CEREBELLUM AND PROPRIOCEPTION

by
Heidi Michelle Weeks

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Abstract

When the cerebellum is damaged, the ability to make coordinated, accurate movements is affected. Motor control and learning following cerebellar damage have been well studied, but less is known about the effect on proprioception (the sense of limb position and motion). In this dissertation, we examine the involvement of the cerebellum in proprioception by assessing the proprioceptive deficits occurring in people with cerebellar damage.

We first investigated multi-joint localization ability (the position of the hand in space) in patients with cerebellar damage and healthy controls. From this, we confirmed that controls showed improved proprioceptive acuity during multi-joint localization when actively moving, as compared to being passively moved. While some cerebellar patients were comparable to controls, others had impaired acuity during active movement. Results did not differ during single-joint localization, suggesting that impairments were due to active movement, rather than multi-joint discoordination. In addition, our results indicated that cerebellar damage may differentially impair components of proprioceptive sense.

Second, we assessed dynamic proprioceptive position sense (the position of the hand during movement) both orthogonal to the direction of movement (only spatial information was relevant) and in the direction of movement (both spatial and temporal
During passive movement, controls had better proprioceptive acuity when only spatial information was needed, regardless of the direction of their movements. In addition, when both spatial and temporal information were relevant, acuity decreased if subjects focused on the spatial information, underscoring the importance of temporal information during movement.

Finally, to determine whether the cerebellum was differentially involved in these tasks, we tested cerebellar patients and controls during both passive and active movements. During passive movement, cerebellar patients had impaired acuity in both tasks. During active movement, impairments in acuity persisted and were worse when temporal information was relevant. Furthermore, acuity worsened when a subject’s active movement time was more variable from trial to trial. Taken together, these results suggest that proprioceptive acuity may depend on the motor system’s ability to predict motor output. Thus, this dissertation provides additional evidence that the cerebellum contains predictive models of movement which contribute to both motor and somatosensory function.

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Dedication

To Margaret, David, Robin, Noel, and Joe.
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Chapter 1

Introduction

1.1 Overview of sensorimotor control

Imagine that you are reaching to turn on a light switch in the dark—even though you are deprived of vision, you are still capable of turning on the light. One reason that you are able to accomplish this is that you have a good sense of where your body is in space (a sense known as proprioception). Now, imagine what would happen if you lost your proprioception. Not only would you lose the sense of where your body is, but you would also lose the capacity to accurately and smoothly control your movements.

The nervous system is an amazing network, which controls our ability to move and interact with the environment. In order to make movements, the nervous system must know where our limbs are and where it wants them to go—information that is constantly updated by sensory feedback. However, it is not simply enough to have the sensory feedback; the nervous system has to be able to properly use the information. When neurological damage occurs (e.g. due to a stroke), it can affect the processing of sensory feedback, which in turn affects movement ability. These movement disorders due to
neurological damage drastically decrease the quality of life of millions of people. In order to further our understanding of movement disorders and develop effective rehabilitative strategies, it is necessary to investigate the relationship between impaired movement and impaired sensation. This dissertation focuses on understanding sensory deficits, specifically deficits in proprioception, in people with movement disorders.

1.2 Overview of proprioception

1.2.1 Definition of proprioception

Proprioception is clearly essential for generating accurate limb movements (Ghez et al., 1995; Gordon et al., 1995); however, defining proprioception is not simple. Proprioception and kinesthesia encompass a wide array of sensations which provide the nervous system continuous feedback about the position and motion of our limbs, as well information about balance, force, and effort (Proske and Gandevia, 2012). Indeed, defining proprioception as the perception of body position and movement also encompasses multiple senses. Studies have shown that limb position and limb motion are two distinct senses (Sittig et al., 1985; Proske and Gandevia, 2009, 2012). Furthermore, limb position sense can be assessed statically (i.e. the fixed position of a limb in space) or under dynamic conditions (i.e. limb position during movement) (Cordo et al., 1994, 2000; Yousif et al., 2015). In this dissertation, we will consider proprioception to be the sense of limb position and limb motion. Our main interest is limb position sense, which we have tested under both static and dynamic conditions.
1.2.2 Peripheral receptors involved in proprioception

Multiple peripheral receptors in both cutaneous and deep tissue contribute to overall proprioception (Purves et al., 2012). These include deep tissue afferents—joint afferents, Golgi tendon organs, and muscle spindle afferents—and cutaneous mechanoreceptors. The main role of joint afferents is to prevent overflexion and overextension. They signal at maximum flexion and extension of the joint, contributing minimally to joint position sense (Freeman and Wyke, 1967; Burgess and Clark, 1969; Clark et al., 1979). Golgi tendon organs (Ib afferents), located in the muscle tendons, also play a smaller role in proprioception. They increase firing rate with increased tension of the muscle (Matthews, 1933; Edin and Vallbo, 1990), and encode muscle velocity well when combined with muscle spindles (Dimitriou and Edin, 2008).

Muscle spindle fibers innervate the intrafusal muscle fibers of the muscle spindle (Matthews, 1933). The two types of muscle spindle fiber afferents, primary (Ia) and secondary (II), encode muscle length and velocity (Goodwin et al., 1972b; Edin and Vallbo, 1990). Slowly adapting type II (SAII) afferents, cutaneous mechanoreceptors, primarily encode lateral skin stretch and direction of stretch in both glabrous and hairy skin (Edin and Abbs, 1991; Edin, 1992; Macefield et al., 1996; Olausson et al., 2000). The integration of feedback from muscle spindles and cutaneous mechanoreceptors is important for joint position and movement sense throughout the body (Collins et al., 2000, 2005).
1.2.3 Accuracy and precision of proprioception

A number of studies have quantified the accuracy (i.e. the systematic error) and precision (i.e. the variability of error) of limb position sense in healthy individuals. These studies differ in the conditions and positions assessed, but are in agreement on the general results. Accuracy, or bias, varies across the workspace and there is less bias when assessing positions closer to the body (Wilson et al., 2010; Rincon-Gonzalez et al., 2011). On average, individuals tend to perceive their right hand to be further right than its actual position (Crowe et al., 1987; Desmurget et al., 2000; Wilson et al., 2010; Jones et al., 2012), as well as closer to them (Crowe et al., 1987; Desmurget et al., 2000).

Given that proprioception can drift over time (Wann and Ibrahim, 1992), the precision, or acuity, of limb position sense may be a more relevant measure than accuracy. Studies have shown that proprioceptive estimates are more precise when estimating positions closer to the body (van Beers et al., 1998; Wilson et al., 2010). Furthermore, Wilson et al. (2010) found that acuity is better in the forward/back axis (i.e. orthogonal to the body) compared to the left/right axis (i.e. parallel to the body), which is consistent with directional differences noted by van Beers et al. (1998).

Early work in assessing limb position sense operated under the implicit assumption that one has to know individual limb angles in order to ascertain distal limb positions (Soechting, 1982). However, a recent study found that assessing the distal limb position (i.e. fingertip position) was more precise than assessing elbow joint angle (Fuentes and Bastian, 2010). It is likely that, while computations regarding limb angles occur, fingertip position is more functionally relevant. Thus, in this dissertation we focus on assessing the precision of position sense at the fingertip.
1.2.4 Passive and active proprioception

Studies of proprioception in healthy individuals have consistently shown that people have better proprioceptive acuity during active movement (i.e. where a person actively moves their own arm) than passive movement (i.e. where a person’s relaxed arm is moved by an external force or device) (Paillard and Brouchon, 1968; Adamovich et al., 1998; Fuentes and Bastian, 2010; Bhanpuri et al., 2013). Various reasons have been posited for the improvement in proprioception during active compared to passive movement. One possibility is due to a peripheral mechanism in which there is an increased sensitivity of peripheral receptors due to the active movement (e.g. modulation of muscle spindles via gamma motor neuron drive) (Matthews, 1988; Jones et al., 2001). An alternative explanation for improved proprioception during active movement is due to central mechanisms in which processing of the sensory signals is improved (e.g. combining efference copy of the motor command with sensory feedback to make predictions of position) (Adamovich et al., 1998; Gritsenko et al., 2007).

While both theories are plausible, there is strong evidence that sensory prediction models combining efference copy with sensory feedback contribute to proprioception during active movement (Wolpert et al., 1995; Bhanpuri et al., 2013). In fact, Bhanpuri et al. (2013) effectively eliminated any proprioceptive improvements in healthy people during a discrimination task by making active movements unpredictable. Given that these sensory prediction models are thought to be located in the cerebellum (Wolpert et al., 1998; Kawato, 1999), it is important to gain further understanding of the cerebellum’s role in both motor control and proprioception.
1.3 Overview of the cerebellum

1.3.1 Cerebellum and motor control

In this dissertation, we study cerebellar involvement in proprioception. However, this involvement should not be studied in isolation. The cerebellum is one of the key neural structures involved with motor control. While it does not directly initiate motor commands, the cerebellum modulates movement via connections with other brain structures, including the cerebral cortex (Purves et al., 2012). With these connections, the cerebellum assists with planning and executing coordinated and accurate voluntary movements. It is also very important for a number of other behaviors, including walking and postural balance (Purves et al., 2012).

It is known that when the cerebellum is damaged, movement becomes uncoordinated and inaccurate, a condition known as ataxia. Ataxia is extremely debilitating—people have difficulty reaching for objects, writing, and maintaining balance when they stand and walk (Ropper and Samuels, 2009). To date, there are no proven pharmacological treatments for ataxia, making rehabilitation the only option for improvement. However, the effectiveness of current rehabilitation methods is minimal (Perlman, 2012). Furthermore, patients with cerebellar ataxia have impairments in motor learning (i.e. the ability to learn and retain new motor patterns) (Martin et al., 1996; Maschke et al., 2004; Smith and Shadmehr, 2005), which may contribute to the limited effectiveness of rehabilitation. This necessitates both a better understanding of cerebellar function and better rehabilitative treatments following cerebellar damage.
1.3.2 Functional anatomy of the cerebellum

The cerebellum can be divided into four functionally distinct regions. It has three lobes—flocculonodular, anterior, and posterior—split by the primary and posterolateral fissures. The anterior and posterior lobes are further split into longitudinal subdivisions—the vermis, paravermis (intermediate zone), and lateral hemispheres. Two cerebellar regions are less important for arm movements. The flocculonodular lobe helps to control eye movements and maintain postural balance. It receives inputs from both the vestibular nuclei and the visual cortex and projects to the vestibular nuclei (Kandel et al., 2000; Purves et al., 2012). Similarly, the vermis controls head movements, eye movements (saccades and smooth pursuit), stance, and gait (Thach et al., 1992; Bastian and Thach, 2002). It receives inputs from the vestibular and reticular nuclei, the spinocerebellar tracts, and visual areas via the pontine nuclei and outputs to the fastigius and vestibular nuclei.

The cerebellar regions which are most relevant to arm movements are the intermediate zone and the lateral hemispheres. It follows that these regions may be involved in proprioception of the arm, which is the focus of this dissertation. The intermediate zone controls multiple aspects of reflexes and voluntary movements, including co-contraction of agonist and antagonist muscles to damp tremor and online corrections during voluntary movements (Schieber and Thach, 1985; Thach et al., 1992). It receives projections from the spinocerebellar tracts and corticopontine input from the motor and somatosensory cortices (Allen et al., 1978), and outputs to the interposed nuclei (globose and emboliform nuclei in humans). The lateral hemispheres are important for planning and regulating movements, as well as some cognitive functions (Kandel et
al., 2000; Purves et al., 2012). They receive corticopontine inputs originating from multiple cerebral cortices—primary motor and somatosensory, motor and somatosensory association areas, visual, and frontal (Allen et al., 1978; Thach et al., 1992)—and output to the dentate nuclei.

1.3.3 Projections to and from the cerebellum

The cerebellum receives information about the motor commands as well as sensory information from both the cerebral cortex and the body. All inputs to the cerebellum are via the cerebellar peduncles (Glickstein and Doron, 2008) and project as either mossy fibers or climbing fibers to both the cerebellar cortex and the associated deep cerebellar nuclei. The middle cerebellar peduncle carries afferents from the cerebral cortex via the pontine nuclei. This includes sensory information from the somatosensory and posterior parietal cortices, the dorsal extra-striate visual areas, and the frontal eye fields. In addition, the pontine nuclei receive projections from the primary motor and premotor cortices and axon collaterals from pyramidal tract fibers, which likely contain an efference copy of the motor commands (Brodal and Bjaalie, 1997; Glickstein and Doron, 2008; Strick et al., 2009).

