



Research paper

Increased activation of the human cerebellum during pitch discrimination: A positron emission tomography (PET) study

Augusto Petacchi ^{a,*}, Christian Kaernbach ^b, Rama Ratnam ^c, James M. Bower ^{a,c}

^a Research Imaging Institute, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA

^b Dept. of Psychology, University of Kiel, Germany

^c Dept. of Biology, University of Texas at San Antonio, USA

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ABSTRACT

Recent years have seen a growing debate concerning the function of the cerebellum. Here we used a pitch discrimination task and PET to test for cerebellar involvement in the active control of sensory data acquisition. Specifically, we predicted greater cerebellar activity during active pitch discrimination compared to passive listening, with the greatest activity when pitch discrimination was most difficult. Ten healthy subjects were trained to discriminate deviant tones presented with a slightly higher pitch than a standard tone, using a Go/No Go paradigm. To ensure that discrimination performance was matched across subjects, individual psychometric curves were assessed beforehand using a two-step psychoacoustic procedure. Subjects were scanned while resting in the absence of any sounds, while passively listening to standard tones, and while detecting deviant tones slightly higher in pitch among these standard tones at four different performance levels. Consistent with our predictions, 1) passive listening alone elicited cerebellar activity (lobule IX), 2) cerebellar activity increased during pitch discrimination as compared to passive listening (crus I and II, lobules VI, VIIIB, and VIIIB), and 3) this increase was correlated with the difficulty of the discrimination task (lobules V, VI, and IX). These results complement recent findings showing pitch discrimination deficits in cerebellar patients (Parsons et al., 2009) and further support a role for the cerebellum in sensory data acquisition. The data are discussed in the light of anatomical and physiological evidence functionally connecting auditory system and cerebellum.

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1. Introduction

For most of the last 150 years, theories of the cerebellum have been dominated by the idea that this structure is responsible for some aspect of motor control, whether timing (Braitenberg 1967, 1983; Braitenberg et al., 1997), learning (Albus, 1971; Marr, 1969; Thach 1998; Thach et al., 1992), or execution (Ito, 1984; Llinas, 1984, 1991). Over the last two decades, however, results obtained from a wide spectrum of studies have begun to call into question the traditional view that the cerebellum is exclusively or even primarily a motor control device (Andreasen and Pierson, 2008;

Bower and Parsons, 2003; Ivry and Fiez, 2000; Manto, 2008; Rapoport et al., 2000; Schmahmann, 1997; Vokaer et al., 2002). While the majority of the resulting new cerebellar theories have emphasized a role for the cerebellum in a wide variety of cognitive processes (Ackermann, 2008; Ackermann et al., 2007; Akshoomoff et al., 1997; Bellebaum and Daum, 2007; Ben-Yehudah et al., 2007; Hallett and Grafman, 1997; Ito, 2008; Ivry and Schlerf, 2008; Ivry et al., 2002; Ramnani, 2006; Ravizza et al., 2006; Stoodley, 2011; Strick et al., 2009; Thach, 1997; Wolpert et al., 1998, 2003), we have suggested that the cerebellum may actually be involved in a much more fundamental computational task related to sensory rather than motor or cognitive function (Bower and Parsons, 2003). Specifically, based on our studies of the responses of the lateral cerebellum to somatosensory (tactile) inputs (Bower and Kassel, 1990; Bower and Woolston, 1983; Hartmann and Bower, 2001; Shumway et al., 2005; Bower, 2011), we have proposed that the cerebellum monitors and optimizes the acquisition of incoming sensory data across all modalities in order to increase the computational efficiency of the rest of the nervous system. Its involvement

Abbreviations: ALE, activation likelihood estimate; BA, Brodmann area; f_0 , fundamental frequency; fMRI, functional magnetic resonance imaging; FWHM, full width at half maximum; MRI, magnetic resonance imaging; PD, pitch discrimination; PET, positron emission tomography; PL, passive listening; rCBF, regional cerebral blood flow; SDT, signal detection theory; SMA, supplementary motor area.

* Corresponding author. Tel.: +1 210 567 8097; fax: +1 210 567 8152.

E-mail address: petacchi@uthscsa.edu (A. Petacchi).

in motor control or higher-order functions is therefore predicted to reflect a more fundamental influence on the acquisition of the sensory data on which these functions depend. If correct, such a more fundamental role might underlie motor, cognitive, as well as a large number of other brain computations but should also be apparent in the most basic forms of sensory-driven behavior, especially those that are computationally more difficult, requiring a finer level of sensory data control (Bower, 1997a, b, 2002). This hypothesis predicts: 1) that the cerebellum will be responsive to any sensory stimulus, 2) that its neuronal activity will increase during active sensory tasks, and 3) that the level of activity will increase with task difficulty.

As a first test of this hypothesis in humans, we have shown in the context of the somatosensory system using functional magnetic resonance imaging (fMRI) that the activation of the cerebellum and cerebellum-related regions of the brain is in fact greater and more closely associated with sensory processing than with motor control per se (Gao et al., 1996; Liu et al., 1999, 2000; Parsons et al., 1997). Specifically, we observed that while cerebellar response to passive cutaneous stimulation of the fingers was already significantly greater than during finger movement alone, tactile sensory discriminations tasks resulted in the largest levels of cerebellar activation. In the current study, we seek to generalize these somatosensory results to the auditory system, where sensory and motor/cognitive components can be more readily dissociated. Unlike the somatosensory system, auditory sensory data acquisition does not require overt movements and cognitive components can be controlled by means of well-established psychophysical methods. Further, the difficulty of auditory discrimination tasks can be more precisely controlled and quantified than is the case for tactile sensory discrimination, allowing us to test the third prediction of our theory, that cerebellar activity levels should increase as task difficulty increases.

As context for the current study, we have previously demonstrated in a quantitative meta-analysis using activation likelihood estimate (ALE) methods (Turkeltaub et al., 2002; for latest developments, see Eickhoff et al., 2009) that several areas of the human cerebellum are consistently activated across functional neuroimaging studies during passive listening and auditory discrimination tasks free of motor and cognitive components (Petacchi et al., 2005). We have also recently shown that dysfunction of the cerebellum impairs auditory performance, as cerebellar patients tested on pitch discrimination exhibited a significant deficit, whose magnitude was strongly correlated with the severity of their cerebellar dysfunction (Parsons et al., 2009). Here we have used positron emission tomography (PET) to investigate and compare cerebellar neural activity during passive listening and pitch discrimination in normal subjects. In this study, healthy volunteers were trained to discriminate small pitch differences in a Go/No Go paradigm chosen to minimize cognitive confounds. A two-step psychoacoustic procedure was used to determine individual psychometric curves and ensure that pitch discrimination would be performed at equivalent levels of difficulty for each subject. Subjects were then scanned with PET for measures of regional cerebral blood flow (rCBF) while: 1) resting in the absence of any sounds (baseline condition); 2) passively listening to standard tones (passive listening condition); and 3) detecting randomly occurring tones slightly higher pitched than the standard tones (pitch discrimination condition). In the discrimination condition, four different difficulty levels were used, corresponding to normalized performance levels across subjects as determined in the pre-scanning psychoacoustic procedure. Functional images were then analyzed using both subtractive and parametric approaches. Based on the proposed role for the cerebellum in sensory data acquisition and our previous somatosensory and

auditory results, we predicted that: 1) passive acoustic stimulation alone would elicit a cerebellar response; 2) the cerebellar response would be greater during pitch discrimination; and 3) the strength of cerebellar response would be positively correlated with the degree of difficulty of the pitch discrimination task.

