

# SENSITIVITY TO MOTOR ERROR IN CHILDREN WITH AUTISM

by

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A dissertation submitted to Johns Hopkins University in conformity with the  
requirements for the degree of Doctor of Philosophy

Baltimore, Maryland

June, 2014

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# Abstract

When making a movement, the brain receives sensory feedback about the consequences of that action. If sensory feedback differs from predicted, the brain experiences an error, driving adaptation and improving subsequent movements. How much the brain adapts to error is governed by its sensitivity. Computationally, sensitivity is a scaling factor, specifying the relative amount of adaptation that occurs, while theoretically it is a quantification of the error's value. In children with autism spectrum disorder (ASD), the response to sensory feedback appears abnormal. In particular, they are hyperresponsive to proprioceptive feedback and hyporesponsive to visual feedback. Here, we hypothesized that these sensory abnormalities would be manifested as an increased sensitivity to proprioceptive error and a decreased sensitivity to visual error. Further, we hypothesized that this pattern of error sensitivity would be related to anatomical abnormalities in the cerebellum, known to be a neural substrate of motor learning.

Typical models of adaptation assume sensitivity to error to be a constant; however several studies contradict this, reporting a non-linear relationship between adaptation and error. Therefore, we first characterized sensitivity in healthy adults with a reach adaptation task, in which we perturbed their movements both proprioceptively and visually. By normalizing the trial-to-trial change in motor commands by the error size, we isolated sensitivity to error. We found that, for both visual and proprioceptive errors, sensitivity declined with increasing error size. Interestingly, the probability of a complex spike in cerebellar Purkinje cells, previously believed to be a neural representation of an

error, declined with increasing error as well. We therefore posited that complex spikes represent sensitivity to error during cerebellar adaptation.

We then repeated our paradigm on children with ASD. As hypothesized, we found increased sensitivity to proprioceptive error and decreased sensitivity to visual error, relative to healthy control children. In these same subjects, we used anatomical MRI to measure the volume of the sensorimotor region of the cerebellum. We found this region was significantly smaller in children with ASD, and that sensitivity was a predictor of volume, identifying a potential neural substrate for the sensorimotor abnormalities seen in ASD.

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# Acknowledgements

Thank you to Dr. Reza Shadmehr, my committee and the Shadmehr lab.

Special thank you to Steven, my family, and Sarah.

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# Chapter 1

## Introduction

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by deficits in social and communication skills, and repetitive and stereotyped patterns of interest and behavior. Theoretically, the social and communication skills that so greatly impact the lives of those with ASD are dependent on the motor system, allowing individuals to map the movements, expressions and body language of others onto themselves, and mentally experience the intentions of others (Baron-Cohen et al., 1985;Gidley Larson and Mostofsky, 2008;Gallese et al., 2004;Iacoboni, 2009). Though motor control is not included in the diagnostic criteria of ASD, many studies have found an array of motor abnormalities in individuals with autism (Jansiewicz et al., 2006;Mostofsky et al., 2006;Dowell et al., 2009;Dziuk et al., 2007;Gowen and Hamilton, 2013). In particular, studies of motor learning suggest that children with ASD show an over reliance on proprioceptive feedback during motor adaptation, the degree of which relates to the degree of overall motor and social impairment (Haswell et al., 2009;Izawa et al., 2012b). This suggests that, just as children with ASD are unable to properly learn social and communication skills, they are unable to properly learn to make movements. Specifically understanding how children with ASD learn from motor error will offer insight and a potential understanding of the difficulties these children face in learning the higher-order skills that govern social interaction, communication, and cognition.

In healthy individuals, learning from motor error to improve motor control is a continuous, ongoing process. Such learning can be characterized with the framework of a forward model, in which the brain maintains an internal mapping about the relationship between movements and sensory feedback (Wolpert and Miall, 1996). When making a movement, the brain uses this internal model to generate a prediction about the sensory consequences of that movement and compares it to the actual, experienced sensory feedback. If the predicted and actual sensory consequences of the movement differ, the brain experiences an error. This error signal drives the brain to adapt its internal model of the environment and generate more accurate motor commands for future movements.

How much the brain adapts to an error depends on two quantities – the size of the error experienced, and the sensitivity to that error. Typical computational models of adaptation assume that sensitivity to error is constant (Thoroughman and Shadmehr, 2000; Scheidt et al., 2001; Cheng and Sabes, 2006; Smith et al., 2006; van Beers, 2009), implying that adaptation would scale linearly in response to increasing error size. However, this is often not the case (Fine and Thoroughman, 2006; Wei and Kording, 2009). In principle, sensitivity is a measure of how much the brain trusts and values that sensory feedback. For instance, imagine reaching for an alarm clock mid-day, in bright lighting. Missing the clock would cause a person to adapt their subsequent reach and improve accuracy. However, missing the clock when getting up early in the morning, with no lights on, would likely cause little to no adaptation, since the error was due to a lack of visual information. This was shown experimentally, with a reach adaptation task by Burge, et al. (2008). When subjects were given clear visual feedback about their movements, indicated by a sharply delineated cursor, they were able to adapt to a

perturbation faster than subjects who were given a blurry cursor. In a different experiment by Smith and Shadmehr (2004), subjects were given errors in different statistical environments. If an error indicated the presence of future, similar errors, subjects learned more from it than from the exact same error when it was a poor indicator of future perturbations. This demonstrates that sensitivity to error is not a simple constant, and that factors beyond magnitude of error can modulate learning by altering sensitivity to error.

In an effort to better examine the exact nature of sensitivity to error, we conducted an experiment in which healthy adults were given a random perturbation to their movements in two different sensory modalities, vision and proprioception. We then measured how much adaptation occurred in response to the given motor errors, and found that sensitivity to error decreased with increasing error size for both modalities (Chapter 2). Additionally, the pattern of decreasing sensitivity to error appeared to match the pattern of neuronal activity in the Purkinje cells of the cerebellum. This neuronal activity is related to error based learning, and was previously believed to act as the brain's error signal (Kitazawa et al., 1998). Our findings suggest that Purkinje cell firing is actually representative of the sensitivity to error, and not the error signal itself. This work provides the framework with which we can better examine motor learning in children with ASD (Chapter 3) and relate our pattern of findings to the anatomy of the brain (Chapter 4).

# **1.1 Sensorimotor Control in Children with Autism**

As with the broad spectrum of cognitive phenotypes in autism, the motor deficits found in ASD are highly variable. Children with ASD repeatedly score worse in a generalized motor battery that measures timed movements, stressed gaits and balance (Jansiewicz et al., 2006; Dziuk et al., 2007; Dowell et al., 2009; MacNeil and Mostofsky, 2012). They also show a generalized impairment on a praxis exam, quantifying their ability to accurately make and imitate gestures that are both social (e.g., waving) and or involving tool use (e.g., brushing teeth) (Mostofsky et al., 2006; MacNeil and Mostofsky, 2012). Furthermore, children with ASD are not only impaired in their ability to perform these skilled gestures but also in representational or postural knowledge of these movements, as performed by others (Dowell et al., 2009). Though overall scores consistently indicate motor impairment, there is no specific or signature motor deficit. Rather, these studies demonstrate broad motor impairments that do not fit into any clear, clinical classification. Given the developmental nature of ASD, these deficits may begin with error-based learning, rooted in an abnormal mechanism for motor adaptation, and an inability to learn how to properly make movements.

The error signals that drive motor learning primarily come through two modalities, vision and proprioception. As with studies of motor control, individuals with ASD show a broad range of sensory processing abnormalities, so much so that “hyper- or hyporeactivity to sensory input” has been added to the DSM-V as part of the diagnostic

criteria for autism (American Psychiatric Association, 2013). For vision, this has been demonstrated with several tasks. For instance, individuals with ASD show worse performance on a visual-temporal integration task (Nakano et al., 2010) and, according to parent surveys, children with ASD tend to both avoid or seek out visual input (Leekam et al., 2007). With regard to the visual aspects of movement, hypo-reactivity to visual feedback has been manifested as an impairment in recognizing biological motion (Cook et al., 2009) and in the recognition and response to visual chains of action (Cattaneo et al., 2007). Additionally, there has also been a tremendous amount of work demonstrating impairments in imitation (Williams et al., 2004; Mostofsky et al., 2006; Vanvuchelen et al., 2007; Stieglitz et al., 2008; MacNeil and Mostofsky, 2012). Taken together, this suggests that there is an inability to properly process and utilize visual information, especially with regard to movement. In contrast, studies of the proprioceptive and haptic response in ASD seem to suggest an overall hypersensitivity. Individuals with ASD are better at haptic-to-visual shape matching (Nakano et al., 2012), have a lower threshold for high frequency vibrotactile stimuli detection (Blakemore et al., 2006), and show diminished effects of perceptual disinhibition (Tannan et al., 2008). It is important to note that these findings are not likely due to a peripheral deficit, as individuals with ASD show normal visual (Tavassoli et al., 2011) and proprioceptive acuity (Fuentes et al., 2011), indicating that sensory abnormalities in ASD are due to differences in central processing of sensory feedback.

The best evidence of how sensory processing can impact motor learning comes from a set of studies that measured generalization, or how much motor learning transfers across different contexts, in children with ASD (Haswell et al., 2009; Izawa et al., 2012b).

In these studies, children were required to learn to compensate for a perturbation against their arm while make a reaching movement to a target. They were then asked to make movements to two additional targets – one which visually matched the learning target, but required a different arm configuration to complete the movement, and one which proprioceptively matched the learning target (required the same joint angles for movement) but was visually different from the learning target. Children compensated for the perturbation when reaching to both the visual and proprioceptive targets, or generalized their learning, even though they had never experienced a perturbation when reaching to these targets. Interestingly, children with ASD showed normal performance at the learning target, but significantly greater generalization to the proprioceptive target, suggesting a greater reliance on proprioceptive feedback during learning (Haswell et al., 2009). A follow up study confirmed this result with larger group numbers, and found it specific to ASD with the addition of a clinical control group (children with attention deficit-hyperactivity disorder, ADHD) (Izawa et al., 2012b). This finding suggests that the abnormalities in sensory processing found in autism may impact how they learn to make movements. Unfortunately, generalization is not a specific measure of visual and proprioceptive sensitivity. Therefore, we examined this more directly (Chapter 3) using our framework for sensitivity to error, as used in our study of adults (Chapter 2). We found that children with ASD do show an increased sensitivity to proprioceptive error and a decreased sensitivity to visual error, as compared to TD controls, during motor learning.

## 1.2 The anatomy of sensitivity to error

Adaptation to motor error is believed to be dependent on the integrity of the cerebellum. For instance, when a perturbation is given to the arm during a reaching task, patients with cerebellar damage are unable to learn to compensate for the perturbation, and continue to make large errors (Smith and Shadmehr, 2005; Criscimagna-Hemminger et al., 2010; Donchin et al., 2012). If the cerebellum is temporarily disrupted using transcranial magnetic stimulation (TMS), the temporal planning of the movement is delayed, indicating that the cerebellum is specifically responsible for the feed forward aspects of movement planning (Miall et al., 2007). Interestingly, individuals with autism show cerebellar abnormalities on the cellular (Ritvo et al., 1986; Bailey et al., 1998; Whitney et al., 2008; Kemper and Bauman, 1998), gross (Murakami et al., 1989; Hashimoto et al., 1995; Courchesne et al., 2001; Scott et al., 2009; Courchesne et al., 2001; Sparks et al., 2002; Stanfield et al., 2008) and functional level (Mostofsky et al., 2009; Allen and Courchesne, 2003), potentially underlying their deficits in motor adaptation.