The inferior cerebellar peduncle contains afferents carrying sensory information from the body, including projections from the inferior olivary and reticular nuclei as well as the spinocerebellar tracts (Wu et al., 1999; Glickstein and Doron, 2008). There are separate direct spinocerebellar tracts for the lower body, the dorsal and ventral spinocerebellar tracts, and the upper body, the cuneocerebellar tract and rostral spinocerebellar tract. All pathways carry information that encodes the endpoint position of the limb (Oscarsson, 1965; Bosco and Poppele, 2001). In addition, an efference copy
of the descending motor command is integrated into the ascending peripheral sensory information in both the ventral and rostral spinocerebellar tracts (Bosco and Poppele, 2001; Casabona et al., 2004).

Axons from the deep cerebellar nuclei exit via the superior cerebellar peduncle, projecting to the contralateral red nucleus and thalamus. Second-order neurons from the thalamus project to numerous cerebral cortical areas, including the primary and premotor motor cortices and the posterior parietal cortex (Tracey et al., 1980; Sakai et al., 1996; Clower et al., 2001, 2005; Glickstein and Doron, 2008; Strick et al., 2009). Thus, the cerebellum receives adequate sensory feedback and is well connected to cerebral areas involved in movement and sensory perception.

1.4 Cerebellum and sensation

1.4.1 Sensory perception

The nervous system receives a multitude of signals from varying sensory modalities—somatic sensation, vestibular sensation, audition, vision, and chemical sensation—which are centrally processed to give rise to specific sensory percepts (Purves et al., 2012). Early studies indicated that the cerebellum was minimally involved in sensory perception (Holmes, 1917; Dow and Moruzzi, 1958). However, recent studies have shown that the cerebellum is likely involved in sensory perceptions in addition to motor control (Paulin, 1993; Baumann et al., 2015). Multiple imaging studies have found cerebellar activation during somatosensation (Gao et al., 1996) as well as visual and auditory motion perception (Baumann and Mattingley, 2010). Furthermore, studies in
patients with cerebellar damage have shown impairments in proprioception (Bhanpuri et al., 2012, 2013) and visual motion discrimination (Händel et al., 2009).

1.4.2 Sensory prediction

As previously discussed, sensory feedback is important for motor control. However, given the time delays in relaying sensory feedback to the nervous system, it is necessary to make sensory predictions about the state of the body and its surrounding environment (Miall et al., 1993; Wolpert and Flanagan, 2001; Shadmehr et al., 2010). This computation is thought to take place in the cerebellum—it may rapidly compute sensory predictions based on the initial body position and the motor command issued during movements (Wolpert et al., 1998; Kawato, 1999). Several recent studies are in agreement on the cerebellum’s involvement in sensory prediction, showing that patients with cerebellar damage are impaired at updating predictions of the visual consequences of movement (Synofzik et al., 2008; Izawa et al., 2012).

1.4.3 Spatial and temporal perception

While the cerebellum is important for sensory prediction and perception, further understanding of its specific involvement is needed (Baumann et al., 2015). One possibility is that the cerebellum is involved in perceptions with a temporal component but not those that are purely spatial. This has yet to be studied in proprioception; however, multiple studies have assessed cerebellar involvement in spatial and temporal-spatial perception in the visual domain (Ivry and Diener, 1991; O’Reilly et al., 2008; Roth et al., 2013). Ivry and Diener (1991) showed that people with cerebellar damage have deficits in perceptual judgments of the velocity, but not the position, of moving
visual stimuli. More recent studies have considered the ability to predict the time (temporal-spatial) or position (spatial) of reappearance of a moving visual stimulus (O’Reilly et al., 2008; Roth et al., 2013). A neuroimaging study in healthy controls showed cerebellar activation during the temporal-spatial task only (O’Reilly et al., 2008). When assessing people with cerebellar damage during the temporal-spatial visual task, researchers found no deficits during the baseline task; however, cerebellar patients were impaired when a recalibration of the sensory prediction was required (Roth et al., 2013). Thus, these studies provide further support for the suggestion that spatial and temporal perceptual signals are processed by distinct neural circuits, with cerebellar involvement when there is a temporal component.

1.5 Cerebellum and proprioception

If cerebellar processing of sensory signals is improved during active movement, then it follows that people with cerebellar damage should have sensory deficits when actively moving. Indeed, there is evidence that cerebellar patients are impaired in sensory perceptual tasks, including force and stiffness discrimination (Bhanpuri et al., 2012), and proprioceptive discrimination (Bhanpuri et al., 2013). However, it is possible that these discrimination deficits (i.e. the ability to detect differences between small movements or forces) do not translate to deficits in a more functional behavior such as assessing the direction or endpoint of a reach. Several studies have assessed the ability to determine reaching direction during baseline active movements and found no impairments in cerebellar patients (Synofzik et al., 2008; Izawa et al., 2012). This poses the question of whether cerebellar damage causes deficits in the ability to localize the hand in space, which is highly important to everyday movement.
The literature regarding proprioceptive deficits during passive movement in people with cerebellar damage is also mixed, and is further confounded by the varied proprioceptive assessments. Multiple studies have shown that cerebellar patients are unimpaired in passive detection and discrimination of elbow angle movements compared to controls (Maschke et al., 2003; Bhanpuri et al., 2012, 2013). Yet an earlier study indicated that cerebellar patients have deficits when assessing the velocity or duration of passive movements (Grill et al., 1994). Thus, the varying results necessitate a systematic assessment of proprioceptive abilities relevant to everyday movement, which we pursue in this dissertation.

1.6 Scope of this dissertation

This dissertation aims to further elucidate the cerebellum’s role in proprioception (i.e. limb position sense). While it is hypothesized that an important function of the cerebellum is predicting limb position, the extent of cerebellar involvement in proprioception has yet to be determined. We investigated how proprioceptive abilities change when the cerebellum is damaged. To do this, we developed psychophysical tasks to measure proprioceptive position sense during varied movement conditions. Our findings have expanded our understanding of the proprioceptive deficits that may result from cerebellar damage and consequently the potential effects on motor control.

In Chapter 2, we investigated whether patients with cerebellar damage have deficits when trying to locate their hand in space (i.e. proprioceptive localization). This type of task is highly important for everyday movements. By comparing performance during passive robot-controlled and active self-made multi-joint movements, we
determined that some cerebellar patients show improved precision during active movement (i.e. active benefit), comparable to controls, whereas other patients have reduced active benefit. Importantly, the differences in patient performance are not explained by patient diagnosis or clinical ratings of impairment. Furthermore, a subsequent experiment confirmed that active deficits in proprioceptive localization occur during both single-joint and multi-joint movements. Consequently, it is unlikely that localization deficits can be explained by the multi-joint coordination deficits occurring after cerebellar damage. Our results suggest that cerebellar damage may cause distinct impairments to different elements of proprioceptive sense. It follows that proprioceptive localization should be adequately accounted for in clinical testing and rehabilitation of people with cerebellar damage.

In Chapter 3, we studied dynamic position sense (i.e. limb position during movement) in both healthy controls and patients with cerebellar damage. We investigated how a person’s estimate of hand position varies when asked to judge the spatial location or timing of the unseen hand during movement. Specifically, we assessed proprioceptive acuity in two tasks. The first task had subjects compare the position of their unseen finger relative to a visual cursor in a direction orthogonal to their hand movement (spatial orthogonal task), which only requires spatial information. The second task had subjects complete this judgment in line with the direction of their hand movement (temporal inline task), which has both temporal and spatial components. Our initial experiments were done in young controls during passive movements to control for variable motor control between subjects. Our results revealed that individuals have better proprioceptive acuity in the spatial orthogonal task compared to the temporal inline task. Importantly, this
result does not change with different movement directions. Furthermore, when subjects
attend to spatial cues rather than temporal cues during the temporal inline task, acuity
decreases.

We subsequently investigated dynamic proprioceptive acuity in patients with
cerebellar damage and age-matched healthy controls during both passive and active
movement to assess the effects of cerebellar damage. We found that cerebellar damage
impairs dynamic proprioceptive acuity compared to controls in both the spatial
orthogonal and temporal inline tasks. This occurs during both passive and active
movement. However, active movement enhances the proprioceptive deficits, which are
most apparent when judgments rely on temporal information about limb movement (i.e.
the temporal inline task). Interestingly, during active movement, patient performance
correlates with clinical ratings of impairment. Furthermore, both patient and control
performance correlates with the trial-to-trial variability of their active movements—
subjects are worse at the proprioceptive tasks when movements are variable. This
suggests that, during active movements, proprioceptive acuity may be reliant on the
motor system’s ability to predict motor output. Thus, the resultant proprioceptive deficits
occurring after cerebellar damage may be related to a more general impairment in motor
prediction.

Finally, in Chapter 4, we summarize the results of our studies and discuss the
implications. This work is important because it suggests that there are predictive models
of movement in the cerebellum which are essential for both motor and somatosensory
function. It also has clinical relevance because it shows that current descriptions of the
signs of cerebellar damage are incomplete.
Chapter 2

Proprioceptive localization deficits in people with cerebellar damage

2.1 Introduction

Accurate movement control depends on our innate knowledge of limb and body position or proprioception (Ghez and Sainburg, 1995; Bosco and Poppele, 2001; Proske and Gandevia, 2009, 2012). Our proprioceptive sense is known to depend on multiple cerebral cortical areas, but historically, has not been thought to involve the cerebellum (Thach et al., 1992). The cerebellum is known to receive substantial projections from the periphery reflecting joint and limb position (Oscarsson, 1965; Bosco and Poppele, 2001). These projections are thought to be important for movement control, but not needed for perception. More recent work, however, has shown cerebellar projections to cerebral sensory areas, bringing into question whether the cerebellum is involved in sensory perception (Dum and Strick, 2003; Strick et al., 2009). This anatomical data is in line with behavioral and imaging studies that strongly suggest cerebellar involvement in
sensory perceptions based on proprioceptive information (Paulin, 1993; Grill et al., 1994; Gao et al., 1996; Hagura et al., 2009; Bhanpuri et al., 2013).

Recently there have been a few papers showing specific proprioceptive deficits in people with cerebellar damage (Bhanpuri et al., 2012, 2013). Cerebellar patients do not perform as well as controls on active proprioceptive discrimination tasks during an elbow joint movement (Bhanpuri et al., 2013). Yet, these patients can perform normally on passive proprioceptive detection and discrimination tasks (Maschke et al., 2003; Bhanpuri et al., 2013). Healthy people normally show better discrimination on active tasks versus passive tasks. However, when their movements are perturbed by small forces, thus becoming less predictable, healthy people lose the benefits of active movements (Bhanpuri et al., 2013). Taken together, these results are consistent with one idea about cerebellar function—namely that it normally acts to predict the sensory consequences of motor commands. Such a prediction could be useful for both motor control and proprioception (Wolpert et al., 1998; Miall et al., 2007; Bhanpuri et al., 2013).

The finding that cerebellar patients do not update sensory predictions following motor adaption (i.e. learning) tasks is also consistent with cerebellar function in predictive control (Synofzik et al., 2008; Izawa et al., 2012). In both Synofzik et al. (2008) and Izawa et al. (2012), healthy people learned a new visuomotor calibration and also recalibrated their proprioceptive estimates. In contrast, cerebellar patients exhibited a perceptual deficit which resulted in much less proprioceptive recalibration. This is in line with another study which showed that cerebellar patients had comparable proprioceptive realignment to controls during a purely sensory task, but less proprioceptive realignment
during a sensorimotor task (Block and Bastian, 2012). Importantly, Synofzik et al. (2008) and Izawa et al. (2012) both found that cerebellar patients did not have proprioceptive deficits during baseline active movements, accurately assessing the direction of their movements. It is possible that when sensory prediction updates are unnecessary (i.e. during baseline assessments), cerebellar patients do not have proprioceptive deficits when only estimating active movement direction. In contrast, when cerebellar patients have to estimate the length of their active movements, proprioceptive deficits occur (Bhanpuri et al., 2013). This may suggest that cerebellar damage induces varied deficits in distinct aspects of proprioception, with a greater effect on movement extent than movement direction.

We are interested in further characterizing cerebellar proprioceptive deficits, with a particular focus on the ability to localize the hand in space. Proprioceptive localization requires estimates of both movement direction and movement length to pinpoint hand position. Previous studies in healthy people have shown that localization is more precise after active movements than passive movements (Paillard and Brouchon, 1968; Adamovich et al., 1998; Fuentes and Bastian, 2010). Given that the cerebellum is involved in active discrimination (Bhanpuri et al., 2013), it may be used during active movements in localization as well. It follows that people with cerebellar damage may exhibit deficits in localization, yet this has not been tested previously. Knowing where the hand is in space (i.e. localization) is very important for making and calibrating real-life movements, so determining whether localization is affected in cerebellar patients will provide further insight into their motor difficulties. Here we asked if there are active
versus passive proprioceptive localization deficits in people with cerebellar damage compared to healthy people.

