Active force perception depends on cerebellar function.

Running title: Active Force Perception and Cerebellum

Nasir H. Bhanpuri,1,2 Allison M. Okamura,3,4 and Amy J. Bastian,2,5

1Department of Biomedical Engineering, The Johns Hopkins School of Medicine, Baltimore MD
2Kennedy Krieger Institute, Baltimore MD
3Department of Mechanical Engineering, The Johns Hopkins University, Baltimore MD
4Department of Mechanical Engineering, Stanford University, Stanford CA
5Department of Neuroscience, The Johns Hopkins School of Medicine, Baltimore MD

Address correspondence to:
A. Bastian, Kennedy Krieger Institute, 707 N. Broadway, G05, Baltimore, MD 21205
Telephone: (443) 923-2718 Fax: (443) 923-2715
Abstract

Damage to the cerebellum causes characteristic movement abnormalities, but is thought to have minimal impact on somatosensory perception. Traditional clinical assessments of patients with cerebellar lesions reveal no perceptual deficits despite the fact that the cerebellum receives substantial somatosensory information. Given that abnormalities have been reported in predicting the visual consequences of movement, we suspect that the cerebellum broadly participates in perception when motor output is required (i.e. active perception). Thus, we hypothesize that cerebellar integrity is essential for somatosensory perception that requires motor activity, but not passive somatosensory perception. We compared the perceptual acuity of human cerebellar patients to healthy control subjects in several different somatosensory perception tasks with minimal visual information. We found that patients were worse at active force and stiffness discrimination but similar to controls with regard to passive cutaneous force detection, passive proprioceptive detection, and passive proprioceptive discrimination. Furthermore, the severity of movement symptoms as assessed by a clinical exam was positively correlated with impairment of active force perception. Notably, within the context of these perceptual tasks, controls and cerebellar patients displayed similar movement characteristics and hence differing movement strategies are unlikely to underlie the differences in perception.

Our results are consistent with the hypothesis that the cerebellum is vital to sensory prediction of self-generated movement and suggest a general role for the cerebellum in multiple forms of active perception.

Keywords
cerebellum; sensory discrimination threshold; proprioception; forward model; ataxia
Introduction

Many sensory percepts involve action and movement—for example, when opening a door we can tell if it is stiff or compliant, heavy or light. This kind of active force perception appears to depend not only on peripheral sensory signals, but also central motor commands (Gandevia and McCloskey 1977; Jones 1983). For example, increased grip force on slippery surfaces produces overestimation of weight (Flanagan et al. 1995) and horizontal load (Flanagan and Wing 1997). This suggests that the nervous system has a means of predicting how motor commands will normally move the arm and hand-held objects (Wolpert and Flanagan 2001). The cerebellum is a likely candidate for this type of prediction, since it is thought to contribute to movement coordination using an internal model of body dynamics (Kawato 1999). In addition, the cerebellum receives both efferent copies of motor commands and sensory information from the periphery (Kawato 1999; Holmes 1917; Dow and Moruzzi 1958) and has distinct projections to brain areas important for perception (Dum and Strick 2003).

Historically the cerebellum has been thought to have a limited role in basic perceptual abilities such as hearing, vision, smell, and somatosensation (Holmes 1917; Dow and Moruzzi 1958; Maschke et al. 2003). Yet, neuroimaging studies have shown that the human cerebellum is active during somatosensory processing (Gao et al. 1996), as well as visual and auditory perceptual tasks (Baumann and Mattingley 2010). It has also been reported that cerebellar patients have some deficits in visual motion perception during a tracking task (Ivry and Diener 1991) and do not properly update the visual consequences of self-generated movements (Synofzik et al. 2008). Thus, the cerebellum may only be important for percepts that involve movement production. One possible mechanism for certain perceptual deficits is that the cerebellum is essential to making sensory predictions of outgoing motor commands (Synofzik et al. 2008; Blakemore et al. 1998; Paulin 1993; Xu-Wilson et al. 2009; Miall et al. 2007). If
cerebellum-dependent sensory predictions are ultimately combined with sensory information from the periphery in order to form percepts, then we predict cerebellar patients should be impaired at an array of active perceptual tasks (including active force perception), but not passive perceptual tasks. On the other hand, it is possible that perceptual tasks do not rely on sensory predictions of motor commands, in which case we would predict that patients would exhibit normal active perception.

Here, we designed experiments to assess active and passive perceptual thresholds in the somatosensory domain with limited visual information. We recruited patients with cerebellar lesions and age-matched controls to participate in the various perceptual tasks. Specifically, we tested for patient impairment with regard to active force perception and also verified that patients had normal passive cutaneous mechanoreception (Holmes 1917) and normal passive position proprioception (Holmes 1917; Maschke et al., 2003).