2. Methods

2.1. Subjects

Ten volunteers participated in the study: 5 males, 5 females, 9 right-handed, 1 left-handed, as assessed by Edinburgh Handedness Inventory (Oldfield, 1971), mean age 25.6 years, age range 20–31 years. All subjects were healthy (no history of medical, neurological, or psychiatric illness) and were taking no medications. For each subject, the normality of brain anatomy was confirmed by anatomical MRI. Furthermore, subjects didn't speak any tonal language and had little (2 subjects, ≤ 4 years) or no music training. Written informed consent was obtained from all participants, and all procedures were approved by the Institutional Review Board and Radiation Safety Committee of the University of Texas Health Science Center at San Antonio.

2.2. Cognitive and audiometric screening

Prior to the imaging experiments, participants underwent Folstein Mini-mental status examinations (Folstein et al., 1975) and standard pure tone audiometry. Inclusion criterion for the former was a score equal to or greater than 25 points (out of 30). Audiometry was performed in a double-walled audiometric sound room using a Grason-Stadler audiometer (GSI 17) and TDH-49 headphones. Air-conduction thresholds were measured at frequencies between 125 Hz and 8 kHz in one-octave steps. Inclusion criterion was normal hearing (≤ 20 dB hearing level).

2.3. Auditory stimuli

The auditory stimuli were harmonic complexes with a fundamental frequency (f_0) and 20 harmonics (3 dB/octave roll-off in the spectrum level), 300 ms duration (rise/fall time = 80 ms), presented at a level of 75 dB SPL (Belin et al., 1998, 2002). The stimuli were generated in Matlab (v7.5; The MathWorks Inc.) at a 24-bit resolution and 44.1 kHz sampling rate, and converted to analogue form via PC-controlled, 24-bit sound-card (CDX-01, Digital Audio Labs) at a sampling rate of 44.1 kHz. They were fed through a headphone buffer (HB7, Tucker-Davis Technologies) and presented binaurally via insert earphones (ER-2, Etymotic Research). The level of the stimuli was calibrated by connecting the headphones to a ¼-in. calibrator adaptor (DP-0775, Brüel and Kjær) which was itself linked to a sound level meter (type 2209, Brüel and Kjær, type 4938 ¼-in. microphone, "A" weighting, fast response).

2.4. Psychoacoustic measures

In the pitch discrimination task used in the imaging session we adopted the same Go/No Go paradigm utilized by Belin et al. (1998, 2002) in their studies on intensity and duration discrimination. In brief, subjects were presented with a series of tones 75% of which had the reference pitch (standard tones) and 25% had a pitch that was higher by a determined amount (deviants). Each trial required a decision as to whether the tone presented had the reference pitch (No Go), or it had a deviant pitch (always higher than the reference pitch, Go). The action taken in a Go trial differed between the psychoacoustic procedure and the imaging task: in order to avoid motor confounds, in the imaging task subjects were instructed to

simply note the change mentally, whereas in the psychoacoustic procedure subjects responded by pressing a computer mouse button. Performance levels were determined for this kind of task with varying pitch differences by means of a Go/No Go adaptive procedure (Step 1) and an extrapolation method (Step 2). The paradigm of choice, a single-interval pitch change detection in one direction, is known for not involving higher-order perceptual phenomena such as sequential analysis, perception of relative pitch, or pitch working memory normally associated with pitch direction judgment and/or multiple-interval choice decisions (Johnsrude et al., 2000; Zatorre et al., 1992, 1994), thus providing control for a range of cognitive confounds. All tasks were programmed and run in Matlab, and performed in the PET room for consistency between psychoacoustic and imaging conditions.

2.4.1. Step 1: measure of pitch discrimination threshold with a Go/No Go adaptive procedure

The sensitivity to pitch change in each subject was determined using a modified version of the single-interval unbiased adaptive procedure developed by Kaernbach (1990). This procedure is based on an adjustment matrix that induces a neutral response criterion and improves efficiency by avoiding redundant presentation time. Stimuli and trial design are schematized in Fig. 1. Subjects pressed the space bar on the computer keyboard to begin each block of trials. A block of trials was defined as a run. In a run, tones were presented at a rate of 1 per s (300 ms stimulus, 700 ms silence). 75% of the tones had the reference pitch ($f_0 = 200$ Hz), 25% had the deviant (higher) pitch. Subjects listened continuously to the stimuli and were instructed to press the button with their right index finger during the 1 s interonset temporal window as soon as they detected a deviant. Subjects were informed that the first four trials in a run were all standard tones. After a deviant there would always be at least one standard tone, both in the psychoacoustic and in the imaging session. The starting f_0 difference (Δf_0) between standard tones and deviants was 100 cents (where 1 cent is a unit of equal log frequency separation and 100 cents = 1 semitone), which is large enough to elicit a correct response in the large majority of listeners. As in signal detection theory (SDT) four events were possible: hit, miss, false alarm, or correct rejection (Green and Swets, 1989; Macmillan and Creelman, 2005). Each outcome was taken into account by decreasing or increasing the deviant f_0 according to the following adjustment matrix: after a hit, the Δf_0 between standard tones and deviants was decreased by one step; after a miss and a false alarm, the Δf_0 between standard tones and deviants was increased by one step and 2/3 of a step, respectively; a correct rejection did not result in a Δf_0 change. These adjustments were already corrected for the uneven occurrences of deviants and standards (25% and 75%, respectively). This matrix leads to

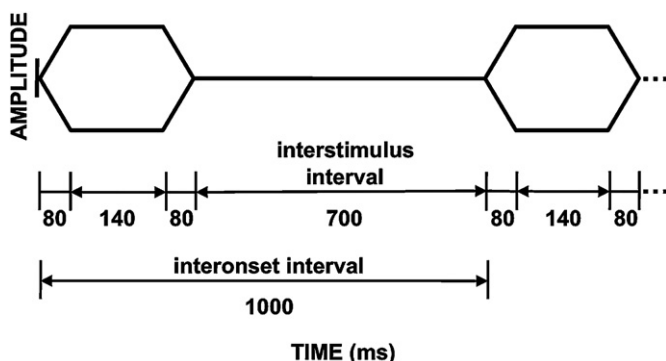


Fig. 1. Schematic representation of the waveform of acoustic stimuli and trial design.

a reduced hit rate (hit rate minus false alarm rate) of 50%. For reasons of simplicity we will refer here to the target performance as $d' = 1.35$. This simplification provides a simple measure of sensitivity whose sole purpose is to reduce inter-subject variability.

Subjects received real-time feedback via the computer monitor: on a hit, the monitor flashed green, on a false alarm, the monitor flashed red, at the end of a miss trial, the monitor flashed yellow, on correct rejections no color change occurred. The Δf_0 associated with a turnaround in the sign of the f_0 change (i.e., an increase or decrease in Δf_0) was defined as a reversal. A step was initially a factor of $10^{1/5}$. This step size was halved a first time after the second reversal, and once more after the fourth reversal, resulting in a final step size of a factor of $10^{1/20}$. A run ended when the 16th reversal was reached. The geometric mean of the last twelve reversals was defined as the difference threshold for that run. Each subject practiced for at least three to five runs. After a few minutes rest period, three to five test runs were then completed. The subject's pitch difference threshold was defined as the mean Δf_0 threshold of the three test runs with a value below the mean obtained in the practice runs.

2.4.2. Step 2: psychometric functions determined using an extrapolation method

Four performance levels were calculated for each subject by linearly increasing the Δf_0 between the reference and the deviant in multiples of the individual thresholds measured in Step 1: levels 1 (threshold), 2, 3, and 4, corresponding to d' 1.35, 2.7, 4.05, and 5.4, respectively. The rationale for the use of this particular extrapolation is that the general form of psychometric functions for frequency discrimination (subjectively, pitch) has been found to be the same across different discrimination paradigms, frequencies, intensities, and stimuli tested, as well as normal-hearing and hearing-impaired listeners, i.e., d' increases linearly with the frequency difference between tones (Harris 1952; Jesteadt and Bilger, 1974; Jesteadt and Sims, 1975; Nelson and Freyman, 1986; Nelson et al., 1983; Sek and Moore, 1995; Turner and Nelson, 1982; Wier et al., 1977). As a consequence, psychometric functions for frequency discrimination can be adequately described with only one parameter, namely, the slope of the psychometric function, which in our case is determined by the individual threshold.

