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Pitch discrimination in cerebellar patients: Evidence for a sensory deficit

Lawrence M. Parsons[a,*], *Augusto Petacchi*[b], *Jeremy D. Schmahmann*[c], *James M. Bower*[b,d]

[a]*Department of Psychology, University of Sheffield, Sheffield S102TP, UK*
[b]*Research Imaging Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[c]*Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[d]*Department of Biology, University of Texas at San Antonio, San Antonio, TX, USA*

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ABSTRACT

In the last two decades, a growing body of research showing cerebellar involvement in an increasing number of nonmotor tasks and systems has prompted an expansion of speculations concerning the function of the cerebellum. Here, we tested the predictions of a hypothesis positing cerebellar involvement in sensory data acquisition. Specifically, we examined the effect of global cerebellar degeneration on primary auditory sensory function by means of a pitch discrimination task. The just noticeable difference in pitch between two tones was measured in 15 healthy controls and in 15 high functioning patients afflicted with varying degrees of global cerebellar degeneration caused by hereditary, idiopathic, paraneoplastic, or postinfectious pancerebellitis. Participants also performed an auditory detection task assessing sustained attention, a test of verbal auditory working memory, and an audiometric test. Patient pitch discrimination thresholds were on average five and a half times those of controls and were proportional to the degree of cerebellar ataxia assessed independently. Patients and controls showed normal hearing thresholds and similar performance in control tasks in sustained attention and verbal auditory working memory. These results suggest there is an effect of cerebellar degeneration on primary auditory function. The findings are consistent with other recent demonstrations of cerebellar-related sensory impairments, and with robust cerebellar auditorily evoked activity, confirmed by quantitative meta-analysis, across a range of functional neuroimaging studies dissociated from attention, motor, affective, and cognitive variables. The data are interpreted in the context of a sensory hypothesis of cerebellar function.

1. Introduction

The cerebellum is amongst the largest, oldest, and most structurally conserved brain regions in the vertebrate nervous system (Llinas, 1969; Matano et al., 1985; Paulin, 1993; Rilling and Insel, 1998; Marino et al., 2000; Matano, 2001; Weaver, 2005). Although classically considered a motor control organ (Luciani, 1891; Marr, 1969; Albus, 1971; Ito, 1984; Llinas, 1985; Glickstein and Yeo, 1990; Thach et al., 1992), debate about cerebellar function has been spurred by a variety of recent

* *Corresponding author*. Fax: +44 0 114 22 26515.
E-mail address: L.Parsons@sheffield.ac.uk (L.M. Parsons).

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findings associating it with numerous nonmotor tasks and systems (Schmahmann, 1997; Ivry and Fiez, 2000; Rapoport et al., 2000; Walker et al., 2000; Vokaer et al., 2002; Bower and Parsons, 2003; Manto, 2008; Andreason and Pierson, 2008). Associated with the wide spectrum of new data there has also been a proliferation of new hypotheses of cerebellar function, postulating a role of cerebellum in timing (Ivry et al., 2002; Ivry and Schlerf, 2008), error monitoring (Fiez et al., 1992; Ben-Yehudah et al., 2007), generation of sensory predictions (Miall, 1997), attentional and executive control (Hallett and Grafman, 1997; Akshoomoff et al., 1997; Bellebaum and Daum, 2007), verbal working memory (Chen et al., 2008; Ravizza et al., 2006; Ben-Yehudah et al., 2007), speech production and perception (Ackermann et al., 2007; Ackermann, 2008), context and response mapping (Thach, 1997; Bloedel and Bracha, 1997), state estimation (Paulin, 2005; Miall et al., 2007), and adaptive forward/inverse models (Kawato et al., 1987; Wolpert et al., 1998, 2003; Ito, 2008), among others.

In general, these new conceptions of cerebellum function tend to emphasize a cerebellar role in higher order cognitive processes, especially in humans. These ideas have been supported specifically by findings from human functional neuroimaging and neurology, with implications for functional topology (see, e.g., Riva and Giorgi, 2000; Steinlin et al., 2003; Exner et al., 2004; Tavano et al., 2007; Baillieux et al., 2008; Habas et al., 2009). For example, recent neurological and neuroimaging studies have been interpreted to suggest a fundamental cerebellar role in nonmotor aspects of temporal processing (Ivry and Fiez, 2000), olfaction (Sobel et al., 1998; Connelly et al., 2003), color discrimination (Claeys et al., 2003), kinesthetic processing (Grill et al., 1994, 1997; Blakemore et al., 1998; Tesche and Karhu, 2000; Restuccia et al., 2001, 2007), sensory processing (Pastor et al., 2004; Harrington et al., 2004a,b), and auditory evoked response (Arai et al., 2003). Similarly, in higher cognition, such implications have been reported for language and verbal working memory tasks (Fiez, 1996; Desmond and Fiez, 1998; Drepper et al., 1999; Fulbright et al., 1999; Leggio et al., 2000; Marien et al., 2001; Gizewski et al., 2005; Jansen et al., 2005; Justus et al., 2005; Hokkanen et al., 2006), declarative memory (Weis et al., 2004), spatial cognition (Parsons and Fox, 1997; Fink et al., 2000; Hulsmann et al., 2003; Imamizu et al., 2003, 2004; Molinari et al., 2004; Lee et al., 2005), sustained attention (Pardo et al., 1991), and executive function (Grafman and Litvan, 1992; Hallett and Grafman, 1997; Burk et al., 1996; Brandt et al., 2004; Gottwald et al., 2004; Kalashnikova et al., 2005). In addition, there have been corresponding reports concerning development (Malm et al., 1998; Karatekin et al., 2000; Scott et al., 2001; Limperopoulos et al., 2005; Gross-Tsur et al., 2006) and a variety of sensory and cognitive functions related to thirst (Parsons et al., 2000), affect (Damasio et al., 2000; Schmahmann and Caplan, 2006; Schutter and van Honk, 2005; Anderson et al., 2005), music (Griffiths et al., 1999; Parsons, 2003; Gaab et al., 2003), pain intensity (Coghill et al., 1999), and hypercapnia and air hunger (Parsons et al., 2001).

