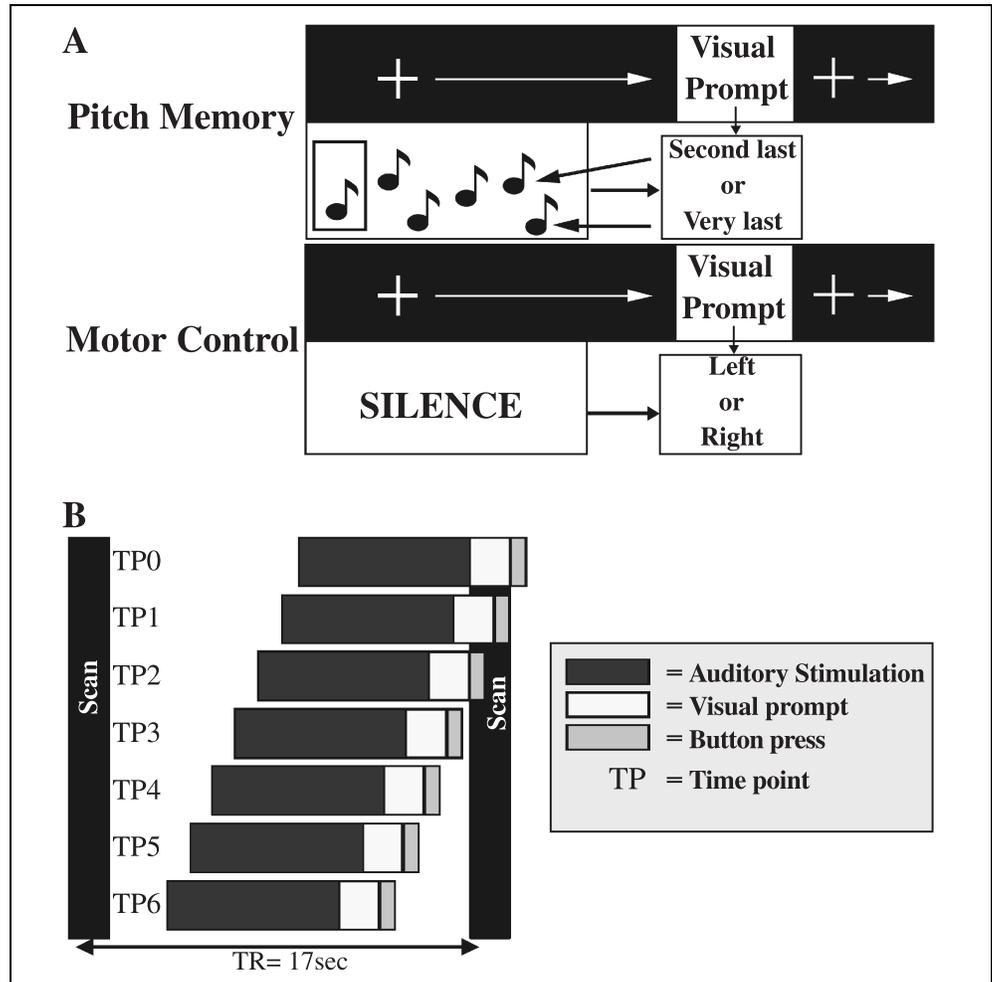
Auditory tasks in the fMRI environment have been regarded as challenging, since MR scanner noise can (1) interfere with the auditory stimulation, (2) lead to auditory activation itself, and (3) mask the auditory activation response. Our sparse temporal sampling technique circumvented these scanner noise interferences by acquiring only one set of 24 axial slices after each event. MR acquisition was kept constant with a fixed TR of 17 sec (all 24 slices were acquired in a cluster over 2.75 sec) while the delay between the auditory stimulation and each subsequent MR acquisition was varied by 0–6 sec between the end of the auditory stimulation and the onset of the scan resulting in seven different imaging time points (see Figure 5B).

A total of 94 events (pitch memory tasks were pseudorandomized with motor control tasks) divided into two runs of 47 each were collected for each subject. In addition to the BOLD data sets, we acquired a high-resolution T1-weighted data set (voxel size: 1 mm^3) for anatomic coregistration.

fMRI Data

Data were analyzed using the SPM99 software package (SPM99, <http://www.fil.ion.ucl.ac.uk/spm>, Wellcome

Figure 5. Task design (A) and MR image acquisition procedure (B) using a modification of a sparse temporal sampling technique.



Department of Cognitive Neurology, London, UK). Each set of axial images for each subject was realigned to the first image, coregistered with the corresponding T1-weighted data set, spatially normalized to the SPM99 template using a nonlinear spatial transformation with $7 \times 8 \times 7$ basis functions, and smoothed with an isotropic Gaussian kernel (8 mm full width half maximum). Condition and subject effects were estimated according to the general linear model at each voxel in brain space (Friston et al., 1995). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Low-frequency drifts were removed using a temporal high-pass filter with a cutoff of 200 sec. We did not convolve our data with the hemodynamic response function and we did not apply a low-pass filter. We applied a box-car function with an epoch length of 1 to the fMRI time series (47 acquisitions within each of the two runs). No temporal derivatives were applied.

Significantly activated brain regions were determined by contrasting pitch memory to the motor control task for all seven imaging time points separately. Initially, all seven imaging time points were explored separately to determine whether or not there was a trend in the

activation pattern over time. For the main analysis of our data, we combined the first to the fourth imaging time point (0–3 sec after the end of the auditory stimulation) and the fifth to the seventh imaging time points (4–6 sec after the end of the auditory stimulation) into two blocks to (1) achieve a higher number of events or acquisitions per block for statistical reasons and (2) reflect the main change over time in the activation pattern, since the initial imaging time points reflected more a perception network while the later time points reflected more a memory network. In the fMRI analysis, we contrasted the pitch memory task with the motor control task for these two combined clusters of imaging time points. Linear contrasts were used to test hypotheses regarding regionally specific condition effects, which produced statistical parametric maps of the t statistics generated for each voxel (SPM $\{t\}$).

Between group differences were determined by examining the interaction between gender and task activations by contrasting the two groups (males and females) for the task-specific activations. Voxels were identified as significant ($p < .05$, adjusted) only if they passed a height threshold of $p < .05$, corrected for

multiple comparisons, and belonged to a cluster of activation with an extent of at least 12 voxels ($k = 12$; number of expected voxels per cluster). Data are also presented derived from a $p < .001$ threshold ($p < .001$, uncorrected) that was not corrected for whole brain space, but all activations discussed in this report were significant after a small volume correction was applied with a spherical region of interest with a radius of 25 mm, centered at the local maximum, for the inferior frontal gyrus, the superior temporal gyrus, and the cerebellum. This analysis was done to examine whether regions (in addition to the superior temporal gyrus) previously shown to exhibit gender-related anatomic differences in some studies (e.g., frontal operculum) would also show functional differences in our pitch memory study. These observations may generate further hypotheses and their significance can be tested in future studies. Both the left frontal opercular and right cerebellar activation were significant when we applied a small volume correction.

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The data reported in this experiment have been deposited in The fMRI Data Center <http://www.fmridc.org>. The accession number is 2-2003-113NF.

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