Materials and Methods

Subjects

We studied 11 patients with cerebellar deficits but no clinical signs of sensory loss, and 11 age-, gender-, and handedness-matched controls without any known neurological impairments (Table 1). All subjects gave informed consent to the protocols approved by the Johns Hopkins Institutional Review Board. Six patients were diagnosed with a genetically defined spinocerebellar ataxia type 6 (n=5) or type 8 (n=1). Four patients presented with symptoms of autosomal dominant cerebellar ataxia type III, an inherited disorder with pure cerebellar signs but no definite genetic testing. One patient presented with symptoms of sporadic adult-onset cerebellar ataxia (sporadic), a disorder with pure cerebellar signs but no familial history. There was no evidence of atrophy to the brainstem or spontaneous nystagmus for these patients. We quantified the severity of cerebellar impairments using the International Cooperative Ataxia Rating Scale (ICARS; Trouillas et al. 1997), which assigns higher scores to
patients with greater impairments in walking, balance, limb control (kinetic), speech, and eye
movements. For the patient group, the mean total ICARS was 45.5 (s.d. 21.8, range 4-79;
maximum possible score = 100). The mean kinetic portion of the ICARS was 19.6 (s.d. 10.8,
range 1-40; maximum possible score = 52).

We evaluated cutaneous mechanoreception based on a monofilament detection
assessment (Semmes et al. 1960). This is a standard clinical examination to determine if
participants display signs of somatosensory loss due to neurological impairment. Typically,
somatosensory loss due to disease and aging occurs distally (fingers and toes) before
proximally (arms and legs). Thus, assessing fingertip mechanoreception, which contributes to
force perception, provides a conservative exclusion criterion. The experimenter performed the
assessment by pushing a given monofilament against the distal segments of the subject’s index
fingers (glabrous side). Subjects gave a response when they felt a force at the fingertip. The
threshold force was recorded for the monofilament that produced the least amount of force and
was correctly detected on at least 3/5 trials. All subjects included in this study had thresholds
that were in the normal range (≤0.4 g). Two subjects, one control and one individual with an
unidentified cerebellar syndrome plus spasticity, had cutaneous sensory loss and were
excluded.

Apparatus

For the experiments, subjects’ perceptive thresholds on the dominant arm were
measured using the KINARM exoskeleton robot system (BKIN Technologies, Kingston,
Canada). The system was calibrated to align the shoulder and elbow joints of the robot with the
corresponding joints on the tested arm. Subjects’ arms rested in arm trays that were chosen to
minimize skin compression (i.e. the trays did not tightly enclose the arm). This is similar to
previous proprioceptive studies at the elbow joint which have attempted to avoid activating
cutaneous mechanoreceptors (Maschke et al. 2003; Zia et al. 2000). In addition, the chair height
was adjusted to constrain arm movement to the shoulder-level horizontal plane. During the test
blocks, vision of the subject’s arm was blocked with a metal screen and subjects wore head
phones playing white noise to occlude the sounds produced by the motors. For all tasks, the
upper arm (i.e. shoulder joint) was fixed at 30° flexion the entire time by a mechanical clamp on
the robot arm. All subjects in both groups experienced the same conditions.

**Task 1 and 2: Torque and Stiffness Discrimination Tasks**

Throughout these tasks, two yellow boundary lines were displayed at elbow angles of
75° and 105°. Subjects were told to stay within the boundary lines, which turned red if their arm
moved outside the designated range. This was the only visual information they were given as
subjects could not see their arm directly nor was it displayed to them. If subjects moved outside
the boundary in more than half the trials within a set, the set was repeated. (This occurred for
less than 15% of subjects). Thus, subjects had to rely on proprioceptive cues to determine arm
location. Each trial consisted of a comparison between two subtrials. As described in Figure 1A,
at the beginning of each subtrial, a blue ring appeared just inside the 75° boundary, at 76°, and
the background was colored red. After the subject moved the elbow to 76°, the ring filled with
color indicating to the subject that he/she was in the start position. Next, the background
changed to green and the robot began to produce torque.

For the torque task, the robot produced a constant extension torque of: 0.40, 0.60, 0.80,
0.90, 1.00, 1.10, 1.15, 1.20, 1.25, 1.30, 1.40, 1.50, 1.60, 1.80, or 2.00 Nm. The torque was
ramped up over one second, remained constant for five seconds, and then ramped down over
one second (Fig. 2 B,C first column). The ramp duration was chosen to be as quick as possible
without introducing unwanted vibrations due to torque discontinuities. Subjects were instructed
to ignore the ramping up of the torque and to focus on the constant “force” during the subtrial,
which would cause extension if they remained passive. As mentioned, subjects were required to
maintain an elbow angle within 75° and 105° and hence, applied flexion torque to counter the
robot. At the end of the subtrial, the background color changed to red. The process was
repeated for the second subtrial with the only difference being the torque magnitude. The torque
magnitude during one of the subtrials was always the “standard,” 1.20 Nm. (The other subtrial
magnitude was the “comparison.”) Each trial was randomized as to whether the standard
subtrial was presented first or second. According to the “Method of Limits for Difference
Thresholds” as described by Gescheider (1997), at the end of each trial, subjects declared
verbally whether the constant torque felt “stronger” on subtrial “one” or “two” or if the torques felt
“equal.” It is unlikely that subjects used the torque increase rate during the ramp phase to
discriminate between the subtrials because the constant phase lasted much longer than the
ramp and they were instructed to attend to the constant phase.