Such roles in nonmotor or cognitive processing are also supported by anatomical evidence in monkeys showing indirect cerebellar connectivity, via thalamus, pons, and basal ganglia, with cerebral cortex (for reviews, see, e.g., Ramnani, 2006; Schmahmann and Pandya, 2008; Habas et al., 2009; Strick et al., 2009).

As a role for the cerebellum has broadened from its traditional role in motor control to a wider and wider range of motor and nonmotor functions, it has increasingly been proposed (often implicitly) that quite different computations (e.g., motor, executive, linguistic semantic, emotion) are performed in different cerebellar regions (e.g., Massaquoi and Topka, 2002). The difficulty with this proposal, as discussed by various commentators (e.g., Eccles et al., 1967; Dow, 1974; Bloedel, 1992; Ramnani, 2006; Ito, 2006), is that it assumes that distinctly different core computations are performed by a neuronal circuitry that is remarkably anatomically and physiologically uniform (Bower, 2002). While it is clear that different regions of the cerebellum receive very different types of afferent inputs, and this could serve as the basis for some kind of functional topology (e.g., Manni and Petrosini, 2004; Stoodley and Schmahmann, 2009; Timmann et al., 2009), we have been pursuing the possibility, as suggested by the remarkably uniform cerebellar cortical circuitry, that there is a single core computation which operates over many different types of information.

Based on anatomical, physiological, and model-based studies of cerebellar cortical circuitry in rats (Morissette and Bower, 1996; Hartmann and Bower, 2001; Santamaria et al., 2007; Lu et al., 2009), one of us (JMB) has proposed that the predominant direct connectivity of the cerebellum with subcortical structures and its uniformity in cortical microcircuitry and physiology are more consistent with a more fundamental role for the cerebellum underlying both higher order and motor functions (Bower, 1997a, 2002). In this view, the cerebellum is involved in regulating the acquisition of incoming sensory data across all sensory modalities, including those associated with motor as well as cognitive activities. It has further been proposed that these sensory data are evaluated in very close to real-time, with cerebellar output then rapidly influencing the peripheral structures acquiring the data (Bower and Kassel, 1990; Bower 2002). Moreover, the overall computational aim is assumed to be to assure that the highest possible quality sensory data are obtained for use by the rest of the nervous system (Bower 1997b, 2002; Bower and Parsons, 2003). This account predicts that cerebellar dysfunction should be apparent in the most fundamental and basic forms of sensory driven discrimination and behavior.

The purpose of this present study was to specifically test this prediction in humans by evaluating primary sensory processing function in individuals with pancerebellar degeneration. (As usual in such cases, there was no evidence in our patients for localized focal lesions of cerebellum.) In order to reduce the number of possible motor and cognitive-related complications in the interpretations of the results, we tested our hypothesis in the context of auditory perception by means of a pitch discrimination task.

Although so far as we know no human study has ever specifically tested for a purely sensory role for the cerebellum in auditory processing, cerebellar activations have been constantly reported across human functional neuroimaging studies including auditory tasks without motor and higher-order components (Griffiths and Green, 1999; Griffiths et al., 1999; Belin et al., 1998, 2002; van Dijk and Backes, 2003; Pastor et al., 2004, 2008; Chen et al., 2008). Furthermore, quantitative meta-analysis has revealed consistent patterns of cerebellar

activations that are specifically associated with the processing of auditory stimuli (Petacchi et al., 2005), suggesting that the cerebellum might have an elemental role in auditory function. The results reported here demonstrate significant elevations in pitch discrimination thresholds in cerebellar patients and show that the extent of this primary auditory sensory deficit is correlated with the severity of cerebellar degeneration as measured by ataxia. We discuss these results in the context of cerebellar function in general and cerebellar function in audition in particular.

2. Results

2.1. *Detection*

Patients and controls were equally accurate at detecting audible noise bursts occurring unpredictably (patients 98% correct, controls 100% correct). This performance confirmed that patients, like controls, were alert and competent for the entire detection task, the overall duration of which equaled that of the pitch discrimination task.