2.2 Methods

2.2.1 Subjects

We recruited 18 patients with cerebellar damage for a multi-joint experiment, excluding two for double vision and three for poor passive proprioception, as assessed either on the task or during clinical examination. We retained 13 patients with cerebellar damage but no upper-limb sensory loss (6 women; mean age: 61.3 ± 12.1 years) and 13 age-, gender-, and handedness-matched controls with no known neurological impairments (6 women; mean age: 56.5 ± 10.2 years). We subsequently tested a subset of patients on a single-joint experiment, retaining 10 patients (5 women; mean age: 58.8 ± 11.9 years) and 11 matched controls (5 women; mean age: 57.2 ± 11.8 years). All subjects were tested on their dominant hands, unless the cerebellar damage only affected the non-dominant side (e.g. in the case of unilateral stroke). All subjects gave informed consent to the protocols approved by the Johns Hopkins Institutional Review Board.

The monofilament test, a standard clinical exam, assessed cutaneous mechanoreception on subject index fingertips to ensure no peripheral sensory loss (Campbell, 2005). All subjects in both groups were within the normal range (≤ 0.40 g) (Thornbury and Mistretta, 1981). The level of cerebellar impairment was assessed with the International Cooperative Ataxia Rating Scale (ICARS; Trouillas et al., 1997), which results in higher scores for more impaired patients in posture and gait, limb control (kinetic), speech, and eye movements. For the patients, the mean total ICARS score was
37.8 ± 16.0 (maximum score = 100). For the kinetic portion of the ICARS, which is relevant for arm movements, the mean subscore was 16.4 ± 6.8 (maximum subscore = 52). Additional details about cerebellar patient characteristics are listed in Table 2.1.

2.2.2 Apparatus

For the following tasks, subjects' proprioceptive localization was measured using the KINARM exoskeleton robot system (BKIN Technologies, Kingston, Canada). The shoulder and elbow joints of the robot were aligned with the corresponding joints on the tested arm. The subject’s arm rested in arm trays with the index finger on a Velcro square. The chair height was adjusted for each subject so arm movements occurred in the shoulder-level horizontal plane. During the test blocks, vision of the subject’s arm was blocked with a metal screen unless otherwise stated. All visual feedback was projected onto the screen surface. All subjects in both groups experienced the same conditions.

2.2.3 Procedure

Experiment 1: Multi-joint

Cerebellar patients and controls completed two multi-joint proprioceptive localization tasks to compare passive robot-controlled movement with active self-movement. We tested localization of fingertip position, which requires knowledge of both shoulder and elbow joint angles and is more precise than joint angle estimation (Fuentes and Bastian, 2010). During both tasks, vision of the arm was blocked by a metal screen. At the beginning of each trial, subjects were moved to the start target, located at a shoulder angle of 60° and elbow angle of 90° for each subject. While at the start target, subjects were shown a depiction of their arm position for 2 seconds, including a white line going
<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>DH</th>
<th>Hand Fine Touch (g)</th>
<th>Diagnosis</th>
<th>ICARS Total (/100)</th>
<th>Kinetic (/52)</th>
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<tr>
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</tr>
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<td>37.8 ± 16.0</td>
<td>16.4 ± 6.8</td>
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<td>L = 1</td>
<td>0.25 ± 0.17</td>
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a: subject also completed the single-joint task; b: subject was tested on the L arm due to unilateral damage; Group data are means ± SD; CB, cerebellar patient; CON, control subject; M, male; F, female; DH, dominant hand; R, right; L, left; g, grams; ADCA, autosomal dominant cerebellar ataxia type II or type III; SCA, spinocerebellar ataxia type 6 or type 8; AVM, cerebellar arteriovenous malformation; Sporadic, sporadic adult-onset cerebellar ataxia; ICARS, International Cooperative Ataxia Rating Scale.
from their elbow to the tip of their index finger, to ensure that their estimate of arm position did not drift over time (Figure 2.1B).

During the passive localization task, subjects were told to relax their arm and let the robot move it. EMG signals from the arm muscles were monitored in this task. The robot then moved the subject’s arm along a smooth trajectory (constant max. velocity) to one of the four end targets, arrayed in Cartesian space, 10 cm in X and 10 cm in Y from the center target (Figure 2.1A). Once the subject’s index fingertip was aligned with the end target, a green visual dot (0.5 cm radius circle) appeared in a pseudo-random location 5.7 – 14 cm away from the target. Subjects used a joystick in their non-dominant hand to move the cursor dot in Cartesian space to their felt fingertip location and clicked a button to indicate their position choice.

During the active localization task, subjects were held at the start position until a green target dot (0.5 cm radius circle) appeared at one of the end targets. Then subjects moved their arm, with zero robot forces, to try to place their unseen fingertip on the target dot. Subjects were told that they could make multiple movements to get their fingertip in the correct location. Once subjects felt that their fingertip was aligned with the target, they clicked a button on the joystick to indicate their decision.

For each task, subjects completed 2 sets of 20 trials. If subjects accidentally clicked the button too soon or showed EMG activity during the passive trials, the trial was discarded. If more than two trials at an end target were discarded, subjects completed an additional set containing only the trials that were previously discarded.
Figure 2.1: Task overview. A. Start targets (white) and end targets (green) for the multi-joint and single-joint proprioceptive localization experiments. The multi-joint start target was at shoulder angle $60^\circ$ and elbow angle $90^\circ$. The end targets were (10 cm, 10 cm) away from the start target. The single-joint start target was at elbow angle $60^\circ$, with the shoulder locked at $75^\circ$. The end targets were at elbow angles 30, 45, 75, and $90^\circ$. B. Task protocol: At the beginning of each trial, the subject’s arm was moved to the unseen start target (gray) and a white stick-figure of the arm was displayed for 2 seconds. Then in the passive task the subject’s arm was moved to an unseen end target (gray) and a green cursor dot appeared. The subject controlled a joystick with the non-dominant hand to move the green cursor dot in Cartesian space as pictured (multi-joint) or along the arc of the fingertip path (single-joint). In the active task, once a green dot appeared at one of the end targets, the subject moved their arm to the visual dot. Subjects clicked a button to indicate that they aligned their fingertip and the green target dot. During the first two sets of each task, vision of the arm was blocked. In the third set, subjects completed the same task while viewing their arm.
Subjects then completed one last set of 8 trials with full vision of the arm. This set served as a control task, to document any visual biases and to ensure that subjects were able to manipulate the joystick to place the dot over their fingertip (passive task) and move their arm to a seen location (active task). The passive task was always completed before the active task to prevent subject exposure to seen target positions prior to the passive task. Before starting the experimental sets, subjects were given a practice set and completed trials until they understood the task and were correctly completing it.

Experiment 2: Single-joint

A subset of cerebellar patients and controls subsequently completed single-joint proprioceptive localization tasks with the same task protocols as described in Experiment 1. The shoulder was locked at 75°, so subjects only moved their forearm. Four end targets were at elbow angles 30, 45, 75, 90°, with the start target at 60° (Figure 2.1A). In the passive task, the green cursor dot only moved along the arc of the fingertip path and initially appeared 15-30° from the end target.

2.2.4 EMG Recordings

Electromyographic (EMG) signals were recorded with the Bagnoli EMG system (Delsys, Boston, MA). Surface electrodes were positioned on five muscles in the dominant arm: brachioradialis, biceps brachii, triceps brachii, pectoralis major, and posterior deltoid. An amplifier gain of 10,000 was applied, and the data was sampled at 1 kHz. EMG signals were monitored online during the multi-joint and single-joint passive localization tasks and trials with muscle activity were discarded.
2.2.5 Analysis

We parameterized error in all tasks by measuring both directional accuracy (bias) and precision. In the multi-joint experiment, we worked in a two-dimensional Cartesian coordinate frame and all calculations were done from a right-handed perspective. As a first step, we calculated the visual bias to the 4 targets for each subject, separately for the active and passive conditions, using the reaches where vision was present. Visual bias at each target was calculated as the average vector between the fingertip position, which was visible, and the visual dot. The visual bias was minimal in patients and controls as is reported in the results. We subtracted the visual bias from the active and passive conditions without vision for each target which allowed us to make a purer measurement of proprioceptive localization sense. Second, we calculated the proprioceptive bias to each target as the average vector between the actual fingertip position (unseen) and the perceived fingertip position (i.e. the position of the visual dot). In the single-joint experiment, a one-dimensional task, we calculated both visual and proprioceptive bias as the perceived elbow angle (i.e. the elbow angle based on the visual dot position) minus the actual elbow angle, again subtracting the minimal visual bias from the conditions without vision.

To assess precision in the two-dimensional space (multi-joint), we computed a 95% confidence ellipse (CE) of the average error at each target location. These can be visualized in Figure 2.2. The CE axes are proportional to the eigenvalues of the variance-covariance matrix, so the area of each CE encompasses the two-dimensional variance at that target (Desmurget et al., 2000; Johnson and Wichern, 2007). To measure each subject’s precision, we calculated the CE area at each end target and then averaged across
Figure 2.2: Representative single subject plots for the multi-joint localization experiment. A. Cerebellar 7, from the impaired subgroup, showed no difference in precision between the passive and active task, as seen by the similar-sized 95% confidence ellipses (CE) of the average error. Cerebellar 10, from the unimpaired subgroup, and the Control had smaller CE for the active task than the passive task, indicating better active precision. B. Importantly, the cerebellar patients performed as well as the control when vision was allowed, suggesting that visual and motor deficits were not limiting factors.
the four end targets. To assess precision in the one-dimensional space (single-joint), we calculated the variance in elbow angle at each of the four end targets and averaged across targets for each subject.

We then determined whether subjects showed active benefit (i.e. improved performance in the active task compared to the passive task), which has been seen in previous proprioceptive studies (Paillard and Brouchon, 1968; Adamovich et al., 1998; Fuentes and Bastian, 2010; Bhanpuri et al., 2013). However, in both of our experiments there was large between-subject variability in passive precision. In order to better compare the amount of active benefit between subjects, we normalized each subject’s active precision to their passive precision by taking a ratio of active precision over passive precision. A ratio close to 1 indicated minimal active benefit, whereas smaller ratios indicated more active benefit. To confirm that both patients and controls showed active benefit, we calculated a confidence interval of each group’s average ratio. The confidence intervals were bootstrapped using 100,000 replications, the BC$_a$ (bias corrected and accelerated percentile) method, and a 99% confidence level (DiCiccio and Efron, 1996). If the confidence interval did not contain 1, the group showed active benefit. To test whether there was a difference in active benefit between groups, we performed a $t$-test for independent samples.

To further investigate the differences in performance in the patient population during the multi-joint experiment, we compared each cerebellar subject’s ratio to the upper bound of the control confidence interval. If patients were below the upper bound, they were classified as unimpaired; if they were above the upper bound, they were classified as impaired. These groups were then used to compare performance within the
patient group for the single-joint experiment. To determine whether the difference between groups was maintained in the single-joint experiment, we performed a nonparametric Kruskal-Wallis ANOVA (3 groups). Post hoc comparisons were done using the Mann-Whitney U test.

2.3 Results

In the first experiment we tested whether cerebellar patients and control subjects performed differently in passive or active proprioceptive localization in a multi-joint movement task. In the passive task, subjects had to localize their unseen fingertip by moving a visual cursor to the location where they felt their finger was moved by the robot. In the active task, subjects had to move their unseen fingertip to place it underneath a stationary visual target. Figure 2.2A shows sample endpoints for three subjects. A CE of the mean error at each target was calculated for individual subjects. Smaller CEs indicate better precision. Note that the CEs for the control subject were smaller for the active endpoints than the passive endpoints. In the cerebellar subjects, some showed CEs comparable to controls (Cerebellar 10), whereas others had similar-sized CEs across the two tasks (Cerebellar 7). Regardless, all subjects were able to perform localization in the full vision condition (i.e. when they could see their finger and the visual cursor; average group error with vision: patients: passive 1.15 ± 0.05 cm SEM, active 0.80 ± 0.02 cm; controls: passive 0.79 ± 0.03 cm, active 0.75 ± 0.02 cm). This control condition was tested to make sure that subjects did not have any fundamental motor or visual problem that could have interfered with the passive or active proprioceptive tasks. Sample endpoints with vision are shown in Figure 2.2B.
Subject bias, or directional accuracy, varied from subject to subject in both direction and extent (Figure 2.3B). However, averages showed a consistent and weak directional trend across tasks and groups—there was no difference between cerebellar patients and controls (Figure 2.3C). Note that all bias was calculated from the right-handed perspective. In addition, bias vectors ran in opposite directions for the passive and active tasks—subjects moved the index finger too far and to the left in the active case, and moved the cursor too short and to the right in the passive case (Figure 2.3A). This means that subjects tended to think their fingertip was closer to them and rightward of their actual fingertip position (Figure 2.3C). This is consistent with previous studies reporting bias (Crowe et al., 1987; Wilson et al., 2010).