To ensure that the performance levels calculated from the thresholds led to the desired degree of variance in the hit rates, constant-stimuli runs identical to those later used in the imaging session as test–retest runs (see below, 2.5.3.) were performed four times at each determined performance level in randomized order, and the d' values for the pooled runs at each performance level were estimated from hits and false alarm rates (Macmillan and Creelman, 2005). For consistency with the imaging session, these runs were performed with eyes closed, no feedback, and with computer mouse response to record performance. Finally, to familiarize the subjects with the imaging task, identical constant-stimuli runs (see below, 2.5.3.) were performed twice at each determined performance level in a random, counterbalanced order. For consistency with the imaging task, these runs were performed with eyes closed, no feedback, and no computer mouse response. Subjects were instructed to mentally detect the tones higher in pitch and after each run they verbally indicated subjective pitch change discriminability to confirm that they were performing the discrimination task.

2.5. Imaging methods

PET was specifically chosen to avoid possible confounds from the acoustic noise generated by fMRI. In a block design, the

presence of this artifact would have resulted in an unwanted listening-against-background-noise auditory modality, and might have masked the responses elicited by stimulus conditions (Gaab et al., 2007a, b, 2008). On the other hand, an alternative of using “sparse” sampling fMRI methods (Belin et al., 1999; Hall et al., 1999) was not necessary as the event-related responses to the deviants (see below, 2.5.3.) were not crucial to evaluating our working hypothesis.

2.5.1. MRI acquisition

An anatomical MRI scan (Elscent 1.9 T; Haifa, Israel) was acquired for each subject for the purposes of spatial transformation of the PET data and parametric image display. A 3D-gradient recalled acquisition in a steady-state (GRASS) sequence was acquired with scan repetition time (TR) of 33 ms, an echo time (TE) of 12 ms, flip angle 60° as a 256 × 256 × 127 mm volume with a spatial resolution of 1 mm³.

2.5.2. PET acquisition

PET data were acquired with a CTI EXACT HR+ scanner (Knoxville, TN). 12 intravenous injections of water labeled with oxygen-15 (H₂¹⁵O, half-life 122 s) were administered (555 MBq H₂¹⁵O dose/scan), corresponding to 12 1-min cerebral blood flow (CBF) measurements using a bolus technique (Fox et al., 1988, 2000, 2006) at inter-scan intervals of 10 min over a total time of about 2 h. Throughout the PET session, participants' heads were immobilized using individually fitted, thermally molded, plastic face masks (Fox and Raichle, 1984). Sixty-three contiguous slices (2.5-mm thick) in a transaxial field of view of 15.5 cm were acquired. Images were corrected by measured attenuation using ⁶⁸Ge/⁶⁸Ga transmission scans and reconstructed at an in-plane resolution of 7-mm full width at half maximum (FWHM) and an axial resolution of 6.5-mm FWHM.

2.5.3. Imaging conditions

Each subject underwent 12 scans, 2 during each of the 6 conditions (randomization of condition sequence and subject assignment to conditions by counterbalanced Latin square). Rest: subjects lay silent and with their eyes closed while no tones were presented through the earphones. Passive Listening (PL): subjects listened continuously to standard tones ($f_0 = 200$ Hz) presented through the earphones over the 1-min scan window at a rate of 1 per s. During this condition subjects were informed that all tones were identical and to avoid potential cognitive contaminations they were instructed to simply attend to the tones, without performing any type of auditory analysis. Pitch Discrimination (PD): during each of the four PD conditions subjects were instructed to mentally detect the deviants, which were randomly intermingled with the standard tones of the PL condition with a 25% probability of occurrence. Deviant and standard tones were identical in all aspects but pitch, which was slightly higher in the deviants. During a given PD condition, all deviants were identical (constant stimuli), with a pitch corresponding to a given performance level for the scanned subject (level 1, 2, 3, or 4), as determined in the psychoacoustic procedure. To avoid possible motor-related confounds subjects did not hold the mouse in their hand, were required to avoid overt responses, and were simply instructed to mentally detect the changes. They were then asked to verbally indicate subjective pitch change discriminability at the end of each PD scan (i.e., subjects had to estimate whether the difficulty level was 1, 2, 3, or 4) to confirm that they were performing the discrimination task as during the psychoacoustic procedure. To have a complementary indicator of subjects' performance, before and after scans involving a PD condition the computer mouse was placed into subjects' hands and they performed test–retest PD runs of the same duration and

performance level as in the corresponding scans. For consistency, subjects performed these runs with eyes closed and no feedback as during the scans, but mouse button responses were acquired. The d' values for the pooled runs at each performance level were estimated from hits and false alarm rates (Macmillan and Creelman, 2005)

2.6. Spatial preprocessing

MRI brain volume was defined using the Brain Extraction Tool (BET) method in FSL software (v. 4.1, Jenkinson et al., 2005; Smith, 2002), applied independently to each individual's data. Each individual's MR was spatially normalized into registration with the Talairach Brain atlas (Talairach and Tournoux, 1988) using the algorithm developed by Lancaster et al. (1995) and implemented in the software SNTM (Research Imaging Institute, University of Texas Health Science Center at San Antonio). This algorithm uses an affine, nine-parameter fit and interactive denotation of the AC-PC line. Images were transformed (i.e., resliced) into 75 slices using trilinear interpolation, with matrix size 128 × 128 × 75 mm 3D spatially normalized image volumes, with isomorphic voxels 2 × 2 × 2 mm, enabling MR grand-averaging.

PET brain volume was defined by an intensity-thresholding of 30% maximum voxel value of the individual data in MANGOTM (Multi Analysis GUI, Research Imaging Institute, University of Texas Health Science Center at San Antonio, TX). Voxels with values lower than the threshold were considered as non-brain regions. Images were further edited, using visual inspection, on a slice-by-slice basis to remove extra-cerebral activity (such as scalp, great vessels, muscles, and sinuses). Inter-scan, intra-subject movement was then assessed and corrected using the MCFLIRT algorithm in FSL (Jenkinson et al., 2002). PET image volumes were independently spatially normalized to matched normalized MR volumes, using the Lancaster et al. (1999) algorithm of convex hulls implemented in the software CHSNTM (Research Imaging Institute, University of Texas Health Science Center at San Antonio). Regional tissue uptake of ¹⁵O-water was globally normalized to whole rCBF brain mean value with images scaled to a mean of 1000 counts. These values and spatially normalized images were tri-linearly interpolated, re-sampled (60 slices, 8 mm³ voxels), and Gaussian filtered to a final resolution of 9.9 mm FWHM.

2.7. PET analysis

The data were analyzed using MIPSTM software package (Medical Image Processing Station, Research Imaging Institute, UT Health Science Center at San Antonio, TX). All steps of statistical analysis considered a threshold of $Z > 3.09$ ($p < 0.001$) at the voxel level. To correct for multiple comparisons across volume, an extension threshold was introduced at the cluster level ($p < 0.05$ corrected, $k > 50$). PET maps were superimposed on the surface-rendered and three-plane sections of the MRI obtained anatomical images averaged across all subjects.

2.7.1. Conditional contrasts analysis

Statistical parametric images for PL relative to Rest (PL vs. Rest), and for the pooled PD conditions relative to PL (PD vs. PL) were computed using voxel-by-voxel group (paired) t -test (SPI{t}) and subsequently transformed into the normally distributed Z statistic (SPI{Z}). A maxima 3D search algorithm (Fox and Mintun, 1989; Fox et al., 1988; Mintun et al., 1989) was then used to identify local extrema within each image. The x , y and z coordinates of each focus were calculated in the Talairach atlas coordinate system (Talairach and Tournoux, 1988). Anatomical labels and Brodmann area (BA) designations were applied automatically using the Talairach

Table 1

Stimulus fundamental frequencies (Hz) corresponding to the deviant tones for detection of pitch changes at each performance level for each subject.