2.2. *Pitch discrimination*

As shown in Fig. 1, mean pitch discrimination threshold in the cerebellar patients (20.9 Hz) was 5.5 times that for controls ($t = 4.34$, $p < 0.0001$). The mean threshold in controls (3.8 Hz, S.D. = 1.6) conforms to long established norms for pitch discrimination (Shower and Biddulph, 1931; Wier et al., 1977; Sek and Moore, 1995). As illustrated in Fig. 2, patients' thresholds varied widely (S.D. = 15.1), but neither patients nor healthy controls showed consistently greater upper or lower thresholds, relative to the standard. The sizes of patient pitch discrimination thresholds were uncorrelated with their hearing thresholds at 500 Hz ($r = 0.02$, $p < 0.79$), which was the

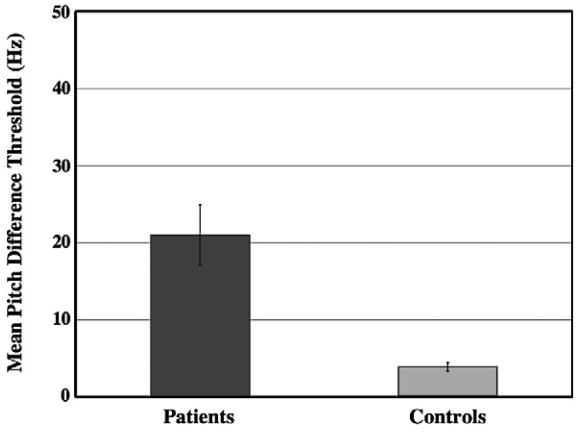

Fig. 1 – Impaired pitch discrimination in pancerebellar degeneration patients. As determined by Parameter Estimation by Sequential Testing (PEST) staircase procedure, the just noticeable difference in pitch between two tones was on average 5.5 times greater for cerebellar patients (black bars) than control subjects (grey bars), indicating that patients' pitch discrimination was significantly impaired compared to controls. Standard deviation bars are shown.

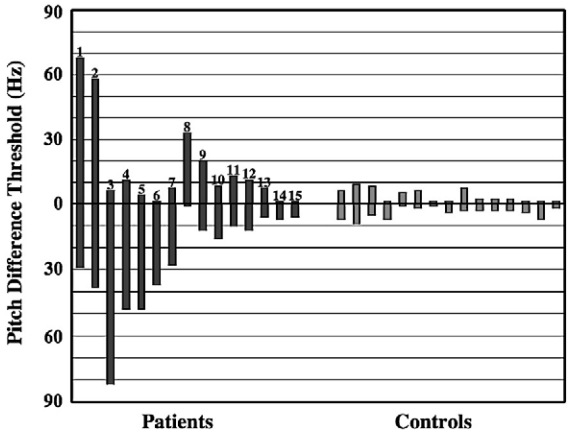

Fig. 2 – Individual pitch discrimination thresholds. Upper and lower pitch difference threshold for each of the 15 controls and 15 patients (with the bars running left to right representing patients #1 through #15 in Table 1).

fundamental frequency (f_0) of the standard tone, and for the wider range 125 Hz–8 kHz ($r = 0.06$, $p < 0.22$). Note that the primary features of the data are unchanged if the six patients who demonstrated noncerebellar signs are withheld from group means: the mean absolute pitch difference threshold is 17.4 Hz, as compared to 20.9 Hz for all 15 patients.

The frequency of time outs (see Experimental procedures) was not correlated with the size of the patients' pitch thresholds ($r = 0.05$, $p < 0.78$). Nine of the patients, like all of the controls, had no time outs; only two of the others had more than 4 and in neither of those patients was the size of the upper or lower threshold correlated with the frequency of time outs.

On average, patients were slower to discriminate pitch (1379 ms, S.D. = 836) than controls (930 ms, S.D. = 208). However, a portion of the patients' slower response time (RT) is due to slower ataxic hand movement as their RTs on the detection task were positively correlated with their degree of ataxia ($r = 0.46$, $p < 0.08$). This motor component of RT can be estimated from RTs in the auditory detection task in which patients' mean RT (469 ms, S. D. = 214) was 166 ms slower than controls (303 ms, S. D. = 97). After accounting for this slowed motor response component, the patients were an additional 285 ms slower to discriminate pitch than controls ($t = 1.35$, $p < 0.10$).

Patients and controls showed similar performance trajectory in progressing from very large pitch differences to successively finer ones across the session. There was no difference between the two groups in the number of trials to achieve asymptotic performance for upper and lower thresholds ($t = 0.12$, $p < 0.90$). For upper threshold, patients' mean was 38.8 trials (S.D. = 6.8) and controls 33.9 trials (S.D. = 3.6); for lower thresholds, patients' mean was 31.5 trials (S.D. = 12.9) and controls 36.9 trials (S.D. = 6.3).