Figure 2.4A shows the precision measurement for every subject tested in the passive and active conditions. In the passive precision (open bars) there was no significant difference between cerebellar patients and controls (t-test, t(24) = 1.14, p > 0.26). However, there was high variability in passive precision across subjects, which made it difficult to compare active benefit. To allow for better between subjects comparison of active benefit, we normalized active benefit to passive precision by taking a ratio of the average CE area for the active task compared to the passive task (Figure 2.4B). All but two control subjects had a ratio below 0.50—they had much better precision on the active task, as expected (Adamovich et al., 1998; Fuentes and Bastian, 2010). The two subjects with higher CE ratios also had the best passive precision, so it is possible that they hit a ceiling on their performance. In other words, rather than indicating lower active benefit, the higher CE ratios reflected better passive precision. The
Figure 2.3: Directional accuracy (bias) across targets for the multi-joint localization experiment. A. Bias was calculated as the average vector between the actual fingertip position (unseen) and the perceived fingertip position (i.e. the position of the green visual dot — target or cursor depending on the task). In the active task, subjects were asked to move their fingertip directly under the green target dot. They tended to move the index finger too far and further left of the green target dot, which suggests that they thought their hand was closer to them and to the right. In the passive task, subjects moved the green cursor dot too short and further to the right of their stationary fingertip. This also shows that they thought their hand was closer to them and to the right. Thus, the bias is the same for the passive and active tasks, even though the bias vectors point in opposite directions. B. Each vector represents an individual cerebellar patient’s (blue) or control subject’s (black) average bias for that target. C. Average group bias was consistent across the target workspace and across patients and controls. On average, subjects thought their fingertip was closer to them and rightward of its actual position (right-handed perspective).
Figure 2.4: Individual subject precision for the multi-joint localization experiment. A. Subject precision (average CE area) for the passive and active tasks. Both the cerebellar patients (blue) and the control subjects (black) showed varying passive precision, but most subjects had at least some active benefit. B. Normalized active benefit to each subject’s passive precision. The CE ratio was calculated as active precision over passive precision, with values close to 1 indicating no active benefit and smaller values indicating more active benefit. Patients showed more variability in CE ratio than controls. The upper bound of the control group’s 99% confidence interval (red dotted line) was used to split patients into two subgroups. Patients over the line were impaired (n = 6), whereas patients under the line were unimpaired (n = 7).
cerebellar patients had more variable CE ratios, ranging from 0.15 to 1.17, with 11 of the 13 patients below 0.82.

Thus, both groups showed clear active benefit, with the upper bound of the confidence interval below 1 (controls: 0.60, patients: 0.78). In addition, there was no significant difference in CE ratio between the patients and controls ($t$-test, $t(24) = 1.30, p > 0.20$; Figure 2.5A). We did not expect any patients to show active benefit, yet the majority of patients had at least some active benefit. However, this did not seem to fully quantify what occurred in the patients. While it is clear that about half of the patients had active benefit to the same level as controls, other patients did not have as much active benefit.

To look at this within group difference, we classified patients into two subgroups by comparing them to the upper bound of the control subject confidence interval (red dotted line at 0.60) around the average CE ratio (Figure 2.4B). Seven patients had a ratio below the upper bound—they had active benefit comparable to controls and were unimpaired. Six patients had a ratio above the upper bound—they had reduced active benefit compared to controls and were impaired. The split group averages showed that there were distinct differences in performance within the patient group (Figure 2.5B). Despite differences in active benefit among the patients, there was no particular diagnosis or distinguishing symptom identifying those with reduced active benefit. Specifically, ICARS scores (total and kinetic) were not correlated with CE ratio (all $p > 0.81$).

To verify that these results were not explained by the difficulty cerebellar patients have with inter-joint coordination (Bastian et al., 1996), we did a second experiment
Figure 2.5: Group averages of normalized active benefit for the multi-joint and single-joint localization experiments. A. Normalized active benefit with all cerebellar patients grouped together. There was no significant difference between patients and controls for either the multi-joint or single-joint experiments (all $p > 0.20$). In addition, all confidence intervals of the group averages had an upper bound below 1, indicating that patients and controls showed active benefit in both experiments. B. Normalized active benefit for the cerebellar patients when split into two subgroups. In the multi-joint experiment, the impaired subgroup ($n = 6$) was outside the control confidence interval for normalized active benefit, whereas the unimpaired subgroup ($n = 7$) was inside the confidence interval. In the single-joint experiment, subjects were grouped according to the multi-joint split. The impaired subgroup ($n = 5$) was significantly worse than the unimpaired subgroup ($n = 5$) and the controls (all $p < 0.03$). Error bars indicate SEM.
using single-joint movement. Here, the shoulder was locked in place, leaving only the elbow joint free to move. Subjects were again asked to localize their fingertip during both passive and active movement. In the passive task, subjects moved a cursor constrained along an arc to their unseen fingertip. In the active task, subjects moved their forearms to a stationary visual target. As in the multi-joint task, all subjects were able to perform the single-joint localization task with full vision (Average group error with vision: patients: passive 0.88 ± 0.09° SEM, active -0.76 ± 0.08°; controls: passive 0.21 ± 0.07°, active 0.05 ± 0.07°). Single-joint bias varied across targets, which is consistent with a previous localization study (Fuentes and Bastian, 2010). Control subjects exhibited the expected bias (passive bias at elbow angle targets 30, 45, 75, and 90°: -5.76 ± 0.58° SEM, -5.20 ± 0.46°, 3.58 ± 0.49°, 3.87 ± 0.51°; active: -4.52 ± 0.26°, -1.42 ± 0.24°, 0.99 ± 0.45°, 4.20 ± 0.55°), with overextension to extension targets (i.e. negative error to target angles 30° and 45°) and overflexion to flexion targets (i.e. positive error to target angles 75° and 90°). While cerebellar patients presented a similar bias trend, they had a small offset in extension (~3.5°) at all targets (passive bias at elbow angle targets 30, 45, 75, and 90°: -8.47 ± 0.84° SEM, -8.47 ± 0.83°, -2.38 ± 0.64°, -1.09 ± 0.66°; active: -8.22 ± 0.61°, -4.43 ± 0.45°, -1.52 ± 0.40°, 0.97 ± 0.53°).

Similar to experiment 1, both the control and patient groups again showed a clear active benefit, with the upper bound of the confidence interval below 1 (controls: 0.59, patients: 0.85). Normalized active benefit in the single-joint experiment did not differ significantly between patients and controls (t-test, t(19) = 1.17, p > 0.25; Figure 2.5A). The patient group was then split based on the experiment 1 classification, with five patients in the unimpaired subgroup and five patients in the impaired subgroup. Within
each subgroup, three patients showed either the same or a slightly worse variance ratio (max decrease 0.15) in the single-joint experiment compared to the multi-joint experiment. However, two patients in each subgroup showed more active benefit in the single-joint experiment compared to the multi-joint experiment, improving their ratio by 0.20 or more. ANOVA of variance ratios in the single-joint task between the two patient subgroups as well as controls resulted in a significant main effect of group (Kruskal-Wallis ANOVA $H(2,21) = 7.45, p < 0.03$). Post-hoc analysis showed this effect to be driven by the impaired patient subgroup performing worse than both the unimpaired patient subgroup and controls (Mann-Whitney U test, $p < 0.03$). Thus, it is unlikely that inter-joint coordination deficits were the main contributor to the impairments exhibited by cerebellar patients in the multi-joint localization task.

2.4 Discussion

In two experiments, we compared proprioceptive localization during both active and passive movement between individuals with cerebellar damage and healthy controls. Our aim was to determine the extent of cerebellar involvement in the localization process. We developed a test of the proprioceptive ability necessary for everyday movements by using a localization task that involved both multi-joint movements and vision. The ability to correctly estimate limb state is essential for the generation of appropriately calibrated motor commands as well as the updating of those commands in response to changing task requirements. Our results showed that while some cerebellar patients had deficits in proprioception during active, multi-joint movements, others did not. Specifically, the patients who did show proprioceptive deficits did so in the precision of localization rather
than bias. Importantly, this within group distinction could not be explained by patient
diagnosis or clinical ratings of impairment.

The division we found in the patient group’s performance is interesting. The
tendency for cerebellar patients to exhibit localization impairments in active, multi-joint
movements was not correlated with clinical ataxia ratings as assessed by the ICARS total
score and kinetic function (limb coordination) subscore. Furthermore, the presence or
absence of localization impairment could not be explained by differential diagnoses (e.g.
degenerative disease vs. cerebellar stroke). Importantly, all patients were pre-screened
using standardized clinical tests of fine-touch sensation as well as proprioception in the
upper extremities (Campbell, 2005). These findings indicate the presence of sensory
deficits following cerebellar damage that are not adequately detected by current clinical
measures of disease type and progression. This is a significant finding because, while
cerebellar damage is well known to impair motor coordination, the precise mechanism
underlying these impairments remains unclear. The ability to accurately sense limb
position is important for the selection and calibration of motor commands (Miall et al.,
2007). Thus, impairments in limb localization are likely to contribute to the motor
symptoms of ataxia.

Bastian et al. (1996) showed that cerebellar damage results in an impaired ability
to compensate for the interaction torques generated in multi-joint movements. These
impairments could have reasonably contributed to the proprioceptive deficits seen in our
patients in the multi-joint localization task. To investigate this possibility, we examined
patient performance in a single-joint localization task that had participants estimate
fingertip position moving only the forearm (i.e. the shoulder angle was locked at 75°).
The performance of some patients improved in the single-joint task (i.e. these patients showed more active benefit in the single-joint compared to the multi-joint task). However, when the patient group was split into the impaired and unimpaired subgroups based on their performance in the multi-joint task, we found that the impaired subgroup continued to show less active benefit in the single-joint task. Therefore, it is unlikely that the localization impairment found in some patients resulted from multi-joint coordination deficits following cerebellar damage.

Our work provides important insights into cerebellar contributions to the proprioceptive localization literature not previously seen in other studies. Studies by Synofzik et al. (2008) and Izawa et al. (2012) focused on cerebellar involvement in updating the sensory consequences of movement. When establishing baseline proprioceptive abilities in cerebellar patients, these authors tested proprioception in terms of movement direction only, and not movement extent. It was clear from these studies that patients did not have deficits in identifying the direction of their movements, as the bias and precision of their directionality estimates was comparable to age-matched controls (Synofzik et al., 2008; Izawa et al., 2012). Here we have shown that patients do not have difficulties with directionality in proprioceptive localization. However, examining performance in a localization task that required subjects to pinpoint their fingertip position (vs. movement direction only) allowed us to calculate a two-dimensional measure of precision. This analysis revealed that a subset of cerebellar patients exhibited deficits in active proprioceptive precision despite showing localization biases comparable to control participants. Overall, this suggests that cerebellar damage may differentially impair component elements of proprioceptive sense.
Previous work from our lab by Bhanpuri et al. (2013) found that cerebellar patients showed clear impairments in a single-joint proprioceptive discrimination task. While these results may seem to contradict those of the present study, distinctions in the experimental protocols used may explain these differences. Our task involved matching the positions of a visual stimulus to a sensed limb position. In other words, our task used a combination of visual and proprioceptive information. In contrast, the task used by Bhanpuri et al. (2013) relied solely on proprioception. Block and Bastian (2012) showed that cerebellar patients are not impaired in their ability to integrate visual and proprioceptive signals. Thus, the use of vision in the present experiment may have allowed other brain areas to compensate for any cerebellar dysfunction. Given that integration of visual and proprioceptive information improves position estimates (van Beers et al., 1999, 2002), this could reasonably explain the varying results in different proprioceptive tasks.