The task began with a practice set to ensure that participants understood the protocol.
The practice set was composed of a random trial sequence with comparison magnitudes of
either 0.40 or 2.00 Nm. The practice set ended when subjects gave five consecutive correct
responses. Next, subjects performed the experimental sets. The order of comparison
magnitudes for a given experimental set was determined using the method of limits (Gescheider
1997). Descending sets began with comparison magnitudes well above the standard and then
on each subsequent trial the magnitude was decreased until the comparison was well below the
standard. (The order of ascending sets was the opposite). For each set, an upper transition
point was computed by taking the highest comparison magnitude for which the subject gave an
incorrect or “equal” response and averaging it with the next highest magnitude tested. A lower
transition point was computed by taking the lowest comparison magnitude for which the subject
gave an incorrect or “equal” response and averaging it with the next lowest magnitude tested.
Each subject completed four sets, alternating between descending and ascending sets. The
upper threshold was estimated by the average of the four upper transition points, and the lower
threshold was estimated by the average of the four lower transition points, for the given subject.
Each set consisted of an average of about 11 trials, ranging between 9-13 trials. Depending on
set length and subject response time, each set took about 5-6 minutes. Subjects were given
breaks of 1-2 minutes between sets and were permitted to take longer breaks if requested.
The stiffness task was similar to the torque task with the exception that the robot torque was not constant during the subtrials but rather, was linearly related to the angular distance from the start position (Fig. 2 B,C, second column). Each subtrial simulated moving against a spring with a specific stiffness such that the torque was zero at the start position and extension (outward) torque was applied as the arm was rotated in flexion (inward). The stiffness magnitude on a given trial was: 1.50, 2.50, 3.00, 3.50, 4.00, 4.25, 4.50, 4.75, 5.00, 5.50, 6.00, 6.50, or 7.50 Nm/rad. The standard stiffness was 4.50 Nm/rad. Subjects were instructed that the robot would provide a force similar to “pushing against a spring” or “stretching a rubber band” meaning that more flexion would result in more “force”. They were encouraged to explore the workspace but as in Task 1, they were required to maintain an elbow angle within 75° and 105°. Once again, the only visual information regarding arm location was the boundary lines that changed color if the arm moved outside of the designated range.

A practice set where the trials had comparison magnitudes equal to 1.50 or 7.50 Nm/rad preceded the experiment. As in Task 1, during the experimental sets, the comparison stiffness was determined using the Method of Limits for Difference Thresholds (Gescheider 1997). Each trial was randomized as to whether the standard subtrial was presented first or second. At the end of each trial, subjects declared verbally whether the external environment felt “stiffer/more resistive” on subtrial “one” or “two” or if they felt “equal.” It is important to note that subjects were not asked to report their intrinsic joint stiffness, but rather, they were asked to discriminate between externally imposed forces that were characterized by stiffness. Thus, success in the task depended on combining information about movement amplitude and external torque (Jones and Hunter 1990), but was unrelated to controlling and maintaining intrinsic joint stiffness. Set length, set duration, break frequency and break duration were similar to the torque task.

**Task 3: Passive Proprioceptive Detection Task**

Subjects were instructed to remain passive and allow the robot to move their arm while vision of the arm was blocked. Before each trial, the forearm was “reset” to a start position of
90° elbow flexion (Fig. 1B). A blue circle appeared briefly, indicating the start of the trial and then the elbow was rotated in flexion to a magnitude of: 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.6, 2.0, 2.4, or 3.0°. A proportional-integral-derivative (PID) feedback controller was implemented in order to move the forearm at a steady velocity with mean 0.3°/s and standard deviation 0.01°/s across trials (Fig. 2 B,C third column). Appropriately tuned PID controllers produce smooth, consistent movements and can correct for external disturbances (Spong et al., 2006). Before each movement, there was a random delay of 1-2 seconds and after the end of the movement there was a random delay of 4-5 seconds before a red circle appeared indicating the end of the trial. Subjects were told that movement could occur at any time before the red circle appeared. Due to the delays of random duration, the latency of the red circle appearance was an unreliable cue for movement length. Thus, although the total trial time varied, duration alone could not provide enough information regarding movement occurrence. (Importantly, in pilot studies we compared the method described here to a similar task where each trial took the same amount of time (i.e. the longest trial duration). We found that both methods resulted in similar thresholds while the latter method took significantly more total time and resulted in greater subject fatigue.)