Within the cerebellum, there appears to be specific regions responsible for reach adaptation. This has been shown a number of ways: first, a patient study examined performance on both a force field adaptation task, which involves adaptation to consistent visual and proprioceptive errors, and visual rotation task, in which subjects experience only visual errors, and related performance on these tasks to the integrity of the cerebellum on a voxel by voxel basis (Donchin et al., 2012). They found regions in lobules IV-VI to be primarily related to each task. Another study, using functional MRI

to examine healthy subjects, gave participants random force field and rotation errors and found similar regions to be related to sensory prediction errors (Schlerf et al., 2012). These regions correspond to the known, proprioceptive maps in the anterior cerebellum, which receive cortical input from the pons and spinocerebellar information directly from the body (Manni and Petrosini, 2004). A recent study found that these regions are functionally coupled to the somatosensory and motor cortices, further validating their relationship to movement and its sensory feedback (Buckner et al., 2011). Alongside their findings, Buckner and colleagues (2011) published an atlas, allowing us to examine the specific regions of the cerebellum most critical for sensorimotor adaptation in our own subjects. Therefore, we hypothesize that in children with ASD, abnormalities in motor adaptation will be reflected in abnormalities of the volume of the sensorimotor region of the cerebellum.



# Chapter 2

## Sensitivity to motor error in healthy adults

### 2.1 Introduction

Theoretically, as the size of a motor error increases, the amount one learns from that error should increase as well. This idea has been formalized with many computational models, which claim that the amount one learns from error is dependent on error size and the sensitivity to that error. In this sense, sensitivity is a scaling factor that determines how error is transformed into adaptation. Commonly, sensitivity to error is assumed to be a constant parameter, simply fit within the model (Cheng and Sabes, 2006; Scheidt et al., 2001; Smith et al., 2006; Thoroughman and Shadmehr, 2000; van Beers, 2009). Such models would predict that adaptation scales linearly with error size; however, many studies have shown that this is not the case. Whether it is a proprioceptive perturbation (Fine and Thoroughman, 2006) or visual perturbation (Wei and Kording, 2009), adaptation saturates as error size increases. Additionally, the amount one learns from a given error can be modulated by a number of factors, such as

the confidence associated with the sensory error experienced (Burge et al., 2008), or the belief that adaptation is beneficial to improving performance (Smith and Shadmehr, 2004). Consequently, it is clear that sensitivity to error is not a simple constant.

Sensitivity to error may be further broken down by considering the modality of the error signal. In other words, how much does the brain learn from a proprioceptive error, or from a visual error? Typical reach adaptation experiments focus on two primary paradigms – those that utilize a force perturbation, which delivers a perturbation to the hand and cursor together, or a visual motor rotation, which perturbs the cursor only. In both paradigms, vision and proprioception are providing feedback to the brain about the position of the arm, but it is unclear how the brain combines these two streams of information. Behavioral research suggests independent mechanisms of learning for proprioceptive based and visual based paradigms (Bock and Thomas, 2011; Pipereit et al., 2006; Krakauer et al., 1999), while lesion studies find that separate regions of the cerebellum are related to performance in force field and visual motor rotation tasks. Here, we attempt to understand not only sensitivity to error, but also sensitivity to specific modalities of error, and how they are combined to generate a single, adapted movement.

With a better understanding of sensitivity to error, we can also look for its neural correlate. On the gross level, motor adaptation depends on the integrity of the cerebellum (Donchin et al., 2012; Rabe et al., 2009; Smith and Shadmehr, 2005; Criscimagna-Hemminger et al., 2010; Taylor et al., 2010). The cortex of the cerebellum contains a simple, repetitive circuit, which has been studied for a variety of error based learning paradigms. In this circuit, climbing fibers deliver input from the inferior olive onto

Purkinje cells via complex spikes (CSs). These CSs are associated with error (Medina and Lisberger, 2008; Kitazawa et al., 1998), and have typically been described as the cerebellar error signal itself (Marr, 1969; Albus, 1971). However, when adapting to a constant perturbation, the probability of a CS begins low and increases with adaptation and the subsequent reduction of error (Catz et al., 2005). Additionally, when errors are random, the probability of a CS decreases with increasing error size (Soetedjo et al., 2008). Both of these findings are inconsistent with the notion that a CS is the error signal itself. Instead, we suggest that CSs represent sensitivity to motor error, which we found to decrease with increasing error size as well.

## 2.2 Methods

### 2.2.1 Experimental Setup

Ten subjects (age  $25.8 \pm 3.7$  yr; 6 women, 4 men) participated in a reaching experiment, in which they held the handle of a robotic manipulandum and made movements towards a target. Subjects sat with a screen over their lap, obscuring their hand and the robot from view, and allowing them to make movements in the horizontal plane (Fig. 2.1A). Projected onto the screen were the target, cursor and information about the task. To start each reaching movement, subjects were instructed to move their hand into a 6x6 mm square. The robot provided a light force to help guide them to the start box. Once they were within 1 cm of the start box, a cursor appeared, indicating the position of their hand. After stopping within the start box, a second 6x6 mm square (the

target box) appeared 8 cm in front of the start box. Subjects were instructed to make a shooting, or a ballistic, movement through the target box. After passing through the target box, a pillow field slowed the hand and helped guide it back to the target box, at which point they received feedback about their movement. If subjects passed through the target within 150-250 ms from movement onset, the target “exploded” and a point was added onto their score. If they reached through the target too quickly (in less than 150 ms) or too slowly (greater than 250 ms), the target box turned red or blue, respectively. Subjects were instructed to get as many points as possible. After stopping in the target box, the cursor was shut off and the robot helped guide their hand back to the start box for the next movement.

The experiment began with a warm up block of 40 movements, allowing subjects to acquaint themselves with the robot and task requirements. Subjects were then given 10 blocks of 80 movements each. The entire experiment lasted about 90 minutes. All subjects were healthy, right hand dominant, and naive for the purpose of the experiment. The protocol was approved by the Johns Hopkins Institutional Review Board, and all subjects provided written informed consent.

## 2.2.2 Perturbations

Throughout each 80 trial experiment block, subjects were randomly exposed to one of 11 different perturbations. Each perturbation type was given to the subject twice, once to the left and once to the right, in each block. This balanced the experiment and each block, such that the mean perturbation was zero (Fig. 2.1B). The perturbations

consisted of both a proprioceptive component and a visual component. The proprioceptive component of the perturbation was created by a velocity dependent force field and applied by the robotic manipulandum. The robot applied a force,  $\mathbf{f}$ , to the hand, perpendicular to the direction of movement:

$$\mathbf{f} = \begin{bmatrix} 0 & b \\ -b & 0 \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} \quad (2.1)$$

where  $\dot{x}$  and  $\dot{y}$  are the hand velocities and  $b$  is the perturbation size. There were three possible perturbation sizes, generating a small proprioceptive error ( $b = \pm 6.5$  N.s/m), a medium proprioceptive error ( $b = \pm 13$  N.s/m) or a large proprioceptive error ( $b = \pm 19.5$  N.s/m) to the left or right. Example hand trajectories for the three field sizes can be seen in Fig. 2.1C.

The visual component of the perturbation was applied through the cursor. During a perturbation trial, the lateral deviation of the hand,  $x$  (as compared to a straight line between the start box and the target box) was scaled by a gain,  $g$ . The resulting cursor position was

$$\mathbf{c} = \begin{bmatrix} g & 0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} \quad (2.2)$$

The visual gain,  $g$ , took on one of five values: 0, 0.5, 1.0, 1.5 or 2.0. Therefore the visual error displayed by the cursor was either smaller ( $g = 0$  or  $g = 0.5$ ), the same ( $g = 1$ ), or larger ( $g = 1.5$  or  $g = 2.0$ ) than the proprioceptive error experienced by the hand. Examples of the cursor trajectories for the five visual gains, as applied to a movement through the small field ( $b = 6.5$ ) can be seen in Fig. 2.1D. These five gains were applied

once to the small and medium field, in each direction, in each block. Additionally, the large field was given once in each direction with gain of 0 only, for a total of 11 potential perturbation types for a given direction. These perturbations generated a variety of errors in both vision and proprioception for the subject, allowing us to measure learning and sensitivity to various error sizes across both modalities.

### 2.2.3 Quantifying learning from error

To quantify how much the brain learns from error, we measured how much the subjects adapted their movements in response to the errors experienced during the perturbation trials. This was achieved through the use of channel trials (Scheidt et al., 2000), which were always given before ( $C_1$ ) and after ( $C_2$ ) any perturbation trial (P). This created triplets of trials, ( $C_1PC_2$ ), which we separated by 0, 1 or 2 null field trials. During a channel trial, the hand moved “through a channel” generated by the robot, forcing the subject to make a straight line movement to the target. The channel walls had a spring force (spring coefficient = 2.5 kN/m) and a damping force (damping coefficient = 25 N.s/m), and prevented the subject from experiencing any errors during their movement. At the same time, a force transducer in the handle of the robotic manipulandum measured the force produced by the subjects against the channel walls. This force acted as a proxy for the subject’s belief about the current state of the experiment, by measuring how much they attempted to compensate for any potential perturbations.

To understand how much learning occurred in response to a given perturbation, we used a state-space model framework for error based adaptation (Donchin et al., 2003):

$$\begin{aligned} f^{(n)} &= \alpha f^{(n-1)} \\ f^{(n+1)} &= \alpha f^{(n)} + \lambda(e_v^{(n)}, e_p^{(n)}) \end{aligned} \quad (2.3)$$

Eq. (2.3) states that the force produce in trial  $n+1$  is a function of the force that was produced in trial  $n$ , adaptation ( $\lambda$ ) to the visual ( $e_v^{(n)}$ ) and proprioceptive error ( $e_p^{(n)}$ ) that were experienced on trial  $n$ , and a constant reflecting the decay of motor memories over time,  $\alpha$ . Put in the framework of the current experiment and a C<sub>1</sub>PC<sub>2</sub> triplet, the force produced by the subject in trial C<sub>2</sub> is a function of the force produced during trial P and the learning that occurred in response to the errors experienced during trial P. Since trial  $n-1$  is a channel trial (C<sub>1</sub>) with no error,  $f^{(n)}$  is purely a function of the decay of  $f^{(n-1)}$ , with no additional adaptation. By rearranging Eq. (2.3), adaptation to the errors caused by the perturbation, P, can be described as:

$$\lambda(e_v^{(n)}, e_p^{(n)}) = f^{(n+1)} - \alpha^2 f^{(n-1)} \quad (2.4)$$

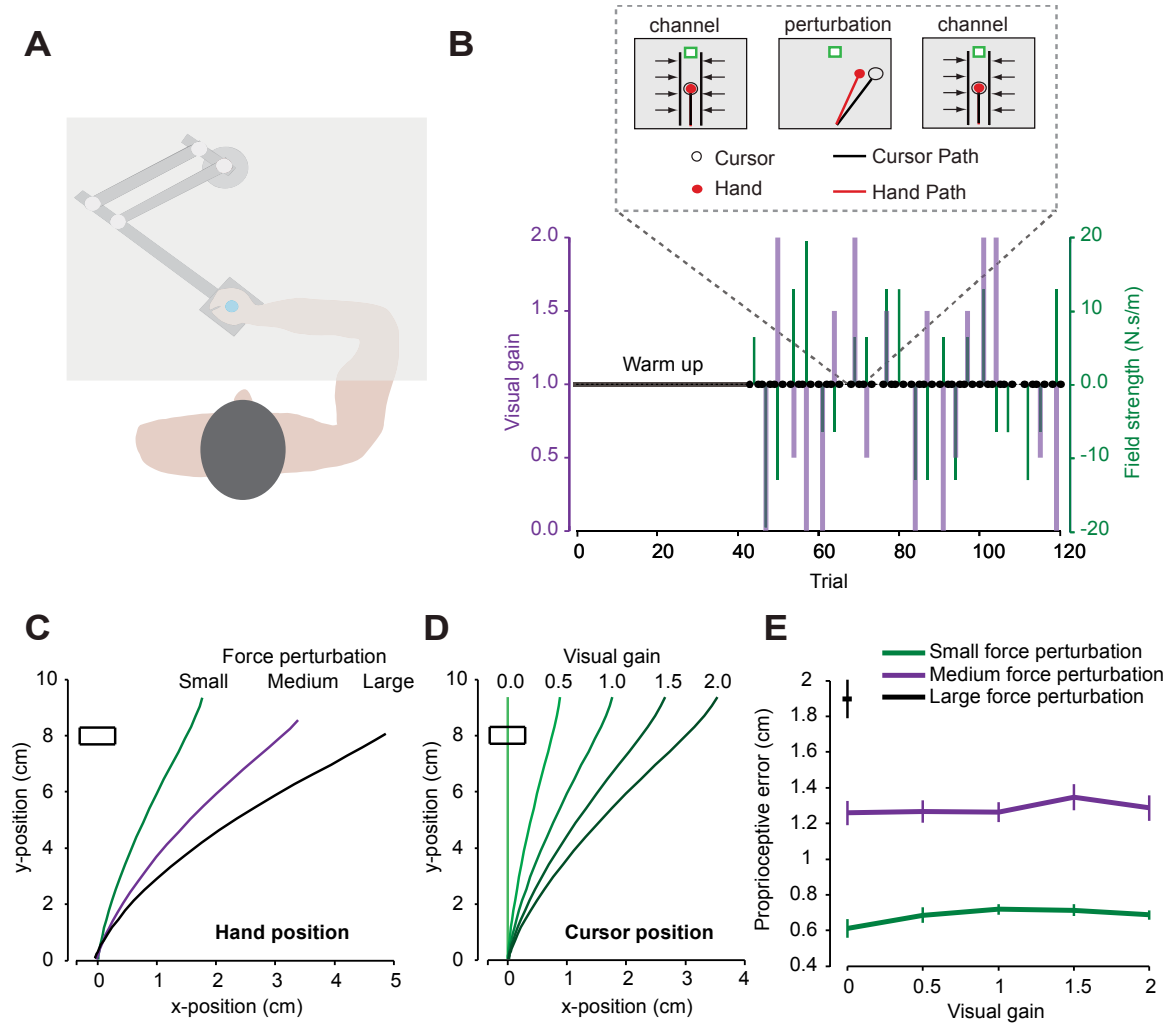
or change in force from C<sub>1</sub> to C<sub>2</sub>.

To find the decay term,  $\alpha$ , we measured the average ratio of force profiles in any instance in which there were back to back channel trials. This occurred when there were two consecutive triplets, 121 times throughout the experiment. We found that  $\alpha = 0.84 \pm 0.07$  (mean  $\pm$  SEM), which is of a similar value to the decay term found when adaptation was fit with the two state model ( $\alpha = 0.85$ ) (Joiner and Smith, 2008).

Since the force produced during a channel trial is a time series, we needed a principled way to choose a scalar value to represent each movement. We opted to use principal component analysis, selecting the time from movement onset in which the first principal component of the change in force had the highest value. We found this to be  $193 \pm 16$  ms (mean  $\pm$  SD). Given our sampling rate of 100 Hz, we used the time point 190 ms from movement onset to measure force and error in a channel or perturbation trial, respectively. This time point allows us to account for the most variability in our data. We further examined the data at various time points and distances from the start of the movement, and found our results to be qualitatively consistent, thus ensuring our results were robust.

When plotting our results, data was corrected for sign collapsed across the left and right perturbation conditions. Although adaptation and error are oppositely signed, all results are plotted in the first quadrant for ease of viewing. Movements that resulted in less than -2N of learning, i.e. movements that showed substantial adaptation in the same direction as the error was experienced, were removed from the analysis. Across all subjects, this excluded 36 movements from 2,200. Analysis and statistics were completed using Matlab (Mathworks), Excel (Microsoft) or SPSS (IBM).





**Figure 2.1: Experimental setup for adults.** **A.** Schematic of the experimental setup: subjects made horizontal reaching movements while holding a robotic manipulandum below an opaque screen. **B.** Perturbation schedule: subjects were presented with movement triplets in a random order separated by zero, one, or two null field trials (the warm up block and the first experiment block are shown in the figure). Triplets consisted of a channel trial ( $C_1$ ), one of the possible perturbations ( $P$ ), and then a second channel trial ( $C_2$ ). The purple trace indicates the size of the visual perturbation and the green indicates the size of the proprioceptive perturbation. Channels are noted by thick black points. **C.** An example of hand trajectories through the small, medium, and large rightward force perturbations. **D.** An example of the cursor trajectory in each of the five possible gains as applied to the small proprioceptive error. Thus, the gain 1 trace in this figure corresponds to the small proprioceptive error trace in part C. **E.** Proprioceptive error resulting from the three different sized force fields, small, medium and large, for all applied visual gains. Error was measured as the lateral deviation of the hand at 190 ms.

## 2.3 Results

### 2.3.1 Adaptive response to error

For our experiment, healthy adults participated in a reaching task in which we perturbed their movements with a force field against the hand, and perturbed the cursor trajectory by scaling the cursor error. We anticipated that these errors would generate adaptation, as described by Eq. (2.4). The resulting proprioceptive errors, or the lateral deviations of the hand at 190 ms after reach onset, are plotted in Fig. 2.1E. A repeated measures ANOVA found no significant effect of gain on error size for the small proprioceptive perturbation ( $F(4,45)=3.08$ ,  $p=0.11$ ) or the medium proprioceptive perturbation ( $F(4,45)=3.00$ ,  $p=0.11$ ), indicating that proprioceptive error was constant within a given perturbation size. Thus, the perturbation conditions can be organized into two groupings – those which produce a constant proprioceptive error but different visual errors (e.g. within a given force field perturbation), and those which produce constant visual error but differing proprioceptive errors (during the three  $g = 0$  conditions).

Data from a typical subject are plotted in Figs. 2.2A-D. Hand (solid lines) and cursor trajectories (dashed lines) are plotted in Fig. 2.2A for the five visual gain conditions for the medium force field ( $b = 13$ ). As demonstrated in Fig. 2.1E, the proprioceptive error experienced by the hand is the same across the different visual gain conditions, while the cursor error increases with increasing visual gain. Noted on the cursor trajectories with circles is the point 190 ms from reach onset. This occurs approximately midway through the reach for all conditions. In Fig 2.2B, we have plotted

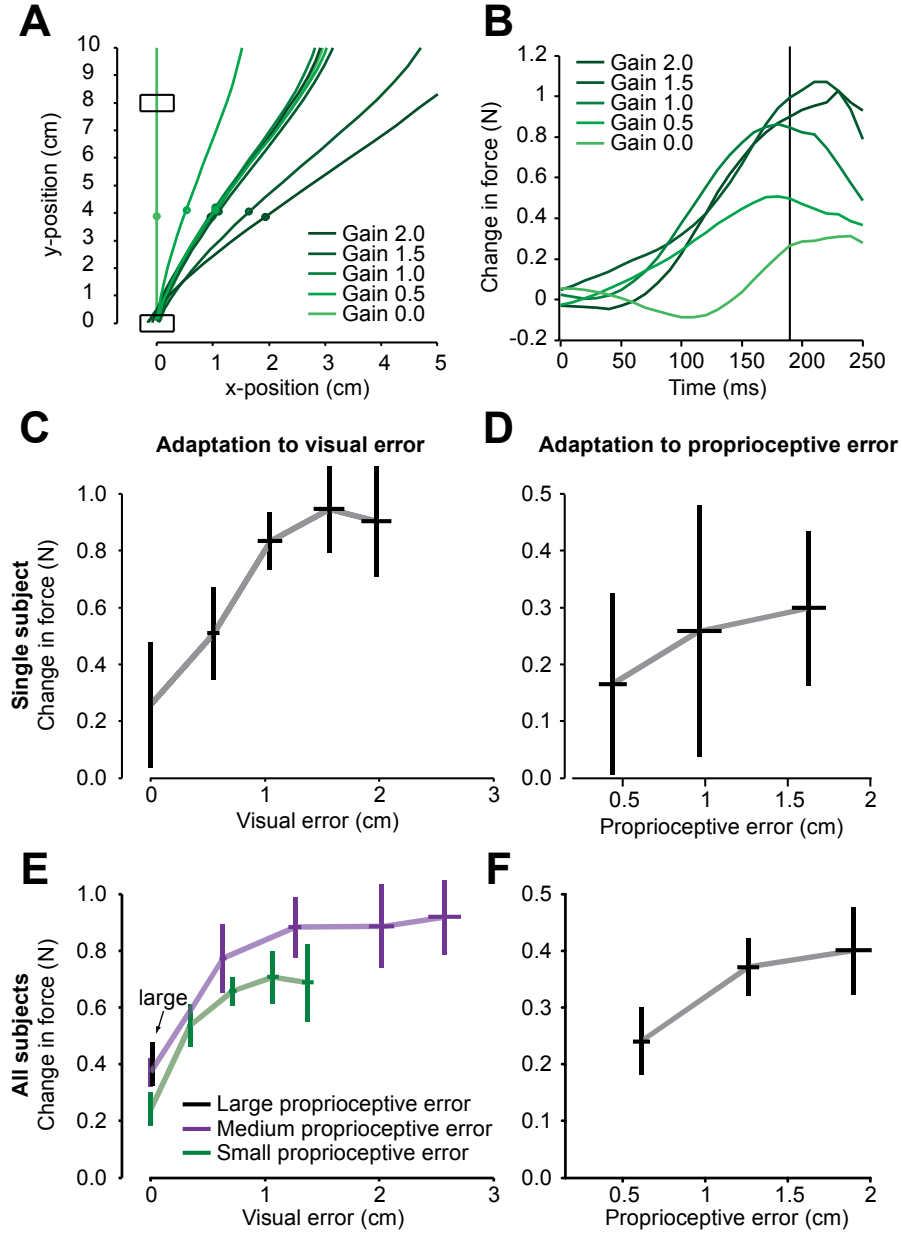
the change in force from  $C_1$  to  $C_2$ , or the adaptation that occurs in response to the perturbation trial,  $P$ , for the entire time course of the movement. We found that as the visual gain increased, the trial-to-trial adaptation initially increased as well, but saturated for large visual gains. Using the force at 190 ms from reach onset as our proxy for each movement, we see a consistent pattern of results (Fig. 2.2C, points represent increasing visual gain): that adaptation saturates when plotted against increasing visual error. This validates our use of the force and error at 190 ms to represent the time series of the movement.

When we repeated this analysis for learning in response to proprioceptive error alone, which occurred during the three  $g = 0$  conditions, we found a similar pattern. The results for our example subject are plotted in Fig. 2.2D, where points represents the small, medium and large force field sizes (increasing  $b$ ), respectively. Similar to visual error, we found that as proprioceptive error increased, adaptation to showed saturation and a sub-linear response to increasing error size.