However, a more likely possibility for the difference in findings of the present study and those of Bhanpuri et al. (2013) comes from the proprioceptive assessments used. Previous literature has shown that cerebellar patients exhibit proprioceptive recalibration deficits in tasks where updating of sensory predictions is required (Synofzik et al., 2008; Izawa et al., 2012). In tasks assessing baseline proprioceptive ability, cerebellar patients show deficits when estimating movement length (Bhanpuri et al., 2013), but not movement direction (Synofzik et al., 2008; Izawa et al., 2012). This suggests that the cerebellum may be more involved in proprioceptive estimates that have a temporal or predictive component (e.g. movement length), but that it may be less involved in generating estimates with only a spatial component (e.g. movement length).
direction). The proprioceptive localization assessed in our task required estimating both movement direction and length. In other words, our task tested proprioceptive estimates with both spatial and temporal components. It is possible that some of our patients relied more heavily on the spatial component when generating their proprioceptive estimates and this could have improved their performance. Conversely, the task used by Bhanpuri et al. (2013) tested proprioceptive estimates that were largely reliant on the temporal component, which could underlie their finding of widespread proprioceptive deficits in the cerebellar patient group. We are currently investigating whether relying on spatial or temporal information differentially influences proprioceptive estimates of limb position as well as the precise role of the cerebellum in processing this information.

In summary, we have shown that some people with cerebellar damage have increased variability in proprioceptive localization during active movements and that this cannot be explained by current tests of clinical impairment. Given that precise estimates of limb position are important for keeping movements well calibrated, deficits in localization likely affect movement ability in daily life. It follows that localization ability should not only be an important consideration during clinical testing of people with cerebellar damage, but should also be taken into account when developing rehabilitation strategies.
Chapter 3

The cerebellum contributes to proprioception during motion

3.1 Introduction

Proprioception is the perception of body position and movement in the absence of vision. It is vital for making accurate reaching movements—without proprioception large errors in movement occur (Ghez et al., 1995; Gordon et al., 1995). Many studies have shown that proprioception, once considered a single sense, can be divided into two distinct senses: limb position and limb motion (Sittig et al., 1985; Proske and Gandevia, 2009, 2012). Evidence for classification of proprioception into two senses includes the capacity to alter the perception of position without changing the perception of motion (Brown et al., 2003; Allen and Proske, 2006), as well as the observation that some cortical neurons only fire for position or motion (Kurtzer et al., 2005). Another distinction often made between the two senses is that limb motion is a dynamic sense,
whereas limb position is a static sense. In fact, if a limb is moved slowly enough, instead of feeling a velocity, subjects will simply feel a change in position (McCloskey, 1973).

Accordingly, the perception of limb position is most often assessed in static situations, where subjects are asked to estimate the fixed position of a limb in space (see studies reviewed in Proske and Gandevia, 2009). Yet recent work suggests that limb position sense should also be thought of in dynamic situations (Goble and Brown, 2009; Yousif et al., 2015). One example of this would be asking a subject to assess where they think that their limb was during a movement—(i.e. were you to the left or right of a fixed target?). In this type of task, only spatial position information is relevant despite the fact that the limb is moving. However, in most natural situations, it is necessary to estimate the position of our hand “on the fly” during a movement. This is clearly a more complicated estimate, which necessarily relies on position and velocity sense (i.e. spatial and temporal information).

There are no studies that directly compare proprioceptive ability in tasks with spatial versus temporal-spatial information. However, work in the visual domain suggests that these two information sources are processed via different neural circuits. Tasks with a temporal component seem to rely on cerebellar processing, whereas those with only a spatial component do not (Ivry and Diener, 1991; O’Reilly et al., 2008; Roth et al., 2013). In line with this, Grill et al. (1994) found that individuals with cerebellar damage have deficits in passive proprioceptive discrimination of movement velocity, which requires updating estimates of limb position over time, but not in discrimination of movement amplitude, which requires assessing the difference between two spatial positions. Interestingly, Bhanpuri et al. (2013) found that discrimination of movement amplitude
was impaired in cerebellar patients when movements were actively generated. Taken together, these results suggest that proprioceptive judgments relying on temporal information may be cerebellum dependent, but it remains unclear how the cerebellar processing of these two sources of sensory information might differ between active and passive movement.

Here we examined the sense of limb position in a dynamic proprioceptive task. First, we sought to quantify proprioceptive acuity, using passive robot-controlled movements to control for variable motor control between subjects. Second, we sought to assess dynamic proprioceptive acuity in both active, self-generated movement and passive movement as well as assay the effects of cerebellar damage. By comparing participants’ ability to judge the position of a visual cursor relative to their unseen hand, we found that regardless of movement direction, proprioceptive acuity is better when assessed orthogonal to movement direction (i.e. when only spatial information is relevant) versus in line with movement direction (i.e. when both spatial and temporal information are important). Additionally, when proprioceptive acuity is assessed in line with movement direction, subjects’ performance improved when relying on temporal cues versus spatial cues. Furthermore, cerebellar damage impairs dynamic proprioceptive acuity during both active and passive movement and this is most apparent when proprioceptive judgments rely on temporal information about limb movement.
3.2 Methods

3.2.1 Subjects

All subjects gave informed consent and protocols were approved by the Johns Hopkins Institutional Review Board. For Experiment 1 we recruited a total of 25 right-handed subjects, ranging in age between 18-33. These subjects were divided into 2 groups each performing different experimental tasks. Group 1 performed 4 tasks (8 females, 4 males, mean age: 25.8 ± 3.9 years). Group 2 performed 2 tasks (7 females, 6 males, mean age: 25.1 ± 4.5 years). For Experiment 2 we recruited 11 patients with cerebellar degeneration and 13 healthy controls matched for age and gender (patients: 3 females, 8 males, mean age: 62.0 ± 10.5 years; controls: 3 females, 10 males, mean age: 62.5 ± 9.6 years). All subjects in Experiment 2 had cutaneous mechanoreception assessed with the monofilament test, a standard clinical exam done on the index fingertips to assess peripheral sensory loss (Campbell, 2005). All cerebellar patients were within the normal range for cutaneous mechanoreception (≤ 0.40 g) (Thornbury and Mistretta, 1981). One older control subject exhibited mild sensory loss due to a cervical spinal fusion; however, clinical proprioceptive tests were normal. Cerebellar patient movement impairments were assessed using the International Cooperative Ataxia Rating Scale (Trouillas et al., 1997). Further details about patient characteristics and other participants are presented in Table 3.1.

3.2.2 Apparatus and Task Considerations

All experimental tasks were performed using the KINARM exoskeleton robot system (BKin Technologies, Kingston, Canada; Scott, 1999). The subject’s arm was supported
**Table 3.1**: Subject characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>DH</th>
<th>Hand Fine Touch (g)</th>
<th>Diagnosis</th>
<th>ICARS Total (/100)</th>
<th>Kinetic (/52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB1</td>
<td>M</td>
<td>61</td>
<td>R</td>
<td>0.16</td>
<td>SCA 6/8</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>CB2</td>
<td>F</td>
<td>66</td>
<td>R</td>
<td>0.07</td>
<td>ADCA III</td>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>CB3</td>
<td>M</td>
<td>63</td>
<td>R</td>
<td>0.40</td>
<td>ADCA III</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>CB4</td>
<td>M</td>
<td>80</td>
<td>R</td>
<td>0.16</td>
<td>ADCA III</td>
<td>45</td>
<td>23</td>
</tr>
<tr>
<td>CB5</td>
<td>M</td>
<td>76</td>
<td>R</td>
<td>0.16</td>
<td>Sporadic</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>CB6</td>
<td>M</td>
<td>43</td>
<td></td>
<td>0.04</td>
<td>SCA 8</td>
<td>59</td>
<td>22</td>
</tr>
<tr>
<td>CB7</td>
<td>M</td>
<td>53</td>
<td>R</td>
<td>0.40</td>
<td>SCA 7</td>
<td>49</td>
<td>15</td>
</tr>
<tr>
<td>CB8</td>
<td>F</td>
<td>64</td>
<td>R</td>
<td>0.16</td>
<td>SCA 6</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>CB9</td>
<td>M</td>
<td>63</td>
<td>L</td>
<td>0.16</td>
<td>SCA 6</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>CB group</td>
<td>F = 2/9</td>
<td>63.2 ± 11.0</td>
<td>L = 2</td>
<td>0.19 ± 0.13</td>
<td>42.0 ± 17.7</td>
<td>15.6 ± 7.8</td>
<td></td>
</tr>
<tr>
<td>OC group</td>
<td>F = 3/10</td>
<td>60.9 ± 9.7</td>
<td>L = 0</td>
<td>0.41 ± 0.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YC group 1</td>
<td>F = 6/10</td>
<td>25.9 ± 4.3</td>
<td>L = 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YC group 2</td>
<td>F = 6/10</td>
<td>25.4 ± 5.0</td>
<td>L = 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group data are means ± SD; CB, cerebellar patient; OC, older control subject; YC, younger control subject; M, male; F, female; DH, dominant hand; R, right; L, left; g, grams; ADCA, autosomal dominant cerebellar ataxia type III; SCA, spinocerebellar ataxia types 6, 7, and 8; Sporadic, sporadic adult-onset cerebellar ataxia; ICARS, International Cooperative Ataxia Rating Scale.
by trays, with the index finger resting on a Velcro square. The shoulder and elbow joints of the subject’s arm were aligned with the corresponding joints on the robot. Arm movements were made in the horizontal plane below a screen which blocked vision of the arm. The projection of the visual feedback onto the screen was calibrated to appear in the same plane as the subject’s arm. Furthermore, the visual display’s inherent lag was compensated for.

In order to assess the necessary range of perceptual shifts, both a large movement length and long movement duration were needed. Consequently, movement velocity needed to be slower than during a typical reaching movement. We specified both movement length and duration during the passive and active tasks, training subjects in the active task to make slow, continuous movements of the correct duration. During active movements at slow speeds, velocity profiles are multi-peaked rather than bell-shaped, resulting in extended time spent near peak velocity. Given this, a constant velocity profile was used for the passive movement rather than a bell-shaped velocity profile.

3.2.3 Procedure

Experiment 1

To assess the differences in proprioceptive acuity due to available proprioceptive information and movement direction, subjects in group 1 performed two tests of proprioceptive acuity during passive robot-controlled movement. One test required estimating limb position in the direction of movement (the temporal inline task) and the other required estimating limb position orthogonal to movement direction (the spatial orthogonal task). Subjects performed the temporal inline and spatial orthogonal tasks
twice over two days to assess different movement directions. In one session participants were moved parallel to the x-axis from left to right (Figure 3.1A). In the other session they were moved parallel to the y-axis from the bottom of the task space to the top. Task order and movement direction order were counterbalanced across subjects.

A trial began with the robot passively moving a subject’s right index finger to the start position. A visual cursor representing the position of the index fingertip (0.5 cm radius blue circle) was then shown for 3 s to ensure that the subject’s estimate of arm position did not drift over time. After this the visual cursor was extinguished for the remainder of the trial. The robot then passively moved the subject’s hand at a constant velocity of 9 cm/s for 3 s (preceded by a 500 ms ramp-up and followed by a 500 ms ramp-down). After constant velocity was reached, a visual dot (0.5 cm radius white circle) appeared on the screen for 600 ms, moving at the same velocity as the subject’s fingertip. The precise timing of this appearance during the constant velocity movement was randomized from trial to trial to prevent the subject from anticipating the dot’s presentation. Subjects were told that the dot represented their index fingertip, but that its position had been shifted relative to their actual fingertip position. They were asked to compare the movement of the dot to the perceived movement of their fingertip.

In the temporal inline task the visual dot’s movement was spatially in line with the subject’s fingertip movement, but its position was shifted in time to appear either too early (i.e. ahead of the fingertip) or too late (i.e. behind the fingertip) (Figure 3.1B). 9 different temporal shifts were tested in a randomized order (-800, -600, -400, -200, 0, 200, 400, 600, 800 ms relative to the fingertip). On each trial, subjects were instructed to
Figure 3.1: Task flow and feedback shifts for x-axis movements. A. Passive tasks: Subjects are moved to the start position. A blue visual dot appears for 3 seconds to show their actual index fingertip position. During the rightward movement, subjects are shown shifted feedback (white dot) for 600 ms. Active tasks: Subjects are moved to the start position and must hold their fingertip there. While in the start target, their actual index fingertip position is shown by a blue visual dot for 3 seconds. Once it disappears, subjects may start their movement, and are constrained to x-axis movements by a force channel. Shifted feedback (white dot) appears for 600 ms during the movement. They continue their movement until they hit the unseen end target and are stopped by the robot. B. Temporal inline feedback shifts (x-axis movements): During the rightward movement, the white visual dot is shifted early or late in time compared to the actual index fingertip trajectory. C. Spatial orthogonal feedback shifts (x-axis movements): During the rightward movement, the white visual dot is shifted either up or down from the actual index fingertip position.
verbally report whether they felt the dot was shifted “early” or “late” relative to their fingertip. In order to implement the early time shifts, each time shift was multiplied by the constant velocity to calculate the corresponding position shift. For consistency, the same procedure was subsequently used for the late time shifts.