Performance level	Subject									
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10
1 (threshold) ($d' = 1.35$)	200.79	201.05	201.54	201.17	202.27	200.81	201.54	201.22	202.18	201.11
2 ($d' = 2.7$)	201.58	202.10	203.08	202.34	204.54	201.62	203.08	204.44	204.36	202.22
3 ($d' = 4.05$)	202.37	203.15	204.62	203.51	206.81	202.43	204.62	203.66	206.54	203.33
4 ($d' = 5.4$)	203.16	204.20	206.16	204.68	209.08	203.24	206.16	204.88	208.72	202.44

Note: The f_0 of standard tones was 200 Hz.

Daemon™ 3D electronic brain atlas (Research Imaging Institute, UT Health Science Center at San Antonio, TX) developed by Lancaster et al. (2000). Cerebellar regions were designated according to the atlas of the human cerebellum by Schmahmann et al. (2000).

2.7.2. Performance correlation analysis

To determine possible cerebral cortical regions in which normalized activity was linearly related with an equivalent level of pitch discrimination performance as determined with the extrapolation method in the psychoacoustic session (see above, 2.4.2.), a statistical parametric image of r values (SPI{ r }) was computed as

a voxel-wise correlation of rCBF with the performance level in the PD conditions using previously described methods (Fox et al., 2000). In brief, SPI{ r } was analyzed for performance level effects first by an omnibus (whole brain) test and, if omnibus significance was proven, then a post-hoc (regional) test was performed and local maxima identified. The SPI{ r } was converted to SPI{ Z }, P values were assigned from the Z distribution, and the volumes and maxima of significant correlations in various brain regions were calculated and graphed in the Talairach atlas coordinate system (Talairach and Tournoux, 1988). Anatomical labels and BA designations were applied automatically using the Talairach Daemon™

Table 2

Summary of PET findings for all contrasts.

Region	BA	Coordinates			Z-value	Cluster size (mm ³)
		x	y	z		
<i>PL vs. Rest</i>						
L Cerebellum vermal lobule IX		−4	−50	−48	5.17	416
L Poscentral gyrus	5	−10	−42	64	4.46	536
R Midbrain		12	−16	−16	3.74	456
R Superior temporal gyrus	42	60	−30	10	3.70	816
L Precuneus	7	−4	−52	48	3.70	440
L Transverse temporal gyrus	41	−33	−36	12	3.36	432
L Superior temporal gyrus	22	−59	−40	12	3.27	640
L Superior temporal gyrus	41	−54	−22	4	3.27	528
R Middle temporal gyrus	22	64	−38	6	3.22	544
<i>PD vs. PL</i>						
L Medial frontal gyrus	6	−4	0	58	5.49	824
L Cerebellum hemispheric lobule VIII B		−14	−62	−48	4.50	408
R Medial frontal gyrus	6	8	−4	54	4.40	736
L Cerebellum hemispheric lobule VI		−26	−64	−22	4.14	712
R Anterior cingulate gyrus	24	2	6	44	4.03	736
L Cerebellum crus I		−32	−78	−34	3.98	408
R Pons		3	−38	−32	3.93	536
R Cerebellum hemispheric lobule VI		34	−49	−32	3.93	416
L Cerebellum crus II		−10	−74	−34	3.88	576
L Cerebellum hemispheric lobule VI		−36	−62	−28	3.77	704
L Cerebellum hemispheric lobule VII B		−32	−58	−42	3.72	616
R Thalamus		16	−17	14	3.67	496
R Cerebellum hemispheric lobule VI		40	−64	−26	3.51	472
L Cerebellum crus I		−48	−59	−26	3.41	408
R Midbrain		8	−26	−8	3.30	480
L Insula	13	−38	8	3	3.30	408
R Superior temporal gyrus	22	50	0	2	3.15	472
<i>Correlation with performance level</i>						
L Cerebellum vermal lobule V		−4	−58	−8	5.83	440
R Middle frontal gyrus	9	48	18	28	5.22	424
R Paracentral lobule	5	9	−40	58	5.09	456
R Cerebellum hemispheric lobule IX		14	−56	−44	5.08	544
R Cerebellum hemispheric lobule VI		14	−76	−24	4.18	408
L Superior frontal gyrus	8	−4	18	50	3.79	424
L Cerebellum hemispheric lobule VI		−32	−60	−32	3.71	440

Note: Z-values refer to the activation maxima within the respective region, $n = 10$, $p < 0.05$ corrected, height threshold $Z > 3.09$, $k > 50$ (400 mm³). Coordinates are in Talairach space (Talairach and Tournoux, 1988). Nomenclature of cerebral areas and corresponding Brodmann areas (BA) are based on Talairach Daemon 3D electronic brain atlas (Lancaster et al., 2000). Cerebellar regions (boldface) are designated according to Schmahmann et al. (2000). L = left, R = right.

3D electronic brain atlas (Lancaster et al., 2000). Cerebellar regions were designated according to the atlas of the human cerebellum by Schmahmann et al. (2000).

3. Results

3.1. Psychoacoustic measures

The thresholds from Step 1 of the psychoacoustic procedure and the calculated performance levels (Step 2) for all subjects are presented in Table 1, which shows that performance was highly variable across subjects. The relation between Δf_0 and d' value for each subject was linear as predicted, both in the psychoacoustic session (see 2.4.2.) and in the corresponding test–retest runs in the imaging session (see 2.5.3.). The regression coefficients for the psychometric functions varied from 0.84 to 0.98 (mean 0.94) for the psychoacoustic session and from 0.80 to 0.93 (mean 0.90) for the imaging session. In the latter, the slopes for the psychometric functions were slightly steeper possibly indicating a moderate improvement in sensitivity over the course of the study, especially at highest Δf_0 's where performance in some instances tended to ceiling. Subjective pitch discriminability reported by subjects corresponded to the previously determined individual's performance level, both in the psychoacoustic (see above, 2.4.2.) and in the imaging session (see above, 2.5.3.), suggesting that the subjects performed the discrimination task similarly with and without mouse response.

3.2. PET results

3.2.1. Passive listening vs. Rest

When compared to the baseline, the PL condition yielded significant rCBF increases in the posterior cerebellum, in several (mostly temporal) regions of the cerebral cortex of both hemispheres, and in the midbrain (Table 2). Primary and secondary

auditory cortices in both hemispheres showed in total the most extensive volume of rCBF change for this contrast (2960 mm³) and the highest number of activations (five), with positive extrema in the left and right superior temporal gyrus (BAs 22, 41, and 42), left transverse temporal gyrus (BA 41), and middle temporal gyrus (BA 22). Additional rCBF increases were found in the left poscentral gyrus (BA 5), in the right precuneus (BA 7), and subcortically in the right midbrain. However, the strongest activation in all structures was observed in a circumscribed medial area of lobule IX in the vestibulocerebellum. Fig. 2 shows the anatomical location of this maximum on a whole brain surface rendering and in the three planes.