The group data are summarized in Fig. 2.2E-F. In Fig. 2.2E we plot the adaptive response (Eq. 2.4) for all conditions against the visual error experienced as a result of the given perturbation. The separate lines represent the different force field sizes and each point along the line represents a different visual gain, increasing from left to right. If sensitivity to error was constant, we would anticipate that as error size increased, adaptation would increase linearly as well. Instead, we see that as visual error increases, adaptation increases initially but then saturates, suggesting that the adaptive response to error is non-linear. To test our observation, we fit a simple linear model and a simple logistic model to the data for the small and medium force fields. We found that the

logistic model yielded a better fit (according to the Akaike information criterion (AIC), for which a lower value indicates a better fit) for both the small (logistic AIC = -37.18, linear AIC = -20.67) and the medium (logistic AIC = -37.4, linear AIC = -17.9) force fields. Thus, as Fig. 2.2E suggests, the relationship between adaptation and visual error size is non-linear.

Figure 2.2F plots adaptation in the three  $g = 0$  conditions, i.e. when visual error is clamped to zero and proprioceptive error is varied with the three different force field sizes. Each point represents a different force field size ( $b$ ) increasing from left to right. Similar to our findings regarding the relationship between adaptation and visual error, adaptation appears to saturate with increasing proprioceptive error. To test this, we again found the AIC for a linear model (linear AIC = -18.4) and a logistic model (logistic AIC - 19.1), and found that the logistic model better characterized the data. This indicates that adaptation to proprioceptive error is non-linear as well, and therefore proprioceptive sensitivity is not constant.



**Figure 2.2: Adaptation saturates as error size increases.** Error bars are SEM. **A.** Hand trajectory (solid lines) and cursor trajectory (dashed lines) for a medium size force perturbation for a representative subject. Circles indicate position at 190ms from start of movement. **B.** Change in force from the trial preceding the perturbation (part A) to the trial after the perturbation trial, or the adaptation in response to the perturbation trial, for the representative subject. Adaptation is small when the visual error is small (gain of 0), increases when visual error increases, but then saturates for large visual errors. Dashed line indicates 190ms into the movement. **C.** Change in force (measured at 190ms) for the same representative subject across all five visual gains (0-2, sequentially from left to right) for the medium force perturbation. **D.** Change in force (measured at 190ms) for the three force perturbation sizes (small, medium and large, left to right) at zero visual gain for the representative subject. **E.** Group data: change in force as a function of visual error size. Lines represent a single force perturbation size, and each point represents a visual gain. **F.** Change in force as a function of proprioceptive error size ( $g=0$ ) for the group.

## 2.3.2 Sensitivity to error

In Figs. 2.2E-F we found that the adaptive response to a perturbation scales with increasing error size for the smallest error sizes only. As error size gets large, adaptation saturates and becomes non-linear. While we find this to be true for both visual and proprioceptive errors, we cannot ignore the possibility that the discrepancy between visual and proprioceptive errors may be modulating learning, not simply error size. It is possible that when vision and proprioception report differing error sizes, the likelihood that the error signals are reliable is reduced (Wei and Kording, 2009). This potential reduced confidence may decrease learning. To examine this, we considered a model of adaptation in which adaptation is a function of both visual ( $e_v$ ) and proprioceptive errors ( $e_p$ ), and their respective error sensitivities ( $\beta_v$  and  $\beta_p$ ) (Thoroughman and Shadmehr, 2000; Cheng and Sabes, 2006; Smith et al., 2006):

$$\lambda(e_v, e_p) = \beta_v e_v + \beta_p e_p \quad (2.5)$$

A simple way to model the potential effect of discrepancy between  $e_v$  and  $e_p$  is to include a term,  $\beta_{vp}$ , which is a function of that discrepancy and has a modulatory effect on the overall amount of adaptation that occurs:

$$\lambda(e_v, e_p) = (\beta_v e_v + \beta_p e_p) \beta_{vp}(|e_v - e_p|) \quad (2.6)$$

In Eq. (2.6),  $\beta_{vp}$  is a function of the absolute difference in magnitude between the visual and proprioceptive errors experienced by the subject. When there is no discrepancy, or  $|e_v - e_p| = 0$ ,  $\beta_{vp} = 1$ . For large discrepancies,  $\beta_{vp}$  approaches zero. This means that

when there is no discrepancy between vision and proprioception, Eq. (2.6) is equivalent to Eq. (2.5). As discrepancy increases,  $\beta_{vp}$  decreases, decreasing the amount of adaptation that occurs in response to the errors experienced. This function is similar to a function of the likelihood that visual and proprioceptive feedback were the result of the same event (Wei and Kording, 2009).

To dissociate the potential effect of discrepancy, or  $\beta_{vp}$ , from error size on the non-linearity observed during adaptation, we examined the sensitivity to error in conditions for which there was no discrepancy. This occurred during the  $g = 1$  conditions, for which the cursor and hand always match. Therefore, Eq. (2.6) can be reduced to:

$$\begin{aligned}\lambda(e_v, e_p) &= (\beta_v + \beta_p) e_v \\ \lambda(e_v, e_p) &= \beta e\end{aligned}\tag{2.7}$$

since  $e = e_p = e_v$ , and therefore  $\beta_{vp} = 1$ . Thus, the overall sensitivity to error,  $\beta$ , can be found as

$$\begin{aligned}\beta &= \frac{\lambda(e_v, e_p)}{e_v} \\ \beta &= \frac{f^{(n+1)} - \alpha^2 f^{(n-1)}}{e_v}\end{aligned}\tag{2.8}$$

If non-linearity in adaptation is due to discrepancy, and not to error size, then sensitivity to error should be constant when discrepancy is zero. To find the sensitivity to error,  $\beta$ , we binned all trials from the  $g = 1$  condition, taking advantage of the natural variability

of error size in response to a force field, and allowing us to find sensitivity at a variety of error sizes. Bin size was 0.25 cm and bins with fewer than 20 total movements were excluded. The results are plotted in Fig. 2.3A. We found that sensitivity to error is not constant, and declines as error size increases (repeated measures ANOVA, main effect of error magnitude,  $F(2,46)=8.95$ ,  $p=0.001$ ). Thus, we find that even when vision and proprioception agree, the brain is more sensitive to small errors than to large errors.

### 2.3.3 Sensitivity to visual and proprioceptive errors

Our results in Fig. 2.3A indicate that sensitivity to error is a nonlinear function of error, even when  $e_v = e_p$ . With no evidence of the modulatory effect of discrepancy, and no evidence that adaptation between visual and proprioceptive errors interferes (Krakauer et al., 1999), we hypothesized that adaptation,  $\lambda$ , is simply the result of the independent sum of adaptation from visual error and proprioceptive error, as described in Eq. (2.5). However, we believe the non-linearity is a result of error size modulating sensitivity. We can describe this hypothesis mathematically as:

$$\begin{aligned}\lambda(e_v, e_p) &= \beta_v(e_v)e_v + \beta_p(e_p)e_p \\ &\equiv \lambda_v(e_v) + \lambda_p(e_p)\end{aligned}\tag{2.9}$$

If Eq. (2.9) is true, it presents an interesting possible result – that sensitivity to a given visual error would be constant regardless of the corresponding proprioceptive error experienced. We can exploit the properties of Eq. (2.9) and our data to see if this is true. Given that proprioceptive error is fixed for a given force field size (Fig. 2.1E), we assume



that the proprioceptive component of adaptation,  $\lambda_p(e_p)$ , is the same for all visual gains within a given field size. Therefore, we can measure  $\lambda_p(e_p)$  in the  $g = 0$  condition, for which  $\lambda_v(e_v) = 0$  and  $\lambda(0, e_p) = \lambda_p(e_p)$ , and subtract this from the measured adaptation during all other conditions in which visual and proprioceptive errors are present concurrently. This allows us to isolate sensitivity to visual error:

$$\beta_v = \frac{\lambda(e_v, e_p) - \lambda(0, e_p)}{e_v} \quad (2.10)$$

For each subject, we subtracted the proprioceptive component of adaptation for two different magnitudes of proprioceptive error (small and medium). The resulting sensitivity to visual error is plotted in Fig. 2.3B. The first thing we noticed was that, as with our finding in Fig. 2.3A, sensitivity to visual error decreased with increasing error size. Additionally, we saw that there was substantial overlap between the curves for sensitivity to visual error experienced with the small proprioceptive error (green line) and medium proprioceptive error (purple line), indicating our assumptions in Eq. (2.9) were correct. To compare the two curves, we fit exponential decay functions to the small and medium visual sensitivity curves for each subject, such that  $\beta_v = \eta \exp(\tau e_v)$ . We found that the regression coefficients  $\eta$  ( $\eta_{small} = 1.39 \pm 0.42$  and  $\eta_{medium} = 1.05 \pm 0.39$ , mean  $\pm$  SEM) and  $\tau$  ( $\tau_{small} = -0.68 \pm 0.34$  and  $\tau_{medium} = -0.27 \pm 0.21$ , mean  $\pm$  SEM) were not significantly different (paired t-test,  $\eta$ :  $t(9) = 0.58$ ,  $p = 0.58$ ,  $\tau$ :  $t(9) = -0.84$ ,  $p = 0.42$ ), despite the medium proprioceptive error being significantly larger than the small proprioceptive error (one tailed paired t-test,  $t(39) = 26.9$ ,  $p < 0.0001$ ). In other words,

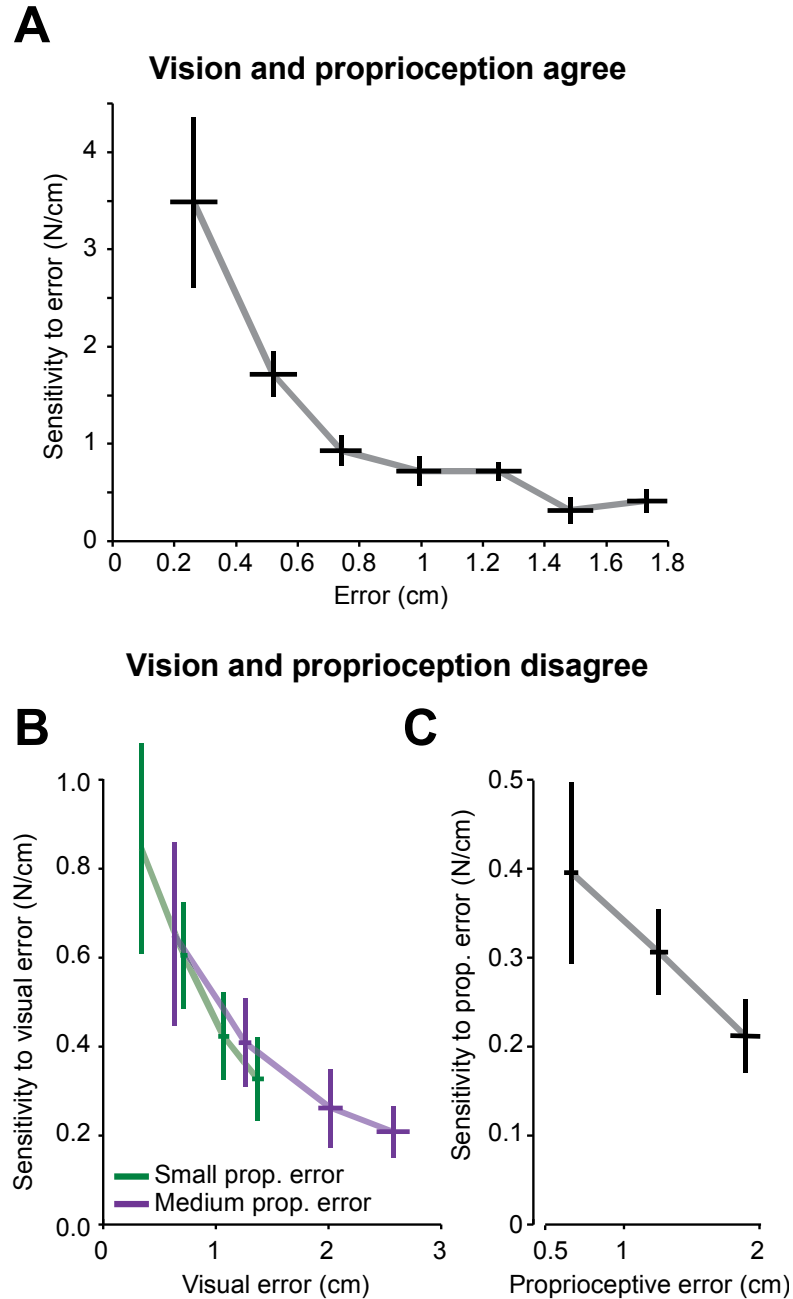
sensitivity to a given visual error is constant regardless of proprioceptive error. This substantiates our assumption that adaptation is the independent sum of visual and proprioceptive components of learning.