In the spatial orthogonal task the visual dot was presented temporally in line with the fingertip movement, but its position was shifted in space orthogonal to the fingertip movement direction. 9 spatial shifts were tested in a randomized order (-30, -20, -13, -7, 0, 7, 13, 20, 30 mm). Here, subjects were instructed to verbally report whether they felt the dot was shifted “up” or “down” (x-axis movement, Figure 3.1C) or “left” or “right” (y-axis movement) relative to their fingertip.

Both the temporal inline and spatial orthogonal tasks used a two alternative forced choice design with the method of constant stimuli. Subjects completed 12 trials at each shift for a total of 108 trials per task. Each task was split into 6 blocks of 18 trials and subjects received breaks between each block. Before starting each task, subjects were given a practice block with larger shift values than in the experimental blocks (temporal shifts of ± 1000 ms, spatial shifts of ± 40 mm), and completed trials until they understood the task and were correctly completing it.

To assess whether proprioceptive acuity in the temporal inline task changed when attending to spatial or temporal cues, a second group of subjects completed both the spatial orthogonal and temporal inline tasks with movement in the x-axis as described above. However, for this group of subjects the temporal inline task directions were changed. Here, subjects were told that the dot had been shifted to the right or left, instead
of early or late, relative to the index fingertip. This served to cue them to spatial signals, rather than temporal signals, to estimate limb movement. The data from these subjects was compared to the x-axis movement data from group 1.

**Experiment 2**

The objectives of this experiment were twofold. First, we sought to assess the influence of active movement on performance of the two dynamic proprioception tasks studied in Experiment 1. Second, we sought to study the contribution of the cerebellum to the dynamic proprioception tasks by comparing the performance of individuals with cerebellar damage and healthy controls matched for age and gender. In two sessions, on separate days, subjects completed the temporal inline and spatial orthogonal tasks during passive, robot-controlled movement, as well as during active, self-generated movement. Movement condition (passive vs. active) and task order (temporal inline vs. spatial orthogonal) were counterbalanced across subjects. Results from Experiment 1 revealed no effect of movement direction (x-axis movement vs. y-axis movement); therefore, subjects in Experiment 2 performed movements along the x-axis only.

The passive movement condition for both the temporal inline and spatial orthogonal tasks was completed as indicated for Experiment 1 with two additional temporal shifts and spatial shifts in each task, respectively. This resulted in 11 temporal shifts (0, ±200, ±400, ±600, ±800, ±1000 ms relative to the fingertip) and 11 spatial shifts (0, ±7, ±13, ±20, ±30, ±40 mm relative to the fingertip position) that were tested in a randomized order within each task. Each task was split into 6 blocks of 22 trials for a total of 132 trials per task. Prior to beginning each task, participants were given a practice
block with larger shift values than those in the experimental blocks (temporal shifts of ±1200 ms, spatial shifts of ±50 mm).

The active movement condition differed from the passive movement condition in that subjects now actively generated the movement of the fingertip along the x-axis. To ensure that all subjects were able to perform the active movement at the desired movement speed, subjects performed 50 trials of the movement only before beginning the perceptual tasks, and were given feedback about their movement duration.

A trial in the active movement condition began with the robot passively moving a subject’s right index finger to the start position (shown as a red circle with a 1.5 cm radius). The subject was then required to actively hold their finger in the start position for 3 s, during which time a visual cursor representing the position of the index finger was shown (0.5 cm radius blue circle). After 3 s both the visual cursor and the start position were extinguished, which cued the subject to begin the active movement along the x-axis. During this movement, an unseen force channel was put in place to prevent any movement of the fingertip that was not in the direction of the x-axis. On each trial, subjects were instructed to move slowly and continuously to the right until they hit an unseen wall (i.e. were stopped by the robot). While subjects were actively moving, a shifted visual dot (0.5 cm radius white circle) appeared on the screen and moved at the same velocity as the subject’s fingertip for 600 ms, disappearing before the movement ended.

The active movement condition of the spatial orthogonal task employed the same spatial shifts as in the passive movement condition. The active condition of the temporal
inline task employed temporal shifts of 0, ± 200, ± 400, ± 600, ± 800 ms, with temporal shifts of ± 1000 ms used for the practice block. As in the passive condition, each time shift was multiplied by the velocity to calculate the corresponding position shift. In order to maintain consistency across subjects regardless of their movement velocity, the constant velocity from the passive task used.

In all tasks, trials where subjects did not see the visual dot, or moved inappropriately during the active tasks (e.g. stopped during the movement or moved too fast, causing the dot to cut off early), were repeated.

3.2.4 EMG Recordings

Electromyographic (EMG) signals were recorded with the Bagnoli EMG system (Delsys, Boston, MA). Surface electrodes were positioned on five muscles in the right arm: brachioradialis, biceps brachii, triceps brachii, pectoralis major, and posterior deltoid. An amplifier gain of 10,000 was applied, and the data was sampled at 1 kHz. During the passive practice trials, EMG signals were monitored online, and subjects were told to relax their arm more if resisting the robot. EMG signals continued to be monitored online throughout all passive tasks to ensure passive behavior.

3.2.5 Analysis

Subjects who could not complete the experiment (e.g. judgments of visual dot position were not different from chance for all shifts) or who had persistent EMG activity during the passive movement were excluded from analysis. This affected data for 3 subjects in Experiment 1, and 2 control subjects and 1 cerebellar patient in Experiment 2.
Data from one additional cerebellar patient was excluded from analysis due to the presence of extracerebellar signs in the clinical exam.

The spatial orthogonal task used position shifts, whereas the temporal inline task used time shifts. In order to compare orthogonal and inline tasks, all shift values had to be represented in the spatial domain. To do this the temporal shifts were multiplied by the movement velocity (9 cm/s). The proportion of trials where a subject reported the visual dot to be “early” (in the temporal inline task with temporal cues), “up” (in the spatial orthogonal task with movement along the x-axis), or “right” (in the temporal inline task with spatial cues and spatial orthogonal task with movement along the y-axis) relative to the finger was determined for each shift value. The data were then fit with a psychometric (logistic) function (Wichmann and Hill, 2001). Individual subject fitting was done for each task and movement direction. If a subject had even one poor data fit, their data was discarded from analysis (Experiment 1: 2 subjects; Experiment 2: 1 control subject discarded after day 1; for poor fit criteria see Wichmann and Hill, 2001). Overall, less than 2.1% of all fits were poor.

From the fitted psychometric function, we calculated two measures to quantify a subject’s sensory predictions, point of subjective equality and just noticeable difference. The point of subjective equality, or bias, is where a subject perceives the visual dot to be aligned with their fingertip. In other words, the bias is the point on the psychometric function equal to a 50% probability (e.g. subjects respond “early” for half the trials and “late” for the other half). To assess bias in both experiments, a one-sample t-test was run on each task’s average group bias to determine whether it was significantly different from zero. In addition, in Experiment 2 a mixed-model ANOVA was used to compare bias in
cerebellar patients and controls separately in the passive tasks and active tasks, with a between subjects factor of group (cerebellar patients, controls) and a within subjects factor of task (spatial orthogonal, temporal inline).

Just noticeable difference (JND), a measure of proprioceptive acuity, quantifies the steepness of the psychometric function. It is calculated as the difference between the 50% and 75% probabilities on the psychometric function. A smaller JND indicates better acuity. To compare JNDs in Experiment 1, a repeated-measures ANOVA was used for group 1, with factors of task (spatial orthogonal, temporal inline) and movement direction (x-axis, y-axis). A mixed-model ANOVA was used for group 2, with a between subjects factor of group (group 1, group 2) and a within subjects factor of task (spatial orthogonal, temporal or spatial inline). To compare JNDs between cerebellar patients and control participants in Experiment 2, mixed-model ANOVAs were used in the passive and active movement conditions, with a between subjects factor of group (cerebellar patients, older controls) and a within subjects factor of task (spatial orthogonal, temporal inline). Post hoc analysis of interactions was done using tests of simple effects. Statistical analysis was completed using Statistica (StatSoft, Tulsa, OK) and SPSS (IBM, Armonk, NY).

3.3 Results

3.3.1 Experiment 1

Here we assessed proprioceptive acuity in two tasks requiring dynamic estimates of limb position. In both tasks, a robot passively moved participants’ hands along a path that paralleled either the x- or y-axis of the task space. The temporal inline task required participants to report the position of a visual dot that was shifted in time along the
movement path relative to their index finger. Conversely, the spatial orthogonal task required participants to report the position of a visual dot that was shifted in space, orthogonal to the movement path, relative to their index finger. A range of temporal and spatial shifts were tested for the two tasks, respectively, and the reported positions of the visual dot on each trial were used to generate a psychometric function for each subject in each task. From these functions we determined each subject’s proprioceptive bias and JND for each movement direction in each task.

Figure 3.2A shows individual fitted psychometric functions for an example subject. Note that in all four tasks there are multiple points at or near both zero and one, indicating that this subject was consistently able to correctly identify the largest temporal and spatial shifts. The 50% probability point for this subject’s psychometric function is close to zero, which means that they did not have any substantial bias in their perception. However, the psychometric functions are sharper for the spatial orthogonal task compared with the temporal inline task, demonstrating better acuity. The direction of movement did not seem to make a difference (i.e. compare x-axis and y-axis movements for each task).

At the group level subjects had minimal proprioceptive bias when they were moved along the y-axis. One sample t-tests showed that these biases were not significantly different from zero for either the temporal inline (t(9) = -0.73, p = 0.48) or the spatial orthogonal (t(9) = 0.50, p = 0.63) tasks. However, when subjects were moved along the x-axis they did show a significant nonzero bias in both tasks. This proprioceptive bias was positive in the temporal inline task (1.22 ± 0.21 cm (SEM); t(9) = 5.83, p < 0.001) and negative in the spatial orthogonal task (-0.73 ± 0.15 cm; t(9) = -4.78, p < 0.001). A positive bias in the temporal inline task meant that subjects thought their
Figure 3.2: Young control experimental results during passive movement. A. Single subject example for the four tasks performed by group 1. The proportion of responses at every shift was calculated separately for individual subjects in each task. A psychometric function was then fit to the data. B. Groups 1 and 2 average JND. In the group 1 tasks, JND was smaller (better acuity) for the spatial orthogonal task than the temporal inline task regardless of movement direction (black significance bars, \( p < 0.001 \)). There was no difference in JND between the x-axis and y-axis movements. In the temporal inline task with spatial cues (group 2 spatial inline task) subjects indicated whether the dot was shifted right/left (instead of early/late as in the group 1 temporal inline task). Cueing subjects to the spatial information in group 2 resulted in larger JNDs (worse acuity) for the temporal inline task (gray significance bars, \( p = 0.055 \)). Both groups ran subjects on the same spatial orthogonal task with no difference in JND. Error bars indicate SEM. *** \( p < 0.001 \).
hand was further rightward than it actually was. A negative bias in the spatial orthogonal task indicated that subjects thought their hand was closer to the body than it actually was. These group level biases align with the proprioceptive biases reported in other studies (Crowe et al., 1987; Wilson et al., 2010).

We focused our analysis on the JND (75% probability minus 50% probability on the psychometric function), which represents proprioceptive acuity. Repeated-measures ANOVA showed a significant main effect of task ($F(1,9) = 36.11, p < 0.001$) driven by a smaller JND for the spatial orthogonal task compared to the temporal inline task (Figure 3.2B). No main effect of movement direction, or interaction between the task and movement direction was found. Therefore, proprioceptive acuity was better in the spatial orthogonal task and worse in the temporal inline task regardless of movement direction.

Given the improvement in proprioceptive acuity in the spatial orthogonal task, we asked whether cueing subjects to spatial signals would change their acuity in the temporal inline task. To test this, we recruited a second group of subjects who performed the temporal inline task, but were told that the dot was shifted to the right or left (spatial) of the index finger instead of early or late (temporal). This was intuitive for the subjects since an early dot appearance would be to the right of a subject’s unseen finger, and a late appearance to the left. As a control, this second group also performed the spatial orthogonal task. However, because the first group’s performance in the two tasks was not differentially influenced by movement direction, subjects in this second group were moved along the x-axis only.
We compared the group mean JND from the temporal inline task with spatial cues to that from the first group who performed the temporal inline task with temporal cues. (Figure 3.2B, compare blue striped bar to solid bar). Mixed-model ANOVA showed a significant main effect of task, where the JND for the spatial orthogonal task was significantly smaller than that for the temporal inline task ($F(1,18) = 24.37, p < 0.001$). The interaction between factors group and task was also significant ($F(1,18) = 4.62, p < 0.05$). Post hoc means comparisons showed that the interaction was driven by significantly greater JND within group 2 for the temporal inline task with spatial cueing compared to the spatial orthogonal task ($p < 0.001$). The comparison between the temporal inline task with temporal cueing (group 1) and the temporal inline task with spatial cueing (group 2) also approached significance ($p = 0.055$). Taken together, these results showed that emphasizing spatial cues in the temporal inline task worsened their performance.