In Fig. 3, the variation amongst patients in pitch discrimination thresholds is compared to an independent (hypothesis blind) measure of eye, hand, gait, and speech motor–sensory ataxias for each patient performed prior to the performance of the tasks (Trouillas et al., 1997; Schoch et al., 2007; Schmahmann et al., 2007; Weyer et al., 2007). There is a strong positive correlation ($r = 0.70$, $p < 0.003$) between the size of patients' pitch

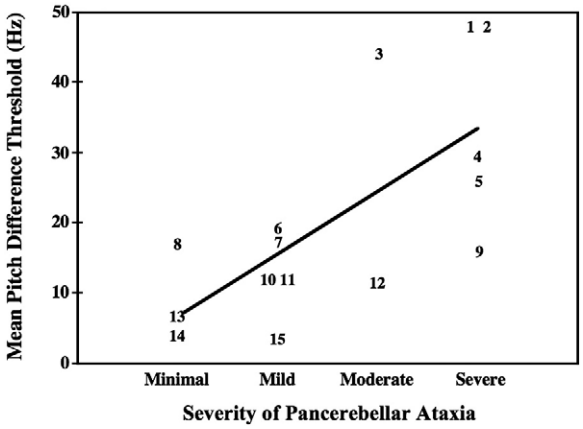

Fig. 3 – Correlation of cerebellar patients' pitch discrimination thresholds and severity of their ataxia. Positive correlation between patients' individual mean pitch difference thresholds and degree of cerebellar degeneration as measured by ataxia. (The numbered points represent patients #1 through #15 in Table 1).

threshold and the ataxia measure. The ataxia measure is a standard technique used to assess the severity of cerebellar degeneration (Klockgether et al., 1994; Tedeschi et al., 1996; Bekkelund et al., 1999; Brenneis et al., 2003; Wollmann et al., 2004; Richter et al., 2005). In this case also, the primary features of the data are unchanged if the six patients who demonstrated noncerebellar signs are withheld from group means: the correlation between those thresholds and severity of ataxia is $r=0.74$, as compared to $r=0.70$. The ages of the patients were unrelated to the severity of ataxia ($r=0.05$, $p<0.84$) and so was the number of years since symptom onset ($r=0.01$, $p<0.65$).

2.3. *WAIS-III digit span*

On the forward series of the WAIS-III Digit Span sub-test, patients' mean was 9.53 (S.D. = 1.99), controls' mean was 10.8 (S.D. = 2.0); on the reverse series, patients' mean was 6.13 (S.D. = 1.5), controls' mean was 6.8 (S.D. = 1.7). The memory spans of patients and controls were not different for series of two to five items, which are equivalent in duration to a pitch discrimination trial. The small difference in mean overall working memory span score between the two groups was due to slightly greater capacity in controls for longer sequences.

2.4. *Audiometry*

Both groups exhibited normal audiograms. Some patients and controls had slightly elevated thresholds at 4 and 8 kHz (Katz, 2002). The threshold at 500 Hz, the standard tone fundamental frequency in the pitch discrimination task, was in the normal range for all patients (14 dB HL) and controls (11 dB HL).

3. Discussion

The primary aim of this study was to test the prediction, originating from the sensory hypothesis of cerebellar function (Bower, 1997a,b, 2002; Bower and Kassel, 1990; Bower and Parsons, 2003), that humans affected with cerebellar disease should have detectable deficits in fundamental auditory tasks. The present study documents an auditory deficit associated with global atrophy of the cerebellum under a range of disease conditions. Specifically, the cerebellar patients have significantly poorer pitch discrimination than healthy controls of matched age and education.

The large differences in pitch discrimination thresholds between the two groups were not likely due to any large or general working memory deficits associated with cerebellar damage (see Discussion section on Limitations) because on the WAIS-III Digit Span subtest patients and controls displayed similar capacities for working memory, in the same range of duration as the pitch discrimination trials. Similarly, performance in the detection task confirmed that patients, like controls, were alert and competent for the entire task, the overall duration of which equaled that of the pitch discrimination task. Thus, the differences between patients and controls in pitch discrimination thresholds were not likely due to differences in the ability to sustain attention. Finally, the normal audiograms exhibited by the cerebellar patients indicate that the pitch discrimination deficit in these patients was unrelated to their ability to hear the tones, which was unaffected by cerebellar degeneration, but instead involved their ability to discriminate between tones. The slightly elevated thresholds recorded in some patients and controls were present only at high frequencies (4000 and 8000 Hz), well above those used in the pitch discrimination task (standard tone fundamental frequency was 500 Hz). Thus, it is safe to consider them irrelevant, consistent with the absence of correlation between pitch discrimination and hearing thresholds, at all the frequencies tested. On the other hand, the positive correlation between patients' pitch thresholds and severity of cerebellar degeneration (Fig. 3) further supports the interpretation that the auditory deficit can be ascribed to the effects of cerebellar disease directly.

3.1. *Auditory deficits in cerebellar patients*

These results are not limited to degenerative disease states, because similar impairments were reported in two studies focused on the ability of patients with focal unilateral hemispheric lesions to discriminate sound duration (Mangels et al., 1998; Casini and Ivry, 1999). These studies, initially designed to dissociate the contribution of various brain areas to attention and time perception, used frequency discrimination as auditory control task and unexpectedly observed that the thresholds for frequency discrimination, just like those for sound duration discrimination, were actually somewhat larger in lesion cerebellar patients than healthy controls. The foregoing findings were noted in these papers with little discussion. The current results confirm and extend those earlier findings, suggest an account for them, and encourage further investigation.