3.2.2. Pitch discrimination vs. Passive listening

When compared to PL, the four PD conditions yielded significant rCBF increases in numerous locations of the cerebellar posterior lobe, in medial frontal areas of the cerebral cortex, and in several subcortical regions, for a total number of seventeen foci and total volume of 9408 mm³ (Table 2). Compared to the previous contrast, this was approximately a twofold increase, most of which was accounted for by changes occurring in the cerebellum. In fact, more than half (nine) of the activations were located in the cerebellar posterior lobe, spanning lobules VI–VIII B and totaling a 4720 mm³ volume, which was 50.2% of the whole brain activation volume and 11.5 times larger than the cerebellar cluster elicited by passive listening. Fig. 3 shows the nine cerebellar foci in horizontal sections. The majority of the peaks was left hemispheric, with a significant concentration in crus I, crus II, and lobule VI between coordinates -22 and -34 in the z-axis. Two of these activations were almost symmetrically in the right ($x = 40$, $y = -64$, $z = -26$) and left ($x = -36$, $y = -62$, $z = -28$) hemispheric lobule VI. The latter, as well as the neighboring cluster in left crus I, were in the vicinity of the most significant cerebellar focus previously found in our ALE metanalysis (Petacchi et al., 2005), and their volumes partially overlapped with that of the ALE cluster. There was one

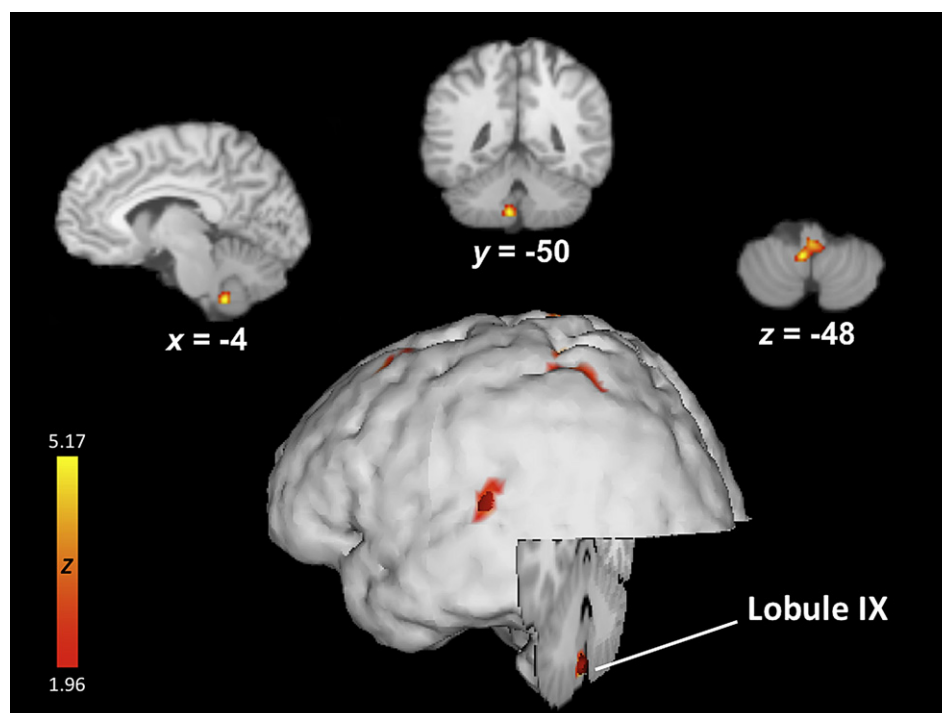


Fig. 2. Cerebellar region significantly more active during passive listening to standard tones than during silent rest is shown in sagittal, coronal, and horizontal plane (top, left to right) and rendered on a whole brain surface and section viewed from the left (bottom center).

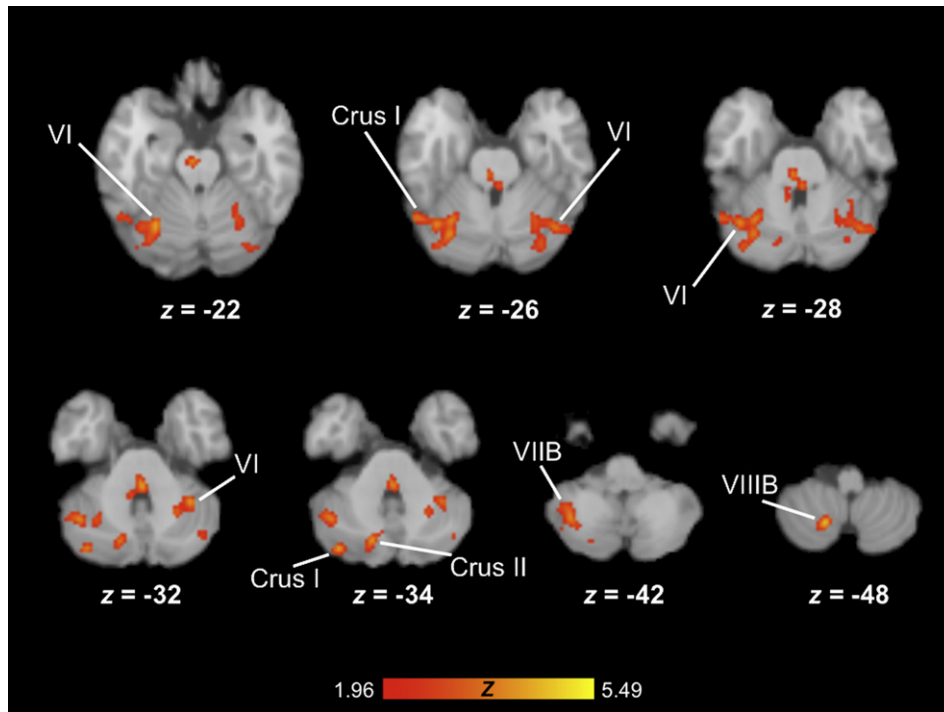


Fig. 3. Cerebellar regions significantly more active during pitch discrimination (all performance levels pooled) than during passive listening are shown in the horizontal plane.

other activation in the right cerebellar hemisphere, which was more caudal (lobule VI; $x = 34$, $y = -49$, $z = -32$) and whose volume extended to the dentate nucleus region (Dimitrova et al., 2002, 2006). The maximum of this right hemisphere caudal cluster was almost symmetrical to that of the foregoing left hemispheric ALE cluster. Two other activations were found in the caudal

part of the cerebellum, one in lobule VIIIB ($x = -32$, $y = -58$, $z = -42$) with volume extending to lobule VIIIA, and adjacent to the other, most caudal, and greatest cerebellar activation in vestibulo-cerebellar lobule VIIIIB ($x = -14$, $y = -62$, $z = -48$) with volume extending to lobule IX. While the cerebellum had the largest total extent of activation, the maximal rCBF change was observed in the

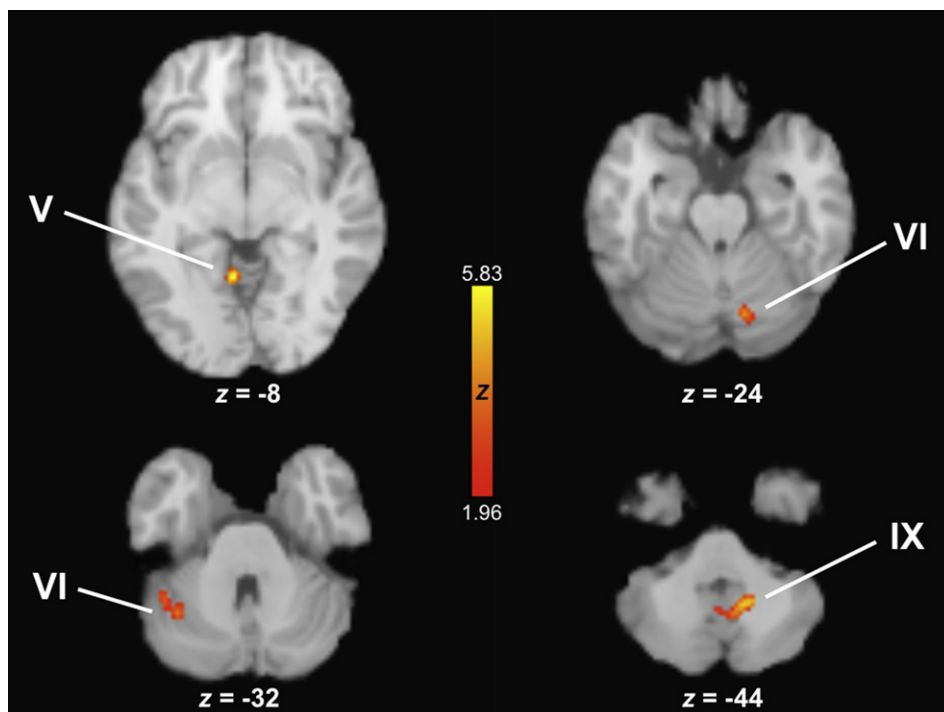


Fig. 4. Cerebellar regions of significant correlation between rCBF and performance level are shown in the horizontal plane.