### 3.3.2 Experiment 2

In this experiment we compared dynamic proprioception during both passive and active movement between patients with cerebellar damage and controls matched for age and gender. Note that we did not compare subject performance between the passive and active movement conditions. This was due to the increased attentional load required during active movement versus passive movement in the dynamic tasks (i.e. subjects had to make a smooth movement in addition to completing the perceptual task). Rather, we compared cerebellar patients and older controls within each movement condition. Figure 3.3 shows example data for a cerebellar patient (Figure 3.3A) and an older control (Figure 3.3B). Both subjects have data points that span the tested shifts, with points near
Figure 3.3: Comparison of cerebellar patient and older control experimental results during passive and active movement. A and B. Single cerebellar subject (A) and control subject (B) examples for the temporal inline and spatial orthogonal tasks during passive movement (left panel) and active movement (right panel). Both subjects spanned the breadth of behavior, with points near zero and one in each task. Each subject’s data was subsequently fit with a psychometric function. C. Group average JND during the passive movement condition. There was a significant main effect of group ($p < 0.05$), indicating that cerebellar patients had worse acuity than controls. There was also a significant main effect of task ($p < 0.001$), indicating that for both groups acuity was better in the spatial orthogonal task than the temporal inline task. D. Group average JND during the active movement condition. There were significant main effects of both group and task (all $p < 0.01$). There was also a significant interaction ($p < 0.05$), which was driven by worse acuity in the cerebellar patients compared to controls for the temporal inline task. Error bars indicate SEM. *$p < 0.05$. 
zero and one for each task. In addition, the psychometric functions match well with the data points. This indicates that we were able to capture proprioceptive ability in all tasks for both groups.

In the example psychometric functions shown in Figure 3.3, the proprioceptive bias varies slightly between tasks, but remains quite small. This is consistent with the group averages for bias, which were all less than 2 cm. Mixed-model ANOVAs comparing proprioceptive bias across the two groups and tasks showed no significant effects and no interaction for both the passive and active movement conditions separately. These results indicate that although participants exhibited proprioceptive biases in some experimental conditions, they were not systematic.

To measure proprioceptive acuity we computed the JND. Analysis of the passive movement condition using mixed-model ANOVA revealed significant main effects of group \((F(1,17) = 5.53, p < 0.05)\) and task \((F(1,17) = 34.53, p < 0.001)\), but the interaction did not reach significance (Figure 3.3C). The main effect of group was driven by significantly greater JNDs (worse acuity) in the cerebellar patients regardless of task. The main effect of task showed that both groups had greater JNDs in the temporal inline task compared to the spatial orthogonal task. In the active movement condition mixed-model ANOVA for JND also resulted in significant main effects of group \((F(1,17) = 9.20, p < 0.01)\) and task \((F(1,17) = 73.86, p < 0.001)\). The main effect of group was again driven by greater JNDs in the cerebellar patients overall. The main effect of task also resulted from greater JNDs in the temporal inline task overall. Here however, the interaction between group and task was significant \((F(1,17) = 4.70, p < 0.05; \text{Figure } 3.3D)\). Post hoc means
comparisons showed that the interaction was driven by JNDs in the temporal inline task, where cerebellar patients had significantly worse acuity than healthy controls \((p < 0.05)\).

To further investigate the reduced acuity in cerebellar patients, we explored the active movement dynamics of the two groups. Subjects were supposed to complete their active movements in 3500-4500 ms. Both groups had an average movement time falling within that time window, with no difference between groups or tasks in movement time (spatial orthogonal task: control = 3961 ± 22 ms (SEM), cerebellar = 4005 ± 26 ms; temporal inline task: control = 4048 ± 27 ms, cerebellar = 4000 ± 38 ms). However, if we consider each subject’s trial-to-trial variance of movement time, a pattern emerges. In the temporal inline task, we found strong positive correlations between JND in the active movement condition and within subject movement time variance for both cerebellar patients and controls (cerebellar: \(r = 0.93, p < 0.001\); control: \(r = 0.95, p < 0.001\); Figure 3.4A). In contrast, within subject movement time variance was not significantly correlated with active JND in the spatial orthogonal task (cerebellar: \(r = 0.27, p = 0.48\); control: \(r = 0.36, p = 0.31\); Figure 3.4B).

In the temporal inline task, JND in the active movement condition was positively correlated with cerebellar patient total ICARS scores \((r = 0.63, p = 0.067); \) Figure 3.5A). There was also a significant positive correlation between cerebellar patient total ICARS scores and active proprioceptive acuity in the spatial orthogonal task \((r = 0.70, p < 0.05); \) Figure 3.5B). The correlation persisted in the spatial orthogonal task when using the kinetic function sub-score, which is a quantification of limb coordination abilities \((r = 0.64, p = 0.064)\). However, proprioceptive acuity in the passive movement condition was
Figure 3.4: Proprioceptive acuity during active movement correlates with movement time variance during the temporal inline task but not the spatial orthogonal task. Plots show correlations between JND in the active movement condition and within subject movement time variance separately for cerebellar patients and older control subjects. A. Temporal inline task. B. Spatial orthogonal task.
Figure 3.5: Proprioceptive acuity during active movement correlates with total ICARS score. Plots show correlations between JND in the active movement condition and the total ICARS score of cerebellar patients. A. Temporal inline task. B. Spatial orthogonal task.
not significantly correlated with cerebellar patient ICARS scores in either task (total and kinetic sub-score, all $p > 0.72$).

### 3.4 Discussion

In two experiments we sought to assess dynamic proprioceptive acuity during passive, robot-controlled movement and active, self-movement in healthy control participants and individuals with cerebellar damage. In Experiment 1, we found that healthy individuals show better proprioceptive acuity when asked to compare the position of a visual cursor to the position of their hand when the cursor was shifted orthogonal to movement direction (i.e. when only spatial information was relevant) versus in line with movement direction (i.e. when temporal and spatial information were relevant). When the cursor was shifted in line with movement, cueing participants to spatial information (rather than temporal information) worsened performance further. Additionally, acuity did not change with different movement directions (i.e. along the x- versus y-axes of the task space). In Experiment 2, we found that patients with cerebellar damage had reduced dynamic proprioceptive acuity compared to age-matched healthy controls in both passive and active movement conditions as well as in both cursor shift conditions. Notably, this impairment was exacerbated during active movement and was most apparent when temporal information was relevant for judgments of hand position.

Overall, our results align with the hypothesis that the cerebellum may be important for sensory perception during movement. Previous work has found that cerebellar damage impairs proprioception in tasks that require the estimation of movement (Grill et al., 1994), but does not impair proprioception in baseline tasks that
require estimating endpoint limb position (i.e. localization; Izawa et al. 2012). This is in line with a general role of the cerebellum in the estimation and online monitoring of movement (Miall et al., 2007). Importantly however, we found that cerebellar damage enhanced proprioceptive deficits when movements were actively generated and that these were most evident when estimates relied on the processing of temporal information. Other work has shown that cerebellar damage specifically impairs judgments of passive movement velocity, which requires the use of temporal information, but found no difference between patients and controls in estimates of passive movement amplitude (Grill et al., 1994). Bhanpuri et al. (2013) found that cerebellar damage did impair estimates of movement extent when movements were actively generated. Taken together with our results, this suggests that the cerebellum may play an integral role in the processing of proprioceptive information during voluntary movement, and that it may be especially important for the perception of temporal properties of that movement.

Of interest was our finding that proprioceptive acuity for both cerebellar patients and healthy controls was related to the reliability of their movement. We found that proprioceptive acuity in the active movement condition of the temporal inline task correlated with movement time variance in both groups. Specifically, individuals with higher variance from one movement to the next had worse proprioceptive acuity overall. We also found that proprioceptive impairments in cerebellar patients were related to their deficits in motor control. Patients’ proprioceptive acuity in the active movement condition of both the temporal inline and spatial orthogonal tasks correlated with their total score on the ICARS, such that patients with worse acuity tended to have higher scores (higher scores denote more severely impaired movement). The motor deficits that
result from cerebellar damage are thought to reflect impaired formation of predictive internal models of limb states (Bastian, 2006). Previous work has shown that the specific proprioceptive deficits seen during single joint, active movements by cerebellar patients can be induced in healthy controls by unpredictably perturbing their movement (Bhanpuri et al., 2013). This suggests that, during movement, proprioceptive acuity may critically depend on the ability of the motor system to predict motor output. In line with this, Synofzik et al. (2008) found that, while cerebellar patients had no baseline deficits in detecting the direction of their active movements, they did show deficits when their direction estimates had to be predictively updated. Furthermore, the proprioceptive deficits seen following cerebellar damage could be related to a more general impairment in motor prediction.

We found that in both healthy controls and cerebellar patients proprioceptive acuity was reduced when estimates required the use of temporal information compared to when they required spatial information alone. One explanation for these results may be that in the temporal inline task the cursor appears along the path of the finger, whereas in the spatial orthogonal task it does not. This means that in the temporal inline task subjects have to make instantaneous estimates of their moving fingertip position in order to compare it to the position of the cursor. Time delays in the processing of proprioceptive feedback would make these inline estimates more variable and subjects more uncertain. In contrast, estimates of fingertip position in the spatial orthogonal task are not continuously changing along the axis in which the comparison is made because participants are not moving in the direction of the cursor shift. This may make it easier for participants to discriminate whether the displayed cursor is shifted in the spatial
orthogonal task. However, variable estimates in the inline task due to delayed proprioceptive feedback should affect acuity no matter if participants were attending to spatial or temporal cues during movement. Thus it remains unclear why performance worsened further in the temporal inline task when participants were asked to focus on spatial cues. Further study is needed to understand more about the processing of temporal and spatial components of proprioception to elucidate the mechanisms underlying this result.

In Experiment 1 proprioceptive acuity was not differentially affected by the direction of movement. This was surprising. Previous work studying proprioceptive localization in the upper extremity has found differences in acuity with different movement directions (van Beers et al., 1998, 2002; Wilson et al., 2010), which potentially resulted from differences in muscle spindle activity for different changes in shoulder and elbow joint angles (Goodwin et al., 1972a; Proske and Gandevia, 2009). In our task, although the shoulder moved through roughly the same angular change for both movement directions, the elbow moved through an angular change that was approximately six times greater in the y-axis movement compared to the x-axis movement. So why were our subjects unable to take advantage of the increased afferent information during the y-axis movement? A possible reason for the discrepancy between previous results and ours might lie in the time at which proprioceptive estimates were made. Previous work showing changes in proprioceptive acuity with different movement directions involved proprioceptive estimates that were made after movement completion. In our task, estimates were generated during movement execution. It is possible that the brain is unable to make use of extra afferent information from larger changes in joint
angle until after a movement is complete. Therefore, the increased change in elbow angle between the two movement directions tested in Experiment 1 could not influence proprioceptive acuity online. It would be interesting for future work to directly compare differences in proprioceptive acuity during movement and after its completion to further our understanding of sensory processing in these two limb states.

In sum, we have found that there is a clear difference in proprioceptive acuity when assessing hand position orthogonal to (spatial) versus in line with (temporal and spatial) the direction of hand movement. Furthermore, individuals with cerebellar damage showed deficits in proprioceptive acuity compared to controls, which were enhanced when hand position was assessed during active movement in line with the direction of movement. We interpret these results as evidence that the inline task requires the brain to use temporal and spatial information to make predictions about the hand while it is in flight and that the cerebellum might play an essential role in this ability. Cerebellar circuits have long been known to be a critical part of a predictive mechanism for motor control. Our results add to this notion by showing that the cerebellar processing may also be part of a predictive mechanism for proprioceptive sense.
Chapter 4

General Conclusions

As we interact with the world, we make countless movements. Sensory feedback, including proprioception, is seamlessly integrated by the nervous system to help make those movements accurate. It has long been known that the cerebellum is involved in motor control, but its role in proprioception is less clear. However, recent work has suggested that the cerebellum plays a bigger role in proprioception than previously thought. It follows that cerebellar damage impairs both motor control and proprioception.