Given our findings that discrepancy does not modulate sensitivity to error, and that sensitivity to error is not a constant even without discrepancy, we can now more closely examine the relationship between sensitivity to error and error size. As with sensitivity to consistent visual and proprioceptive error,  $\beta$ , we found that sensitivity to visual error declined with increasing error size (comparison of the first and last points in Fig. 2.3B:  $t(9)=2.59$ ,  $p=0.01$ ). Thus, the brain appears to be more responsive to small visual errors than to large visual errors.

Finally, we considered sensitivity to proprioceptive error. We focused on the three  $g = 0$  conditions, in which visual error was clamped to zero but proprioceptive error increased with increasing force field size. Using Eq. (2.9) and the fact that  $e_v = 0$ , we found sensitivity to proprioceptive error as:

$$\beta_p = \frac{\lambda(0, e_p)}{e_p} \quad (2.11)$$

The results of this analysis are plotted in Fig. 2.3C. We found that, as with visual error, sensitivity to proprioceptive error decreased with increasing proprioceptive error size (one tailed paired t-test between the first and last points:  $t(9)=-2.03$ ,  $p=0.036$ ). Therefore for both vision and proprioception, the brain learns relatively more from small errors than large errors.



**Figure 2.3: Sensitivity to error declines as error size increases.** **A.** Sensitivity to error when visual and proprioceptive modalities are matched. Movements from all subjects were binned and bins with fewer than 20 movements were excluded. Bin size was 0.25 cm. Error bars represent SEM for each bin. **B.** Sensitivity to visual error. Sensitivity declines with increasing visual error, independent of proprioceptive error, as evidenced by the fact that the two curves coincide. Error bars are between subject SEM. **C.** Sensitivity to proprioceptive error also declines with increasing error size. Error bars are between subject SEM.

## 2.3.4 Analysis of previously published psychophysical results

In our results, we have found that sensitivity to error declines with increasing error size, regardless of the presence of discrepancy between modalities of error. To determine if our findings were a generalized occurrence, we reanalyzed data from previous publications and found that sensitivity to error declines with error size for multiple paradigms. We began with two, single trial adaptation tasks that were similar to ours. The first examined adaptation in response to a visual error alone (Wei and Kording, 2009) and the second measured adaptation in response to consistent visual and proprioceptive error (Fine and Thoroughman, 2006). As with our analysis, error experienced on trial  $n$  was measured as the lateral deviation of the cursor relative to a straight line between the start and target. Adaptation, which we will term  $\Delta x$ , was quantified as the perpendicular change in reach direction from the trial before the perturbation,  $n-1$ , to the trial after the perturbation,  $n+1$ , i.e.,  $\Delta x = x^{(n+1)} - x^{(n-1)}$ . This is analogous to our measurement of change in force to quantify adaptation. Likewise, adaptation is a product of the error experienced on trial  $n$  and the sensitivity to that error,  $\beta$  (Eq. 2.7):

$$\begin{aligned}\Delta x &= \beta x^{(n)} \\ \beta &= \frac{\Delta x}{x^{(n)}}\end{aligned}\tag{2.12}$$

Sensitivity can be found as before, by normalizing adaptation by error size. The results of our analysis are plotted in Figure 2.4A and 2.4B. In Wei and Kording (2009), subjects

made horizontal reaching movements without cursor feedback. At the end of their reach, they were briefly given endpoint feedback with the appearance of a cursor. The cursor position was shifted perpendicular to the reach direction by various amounts, as indicated by the x-axis in Fig. 2.4A, while the hand displacement was approximately zero throughout the experiment. Thus, subjects experienced visual errors only. This paradigm was carried out twice, once for 15 cm reaches and once for 5 cm reaches. As shown in Fig. 2.4A, for both reach amplitudes, sensitivity to error declines with increasing error size. This supports our findings in Fig. 2.3B, in which we find that visual sensitivity decreases with increasing error size as well. Importantly, this analysis quantifies sensitivity to visual error, without the presence of proprioceptive error, a condition that was not included in our experiment. Thus, our findings regarding sensitivity to visual error are robust to the presence or absence of proprioceptive error.

In Fine and Thoroughman (2006), errors were generated with a force pulse to the hand, and while veridical feedback was provided with a cursor. Therefore, visual and proprioceptive feedback was consistent and there was no discrepancy between modalities. This is similar to our  $g = 1$  condition. Our analysis of their results, shown in Fig. 2.4B, again finds that sensitivity to error declines with increasing error size. This offers further support to our findings in Fig. 2.3A, and to the hypothesis this pattern of sensitivity exists independent of discrepancy between modalities.

Finally, we considered a different type of paradigm, in which the goal was to estimate a loss function. A loss function is a computational construct that specifies costs associated with prediction errors. In other words, it quantifies how much worse is it to have a large prediction error vs. a small prediction error. Loss functions are often chosen

to be quadratic functions of error, such that the loss,  $\Psi$ , is  $\Psi = (y - \hat{y})^2$ . In a study by Kording and Wolpert (2004), subjects participated in a pea shooting task in which they were given various distributions of error sizes. How the subject adjusted their movements to maximize their success, or the probability of landing a pea in the target area, allowed the authors to estimate the actual loss function assumed by the subject. They found that loss was not quadratic, and instead could be approximated as  $\Psi = |y - \hat{y}|^{1.72}$ .

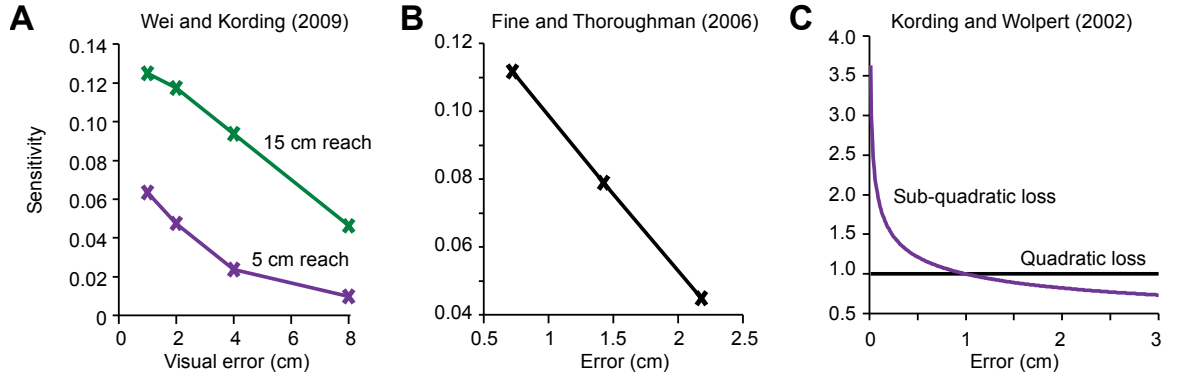
To find sensitivity to error using a loss function, imagine that the subject's prediction on trial  $n$  is a function of some parameter,  $\mathbf{w}^{(n)}$ , such that the prediction,  $\hat{y}$  is  $\hat{y}^{(n)} = g(\mathbf{w}^{(n)})$ . To minimize loss after experiencing an error,  $\tilde{y}$ , subjects change  $\mathbf{w}$  in the direction opposite to the gradient with respect to the parameters, or along the gradient of steepest descent:

$$\begin{aligned}\mathbf{w}^{(n+1)} &= \mathbf{w}^{(n)} - \eta \frac{d\Psi}{d\mathbf{w}} \\ &= \mathbf{w}^{(n)} - \eta \frac{d\Psi}{d\hat{y}} \frac{d\hat{y}}{d\mathbf{w}}\end{aligned}\tag{2.13}$$

In this framework, adaptation can be thought of as the change in  $\mathbf{w}$ , or  $\Delta\mathbf{w} = \mathbf{w}^{(n+1)} - \mathbf{w}^{(n)}$ . As before, we can find sensitivity to prediction error as the ratio of adaptation to error:

$$\begin{aligned}\beta(\tilde{y}) &= -\eta \frac{d\Psi}{d\hat{y}} \frac{d\hat{y}}{d\mathbf{w}} \frac{1}{\tilde{y}} \\ &\propto \frac{d\Psi}{d\hat{y}} \frac{1}{\tilde{y}}\end{aligned}\tag{2.14}$$

If the loss function is in fact quadratic, then  $\frac{d\Psi}{d\tilde{y}} = -2\tilde{y}$ . When substituted into Eq. (2.14),  $\beta(\tilde{y})$  reduces to a constant, which would imply that adaptation is linearly related to error size. However, using the loss function as determined by Kording and Wolpert (2004),  $\Psi = |y - \hat{y}|^{1.72}$ , we find that  $\beta(\tilde{y}) \propto |\tilde{y}|^{-0.28}$ , and sensitivity declines with increasing error size. Both calculations for sensitivity to error are shown in Fig. 2.4C. Using the sub-quadratic loss function, we again find that sensitivity to error declines with increasing error size, a finding that is consistent across multiple modalities and now, multiple paradigms.



**Figure 2.4: Re-analysis of previously published psychophysical results.** **A.** From Wei and Kording (2009). Adaptation to a visual shift perturbation of increasing size was measured without the presence of proprioceptive error. Sensitivity was calculated as adaptation normalized by the visual perturbation for each reach distance, 15 cm and 5 cm. **B.** From Fine and Thoroughman (2006). Adaptation to force pulses, generating consistent visual and proprioceptive errors. Sensitivity was calculated as this adaptation normalized by error size. **C.** Sensitivity to error as described by the loss function measured in Kording and Wolpert (2004). Subjects adjusted their hand position in a pea shooting task depending on the distribution of errors. From this, a loss function was estimated and found to be a sub-quadratic function of error. We calculated the sensitivity for two potential loss functions.