Consistent with our findings and with the more general hypothesis of a role for the cerebellum in the control of sensory data acquisition, recent studies have also documented impairments for cerebellar degeneration and lesion patients in other sensory domains such as, for instance, the perception of lower-

level visual information (motion, speed, direction, coherence, duration), as dissociated from motor and attentional factors (Thier et al., 1999; Jokisch et al., 2005; Livesey et al., 2007; Liu et al., 2008; Shih et al., 2009, in press). Likewise, the pitch discrimination impairment here is unaccompanied by evidence in control tasks for deficits in attention, verbal working memory, or hearing thresholds.

3.2. *Support from neuroimaging studies*

The results presented here complement studies of healthy subjects performing auditory perceptual tasks while being scanned by functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Discrimination tasks involving pitch or melody, as dissociated from motor factors, elicit strong activations in lateral aspects of cerebellar regions V and VI bilaterally (Griffiths et al., 1999; Parsons, 2003; Gaab et al., 2003) or on the left (Holcomb et al., 1998). Indeed, in the latter study activity in those regions was present for a similar pitch discrimination task as used here, in which subjects discriminated between a 1500 Hz reference tone and comparison tones (differing by 700, 300, or 100 Hz from the reference tone), all embedded in a noisy background. Moreover, in a second study, activation in those regions was correlated with subjects' accuracy in a melody discrimination task (Gaab et al., 2003). Similar patterns of hemispheric cerebellar activation were also reported in studies focused on the processing of other sound parameters, such as intensity discrimination (Belin et al., 1998), duration discrimination (Belin et al., 2002; Griffiths et al., 1999), and sound movement (Griffiths et al., 2000). Even passive listening to instrumental music induces activity in lateral aspects of the posterior cerebellar hemispheres in lobules VI, IV, V, and Crus I, as well as the dentate nuclei (Brown et al., 2004). Similar activity is observed during passive listening to speech (Callan et al., 2006, 2007) or synthesized sounds such as clicks (Ackermann et al., 2001; Ortuño et al., 2002; Pastor et al.; 2002), amplitude modulated tones (Reyes et al., 2004), and pure tones (Rao et al., 1997; Lockwood et al., 1999).

The latter coherent pattern of findings is confirmed rigorously in a recent quantitative meta-analysis, using activation likelihood estimate (ALE) methods (Turkeltaub et al., 2002; Eickhoff et al., 2009), of PET and fMRI studies of auditory perception excluding experimental designs with cognitive, emotion, or motor confounds (Petacchi et al., 2005). The meta-analysis revealed ALE maxima in posterior cerebellar cortex in crus I, crus II, and lobule V (with volumes extending to lobule VI) that were present across a set of studies with varying contrasts, stimuli, and tasks, from passive listening to clicks or pure tones to discrimination and masking tasks. Furthermore, subanalyses of the data set ruled out a role in attentional mechanisms, which is consistent with the absence of attentional deficits in the present study. This quantitative meta-analysis, based on an extensive review of available published functional neuroimaging findings, implicates the regions of posterior cerebellum in aspects of primary auditory processing, a pattern that has been further confirmed in subsequent studies (Chen et al., 2008; Pastor et al., 2008).

Such findings with healthy individuals also fit with neuroimaging studies of patients with Williams Syndrome. This genetic disorder spares abilities in music, with extraordinary sensitivity to sound (Levitin and Bellugi, 1999; Bellugi et al., 2000; Levitin, 2004), and relative to controls, they show greater activation to music and noise in the cerebellum (Levitin et al., 2003), as well as greater grey matter density, in lobules VI and VII (Reiss et al., 2004).

3.3. *Limitations*

Although the findings from the present study are consistent with our hypothesis, they provide no insight into what particular cerebellar regions might be involved in the auditory deficits we report, as a fine-grained analysis of cerebellar subregions is precluded in pancerebellar degeneration patients. On the other hand, their symptoms are more stable and persistent than those of patients with focal lesions who can be relatively asymptomatic after extended recovery periods (Schmahmann and Sherman, 1998). Until we have a better understanding of any functional regionalization in cerebellar auditory function, data obtained from patients with focal lesions could in principle lead to the misinterpretation of negative results. This may be the case in the study by Harrington et al. (2004a,b) who failed to replicate previously reported cerebellar impairments in identical auditory tasks (Mangels et al., 1998; Casini and Ivry, 1999; for discussion, see Ivry and Spencer, 2004). Given the general nature of our working hypothesis and the fact that we wanted to use ataxia as an independent and quantifiable measure of cerebellar dysfunction, we valued symptoms stability and consistency of sampling over localization.