supplementary motor area (SMA) of the left medial frontal gyrus (BA 6) close to the interhemispheric fissure, paralleled by a comparable cluster extending and peaking almost symmetrically in the right hemisphere. There was one activation in the auditory cortex in the laterorostral portion of the right superior temporal gyrus (BA 22). Additional activations were observed in a circumscribed area of the left anterior insula, in the right anterior cingulate gyrus (BA 24), and subcortically in the right thalamus, right pons, and right midbrain.

3.2.3. Performance correlation

Neural activity in several cerebellar and cerebral regions was linearly related with the difficulty of the pitch discrimination task, as measured by the negative correlation between rCBF and the four performance levels. In each case, decreasing performance level (lower performance level = lower discriminability = greater task difficulty) corresponded with increase in rCBF (Table 2). Overall, the cerebellum showed the greatest total volume (1832 mm³) and number of areas (four) in which increase in neural activity was correlated with task difficulty (Fig. 4). In addition, the cerebellum included both the highest correlation maximum, found in a circumscribed area of vermal lobule V ($x = -4, y = -58, z = -8$), and the largest cluster, peaking in the medial aspect of right vestibulocerebellar lobule IX with volume extending caudally deep into lobule IX and rostrally into the dentate nucleus region. Two other cerebellar regions showed a significant correlation: two small clusters were located bilaterally in lobule VI. The leftmost ($x = -32, y = -60, z = -32$) was proximal to an area of crus I where the main ALE cluster found in the meta-analysis of Petacchi et al. (2005) was located. Additional correlation maxima were identified in the right middle frontal gyrus (BA 9), in the right paracentral lobule (BA 5), and in the left superior frontal gyrus (BA 8).

4. Discussion

This study tested the general hypothesis that the cerebellum is involved in monitoring and optimizing the acquisition of incoming sensory data (Bower, 1997a, b, 2002; Bower and Parsons, 2003). Using PET, we measured the rCBF of healthy human subjects while they were passively listening to tones and while they were performing a pitch discrimination task. We predicted that 1) passive listening would elicit cerebellar activity, 2) pitch discrimination would result in a higher degree of cerebellar activity, and 3) cerebellar activity would scale with the degree of difficulty of the pitch discrimination task. Paralleling our somatosensory fMRI studies, the data presented here confirmed the first two predictions, revealing cerebellar activation in response to passive acoustic stimulation, which increased when subjects performed the pitch discrimination task. Extending the previous somatosensory imaging results we have also shown that the level of cerebellar activation during pitch discrimination was correlated with the difficulty level of the task, as determined by independent psychoacoustic measures. The absence of motor components in the auditory tasks rules out the possibility that changes in cerebellar activity were associated with differences in motor performance. Similarly, the minimal cognitive demand of the pitch discrimination paradigm adopted makes it less likely that the significant increase in cerebellar response during pitch discrimination can be explained by higher-order processes. On the other hand, the correlation between cerebellar activity and the degree of difficulty of the pitch discrimination task further supports the interpretation that the observed cerebellar increases were related to the sensory aspects of the stimulus conditions.

4.1. Cerebellar response to passive auditory stimulation

A core tenet underlying the sensory data acquisition hypothesis is that the cerebellum will respond to simple sensory inputs from all modalities even in the absence of any overt movement or higher-order cognitive task component (Bower, 1997a, b, 2002). Consistent with this prediction, we have previously reported strong human cerebellar responses to passive cutaneous stimulation (Gao et al., 1996; Liu et al., 2000; Parsons et al., 1997), while other investigators have shown that the cerebellum is also activated by passive visual (Clarke, 1974; Mori, 1993; Reid and Westerman, 1975), gustatory (Cerf-Ducastel and Murphy, 2001) and olfactory stimulation (Ferdon and Murphy, 2003; Sobel et al., 1998).

With respect to auditory stimuli, there is a long, if somewhat neglected history of cerebellar auditory studies in animal models. In fact, the first electrophysiological report showing auditory evoked responses in the cat cerebellum was published nearly 70 years ago (Snider and Stowell, 1944). This study was one of the first neurophysiological investigations questioning the sole function of the cerebellum as a motor device (Bower, 2011). Although strong auditory signals have subsequently been shown in numerous other animal studies (Aitkin and Boyd, 1975; Jen and Schlegel, 1980; Huang and Huang, 2007; Huang and Liu, 1990; Sun et al., 1983; Wolfe, 1972; and Wolfe and Kos, 1975; Xi et al., 1994), most human imaging studies have interpreted auditory-related cerebellar activations in terms of higher-level aspects of auditory perception, such as timing (Jueptner et al., 1995; Pastor et al., 2008), attention (Sevostianov et al., 2002; Zatorre et al., 1999), speech (Ackermann et al., 2001, 2007; Mathiak et al., 2002, 2004), learning (Christian and Thompson, 2005; Woodruff-Pak et al., 1996), or the analysis of sound movement (Griffiths et al., 1998, 2000). In this study, we have shown strong activation of the human cerebellum by auditory stimuli even during passive acoustic stimulation alone and in the absence of any motor or specific cognitive component. In fact, under passive listening condition, the greatest rCBF increase in the entire brain was observed in the medial aspect of vestibulocerebellar lobule IX.

Since the cerebellum has been associated with timing (for reviews, see Ivry and Fiez, 2000; Ivry et al., 2002), it could be argued that the constant stimulus presentation rate of 1 standard tone per s used here introduced a regular timing pattern that could confound our results. However, the timing hypothesis does not claim or require that the cerebellum is intrinsically sensitive to the temporal organization of sensory inputs, rather, it posits that the cerebellum itself generates a clock signal used in motor (Ivry and Keele, 1989; Spencer and Ivry, 2005; Schlerf et al., 2007) or perceptual tasks (Casini and Ivry, 1999; Mangels et al., 1998; Nichelli et al., 1996) requiring timing computations. Moreover, imaging studies on timing and time perception (Belin et al., 2002; Bueti et al., 2008; Jäncke et al., 2000; Jueptner et al., 1995; Mathiak et al., 2002, 2004; Rao et al., 1997) have documented highly distributed patterns of hemodynamic response typically including lateral cerebellar lobule VI, basal ganglia, prefrontal, right frontoparietal, sensorimotor, and/or insular areas, whereas none of these regions resulted activated in this contrast. As a result, since our passive listening task did not involve any timing requirement (either explicit or implicit), nor did it elicit any of the responses (either cerebellar or cerebral) typically associated with timing tasks, we think it is more parsimonious to interpret the vestibulocerebellar activation reported here as reflecting a basic response of the cerebellum to the acoustic stimulation rather than a response to some higher-order feature of the presented stimuli.

Anatomical and physiological evidence for direct interaction between the auditory system and vestibulocerebellum obtained in anesthetized animals seems to further support this interpretation.