According to the “Method of Limits for Absolute Thresholds” (Gescheider 1997), subjects then expressed verbally “yes” or “no” as to whether or not they felt a movement during the trial. Prior to the experimental sets, subjects conducted a practice set that consisted of a random sequence of trials with the extreme magnitudes, 0.0 and 3.0°. During experimental sets, the order of magnitudes presented to the subjects followed the method of limits (Gescheider 1997). The procedure begins by first presenting a stimulus well above (descending set) or below (ascending set) threshold and then with each following trial, the stimulus strength is changed by a small amount in the direction of the threshold. The set ends when the subject’s response changes. The two magnitudes between which a response change occurs are averaged to compute the transition point. Each subject completed four sets, alternating between descending
and ascending sets. The average of the four transition points provided the estimate of the absolute threshold for the given subject. Each set consisted of an average of about 6 trials, ranging between 3-9 trials. Depending on set length and subject response time, each set took about 5-7 minutes. Subjects were given breaks of 1-2 minutes between sets and were permitted to take longer breaks if requested. Due to limited availability of one patient, only 10 patients and 10 matched controls completed this task.

**Task 4: Passive Proprioceptive Discrimination Task**

Six patients and six matched control subjects performed Task 4 on a return visit to the laboratory. Each trial consisted of two subtrials during which the subject’s forearm was rotated different magnitudes while the subject remained passive and vision of the arm was blocked (Fig. 1C). First the subject was moved to the start position (75°) and a blue circle appeared briefly to indicate the beginning of the subtrial. Next, using the PID controller, the commanded velocity was ramped up over 250 ms (to minimize possible torque transients), and held constant at 5°/s (standard deviation 0.05°/s), until the desired displacement was achieved (Fig. 2 B,C fourth column). After a random delay between 7.5 and 8 seconds from the start of the subtrial, a red circle appeared to indicate the end of the subtrial. (In contrast to task 3, the latency of red circle appearance was consistently longer than the duration of the longest possible movement. In this case we used a more conservative approach to the timing of task events because subjects did not express excessive fatigue during pilot experiments—presumably due to higher velocity, shorter duration movements.) The designated magnitude for a trial was: 2.0, 4.0, 6.0, 7.0, 8.0, 9.0, 9.5, 10.0, 10.5, 11.0, 12.0, 13.0, 14.0, 16.0, or 18.0°. For each trial, one of the randomly chosen subtrials moved the subject the standard distance of 10.0°.

The magnitude of the comparison distance was determined using the Method of Limits for Difference Thresholds (similar to Task 1 and 2). At the end of each trial, subjects declared verbally whether the movement was “farther/ longer distance” on subtrial “one” or “two” or if they felt “equal.” The task began with a randomized practice set in which the comparison magnitudes
were either 2.0 or 18.0°, and five consecutive correct responses were required before the
experimental sets began. Each set consisted of an average of about 11 trials, ranging between
9-13 trials. Depending on set length and subject response time, each set took about 5-6
minutes. Subjects were given breaks of 1-2 minutes between sets and were permitted to take
longer breaks if requested.

It should be noted that any magnitude (i.e. distance) comparison must inevitably involve
velocity and duration comparisons as well. In the task described here, velocity was constant and
duration varied for different magnitude trials. Alternatively, duration could have been constant
and velocity could have varied for different magnitude trials, or a third possibility is that velocity
(and the corresponding duration) could have been randomized from trial to trial to reach
different magnitudes. In all cases, if subjects are not explicitly told which parameters are being
varied or held constant, subjects could use information regarding all three parameters to assess
movement magnitude. Thus, passive proprioception as described here, specifically involves
position sense, duration sense and velocity sense. We opted to keep velocity constant because
the robot controller was less optimal at high velocities.

**EMG Recordings**

Electromyographic (EMG) recordings were collected using the Bagnoli EMG system
(Delsys, Boston, USA). Surface electrodes were placed on three muscles in the tested arm:
brachioradialis, biceps brachii, and triceps brachii. The amplifier gain was 10,000 for all
channels and the sampling rate was 1 kHz. For tasks where subjects were instructed to remain
passive, EMG signals were monitored and trials with muscle activity during these tasks were
discarded (typically ≤ 5% of trials for a given subject).

**Analysis**

*Discrimination Tasks:* The average upper and lower thresholds (UT, LT) were calculated
for each subject. The point of subjective equality (PSE) was estimated as the average of the UT
and LT for each subject. The Weber Fraction (WF) was computed as
WF = (UT-LT) / (2*PSE).

The individual subject WFs were then used to compute the average WF for each of the groups (patients and controls).

Detection Task: For each subject, the average absolute threshold was calculated across the four sets. The individual subject means were then used to compute the averages for each of the groups. Group differences in various parameters (WF, PSE, position threshold, movement metrics) for each task were computed using a $t$-test for independent samples with separate variance estimates after testing for normality of data distribution with Lilliefors test (Statistica, Tulsa, USA). Within group comparisons of parameters (WF, PSE, and position threshold) were computed using a $t$-test for dependent samples. In addition, correlation analyses were performed on the parameters (WF, PSE, position threshold, movement metrics) with respect to other parameters and with respect to ICARS subscores for patients by computing Pearson’s product-moment correlation coefficient and corresponding significance levels.