Another important issue in relying on cerebellar patients suffering from global cerebellar degeneration results from the fact that diffuse degenerative cerebellar disease states can extend beyond the cerebellum and concern other brain regions. This is known to be the case, for example, in patients suffering from one of the forms of genetically determined spinocerebellar ataxia, who have also been known to present noncerebellar symptoms (Klockgether, 2008; Schmitz-Hübsch et al., 2008). We are relatively confident that impaired performance in the auditory task was not due to extracerebellar pathology. In particular, the MRI examination of each patient revealed no obvious evidence of damage in other brain regions, all patients had normal hearing thresholds as well as cognitive and attention abilities, and our major findings are unchanged when we excluded patients with noncerebellar symptoms from group means. However, because of the close association between cerebellum and auditory system at a developmental and genetic level (Altman and Bayer, 1997; Bell et al., 2008), it cannot be excluded that the pitch discrimination impairments might be caused by some degree of concurrent degeneration in the auditory system of a size that escapes MRI examination.

Similarly, it cannot be excluded that the diffusely degenerative cerebellum interferes with auditory functionality indirectly, via other systems, for example through the well-known somatosensory projections to the cochlear nucleus (Wright and Ryugo, 1996; Young et al., 1995), although we would point out that the cerebellar degeneration of patients in this study were a result of a range of different genetic and disease conditions.

Linked to this somatosensory scenario is another possible confound, namely, that the cerebellar involvement may be actually related to the proprioceptive component of the middle ear reflex, as also previously speculated (Jastreboff, 1981). The fact that divisions of the cochlear nucleus that are connected with the cerebellum (Huang et al., 1982) also project both directly and indirectly, by way of the medial superior olive, to the motor neurons that control the tensor tympani and stapedius muscles in the middle ear (Borg, 1973; Billig et al., 2007), may provide a possible neuroanatomical substrate for such a proposed relationship. However, if the cerebellum is involved in the middle ear reflex, it is not likely to be exclusively so, because (1) the extensive neuroanatomical connectivity between cerebellum and virtually all levels of the auditory system (Brozoski et al., 2007; Gacek, 1973; Huang et al., 1982; Huffmann and Henson, 1990; Morest et al., 1997; Rossi et al., 1967; Wang et al., 1991) and (2) the wide range of central and peripheral cerebello-auditory interaction repeatedly documented in electrophysiological studies across different animal species (Crispino and Bullock, 1984; Huang and Liu, 1990; Lee and Bullock, 1984; Snider and Stowell, 1944; Sun et al., 1983, 1990; Teramoto and Snider, 1966; Velluti and Crispino, 1979; Wang et al., 1991; Wolfe and Kos, 1975; Xi et al., 1994) are both well beyond what normally found in a simple reflexive phenomenon. Further anatomical and physiological investigations will be needed to clarify these points and the role of the cerebellum in auditory function.

Another limitation concerns the possible role in the deficits observed here of pitch working memory, as distinct from sensory aspects of pitch perception. Our patients had global cerebellar atrophy, which would affect both the left and right areas of cerebellum. Pitch working memory and verbal auditory working memory appear to be distinct in non-musicians (e.g., Zatorre et al., 1992, 1994), and have been proposed to be subserved respectively by (a) left cerebellar–right prefrontal and (b) right cerebellar–left prefrontal circuits. Because of the global cerebellar damage in our patients, any impairment should be present for cerebellar regions supporting either pitch or verbal working memory processes. By evaluating any deleterious behavioral effects of the damage in right cerebellar regions that have been proposed to support left prefrontal regions for verbal working memory, we have an approximate representative measure of such effects for the corresponding left cerebellar–right prefrontal circuits for pitch working memory. However, although we observed no relevant impairment in verbal working memory span in our patients, even a preserved digital span performance does not exclude possible subtle qualitative impairments in verbal working memory of cerebellar patients (Justus et al., 2005). Be that as it may, we minimized reliance on pitch working memory by using brief interstimulus intervals between standard and comparison tones and by representation of the standard tone on every trial. On balance, we think it is not unreasonable to interpret the elevated pitch thresholds to be more likely due to pitch perceptual processing deficits, than pitch working memory deficits. Nonetheless, these experiments cannot rule out the contribution of a possible pitch working memory deficit to the observed elevated thresholds.

3.4. *Functional significance*

Under our working hypothesis, neither cerebellar activations nor the discrimination deficits observed here should be taken to imply that the cerebellum directly takes part in the computations involved in the discrimination or perception tasks. Instead, we propose that cerebellar involvement is related to the initial acquisition of the sensory data on which these tasks depend (Bower, 1997a, 1997b, 2002; Bower and Kassel, 1990; Gao et al., 1996; Bower and Parsons, 2003).