### 2.3.5 Neural correlate of sensitivity to error

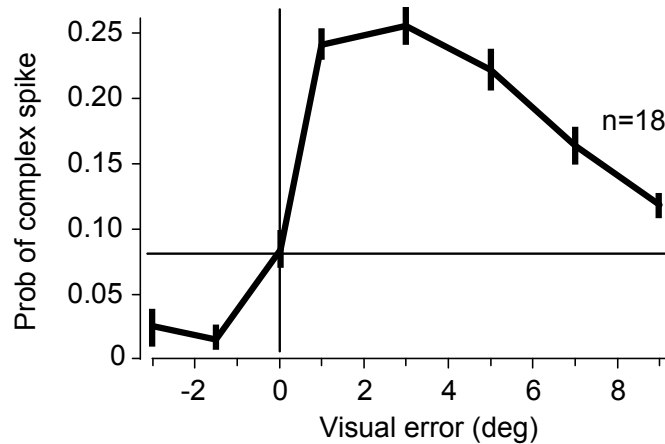
Error dependent adaptation in reaching is known to depend on the cerebellum (Smith and Shadmehr, 2005; Rabe et al., 2009; Criscimagna-Hemminger et al., 2010; Donchin et al., 2012; Schlerf et al., 2012). The errors that drive adaptation are typically believed to be signaled to the cerebellum by climbing fiber input to the Purkinje cells, which cause complex spikes (CSs) (Marr, 1969; Albus, 1971; Ito, 1972). These CSs are believed to represent an error, or a difference between the predicted sensory feedback and an experienced sensory feedback (Kawato, 2003). If this hypothesis were true, the occurrence of a CS might show a linear relationship to error. While CSs are definitively related to the presence of an error (Medina and Lisberger, 2008), there is considerable evidence that they do not represent the error signal itself (Ojakangas and Ebner, 1992; Catz et al., 2005; Soetedjo and Fuchs, 2006). In light of our results, we suggest that CSs are actually representative of sensitivity to error.

Soetedjo et al. (2008) used a saccade paradigm to examine the relationship between error size and the occurrence of a CS. For this task, monkeys made 15 degree saccades, during which the target was jumped forward or backwards by a random amount, leading to a visual prediction error at the end of the eye movement. This led to CSs in the Purkinje cells of the oculomotor cerebellum. The authors found two groups of Purkinje cells, those who showed CSs early and with low variability in their timing (early-compact), and those with late responding CSs and high variability (late-broad). When the relationship between the probability of a CS and error size was considered, the early-compact group showed its highest probability for small errors while the late-broad group showed a relatively flat distribution across error sizes. However, the authors



described this distinction as “somewhat arbitrary.” In Fig. 2.5, we collapse these both groups by taking the weighted average of the two populations. The results indicate that the probability of a CS declines with increasing error size.

In the analysis of our psychophysical results, we have found that the amount that one adapts to an error is driven by two factors – the magnitude of the sensory prediction error and the sensitivity to that error. In principle, sensitivity to error reflects the confidence associated with that error. In other words, it is a quantification of how much the brain believes it should learn from a given error. In our results, we found that this value was not a constant, as it is often assumed to be (Cheng and Sabes, 2006; Scheidt et al., 2001; Smith et al., 2006; Thoroughman and Shadmehr, 2000; van Beers, 2009). Instead, sensitivity to error declined with increasing error size. Presumably, CSs could represent either quantity and still be found to be related to error during motor adaptation. However, the relationship between the probability of CSs and error size suggest that they are the neurological signal for error sensitivity, rather than the error itself.



**Figure 2.5: Analysis of data from Soetedjo et. al. (2008).** Average probability of a complex spike from  $n=18$  Purkinje cells in the cerebellum in response to visual errors of various sizes. The probability of a complex spike peaks for small errors, and then declines as error size increases. This corresponds to sensitivity to error, and not error itself.

## 2.4 Discussion

When making a movement, the brain makes a prediction about the anticipated sensory consequences. When the actual sensory consequences differ from predicted, an error signal is generated and the brain updates subsequent motor commands for improved performance. Essential to this process is the sensitivity to error, or rather, the amount that the brain learns from a given error. Typical models of motor adaptation assume that sensitivity to error is constant with respect to error size (Cheng and Sabes, 2006; Scheidt et al., 2001; Smith et al., 2006; Thoroughman and Shadmehr, 2000; van Beers, 2009). Here, we attempted to quantify the value of sensitivity to error, and found that sensitivity to error is not constant, and instead declines with increasing error size. We found this to be true for both visual and proprioceptive errors, and to occur even when there was no discrepancy between modalities of error.

## 2.4.1 Perception of error

One potential alternative explanation for the pattern of sensitivity error that we find may relate to the perception of errors. If the brain is less able to perceive large errors, it would be expected that the brain would learn less from them. For our study, we assumed that sensing of error was unbiased, and that the brain received accurate sensory feedback regarding the movement error. One potential way to assess this possibility is to look at within trial feedback correction. If the brain can correct for both large and small errors alike, then perhaps we can assume that perception of error is unbiased. Our study utilized ballistic movements (150-250 ms reach duration), specifically trying to minimize the opportunity for online feedback correction, in the hopes that we could isolate trial-to-trial adaptation. However, other publications can offer insight to this issue.

Scheidt et al. (2005) examined force field adaptation for point-to-point reaching movements through a force field that was similar to our medium strength perturbation condition. The perturbation was turned on abruptly and maintained. Importantly, the authors also removed visual feedback. At the start of adaptation, when errors were largest, subjects successfully corrected for their proprioceptive errors and accurately returned the perturbed hand to the target (column 2 of their Fig. 2B, and row 5 of their Fig. 4). As training continued, errors were reduced and subjects continued to successfully correct for the perturbation by returning their hands to the target, but without any change in accuracy (column 3 of Fig. 2B, and row 5 of Fig. 4). This suggests that the brain can accurately perceive and therefore, correct for, both large and small errors in proprioception. A second example, allowing us to examine this in visual errors, comes from the work of Veerman et al. (2008). For this study, the authors generated a visual

error by jumping the position of the target during the reach. They found that doubling the imposed visual error caused the online motor response to double as well. Therefore, it appears that the brain can accurately detect and correct for a range of visual error sizes, in addition to proprioceptive error sizes. This tells us that our findings about sensitivity to error are likely not due to a bias in the perception of error size.

## 2.4.2 Additional factors modulating sensitivity to error

Though we believe that there is no bias in the perception of large and small errors within a given experiment, there may be biases that occur between different experiments. For example, consider the two lines in Fig. 2.4A, which display the sensitivity to endpoint visual error for two tasks that were identical with the exception of reach amplitude. For a given perturbation, the sensitivity to error for the 5 cm reach is smaller than the sensitivity to error for a 15 cm reach, though the absolute error size (lateral deviation of the cursor) was identical. What could cause these differences? The authors note that the end point reach variability was significantly smaller for the 5 cm reach than for the 15 cm reach (Wei and Kording, 2009). If we consider the visual errors (the x-axis of Fig. 2.4A) in terms of z scores for their respective experiment, then the z-scores for the 5 cm reach are larger than for the 15 cm reach, potentially causing the smaller sensitivity. Alternatively, we can consider the visual errors with respect to reach amplitude by taking the angular error, and not simply the lateral deviation. Then, for example, the angular error of the 4 cm perturbation on a 5 cm reach is larger than the same perturbation applied to a 15 cm reach, potentially explaining the smaller sensitivity to error during 5 cm reaches. These are only two examples of how task parameters as simple as reach

amplitude can alter the brain's perception of an error size. It is likely that an error signals are complex, and dependent on many parameters, many of which can alter ones sensitivity to error.

Additionally, the structure of a task can alter error sensitivity. Previous work has shown that learning increases when perturbations have a positive trial-to-trial autocorrelation, and decreases when perturbations have a negative trial-to-trial autocorrelation (Smith and Shadmehr, 2004). In other words, if a given error indicates the presence of similar errors in the future, the brain will learn relatively more from that error. If that same error poorly predicts future errors, the brain will learn relatively less from it. Thus, sensitivity to the same error can be altered, depending on the history of errors experienced.

Finally, consider the variance in our measure of sensitivity to error. We find larger variance for small errors as compared to large errors (Fig 2.3). This is a result of the nature of our sensitivity calculation. Sensitivity, in simplest terms, is the ratio of trial-to-trial change in force and error, both of which are random variables. When taking the ratio of any two Gaussian random variables, with an arbitrary but constant standard deviation, as the mean of the random variable in the denominator becomes smaller (for our purposes, as the error becomes smaller), the variance of the ratio becomes larger (Hinkley, 1969). Therefore, our increased variance surrounding our calculation of sensitivity to small errors relative to large errors is a reflection of our analysis, which requires us to take the ratio of two random variables.

### 2.4.3 The effect of forward models on sensitivity to error

Studies of generalization have found that when people adapt to an imposed perturbation, they learn the greatest amount along the path which their hand actually traveled (where they experienced the error due to the perturbation), and relatively less where they intended to move (along the path to the target) (Izawa and Shadmehr, 2011; Izawa et al., 2012a; Gonzalez Castro et al., 2011). This has been attributed to learning with a forward model, which suggests that the brain learns a mapping between motor commands and sensory feedback. To understand this, imagine a person is making a reach to a target at zero degrees. When a force field is turned on, the hand is perturbed approximately 30 degrees from the target, and the subject uses the experienced error to update their motor-sensory map. In the context of a forward model, what that subject has learned is that the motor command that was generated to reach zero degrees (the intended state) actually generates a movement to 30 degrees (the experienced state). Selecting a motor command that will bring the hand to the target requires generalization of the learned, and experienced, motor-sensory mapping to a desired, and previously unexperienced, sensory state. If forward model generalization declines with distance, then this model would imply that sensitivity to error would decline with increasing error size as well.

Though intriguing, the forward model framework for decreasing sensitivity to error with increasing error size is not likely the only explanation for our current findings. Izawa and Shadmehr (2011) measured adaptation to a gradually introduced visual rotation in two groups – one which had full cursor feedback throughout the reach, and another which had only endpoint visual feedback. When measuring generalization, the

group which had full cursor feedback showed a shift in the peak of generalization, away from the target and towards the direction of the experienced errors, supporting the forward model hypothesis. However, the group that had only endpoint visual feedback showed a peak at the target direction, suggesting that this effect requires full, online sensory feedback. In our analysis of previous published results, we include a study in which only endpoint visual feedback was provided (Fig. 2.4A). Despite the lack of online visual feedback, subjects still demonstrated decreased sensitivity to error with increasing error size. This demonstrates that our findings are consistent even in instances where this effect is not present, and that forward model generalization likely cannot fully explain the given results.

#### 2.4.4 The impact of discrepancy on adaptation

A key feature of our paradigm was to vary visual and proprioceptive errors independently of each other. While this allowed us to find sensitivity to visual and proprioceptive error alone, it also introduced a question the effect of discrepancy between visual and proprioceptive error signals on adaptation. The causal inference model would suggest that sensitivity declines as discrepancy increases (Wei and Kording, 2009), implying that the brain maps both sensory errors onto a common metric for comparison. However, a study of cerebellar patients found separate regions of the cerebellum to be responsible for visual rotation (visual error only) adaptation and force field (consistent visual and proprioceptive error) adaptation, and found that performance in the two tasks were not correlated (Donchin et al., 2012). This indicates that there is no common neural

substrate for which errors will be compared. Behaviorally, learning and consolidation of rotations and force perturbations do not interfere with each other, further suggesting separate mechanisms of adaptation (Krakauer et al., 1999). Additionally, degradation of proprioceptive information does not encourage adaptation in a visual rotation experiment, indicating that adaptation occurs in response to visual error is independent of the proprioceptive feedback (Bock and Thomas, 2011; Pipereit et al., 2006). Without any behavioral or anatomic link between visual and proprioceptive errors, it seems unlikely that the brain could quantify discrepancy and utilize it for adaptation. Finally, saturation of adaptation occurs even without the presence of discrepancy (Fine and Thoroughman, 2006). However, it is worth noting that though we found no significant effect of discrepancy on sensitivity to error, our findings were negative and we only explored a small range of discrepancies. We cannot exclude the effect that large discrepancies may have on adaptation.