Results

In Task 1, subjects pushed against a constant torque produced by the robot about the elbow, while keeping the forearm within the designated 30° range. Using the paradigm illustrated in Figure 1A, we measured the difference threshold, which is the magnitude of stimulus that could just be distinguished from a fixed standard stimulus of 1.2 N-m. The difference thresholds were then used to compute Weber Fractions (WFs), a metric for comparing perceptual sensitivity across different magnitudes and modalities (Gescheider 1997). Low WFs indicate greater sensitivity, (i.e. smaller differences between the standard and test magnitudes are required for discrimination), whereas high WFs indicate less sensitivity. In contrast to their success in perceiving passive forces (discussed below), patients were impaired
at discriminating between constant torques when muscle activity was required to resist external
torques ($P = 0.021$; Fig. 3A). Thus, cerebellar degeneration appears to worsen active force
discrimination. Furthermore, within the patient group, torque WFs were significantly correlated
with the ICARS kinetic functions score (Pearson’s correlation $r = 0.72, P = 0.013$; Fig. 3B).
Patients with more severe cerebellar signs were more impaired at torque discrimination.

We used two metrics, maximum elbow angle and standard deviation of elbow angle, to
test for discrepancies in the amount of movement between groups. Control subjects and
cerebellar patients exhibited a variety of different position profiles as demonstrated by
exemplary trials for Task 1 (Fig. 4A). The metrics for these example trials are shown in Figure
4B and C to show how they correspond to different position profiles. Importantly, the movement
metrics of all subjects, averaged across all trials, in Task 1 (and Task 2, described below)
showed no systematic differences across groups (all $P > 0.19$; Fig. 4D and E). Consequently,
differences in perceptual thresholds between controls and cerebellar patients cannot be
attributed to differing movement strategies. Additionally, among the patient group neither
maximum elbow angle nor standard deviation of elbow angle was significantly correlated to
ICARS scores for Tasks 1 and 2 (all $P > 0.21$). Therefore, although certain patients
demonstrated more variability and intention tremor during rapid, targeted movements (one of
the key assessments for the ICARS rating) relative to their peers, those patients did not
systematically move more erratically within the context of these tasks.

In Task 2, we assessed stiffness discrimination, a second, more complex form of active
force perception. Stiffness perception requires a direct comparison between sensed force and
position information (Jones and Hunter 1990). The Task 2 trial sequence was the same as
Task 1 (Fig. 1A), but the applied torques were not constant. Instead they scaled with elbow
angle, thereby simulating a virtual spring with a different stiffness (N-m/rad) on each trial.
Subjects were encouraged to move away from the start position in order to feel the stiffness on
each trial, but were restricted to the same $30^\circ$ range as in Task 1. For a given group, stiffness
WFs significantly greater than torque WFs would indicate that those subjects were impaired at estimating the ratio between sensed torque and displacement. While the patients’ stiffness WFs were higher than those of controls ($P = 0.026$; Fig. 3C), both patients and controls were not different from their respective torque WFs (patients $P = 0.12$, controls $P = 0.82$, compare Fig. 3A and C). Moreover, across all subjects, stiffness perception was significantly correlated with torque perception (Pearson’s correlation $r = 0.80$, $P < 0.001$). Although stiffness WFs were positively correlated with ICARS kinetic functions score among the patient group, the correlation was not significant (Pearson’s correlation $r = 0.49$, $P = 0.12$). In sum, the Task 2 results confirm that the cerebellum contributes to active force perception, but indicate that it is not important for gauging the relationship between sensed torque and movement amplitude. This form of multimodal perception may be a function of posterior parietal cortex (Stein and Stanford 2008).

To ensure that movement detection was intact in patients, we performed Task 3 to measure the absolute threshold for position proprioception (i.e. the smallest detectable change in elbow angle, Fig. 1B). There was no difference between groups ($P = 0.89$; Fig. 3D). In fact, the observed values (mean ± standard error: patients $= 0.91 ± 0.17^\circ$; controls $= 0.88 ± 0.13^\circ$) were similar to those reported previously despite differences in the robot apparatus and psychophysical methods ($1.15^\circ; 1.03^\circ$) (Maschke et al. 2003). Thus, this facet of passive proprioception does not appear to be cerebellum dependent, though it has been reported that, with regard to proprioception, both duration sense and velocity sense may involve the cerebellum (Grill et al. 1994).

After the initial finding that patients performed worse than controls at Tasks 1 and 2, but not Task 3, we designed Task 4 to examine patients’ ability to recall and compare sensations in a passive task. In Task 4, proprioceptive difference thresholds were measured by instructing subjects to compare passive displacements of different amplitudes (Fig. 1C). Again, the method of limits protocol for discrimination thresholds was employed to compute the WF. We were able to retest a subgroup of six patients with impaired torque perception (torque WF > mean control...
torque WF) and matched controls. The results clearly indicate that patient impairments in torque
and stiffness thresholds (Tasks 1 and 2) were not due to memory problems, because the patient
subgroup was significantly worse at Tasks 1 and 2, (Task 1 $P = 0.0011$, Task 2 $P = 0.0061$; Fig.
5A and B) but similar to their control counterparts at Task 4 ($P = 0.83$; Fig. 5C) which included a
comparable memory demand. Furthermore, potential disruption of duration and velocity sense
due to cerebellar damage (Grill et al. 1994) did not seem to impair patient performance in this
task, even though duration and velocity information could, theoretically, be combined with
position sense in order to complete the task (see Methods: Task 4). Lastly, similar to the larger
groups, the subgroups were not significantly different with regard to Task 3, movement
detection ($P = 0.47$; Fig. 5D).