This distinction between direct involvement in a particular sensory task and indirect involvement through the monitoring and control of sensory data acquisition may also be relevant to the interpretation of other auditory discrimination and perception studies exploring nontraditional roles for the cerebellum. For instance, it has been shown that cerebellar degeneration patients exhibit deficits in the discrimination of phonemes distinguished by closure time (Ivry and Gopal, 1992; Ackermann et al., 1997), a result supported by neuroimaging studies in healthy individuals (Mathiak et al., 2002, 2004). However, this result has been interpreted to support a direct role for the cerebellum in timing (Ivry and Fiez, 2000; but see Pastor et al., 2002; Harrington et al., 2004a,b). In light of the observed auditory impairments, the effects of cerebellar damage on speech perception may actually reflect a more fundamental cerebellar involvement in audition, operating at the level of the basic mechanisms of active sensory data acquisition. Accordingly, we suggest that patient studies built around hypotheses for cerebellar involvement in very specific sensory or cognitive functions should control for such a proposed more generalized (or indirect) function. It should also be pointed out that experimental procedures using auditory stimuli to probe possible cerebellar learning mechanisms (Thompson and Steinmetz, 2009) should also probably consider the possibility that cerebellar lesions could interfere with subjects primary perception of the auditory stimulus.

3.5. *Anatomical and physiological connections between cerebellum and auditory system*

With respect specifically to the auditory system, distinguishing between direct and indirect cerebellar contributions to pitch (or other) perceptions will depend on a closer examination of the actual circuitry amongst cerebellar and auditory structures and its functions. Although scant, there is evidence for direct cerebellar influence on the olivocochlear system, the auditory network responsible for control of the sensory transduction properties of the auditory periphery (Warr, 1992). Anatomical studies have shown that the cerebellum has direct and often reciprocal connectivity with all the auditory structures involved in the functioning of the olivocochlear system, namely, cochlea (Morest et al., 1997; Brozoski et al., 2007), cochlear nucleus (Rossi et al., 1967; Gacek, 1973; Huang et al., 1982; Wang et al., 1991), superior olive (Rossi et al., 1967; but see Gacek, 1973), and inferior colliculus (Huffmann and Henson, 1990). Importantly, there is evidence that cerebellar output influences auditory peripheral activity, as it has been shown that electrical stimulation of the cerebellar cortex reduces auditory brainstem responses in rats (Crispino and Bullock,

1984) and inhibits cochlear microphonics and auditory nerve responses in guinea pigs, whereas cooling the cerebellar cortex enhances them (Velluti and Crispino, 1979). Of course, determining the exact mechanism by which the cerebellum contributes to the acquisition of sensory data in audition, or in any other form of sensory (or motor/cognitive) processing, will require both a better understanding of the computational structure of the cerebellum (Bower, 2002; Sims and Hartell, 2005), as well as its efferent and afferent influences.

4. Experimental procedures

4.1. *Participants*

4.1.1. *Patients with cerebellar degeneration*

Fifteen patients who demonstrated features of degenerative cerebellar dysfunction (Trouillas et al., 1997) on examination participated in the study (Table 1). Clinical signs included dysmetria of the extremities, gait ataxia, dysarthria, as well as eye movement abnormalities. The symptoms were exclusively cerebellar in the nine patients with idiopathic or familial cerebellar cortical atrophy (Villanueva-Habas et al., 2001; Hammans, 1996; Schols et al., 1997; Nance, 1997; Klockgether et al., 1998), and in postinfectious and paraneoplastic cerebellar degeneration (Peterson et al., 1992; Shams'ili et al., 2003). The six patients with spinocerebellar ataxia (SCA) type 1 (Greenfield, 1954; Koeppen and Barron, 1984; Zoghbi and Ballabio, 1995), SCA-3 (Lima and Coutinho, 1980; Burk et al., 1996), SCA-7 (Gouw et al., 1994; Harding and Deufel, 1993), and Friedreich variant (Geoffrey et al., 1976; Harding, 1981, 1993a,b) demonstrated noncerebellar features but hearing thresholds, cognitive, and attention abilities were normal. (The latter patient, in particular, was gene-negative, with symptom onset 10 years prior to study and had been stable with no noncerebellar signs.) Magnetic resonance imaging (MRI) of the brain was consistent with the clinical diagnosis in all instances (Döhlinger et al., 2008).

No patient possessed any of the following conditions: preexistent psychiatric diagnoses; major neurological diseases (Parkinson's, Alzheimer's, epilepsy); history of drug or alcohol abuse; head trauma or central nervous system infection; current use of psychoactive or sedating medications; noncerebellar white matter hyperintensities on MRI; other areas of lesions such as infarction or hemorrhage involving the cerebral hemispheres; or medical conditions such as hepatic, renal and pulmonary disease, systemic infection, or metabolic encephalopathy.

Patients ranged in age from 28 to 67 years (mean=47.7). Their level of education ranged from 13 to 22 years (mean=14.7). The mean number of years since symptom onset across patients was 5.5 years (S.D.=3.1). The patients were all known to have normal hearing and little or no musical training or experience. They were all high functioning and showed excellent general compliance in each task.

The four levels of functional staging of ataxia used in this study were determined by clinical examination with reference to the International Cooperative Ataxia Rating Scale (Trouillas et al., 1997). Ataxia evaluations were conducted independently, and without knowledge of the results of the pitch discrimination tasks. The mean ages for the Minimal, Mild, Moderate and Severe groups were 44, 48, 58, and 46 years, respectively. There was a similar distribution of males and females in all groups (Table 1).

Table 1 – Cerebellar patients.