### 2.4.5 Complex spikes and error dependent learning

Models of cerebellar learning suggest that complex spikes of the Purkinje act as the brain's error signal (Kawato, 2003). For this to be true, one would anticipate that the occurrence of a CS would scale with error size, such that the probability of a CS is large when errors are large, and small when errors are small. However, there are several examples in which this theory has failed. For instance, consider the saccade adaptation task by Catz et al. (2005). At the onset of adaptation, when the perturbation is first introduced and errors are largest, the probability of a CS is at its lowest. As training



continued, errors were reduced but the probability of a CS increased. In another study by Soetedjo and Fuchs (2006), error was reduced with no corresponding changes in the probability of a CS. In a study of reach adaptation by Ojakangas and Ebner (1992), the probability of a CS initially increased at the beginning of training but did not change as errors were reduced and adaptation progressed. In fact, to our knowledge, only one study (Gilbert and Thach, 1977) found a reduction in the probability of CSs during adaptation. Therefore, while it appears that CSs are related to motor adaptation, it seems unlikely that a CS encodes a prediction error.

What then, do complex spikes encode? When we analyzed the findings of Sotetedjo et al. (2008) (Fig. 2.5), we found an inverse relationship between the probability of a CS and error size, similar to the relationship between sensitivity to error and error size. Therefore, we propose a new idea – that CSs do not encode error, but rather sensitivity to error, modulating the amount one learns from an error signal.

Our proposed model can potentially account for an interesting finding in neurophysiology experiments. Consider a rightward horizontal saccade in which the target is stepped back (gain-down) and a leftward horizontal saccade in which the target is stepped-forward (gain-up). In both instances, the perturbation would generate the same error vector, despite the fact that the initial saccades were in opposite directions. Although the errors are the same in magnitude and direction, monkeys tend to adapt less to a gain-up error as compared to a gain-down error (Robinson et al., 2003). If CSs encode error, then for both conditions, the probability of a CS should be the same, reflecting the consistent error magnitudes. Instead, the authors found that a gain-down error causes a greater and more sustained increased in CS activity than a gain-up error

(see Fig. 4 in Soetedjo and Fuchs (2006)). Thus, when sensitivity to error was greater, there was a greater CS response, supporting our hypothesis that CSs encode sensitivity to error and not error magnitude.

## 2.4.6 Implications for patients

In the presence of an abruptly introduced force field perturbation, patients with cerebellar degeneration are unable to adapt their movements and compensate for the field (Smith and Shadmehr, 2005; Criscimagna-Hemminger et al., 2010). However, when this perturbation is introduced gradually, patients are able to adapt their movements (Criscimagna-Hemminger et al., 2010). In other words, when faced with widespread cerebellar degeneration, patients were able to learn from small errors, but not large errors. Given that smaller errors are more likely to induce a complex spike, it is possible that adaptation in these patients is a reflection of greater engagement of the residual functionality of the cerebellum. A greater understanding as to how the brain determines an error to be large or small may provide insight into how patients with cerebellar damage adapt, and may lead to improvements in therapeutics.

Additionally, abnormalities in the weighting of sensory feedback during motor tasks are present in disease populations. For instance, when visual feedback is rotated from the hand position, patients with schizophrenia show increased confidence in visual feedback relative to controls (Synofzik et al., 2010). In contrast, when children with autism spectrum disorder adapt to a force field, they show increased generalization of this learning in proprioceptive coordinates, relative to controls. This suggests an overreliance

on proprioception during motor learning (Haswell et al., 2009; Izawa et al., 2012b). For both patient groups, these results may stem from an increased sensitivity to visual or proprioceptive error, respectively. Specifically measuring the sensitivity to visual and proprioceptive error will allow for a greater understanding of how these abnormalities in sensory processing impact motor learning in patients.

# Chapter 3

## Sensitivity to motor error in children with autism spectrum disorder

### 3.1 Introduction

Autism spectrum disorder is a developmental disorder, characterized by deficits in social and communication skills, and repetitive and stereotyped patterns of behavior. Though motor impairments are not considered a diagnostic feature of ASD, motor deficits have been widely reported in ASD (Jansiewicz et al., 2006; Mostofsky et al., 2006; Dowell et al., 2009; Dziuk et al., 2007; Gowen and Hamilton, 2013). These impairments are broad and generalized, and lack any clear clinical classification (described in Chapter 1). Likewise, abnormalities in sensory function have been repeatedly demonstrated, but lack any clear signature impairment (Leekam et al., 2007; Williams et al., 2004; Nakano et al., 2010; Nakano et al., 2012; Tannan et al., 2008; Blakemore et al., 2006; Paton et al., 2012). Impairments in motor abilities can have far reaching effects, as motor control is believed essential for communication, language,

and potentially even the understanding of others thoughts and intentions (Iacoboni, 2009;Gallese et al., 2004).

To better understand the cause of this motor dysfunction, one must consider the developmental nature of ASD. It is likely that motor impairments, present even in infancy (Provost et al., 2007;Teitelbaum et al., 1998), are rooted in the ability to acquire motor skills, or motor learning. As described in Chapter 2, motor learning is believed to be driven by the formation of internal models, which contain a mapping of action onto expected sensory feedback (Wolpert and Miall, 1996). Prior to making a movement, these models are used to formulate a prediction of the sensory consequences of the movement. If the actual sensory feedback differs from what is predicted, an error is experienced and motor adaptation ensues, updating the internal model of action. Given that motor learning is driven by sensory feedback, abnormalities in sensory processing have the potential to disrupt the proper formation of internal models and motor learning. On a developmental timescale, such impairments may lead to global motor deficits.

Interestingly, in sensorimotor tasks, the effect of these abnormalities can sometimes lead to improved performance relative to healthy controls. For instance, when measuring generalization of motor learning during reach adaptation, children with ASD show increased learning in proprioceptive coordinates (Haswell et al., 2009;Izawa et al., 2012b). Similarly, in a haptic-to-visual shape matching task, in which subjects explored an object by tracing it with their finger, individuals with autism are better able to identify the object (Nakano et al., 2012). Further, individuals with ASD show lower thresholds in measures of tactile perception of vibro-tactile stimuli (Tannan et al., 2008;Blakemore et al., 2006), and less susceptibility to proprioceptive drift during the rubber hand illusion

(Paton et al., 2012). We hypothesize that this oversensitivity to somatosensory feedback will be reflected in an increased sensitivity to proprioceptive error during motor adaptation.

In contrast, individuals with autism show deficits in their ability to utilize visual feedback. For example, individuals with ASD have well documented difficulties with imitation (Dowell et al., 2009; Vanvuchelen et al., 2007; Stieglitz et al., 2008; Williams et al., 2004). Imitation, however, is a complex process involving the translation another's actions to one's own body mapping, and reproducing them. Related efforts to identify a core visuomotor deficit have examined the ability of individuals with ASD to properly respond to biological motion. They found that adults with ASD are less able to recognize biological motion (Cook et al., 2009) and children with ASD show preferential attention to motion of objects rather than biological motion, unlike their TD controls (Annaz et al., 2012). This hyporeactivity to the visual feedback of movement is believed to relate to deficits in imitation and social cognition (Dziuk et al., 2007; MacNeil and Mostofsky, 2012; Mostofsky et al., 2006). We hypothesize that, during simple motor adaptation, children with ASD will show a decreased sensitivity to visual error, providing a quantification of the hypo-responsiveness to visual feedback of motion. Understanding sensitivity to visual and proprioceptive error in children with ASD will not only offer a better understanding as to how individuals with ASD learn to make movements, but also provide insight into how they learn from and interact with their surroundings.

## 3.2 Methods

### 3.2.1 Subjects

We recruited  $n=40$  children, ages 8-12.  $N=20$  were typically developing (TD, 16 male, age  $10.3 \pm 0.3$ , mean  $\pm$  SEM, one left handed), and  $n=20$  were diagnosed with ASD (18 male, age  $10.95 \pm 0.2$ , one left handed). ASD diagnosis was based on DSM-IV criteria and established using both the Autism Diagnostic Observation Schedule (ADOS-G: first 9 participants,  $14.6 \pm 1.8$ , mean  $\pm$  SEM, or ADOS-2: final 11 participants,  $11.4 \pm 1.3$ , mean  $\pm$  SEM) and was confirmed by ADI-R (Autism Diagnostic Interview, Revised) and a pediatric neurologist. Children were excluded if they had a known etiology for autism, or a documented prenatal/perinatal insult. Children from either group were excluded if they scored  $<80$  on the Wechsler Intelligence Scale for Children - IV (WISC-IV) Full Scale IQ. Subjects were matched for gender (Fischer's exact test,  $p=0.66$ ), age ( $t(38)=1.70$ ,  $p=0.09$ ), Perceptual Reasoning Index ( $t(38)=1.74$ ,  $p=0.09$ ), and Edinburgh Handedness score, ( $t(38)=-0.64$ ,  $p=0.52$ ) (see Table 3.1). All protocols were approved by the Johns Hopkins Institutional Review Board and a legal guardian for all participants provided written, informed consent.

	<b>ASD</b>	<b>TD</b>
<b>n</b>	20	20
<b>Males</b>	18	16
<b>Age</b>	10.95±0.22	10.30±0.30
<b>Perceptual Reasoning Index</b>	109.6 ± 2.9	117.7 ± 3.6
<b>Edinburgh Handedness Score</b>	0.737 ± 0.1	0.828 ± 0.1
<b>ADOS-G/ADOS-2</b>	14.6 ±1.8/11.4 ±1.3	N/A

**Table 3.1: Participant information.** There were no significant differences in gender, age, perceptual reasoning index or handedness between groups. Children with ASD were diagnosed with the ADOS-G or ADOS-2 and by physician examination.

### 3.2.2 Psychophysical task

The robot task for the children was a modified version of the robot task used for the adults (Chapter 2). Briefly, children sat in front of a robot with a screen over their arm, and made reaching movements to a target as it appeared on the screen (Fig 3.1A). On random trials, their arm was perturbed with a force field to the left and right of various different sizes (Eq 2.1) generating a small proprioceptive error ( $b = \pm 6.5$  N.s/m), a medium proprioceptive error ( $b = \pm 13$  N.s/m) or a large proprioceptive error ( $b = \pm 19.5$  N.s/m). At the same time, they had a visual gain applied which scaled the lateral deviation of the cursor (Eq. 2.2) by 0, 1 or 2. Before and after each perturbation trial was a channel trial, with which we could measure the motor output of the subject (Fig. 3.1A). This created triplets of trials, or  $C_1PC_2$  triplets, which were randomly separated by 0, 1 or 2 null field trials. Trajectories through all perturbation conditions for the hand and cursor can be seen in Fig. 3.1B for a representative subject, and in Fig. 3.1C for the group.