As mentioned, the patients showed no deficits in passive cutaneous mechanoreception
based on a monofilament detection assessment at the index finger of the dominant hand. The
threshold for all subjects was $\leq 0.4$ grams, which is normal for the given subject age (Semmes
et al. 1960). Thus, the component of force perception mediated by cutaneous
mechanoreceptors was not disrupted in patients. It is therefore unlikely that the cause of
impaired torque discrimination in patients is due to poor mechanoreception.

Discussion

The key finding in this study is that cerebellar patients were impaired in the perception of
external torque and stiffness, but unimpaired in passive position proprioception at the same joint
and passive mechanoreception at the same hand. Thus, the deficit is specific to active force
perception. The severity of ataxia (kinetic score) was significantly correlated with reduced
torque perception. Additionally, our results suggest that within the constraints of the experiments
described, stiffness discrimination is closely related to torque discrimination for both controls
and patients. Thus, perceiving torque during self-generated movement appears to be
cerebellum dependent while perceiving the ratio between torque and displacement seems to
depend on other brain areas. The results predict that patients would also have difficulty with other types of load discrimination that require movement such as object heaviness during wielding (Dow and Moruzzi 1958; Angel 1980), but not passive heaviness perception (e.g. when an object is placed on the hand supported by a solid surface).

As mentioned previously, the proprioception discrimination task (Task 4) may have involved a mix of information including position and velocity proprioception and duration sense, even though subjects were instructed to focus on movement distance. Presumably, the same information contributes to position sense during the torque and stiffness tasks (Tasks 1 and 2). Our results indicate that deficits in torque and stiffness discrimination are not due to underlying problems with position perception (arising from a combination of position and velocity proprioception and duration sense). Additionally, since it has been suggested that velocity proprioception and duration sense are indeed impaired following cerebellar damage (Grill et al. 1994), it is likely that within the context of the experiments described here, subjects relied more heavily on position sense rather than velocity or duration sense. Otherwise, we would have expected control subjects to perform better at Task 4 relative to the patient group.

The specific thresholds and Weber Fractions computed in this study undoubtedly depend on the specific details of the task sequence and overall methodology. The method of limits was chosen as a compromise between overall task duration and sensitivity of perceptual measurements. It is possible that a more rigorous and time-consuming methodology (e.g. “Method of Constant Stimuli”; Gescheider 1997) would have resulted in slightly different WFs than those computed here (perhaps shifted up or down). However, the important conclusions of this study are based on the perceptual differences observed between the patient and control groups, which would presumably have been seen if a different psychophysical method had been employed.

An important consideration is that the amount of movement during force and stiffness discrimination tasks can influence subjects’ ability to resolve external loads (Tan et al. 1995). It
is possible that differences in movement or exploration strategy during the constant torque
(Task 1) and stiffness (Task 2) tasks caused the observed group differences in perceptual
sensitivity. In Tasks 1 and 2, subjects employed varying movement strategies, as they were not
given explicit instructions other than to stay within the 30° range. However, we found no
differences between patients and the matched control group in the maximum elbow angle, and
standard deviation of elbow angle for either of the two tasks. Therefore, we concluded that the
impairments in torque and stiffness discrimination were not due to differing movement patterns
between groups.

Perceptual differences observed in this study could potentially be attributed to
differences in onset acceleration between tasks. In other words, abrupt changes in acceleration
or external torque could activate different sensory signals and perhaps elicit reflexes that could
influence perception. However, as explained in the task description and demonstrated in Figure
2 B,C third row, all of the tasks were designed to have gradual changes in externally applied
torque and thus, onset acceleration was relatively low across all of the different tasks described.
Therefore, we concluded that the observed perceptual thresholds were not impacted by abrupt
changes in acceleration.

It is possible that the perceptual deficits we observed in cerebellar patients were due to
changes in fusimotor drive (Gilman & McDonald 1967). Within the fusimotor system, gamma
motor neurons modulate muscle spindle sensitivity (important for proprioception) by altering the
tension in intrafusal muscle fibers. If the cerebellum is specifically important for gamma
motorneuron-driven increases in sensitivity during self-generated movement but not during rest,
then cerebellar patients would show impaired active but not passive perception as seen here.

However, we favor the possibility that the role of the cerebellum in active force
perception is more sophisticated than simply increasing receptor sensitivity during movement
based on its putative function in motor control. We propose that the cerebellum may be
important for sensory prediction, which is important for accurate movement control (Wolpert and
Flanagan 2001; Kawato 1999; Miall et al. 2007; Xu-Wilson et al. 2009), and might be essential for distinguishing internal from external sensation (Blakemore et al., 1998; Gellman et al. 1985).