Previous reports in a variety of animal species have in fact demonstrated strong auditory signals in lobule IX (Azizi and Woodward, 1990; Azizi et al., 1985; Huang and Liu, 1985). Further, the presence of these responses is supported by evidence for extensive neuroanatomical connectivity between the vestibulocerebellum and the auditory system. Specifically, tracts originating from the cochlear nucleus (Huang et al., 1982) and even from the cochlea itself (Brozoski et al., 2007; Morest et al., 1997) have been shown to target this cerebellar region directly, and the auditory cortex is also known to send projections via the dorsolateral pontine nuclei (Azizi et al., 1985; Brodal, 1979; Brodal and Jansen, 1946). The current finding corroborates this intimate neuroanatomical and physiological connection between auditory system and vestibulocerebellum found in animal studies and for the first time demonstrates an analogous result in humans, suggesting that neural activity in this caudal cerebellar region may be considered part of the basic characteristic response of the brain to an auditory input. Accordingly, we suggest that future studies using auditory stimuli to explore the involvement of the cerebellum in higher-order functions should probably consider (and control for) such more fundamental association between cerebellum and physical stimuli.

4.2. Cerebellar response during pitch discrimination

Another core prediction of the cerebellar sensory acquisition hypothesis is that cerebellar activity should increase when sensory data are being used explicitly for a behavioral task, like, for example, sensory discrimination (Bower, 1997a, b, 2002; Bower and Parsons, 2003). This prediction is based on the assumption that the requirements for accurate control of sensory data increase when the data are being actively used by other parts of the brain and that the cerebellar control of sensory data acquisition should accordingly ramp up. In previous human somatosensory imaging studies, we demonstrated a significant increase in cerebellar response when subjects performed tactile discrimination tasks as compared to passive cutaneous stimulation (Gao et al., 1996; Liu et al., 1999, 2000; Parsons et al., 1997). In parallel with these previous reports, the results presented here show that cerebellar activity increased significantly during the pitch discrimination task as compared to passive auditory stimulation. Specifically, the pitch discrimination task elicited strong and extensive activity through the cerebellar posterior lobe, accounting for more than half of the activation maxima and volume found in the whole brain. These activations spread from the already noted medial vestibulocerebellum rostrally up to bilateral hemispheric aspects of lobule VI and crus I, with the volume of each activation extending considerably.

Considered simply from a sensory point of view, it could be argued that the rCBF changes observed in this contrast, might be due to subtle differences in the stimuli presented in each condition, as the pitch discrimination task contained pitch irregularities (deviants) that were not present in the passive listening task. It seems however unlikely that the infrequent occurrence of the deviants alone (only 25% of the time) can account for the significant increase in number, volume, and magnitude of the cerebellar activations we have reported here, suggesting that the differences in cerebellar activation are more likely related to changes in the task and not (or at least not only) subtle changes in the stimulus. Similarly, given the total absence of motor components in the pitch discrimination task, the cerebellar activity observed in the present study cannot be ascribed to motor function. With respect to possible cognitive confounds, we specifically chose a simple single-interval pitch change detection task in one direction only to reduce to a minimum the likelihood that the cerebellar activation pattern

was contaminated by activity specific to higher-order perceptual phenomena such as sequential analysis, perception of relative pitch, pitch working memory, or by any significant cognitive load in general (Johnsrude et al., 2000; Zatorre et al., 1992, 1994). The absence in our results of activations in any of the right hemispheric frontoparietal areas classically associated with attentional mechanisms (Helton et al., 2010; Paus et al., 1997; Pardo et al., 1991; Sturm et al., 2004; Thakral and Slotnick, 2009; Zatorre et al., 1999) further supports our interpretation that the enhanced cerebellar response we report here was not directly associated with any general increase in cognitive activity (Akshoomoff and Courchesne, 1992; Allen et al., 1997; Gottwald et al., 2003; Le et al., 1998). Taken together, these facts lead us to conclude with greater confidence that the higher degree of cerebellar involvement found during pitch discrimination was most likely due to the increased sensory demands of the auditory task. In fact, similar strong activations in hemispheric aspects of lobule VI have been previously found in association with discrimination tasks involving pitch (Gaab and Schlaug, 2003; Gaab et al., 2003; Griffiths et al., 1999; Holcomb et al., 1998; Schulze et al., 2009). In particular, in the PET study by Holcomb et al. (1998) activity in those regions was present for a similar pitch discrimination task as used here, in which subjects discriminated between a 1500 Hz standard tone and deviant tones (differing by 700, 300, or 100 Hz from the standard tone), all embedded in background noise.

As previously noted, however, in the current study cerebellar responses associated with pitch discrimination were not limited to lobule VI, rather they were also present in crus I and II, and in other more caudal regions of the posterior lobe, including lobule VIIIB and vestibulocerebellar lobule VIIIIB, the latter showing the greatest maximum amongst the cerebellar areas and the second greatest for all brain regions. Additional evidence that these regions of the cerebellum may influence actual pitch discrimination comes from the clinical literature. Specifically, damage involving hemispheric regions of the cerebellar posterior lobe has been shown to impair the ability of patients to detect small frequency differences between sounds¹ (Casini and Ivry, 1999; Mangels et al., 1998), whereas anterior lobe lesions do not (Harrington et al., 2004). Our own recent auditory study focusing on pitch discrimination in cerebellar patients confirmed a severe auditory perceptual deficit (Parsons et al., 2009), but no measurable deficits in attention, or other cognitive processes. The current imaging results complement the findings in cerebellar patients and demonstrate, reversely, that the regions of the cerebellum associated with patients' deficit were active in healthy subjects, thus providing convergent evidence that this structure influences processes involved in pitch discrimination. It is important to note, however, that we are not proposing that pitch discrimination itself takes place in the cerebellum. Rather, as discussed in more detail below (see 4.4.), we suggest that the ability of other regions of the brain to perform pitch discrimination is facilitated by an intact cerebellum.

4.3. Cerebellar response to varying difficulty levels of pitch discrimination

In addition to supporting our previous somatosensory imaging results, the use of psychoacoustic methods in the current study has also allowed us to test an additional and central prediction of the sensory data acquisition hypothesis: that cerebellar activity should

¹ It is interesting to note that these results were obtained in frequency discrimination tasks used as a control for the auditory processing and sensory discrimination requirements of time perception tasks which were the main focus of the studies.

increase with the level of difficulty of the task (Bower 1997a, b, 2002). The argument in this case is that the more computationally difficult the discrimination task, the higher quality sensory data are necessary, and therefore the higher the degree of cerebellar involvement required. We show here, as predicted, that activity in cerebellar regions including lobules V, VI, and IX correlated significantly with task difficulty. This specific prediction of our hypothesis has also recently been tested by an independent laboratory with similar results (Baumann and Mattingley, 2010). Specifically, Baumann and Mattingley (2010) used fMRI to monitor cerebellar activity while subjects discriminated the direction of an auditory motion signal embedded in noise, varying the signal-to-noise ratio to test different levels of demand for sensory data control associated with the varying difficulty of the task. Consistent with our results, these authors also reported a cerebellar area in left crus I whose hemodynamic response was significantly correlated with the difficulty level of the discrimination task. This activation was 5.5 mm apart from the region in left lobule VI we report (transformation of original coordinates into Talairach space using procedure of Lancaster et al., 2007). Our previous meta-analysis (Petacchi et al., 2005) also found that this left hemispheric region extending from crus I to lobule VI had the highest probability of being involved in auditory processing. Accordingly, the results of Baumann and Mattingley (2010) support both the influence of task difficulty on the degree of cerebellar activation, and also identify nearly identical regions of the cerebellar cortex as being involved. Similarly, Holcomb et al. (1998) and Gaab et al. (2003) have reported a correlation between activity in lobule VI of the cerebellum (in a location very close to one of our maxima regions) and subjects' performance in a similar pitch discrimination task as well as in a melody discrimination task, respectively. It may be equally important to note that the area of greatest correlation in the present study was actually in the cerebellum (lobule V), which in total accounted again for more than half of the maxima and volume found in the entire brain. The cerebellum also included the largest correlation cluster, in vestibulocerebellar lobule IX.

