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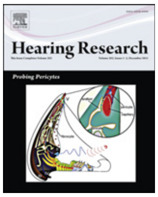

Research paper

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

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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, VIIB, 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.

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

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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.

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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 metanalysis 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, $\leq$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 ($\leq$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