It is possible that the cerebellum modulates the fusimotor system based on predictions of movement outcomes rather than simply causing an increase in receptor sensitivity, or perhaps the cerebellum sends signals of movement prediction directly to the parietal cortex.

The results presented here build upon findings that the cerebellum is important for updating predictions of movement outcome following a visual rotation (Synofzik et al. 2008). Theoretically, predictions of sensory changes due to self-generated movement would rely on a forward dynamic model which receives copies of motor commands and has knowledge of the limb’s physical properties (Kawato 1999; Wolpert and Flanagan 2001). These sensory predictions could contribute to active force discrimination by providing an error signal between predicted and expected movements, and hence indicate changes in external load. A malfunctioning (i.e. unreliable) forward model would account for movement variability characteristic to cerebellar damage (Holmes 1917; Dow and Moruzzi 1958; Trouillas et al. 1997) and the impaired active force perception observed in this study. Importantly, our results from the passive tasks are in line with the notion of the cerebellum acting as a forward model, because a corrupt forward model would not impair passive somatosensory perception. In addition, the results presented here are in accordance with the finding that the size-weight illusion is preserved in patients with cerebellar degeneration (Rabe et al. 2009), which is thought to rely more on cognitive expectations of constant material density than on accurate forward models (Flanagan and Beltzner 2000). We do not propose the cerebellum is itself integrating and processing different modes of information that lead to perception, but rather, it is likely providing one of several signals that may be integrated by the parietal cortex (Stein and Stanford 2008). Similarly, evidence from a recent study suggests that visual motion perception in cerebral cortex relies on relevant signals from the cerebellum (Händel et al. 2009). If the cerebellum is indeed critical to sensory predictions of self-produced movements, or simply increasing receptor
sensitivity during all movements, it is likely to play a role in other forms of active sensory perception (e.g. active proprioception, stereognosis).

Finally, the results of this study have clinical relevance. They suggest that in addition to well-known movement abnormalities, cerebellar patients have clear perceptual deficits during self-generated movement. They have difficulty perceiving differences in externally applied forces and likely have difficulty discriminating between the heaviness of different objects (during movement, Angel 1980). For example, during lifting patients may not be able to readily perceive whether an opaque cup is full or empty, which would serve to exacerbate problems with moving the cup accurately. Another practical example is that patients may have difficulty distinguishing whether an accelerator pedal is stiff or compliant and thus would presumably struggle with driving an unfamiliar car.
Acknowledgements

We thank D. Grow, T. Gibo, S. Charles, and N. Gurari, for consultation on experimental design.
We also thank J. Bastian, C. Connor and D. Wolpert for comments on previous versions of this
manuscript. In addition, we thank the patients who participated in this study.

Grants

This work was supported by the National Institutes of Health [R21NS061189 to A.M.O.,
R01HD040289 to A.J.B, F31NS070512 to N.H.B, T32EB003383 to N. Thakor].

Author Contributions

All three authors designed the study. N.H.B. performed the experiments and conducted the data
analysis. All three authors contributed to interpretation and writing of the paper.
References


Figure 1 Task descriptions. (A) Tasks 1 and 2: torque and stiffness discrimination. After subjects moved to start location, the robot applied elbow torques for five seconds. Subjects were instructed to keep movements within boundary lines (elbow angle 75° and 105°). Two environments were presented sequentially in each trial and subjects reported which one was stronger. The label for each stimulus was indicated in the black square at the upper-left corner (I: magnitude one, II: magnitude two). (B) Task 3: position detection task. Robot-driven movements occurred while subjects remained passive; subjects reported if they felt a movement or not. (C) Task 4: position difference threshold task. Same as B with addition of second movement and subjects reported which movement went farther. Gray arrows indicate passive, robot-driven movement and black arrows indicate active, subject-driven movement. The white dotted lines depicting the arm of the subject are for illustrative purposes only, as vision of the arm was occluded throughout all tasks.

Figure 2 Conventions and example trials of perceptual tasks. (A) Schematic of conventions used to report elbow angle (θ_e) and applied torque (τ_e). The shoulder angle (θ_s) was fixed at 30° for all of the tasks. (B) Example trials of control and (C) cerebellar subjects for: torque discrimination task (1.20 Nm; first column), stiffness discrimination task (4.5 Nm/rad; second column), position detection task (1.0° trial; third column), and position discrimination task (10.0° trial; fourth column). Overhead view of fingertip position (top row), elbow angle (middle row), and commanded torque (bottom row), are shown for given trials. Gray lines correspond to the visual boundary.

Figure 3 Cerebellar patients have impaired torque and stiffness perception but normal proprioception. (A) Torque WF was significantly higher for patient group (n = 11, P = 0.021). (B) Torque WFs were significantly correlated to ICARS Kinetic subscore of patients (n = 11, Pearson’s correlation r = 0.72, P = 0.013). (C) Patients had a significantly higher average
stiffness WF as compared to matched controls ($n = 11$, $P = 0.026$). (D) Absolute threshold for position was similar across groups ($n = 10$, $P = 0.89$). Note that, due to limited availability, only 10 of 11 subjects from each group participated in Task 3 (position detection). (*$P < 0.05$). Error bars indicate standard error.