Patient	Age	Sex	Diagnosis	Years from symptom onset	Severity of ataxia
14	53	M	I-CCA	2	Minimal
8	51	M	GNFV	10	Minimal
13	28	F	I-CCA	3	Minimal
6	50	M	SCA-7	3.5	Mild
15	34	F	F-CCA	8	Mild
10	39	F	I-CCA	4	Mild
11	62	M	I-CCA	7	Mild
7	53	M	SCA-1	6	Mild
12	67	M	SCA-3	11	Moderate
3	50	F	SCA-7	9	Moderate
1	61	F	SCA-3	4	Severe
2	36	F	Postinfectious Cerebellitis	2	Severe
5	61	F	PCA	1	Severe
4	40	M	I-CCA	7	Severe
9	30	M	I-CCA	5	Severe

Abbreviations: F-CCA, familial cerebellar cortical atrophy; GNFV, gene negative Friedreich variant; I-CCA, idiopathic cerebellar cortical atrophy; SCA, spinocerebellar ataxia; PCA, paraneoplastic cerebellar ataxia.

4.1.2. *Control group*

Fifteen healthy volunteers participated in the study as a control group. They were matched to the patients with respect to age (26–63 years, mean=43) and level of education (12–18 years, mean=13.8). Like the patients, all the healthy controls were known to have normal hearing and little or no musical training or experience.

4.2. *Tasks*

Participants gave informed written consent and performed the following sequence of tasks: (1) auditory detection to control for attentional deficits in the duration range of a block of pitch discrimination trials, (2) pitch discrimination, (3) Weschler Adult Intelligence Scale-III (WAIS-III) Digit Span to assess working memory capabilities in the duration range of a pitch discrimination trial, and (4) audiometry to assess hearing sensitivity.

4.2.1. *Detection*

The detection task was programmed in Java and completed on a Pentium II 300 MHz computer, with stimuli created via Cooledit (Syntrillium) and presented binaurally over headphones (MDR-V200, Sony). Participants responded by pressing a computer key when they detected a sound (400 ms white noise burst at 75 dB SPL). The stimuli were presented in a pseudorandom design during a 10-min epoch, such that they were always at least 3 s apart. On average, there was one stimulus every 6 s. In total, 100 stimuli were presented.

4.2.2. *Pitch discrimination*

The pitch discrimination task was also programmed in Java and completed on a Pentium II 300 MHz computer, with stimuli created via Cooledit (Syntrillium). The stimuli were 400 ms complex tones ($f_0+3f_0+5f_0$) presented binaurally over headphones (MDR-V200, Sony) at a level of 75 dB SPL. Participants performed a discrimination task measuring pitch difference thresholds. Each trial required a forced-choice decision as to whether a comparison tone was higher or lower in pitch than a preceding standard tone with a 500-Hz fundamental frequency. This frequency is within a range that is less affected by age-related changes in hearing sensitivity (Olsho et al., 1985) and in which discriminability is finest (Dye and Hafter, 1980). Tones in the trials were presented with a silent 400 ms interstimulus interval. Participants responded by pressing either a left or right computer key with the left or right index fingers. A response was accepted only from one of the two designated computer keys during the six seconds following the comparison tone. The leftward key indicated the comparison tone was lower in pitch than the standard tone; the rightward key indicated it was higher.

Pitch difference thresholds were determined by Parameter Estimation by Sequential Testing (PEST) staircase procedure (Taylor and Creelman, 1967), an adaptive procedure that estimated how small a difference can exist between two pitches for a subject to decide correctly 75% of the time that the pitches are different. Subjects performed up to 110 trials, with threshold trials from above and below the standard tone, mixed together in pseudo-random order. The task terminated the probe of a threshold if the participant had failed to improve according to the statistical criterion to the next threshold after reaching a plateau for sufficiently long (i.e., 20 trials). If the probe for the upper bound terminated before that for the lower bound, pitches near the upper bound were randomly selected for discrimination as foil trials until the lower bound was determined. The reverse was true if the probe for the lower bound terminated first. Because an identical standard tone was repeated on every trial and there was a very brief interval between standard and comparison tones, this task likely had very little reliance on perceptual phenomena such as sensory memory trace, working memory or sequential analysis. Additional studies will need to be designed to clarify whether such patients have difficulties maintaining a sensory memory trace for pitch, for example. A pitch discrimination trial would "time out" if a participant pushed a different key or failed to press a designated key in time. Timed out trials were discarded and had no impact on threshold estimation.

4.2.3. *WAIS-III digit span subtest*

In the digit span subtest task (Wechsler, 1997) participants heard strings of random digits, varying in length from two to nine items, presented in spoken form at a rate of 1/s. At the conclusion of each string, participants recalled the items in forward or reversed order, according to prior instruction. The spoken stimuli were digitized and presented via a Pentium II 300 MHz computer. Participants' spoken recollections were recorded by the experimenter.

4.2.4. *Audiometric test*

Standard pure tone audiometry (Katz, 2002) was performed on a Grason-Stadler GSI 17 audiometer, testing hearing thresholds at frequencies between 125 Hz and 8 kHz in one-octave steps.

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