In this dissertation, we investigated cerebellar involvement in proprioception. We assessed proprioceptive ability in multiple tasks that are functionally relevant to everyday movements and found varied deficits in people with cerebellar damage. Importantly, this work suggests that the cerebellum contains predictive models of movement which contribute to both motor and somatosensory function. Furthermore, these findings have clinical implications for both determining the presence of sensory deficits and informing future rehabilitative strategies. Lastly, this work advances our knowledge of proprioceptive ability in healthy individuals.
4.1 Cerebellar contributions to proprioception

It is well documented that healthy individuals have improved proprioceptive acuity during active movements compared to passive movements (Paillard and Brouchon 1968; Adamovich et al. 1998; Fuentes and Bastian 2010; Bhanpuri et al. 2013). However, proprioceptive deficits have been seen in people with cerebellar damage during both passive and active movements (Grill et al. 1994; Bhanpuri et al. 2012, 2013). Due to variations between previous studies, the basis for proprioceptive deficits in cerebellar patients remains unclear. In Chapter 2, we first assessed proprioception in a multi-joint localization task where people were asked to locate their fingertip position in space. We chose this task due to its functional relevance to everyday movements—people need to know where their hand is in order to make reaching movements. We found that cerebellar patients were comparable to control subjects in the precision of multi-joint localization during passive movement. However, some, but not all cerebellar patients had deficits in precision during active movement. Importantly, the localization deficits were still present during single-joint active movement, which suggests that the deficits result from active movement rather than from difficulties in coordinating multi-joint limb movements (Bastian et al. 1996). In addition, cerebellar patients were comparable to control subjects in the bias of their proprioceptive estimates. This is consistent with previous studies (Synofzik et al. 2008; Izawa et al. 2012), and suggests that cerebellar damage may differentially impact proprioceptive acuity and bias.

Given the functional relevance of localization, it would be useful to understand why some patients have deficits and others do not. We compared our study to previous proprioceptive studies (Grill et al. 1994; Synofzik et al. 2008; Izawa et al. 2012; Bhanpuri et al. 2013).
et al. 2013), considering the differences between the proprioceptive assessments used and the corresponding results. Consequently, we hypothesized that the level of cerebellar involvement may vary depending on the proprioceptive assessment, with more involvement if there is a temporal or predictive component to the proprioceptive estimate, as compared to a spatial component. In line with this, previous research has suggested that the cerebellum contains sensory prediction models to compensate for time-delayed feedback (for review see Shadmehr et al. 2010). This would provide a straightforward explanation for our localization results. During active movement, localization utilizes both spatial and temporal information; thus, the more reliant cerebellar patients are on the temporal information, the more impaired they are at active localization. In contrast, the passive localization task is a static assessment of limb position, likely involving only spatial information.

To test our hypothesis, in Chapter 3 we investigated limb position sense when both temporal and spatial components are relevant (i.e. in the direction of movement) compared to when only the spatial component is relevant (i.e. orthogonal to movement direction). As before, we chose a task with functional significance, assessing limb position sense as a movement occurs. Again, there were no bias differences between patients with cerebellar damage and control subjects; however, consistent deficits in proprioceptive acuity occurred. During passive movement, we found that cerebellar patients had reduced proprioceptive acuity compared to controls regardless of whether temporal information was relevant to the limb position estimate. Due to the dynamic movement, there was still temporal information available; accordingly, this was not unexpected. Importantly, during active movement, cerebellar patients exhibited larger
deficits when temporal information was relevant. Furthermore, in both patients and
control subjects there was a strong relationship between dynamic proprioceptive acuity
and active movement reliability. The more variable a subject’s movement time was
between trials, the worse their proprioceptive acuity. Therefore, these results provide
compelling evidence in support of the cerebellum’s involvement in sensory prediction.

4.2 Clinical implications

Given the importance of sensory feedback in making well calibrated movements,
it is likely that impaired proprioception impacts movement ability. Thus, in addition to
assessing movement impairments, it is also necessary to identify any underlying
proprioceptive deficits. This work has shown that people with cerebellar damage may
have proprioceptive deficits that are not evident with current clinical assessments. We
assessed all cerebellar patients using standard clinical assessments of fine-touch sensation
and proprioception for the upper extremities (Campbell 2005), with no loss detected. Yet,
during our experiments numerous proprioceptive deficits were found.

In Chapter 2, we showed that only some cerebellar patients had deficits in
proprioceptive localization during active movement. The distinction between those with
deficits and those without could not be explained by patient diagnosis. In addition, there
was no relationship between clinical ratings of impairment as assessed by the ICARS.
Conversely, in Chapter 3, we found that dynamic proprioceptive acuity during active
movement correlated with the total ICARS score. Patients with higher scores, indicating
more severe motor impairments, also had worse proprioceptive acuity. However, there
was no relationship between the ICARS and proprioceptive acuity during passive
movement. Taken together, these findings suggest that, while current clinical assessments relate to some proprioceptive measures, they should be reevaluated in order to fully capture impairments in proprioception. Furthermore, this dissertation has expanded the characterization of proprioceptive deficits in cerebellar patients, which should be utilized when developing future rehabilitative strategies. It is possible that improving or compensating for proprioception (e.g. increasing reliance on vision) will improve motor performance in people with cerebellar damage, which will be an important focus for future studies.

4.3 Proprioception in healthy individuals

In Chapter 3, we conducted multiple experiments in healthy young control subjects during passive movement in order to establish baseline performance in dynamic position sense. We found that acuity did not change when different movement directions were tested, despite large differences in joint angle movements. Furthermore, subjects had better acuity when fingertip position was queried orthogonal to movement direction rather than in the direction of movement. A reasonable explanation for the difference comes from sensory prediction. Sensory predictions were needed in the latter task due to time-delayed sensory feedback. Hence, position estimates would be more variable than in the task for which sensory feedback was up to date. Additional tasks further confirmed that it is important to utilize temporal information during tasks in which it is relevant. When spatial information is emphasized instead, acuity decreases. The exact mechanisms for this are unknown, but may relate to the relative uncertainty and subsequent preferential weighting of the different types of information. In sum, we found several surprising results, which should be examined further in future work to understand the
underlying mechanisms. Nevertheless, a number of our findings can be plausibly explained by sensory predictions, lending further support to the idea that predictive models contribute to proprioception in addition to motor control.
Appendix A

Appendix for Chapter 2 bias figures

In Chapter 2, biases in both multi-joint and single-joint localization are discussed in section 2.3. Multi-joint bias is visualized in Figure 2.3. The single-joint bias, Figure A.1, is included here for visual reference.
Figure A.1: Bias across targets for the single-joint localization experiment. Bias is represented in these plots as elbow angle error. A positive (flexion) error indicates that the subject thinks their elbow is more flexed than its true angular position. A negative (extension) error indicates that the subject thinks their elbow is more extended than its true angular position. In both passive and active movement conditions, controls show flexion errors when the elbow is more flexed (75°, 90°) and extension errors when the elbow is more extended (30°, 45°). Cerebellar patients show similar trends, but exhibit a small offset towards extension. Error bars indicate SEM.
Appendix B

Appendix for Chapter 3 bias figures

In Chapter 3, biases in Experiment 1 were discussed in section 3.3.1, whereas biases in Experiment 2 were discussed in section 3.3.2. The following figures, Figure B.1 for Experiment 1 biases and Figure B.2 for Experiment 2 biases, are included for visual reference.
Figure B.1: Young control average bias during passive movement. Minimal bias occurred during movements along the y-axis. Significant non-zero bias occurred during movements along the x-axis. Positive bias in the temporal inline task and negative bias in the spatial orthogonal task indicate rightward and inward biases, respectively. Error bars indicate SEM.
Figure B.2: Comparison of cerebellar patient and older control bias during passive and active movement. There were no significant differences in bias between groups or tasks for either movement condition. A. Group average bias during the passive movement condition. B. Group average bias during the active movement condition. Error bars indicate SEM.
Appendix C

Appendix for Chapter 3 supplementary experiment

As discussed in Chapter 3, Experiment 1, subjects showed reduced acuity in the temporal inline task with temporal cues compared to the spatial orthogonal task as well as an additional drop in acuity in the temporal inline task with spatial cues. This suggested that subjects did not use both temporal and spatial information during the temporal inline task. Additional experiments were done to further investigate whether proprioceptive acuity in the temporal inline task relies on both temporal and spatial information.

We moved subjects at different velocities, but kept the time shifts the same (-800, -600, -400, -200, 0, 200, 400, 600, 800 ms relative to the fingertip), resulting in different position shifts for each velocity. The faster the subject was moved, the larger the position shifts. As a result, if a subject utilized the spatial information in addition to the temporal information, it was possible that they would perform better during faster velocities because the position shift was large and easy to see. However, if a subject ignored the spatial information and only used the temporal information, performance would not differ
across velocities. We tested one group of subjects in a separated design, with each velocity tested separately. Another group of subjects was tested in an interleaved design—trials of all three velocities were mixed together—to determine whether results were affected by velocity predictability.

12 healthy young control subjects (8 women; mean age: 23.5 ± 3.6 years) completed the temporal inline task with temporal cues during passive horizontal movement, as described in Chapter 3, Experiment 1. They completed the task at three different constant velocities (7, 9, or 11 cm/s), and trials from the three velocities were interleaved. Subjects completed 12 blocks of 27 trials. For the interleaved trials the start position was varied by velocity to align movements around appearance of the shifted feedback. 12 additional subjects (7 women; mean age: 24.8 ± 3.7 years) completed the temporal inline task at the same three constant velocities; however, trials were separated by velocity and all trials of each velocity were grouped together. For each velocity, subjects completed 6 blocks of 18 trials. The start position was held constant across velocities. Velocity order was counterbalanced across subjects.

In order to determine the effect of the differently-sized position shifts, comparisons between the velocities were made in the temporal shift domain. Regardless of whether the trials were interleaved or separated, for each velocity the proportion of trials where a subject reported the visual dot to be “late” relative to the finger was determined at each shift value. Then a separate logistic function was fit for each subject at each velocity. To compare JNDs, a mixed-model ANOVA was used, with between subjects factor task design (interleaved, separated) and within subjects factor velocity (7, 9, or 11 cm/s).
Figure C.1A shows the psychometric functions for an example subject during the interleaved design. The curves are similar across velocities, though that of the slowest velocity is not as steep as the other two curves, indicating that this subject has poorer acuity for the slowest velocity. Overall, our results showed no effect of task design (Figure C.1B, F(1,22) = 0.91, p = 0.35) and no interaction (F(2,44) = 1.62, p = 0.21). Thus, regardless of whether the velocity is consistent or unpredictable, proprioceptive acuity does not change. However, there was a significant effect of velocity (F(2,44) = 6.36, p < 0.01), driven by worse acuity during slower velocities.

Slower velocities have smaller spatial shifts than faster velocities. Thus, the main effect of velocity suggests that the position shifts can affect judgments in the temporal inline task with temporal cues. This corresponds with our earlier finding—when we asked subjects to focus on spatial cues (i.e. the temporal inline task with spatial cues), they had reduced acuity. In addition, we saw no effect of velocity predictability, which indicates that subjects do not change their strategy under more uncertain conditions.
Figure C.1: Young control experimental results for the temporal inline task tested at multiple velocities. A. Single subject example of the three movement velocities tested. The proportion of responses at every shift was calculated separately at each velocity for individual subjects. A logistic function was then fit to the data. B. Group JND averages for the three movement velocities tested on two task designs, interleaved and separated. There is no difference in JND between the two task designs but there is a significant main effect of movement velocity ($p < 0.01$). Error bars indicate SEM.
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Curriculum Vitae

Heidi M. Weeks was born on March 25, 1987 in Evanston, Illinois. She graduated as salutatorian of Northwest School of the Arts in Charlotte, NC in 2005. She received a National Merit Finalist Scholarship and a Dean’s Honorary Scholarship to attend Washington University in St. Louis. She graduated *cum laude* from Washington University in 2009 with a Bachelor of Science in Biomedical Engineering. While at Washington University, she was selected to participate in the HHMI Summer Scholars Program in Biology and Biomedical Research and the Summer Exchange Program at Hong Kong Polytechnic University. She also conducted research and spent a semester as a teaching assistant for the Department of Biomedical Engineering. She began the Biomedical Engineering PhD program at Johns Hopkins University in the fall of 2009. She subsequently joined the Motion Analysis Lab, headed by Dr. Amy Bastian, in the spring of 2010. She was supported by the NIH funded Neuroengineering Training Initiative Grant at Johns Hopkins from 2009 to 2011. In 2014, she received the Ruth L. Kirschstein National Research Service Award fellowship from the NIH. During her time in the PhD program, she completed two semesters as a teaching assistant for undergraduate biomedical engineering courses.