**Figure 4** Comparison of movement strategies during perceptual tasks. (A) Elbow angle versus time profiles during example trials of Task 1 for all subjects. Each subject is offset vertically from the others. Scaling is indicated by bars below panel A. (B-C) Maximum angle attained and standard deviation of angles sampled during the single example trials. The vertical position corresponds to the profiles in A. (D-E) Comparison across groups of different average metrics across all trials for Tasks 1 and 2 (torque and stiffness tasks): (D) Maximum angle and (E) standard deviation of angle. Error bars indicate standard error. All comparisons between groups were not significant.

**Figure 5** Comparison across tasks of subgroups that conducted the position discrimination task. (A) Torque Weber Fraction (WF) was significantly higher for the patient subgroup ($n = 6$, $P = 0.001$). (B) Patient subgroup also had a significantly higher average stiffness WF as compared to matched controls ($n = 6$, $P = 0.006$). (C) WFs were similar in the proprioception task with a memory component ($n = 6$, $P = 0.83$). (D) Absolute threshold for position was similar across subgroups ($n = 5$, $P = 0.56$). Note that, due to limited availability, only 5 of 6 subjects from each subgroup participated in Task 3 (position detection). (*$P < 0.05$). Error bars indicate standard error.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>DH</th>
<th>Diagnosis</th>
<th>ICARS</th>
<th>Kinetic (/52)</th>
<th>Cutaneous threshold (R-L, g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRB01</td>
<td>58</td>
<td>M</td>
<td>R</td>
<td>ADCA III</td>
<td>4</td>
<td>1</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB02</td>
<td>68</td>
<td>F</td>
<td>R</td>
<td>SCA 6</td>
<td>13</td>
<td>4</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB03*</td>
<td>57</td>
<td>F</td>
<td>R</td>
<td>SCA 6</td>
<td>38</td>
<td>15</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB04</td>
<td>61</td>
<td>F</td>
<td>R</td>
<td>ADCA III</td>
<td>38</td>
<td>18</td>
<td>0.07-0.4</td>
</tr>
<tr>
<td>CRB05*</td>
<td>37</td>
<td>M</td>
<td>L</td>
<td>SCA 8</td>
<td>45</td>
<td>20</td>
<td>0.07-0.07</td>
</tr>
<tr>
<td>CRB06*</td>
<td>74</td>
<td>M</td>
<td>R</td>
<td>SCA 6</td>
<td>52</td>
<td>20</td>
<td>0.07-0.07</td>
</tr>
<tr>
<td>CRB07*</td>
<td>69</td>
<td>F</td>
<td>R</td>
<td>ADCA III</td>
<td>60</td>
<td>20</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB08</td>
<td>56</td>
<td>M</td>
<td>R</td>
<td>SCA 6</td>
<td>62</td>
<td>23</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB09</td>
<td>57</td>
<td>F</td>
<td>R</td>
<td>SCA 6</td>
<td>59</td>
<td>27</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB10*</td>
<td>47</td>
<td>M</td>
<td>R</td>
<td>Sporadic</td>
<td>51</td>
<td>28</td>
<td>0.4-0.4</td>
</tr>
<tr>
<td>CRB11*†</td>
<td>66</td>
<td>M</td>
<td>R</td>
<td>ADCA III</td>
<td>79</td>
<td>40</td>
<td>0.4-0.4</td>
</tr>
</tbody>
</table>

**Table 1 Characteristics of subjects**

| CRB Group | 59.1 ± 10.5 | M=6/11 | L=1/11 | 45.5 ± 21.8 | 19.6 ± 10.8 |
|CNT Group  | 56.7 ± 10.5 | M=6/11 | L=1/11 |             |             |

ICARS, International Cooperative Ataxia Rating Scale; CRB, cerebellar subject; CNT, control subject; g, grams; M, male; F, female; DH, dominant hand; L, Left; R, Right; ADCA III, autosomal dominant cerebellar ataxia type III; SCA, spinocerebellar ataxia; Sporadic, sporadic adult-onset cerebellar ataxia; *, performed Task 4 (position difference threshold); †, did not perform Task 3 (movement detection threshold), group data: mean ± (standard deviation).
Task 1 & 2: torque & stiffness discrimination

- Hold
- Stimulus 1
- Hold
- Stimulus 2
- Choice

Task 3: joint position detection

- Start position
- Arm moved
- Choice

Task 4: joint position discrimination

- Start position
- Movement 1
- Stop
- Start position
- Movement 2
- Choice

Figure 1
Figure 2
Figure 3
Figure 4
Position Discrimination

Torque Discrimination

Stiffness Discrimination

Position Detection

* control subgroup (n = 6)
△ cerebellar subgroup (n = 6)
○ control subgroup (n = 5)
▽ cerebellar subgroup (n = 5)

Figure 5