As in the previous contrast between pitch discrimination and passive listening, we did not find significant activity in any region of the right hemispheric frontoparietal attentional network, suggesting again that the cerebellar effects are unlikely to be accounted for by a simple increase in attentional load. We do however report a significant correlation in the right middle BA 9 of prefrontal cortex. Previous anatomical and imaging studies have shown that this and other cortical regions are interconnected with the cerebellum of monkeys (for a review, see Strick et al., 2009) and humans (Habas et al., 2009; Krienen and Buckner, 2009) via thalamus and pons, and interpreted these indirect cerebro-cerebellar pathways as the basis for cerebellar involvement in cognition (for a review, see Ramnani, 2006). One hypothesis in particular evokes an analogy between motor control and mental representations to suggest that the cerebellum encodes internal models of mental activities, a theoretical construct taken to encompass a fairly broad range of activities, including error prediction, attention, language generation, mental calculations, planning and working memory, chess playing, and mentation on the future (for reviews, see Ito, 2008; Stoodley, 2011). Based in large part on physiological evidence from the somatosensory system (Brown and Bower, 2001, 2002; Morissette and Bower, 1996), we have suggested the somewhat more fundamental alternative, that these indirect cerebro-cerebellar pathways instead, simply serve as the basis for cerebral cortical modulatory influence on cerebellar activity (Bower, 1997a). Evidence for such a modulatory role has also been reported for the auditory system (Sun et al., 1990). With respect to the sensory hypothesis of cerebellar function, such a cerebral cortical influence would have an effect on cerebellar control over the acquisition of

sensory data being used by the rest of the nervous system (Bower, 1997a, 2002). We have further suggested that this influence might be specifically responsible for the increase in cerebellar activity we have shown with somatosensory discrimination tasks (Gao et al., 1996; Parsons et al., 1997; Liu et al., 2000), and now for auditory discrimination tasks as well. The data presented here and elsewhere (Baumann and Mattingley, 2010) extend these results to show that cerebellar activity ramps up with task difficulty. Experiments to determine if this increased cerebellar activity is a result of a direct cerebral cortical influence are currently underway.

4.4. *The anatomical and physiological basis for cerebellar interaction with the auditory system*

Although the results from the present study are consistent with our working hypothesis, it is important that functional interpretations based on imaging data are also solidly grounded in the anatomy and physiology of the neural circuits under study. While imaging and even electrophysiological studies can suggest, as they do here, involvement in some task or behavior, it is the actual functional anatomy of the networks involved that ultimately determines the role played (Bower, 2011). With respect to the auditory system, anatomical data show that the cerebellum sits in a somewhat unique anatomical position with respect to its sensory inputs and its outputs. Specifically, there is strong evidence for a subcortical short loop between cerebellum and auditory system possibly involving the olivocochlear system responsible for fine control of sensory transduction properties of the hearing organ (Warr, 1992). Animal studies have in fact shown that the cerebellum receives direct afferents from both the cochlea (Brozoski et al., 2007; Morest et al., 1997) and the cochlear nucleus (Huang et al., 1982). The cerebellum in turn sends direct efferent projections to the superior olive (Earle and Matzke, 1974; Rossi et al., 1967; but see Gacek, 1973), as well as to those divisions of the cochlear nucleus (Gacek, 1973; Rossi et al., 1967) and of the inferior colliculus (Huffman and Henson, 1990) that are directly connected to the superior olive (Cant and Benson, 2003; Schofield and Cant, 1999; Thompson and Thompson, 1991, 1993) and involved in olivocochlear function (De Venecia et al., 2005; Groff and Liberman, 2003; Huffman and Henson, 1990). Interpreted in the context of the hypothesis being tested here, this pathway provides the cerebellum an opportunity to evaluate the incoming auditory data and influence the way in which those data are subsequently acquired by auditory structures (Bower, 1997a). Moreover, the cerebellar regions showing this subcortical connectivity are the same that were found activated in the present study, namely, posterior lobe lobules VI to IX and in particular, vestibulocerebellar lobules VIII and IX. It is interesting to note that the vestibulocerebellum was the most consistently activated region in the present study, exhibiting significant effects for both conditional contrasts and for correlation analysis. Beyond the anatomical connectivity with the olivocochlear pathways, it has also been shown that cerebellar output does, in fact, influence auditory peripheral activity, as demonstrated by the fact that electrical stimulation of the cerebellar cortex reduces auditory brainstem responses (Crispino and Bullock, 1984), and inhibits cochlear microphonics and auditory nerve action potentials, whereas cooling enhances them (Velluti and Crispino, 1979).

Such a primary anatomical and physiological association between cerebellum and auditory system at the subcortical level is also consistent with existing knowledge regarding the auditory percept at task in this study. While the exact nature of the pitch-extracting mechanism in the auditory system itself (whether spectral, temporal, or some spectro-temporal combination) is still

an open question especially for harmonic complex tones (for excellent reviews, see Cedolin and Delgutte, 2005; de Cheveigné, 2005; Oxenham, 2008; Walker et al., 2011), clear evidence exists that the processing, formation, and ultimately fine-grained resolution of the “pitch percept” by higher centers in the auditory system (Barker et al., 2011; Bendor and Wang, 2005; Hall et al., 2006; Hyde et al., 2008; Johnsrude et al., 2000; Patterson et al., 2002; Tramo et al., 2002) depends strongly on the coding of both frequency and time domain information already at the earliest level of the cochlear nucleus (Rhode, 1995; Sayles and Winter, 2008; Winter et al., 2003) and the auditory nerve (Cariani and Delgutte, 1996a, b; Cedolin and Delgutte, 2010). As already pointed out, these are the same auditory structures with which the activated cerebellar areas, and in particular the vestibulocerebellum, have direct and reciprocal connectivity, and whose neuronal activity is influenced by cerebellar output.

It is worth stating explicitly again that we are not proposing a direct role for the cerebellum in fine-grained pitch resolution or any other perceptual processing or discrimination computation. Our hypothesis is instead that the cerebellum interacts with the auditory system at a more fundamental level, subserving the structures directly involved in pitch or in any other auditory processing by optimizing the acquisition of sensory data on which their computations rely (Bower, 2002; Bower and Kassel, 1990).

4.5. Conclusions and future directions

The current results are consistent with, although they do not of course prove, the cerebellar data acquisition hypothesis, identifying a region in the vestibulocerebellum that responded to passive acoustic stimulation alone, and further showing that this and new cerebellar regions were increasingly activated during pitch discrimination. Furthermore, we found that activity within some of the previously noted cerebellar regions, including the vestibulocerebellum, scaled with the degree of difficulty of the pitch discrimination task.

We believe that the results presented here set a basis for future investigations on the role of the cerebellum in auditory function that may also have significant clinical implications. In particular, convergent evidence from animal models and human studies indicated a relationship between abnormal tinnitus-related activity in the auditory system and the cerebellum as a potential source of aberrant input (Brozoski et al., 2007; Lanting et al., 2009, 2010; Morest et al., 1997; Shulman and Strashun, 1999; Shulman and Goldstein, 2010; Shulman et al., 2009). Similarly, the auditory deficits we reported in patients with cerebellar degenerative conditions (Parsons et al., 2009) suggest that it will also be important to determine if age-related degeneration of the cerebellum may contribute to auditory disfunctions. The cerebellum is in fact one of the structures with the earliest and greatest senescence in the nervous system (Andersen et al., 2003; Larsen et al., 2000; Woodruff-Pak et al., 2010), and an association between sensory deficits and aging cerebellum has already been documented in the olfactory system (Ferdon and Murphy, 2003).

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