To modify the paradigm to make it more suitable for children, we eliminated the gains of 0.5 and 1.5 from the paradigm that were present in the adult version of the task (Chapter 2). This was an effort to shorten the experimental duration. Additionally, we split the experiment into two sessions. Both sessions began with a warm up block, and then consisted of five experiment blocks. As with the adults, in each experiment block, all perturbations were given once in each direction. This ensured that each block, and the overall experiment, was balanced with a mean perturbation of zero. Finally, in addition to feedback about movement timing (the target square turning red, blue or exploding for movements that were too fast, slow or correctly timed, respectively), an animated coin appeared for each movement that successfully crossed through the target between 150-250 ms. Children were instructed to collect as many coins as possible.

### 3.2.3 Quantifying adaptation to error

As evidenced in Chapter 2, this random perturbation schedule will produce learning from error that can be measured as the difference in force from the channel before ( $C_1$ ) to the channel after ( $C_2$ ) the perturbation (P). Specifically, adaptation can be found using a state space framework for error dependent learning (Donchin et al., 2003), and from Eq (2.4):

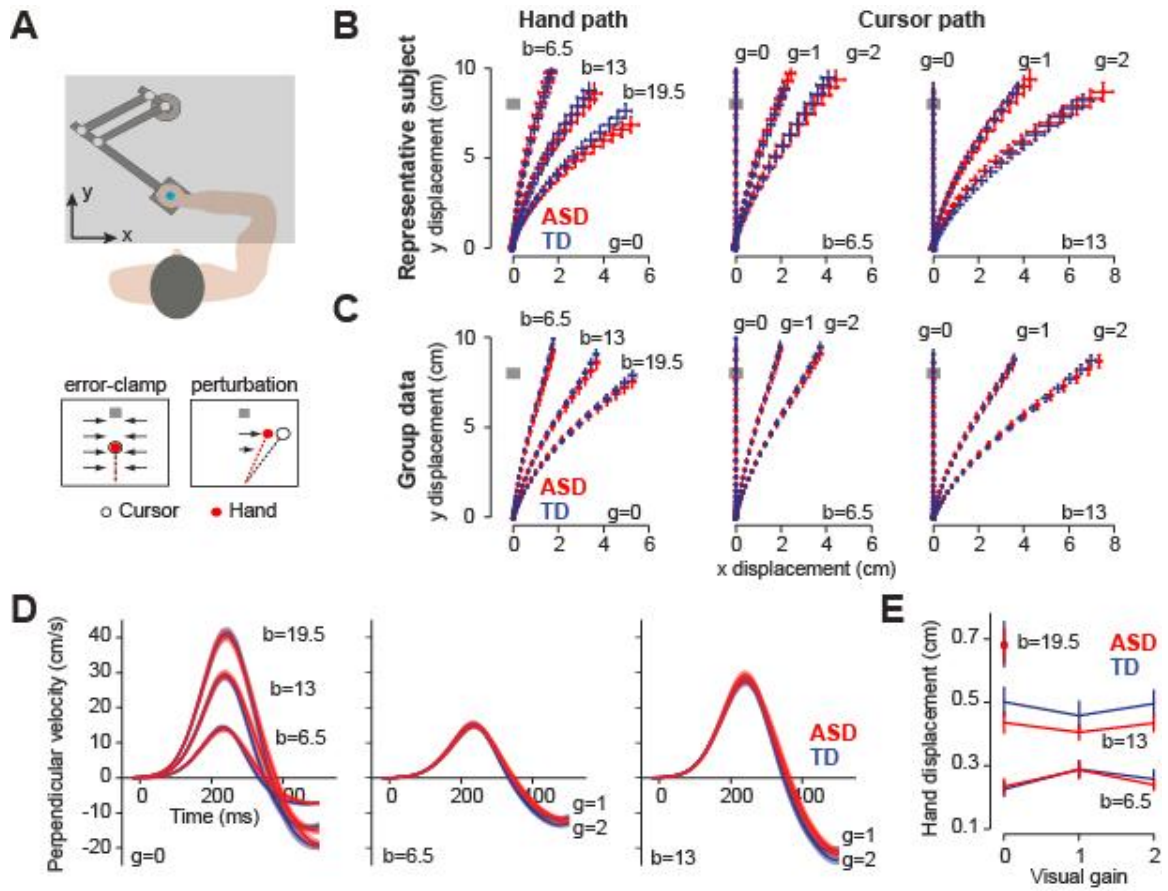
$$\lambda(e_v^{(n)}, e_p^{(n)}) = f^{(n+1)} - \alpha^2 f^{(n-1)} \quad (3.1)$$

where  $f^{(n-1)}$  is the force measured during  $C_1$ ,  $f^{(n+1)}$  is the force measured in  $C_2$ , and  $\lambda$  is the adaptation that occurs in response to the visual and proprioceptive errors,  $e_v$  and  $e_p$ , experienced from the perturbation on trial  $n$ .

The decay term,  $\alpha$ , quantifies how much force production of the subject decays from trial to trial. This was found using any instance in the experiment when there were two consecutive error-clamp trials, which occurred 52 times across the duration of the experiment. To quantify  $\alpha$ , we regressed the force profile in the second of the consecutive error-clamp trials onto the first, telling us how much of the motor output was retained in two consecutive movements. We found that  $\alpha = 0.91 \pm 0.05$  (mean  $\pm$  SEM). There was no significant difference in the value of alpha between groups ( $t(38)=0.60$ ,  $p=0.55$ ).

To find a single value to represent motor output or error for a given trial, we used the measured force or lateral deviation of the hand/cursor at 50% of the maximum speed of the movement (Taig et al., 2012). There was no difference between groups in time to 50% of max speed ( $t(38)=-0.12$ ,  $p=0.91$ ), which occurred an average of 149 ms after movement onset. Thus, using Eq. (3.1), we could find  $\lambda(e_v^{(n)}, e_p^{(n)})$  as a scalar value. Triplets were removed from analysis if 50% of max speed occurred prior to 100 ms from movement onset, if they did not successfully complete the 8 cm reach, if the hand moved further than twice the width of the target box (0.6 cm) from the midline during a channel trial, or if the hand experienced a substantial error in the wrong direction ( $>\pm 0.5$  cm) in response to a perturbation. Additionally, within each condition, outliers were identified and removed using the  $p < 0.001$  criterion of the median absolute deviation. Together,

this removed  $6.6\% \pm 0.76\%$  (mean  $\pm$  SEM) of triplets per subject, with no difference in percentage of removed triplets between groups ( $t(38)=-1.1, p=0.29$ ). Learning from error and error size were corrected for sign and collapsed to one direction. Though adaptation and error are oppositely signed, data will be plotted in the first quadrant for ease of viewing. All analysis was completed using Matlab (Mathworks), Excel (Microsoft), or SPSS (IBM).



**Figure 3.1: Task and performance for children.** **A.** Children participated in a reach adaptation task in which they held a robotic manipulandum and made reaching movements to a target that appeared on a horizontal screen. **B.** Hand and cursor trajectories for a representative ASD and TD subject display no differences in online response to error. **C.** Group data for hand and cursor trajectories display no obvious differences in speed or lateral deviation, indicating no difference in online response to error between groups. **D.** Perpendicular velocity of the hand for all perturbation conditions, a sensitive measure of online feedback response, again shows no difference between groups. **E.** Lateral deviation of the hand, measured at 50% of max speed, shows no effect of gain or group on hand error.

## 3.3 Results

### 3.3.1 Feedback response during a perturbation

When quantifying the sensitivity to error during reach adaptation, it is important to distinguish between the effects of online error correction within a movement, and the trial to trial response to error we describe in Eq. (3.1). We anticipated that the applied perturbations and their resulting sensory feedback would engage reflex pathways, generating motor commands that partially corrected for the perturbation as the movement proceeded. Though we attempted to minimize this with short duration, ballistic movements, it is important to ensure there are no confounding effects of online feedback response in our trial-to-trial measurement of adaptation.

To examine the online response to error, we plotted the hand and cursor trajectories during the perturbation trials. Figure 3.1B shows the hand and cursor path for a representative subject from each group, and Fig. 3.1C shows the group data, for all possible perturbation conditions. We detected no obvious difference between the trajectories, indicating there was no difference in the nervous system's response to an error during the perturbation. A more sensitive measure of the motor system's response to sensory feedback is perpendicular velocity of the hand, which is plotted in Fig 3.1D. Again, we see no discernable differences in perpendicular velocity between groups, further demonstrating that both the short and long latency feedback response to error is similar for ASD and TD children.

As a scalar proxy for the error induced by the perturbations, we used displacement of the hand or cursor, perpendicular to a straight line reach to the target, at 50% of max speed. The value of the hand error using this metric is plotted for all conditions in Fig. 3.1E. We found that while increasing field strength increased proprioceptive error, there was no difference in errors between groups. Further, there was no effect of visual gain on hand displacement, indicating that proprioceptive error for a given field size is constant, regardless of the applied visual gain: ANOVA with a within-subject measure of hand displacement for visual gain, and between-subject factor of group showed a significant effect of field strength ( $F(1,38)=1575.1, p<0.001$ ), but found no effect of visual gain ( $F(2,37)=.623, p=0.54$ ), and no effect of group ( $F(1,38)=0.66, p=0.42$ ). Thus, we have found that during a perturbation trial, children with ASD responded normally to a visual or a proprioceptive perturbation. This implies that the visual and proprioceptive reflex gains of the motor system are similar across groups, and the errors experienced between the two groups were comparable.

### 3.3.2 Learning from proprioceptive error

Although demonstrating similar online responses to motor error, we hypothesized that children with ASD would show an increased trial-to-trial response to proprioceptive error. To examine this, we utilized the framework discussed in Chapter 2 and defined the adaptation, described in Eq. (3.1), as the independent sum of a visual and proprioceptive component of adaptation:

$$\begin{aligned}\lambda(e_v, e_p) &\equiv \lambda_v + \lambda_p \\ &\approx \beta_v(e_v)e_v + \beta_p(e_p)e_p\end{aligned}\tag{3.2}$$

As demonstrated previously, each component of adaptation is the product of the error experienced in that modality, and error sensitivity, which is a function of the error experienced (Marko et al., 2012). We were able to quantify the response to proprioceptive error using the three zero gain conditions ( $g = 0$  for all three values of  $b$ ). When the visual gain is zero, the visual error is clamped to zero as well, and Eq. (3.2) can be reduced:

$$\begin{aligned}\lambda(0, e_p) &= \beta_v(0)0 + \beta_p(e_p)e_p \\ &= \lambda_p\end{aligned}\tag{3.3}$$

Figure 3.2A, left, shows adaptation to proprioceptive error alone,  $\lambda_p$ , for the three different field sizes for both groups. We found that children with ASD learned more from a given proprioceptive error than TD controls. An ANOVA with a within subject repeated measure of field strength and a between-subject factor of group resulted in a significant main effect of group ( $F(1,38)=5.7, p=0.022$ ), but no significant effects of field size ( $F(2,37)=1.36, p=0.27$ ) or group by field interaction ( $F(2,37)=0.009, p=0.99$ ). In other words, the ASD group learned significantly more from proprioceptive error than the TD group.

We further examined this learning by calculating the proprioceptive sensitivity, or  $\beta_p$ , at each error size:

$$\beta_p(e_p) = \frac{\lambda(0, e_p)}{e_p}\tag{3.4}$$

Proprioceptive sensitivity represents adaptation that has been normalized to the specific error experienced, or how much learning occurs in response to a specific proprioceptive error. The results are shown in Fig. 3.2A, right, for each field size. As with the adults (Chapter 2), we found that sensitivity to error decreased with increasing error size. Importantly, we found that sensitivity to error was significantly larger for children with ASD than for TD controls, echoing the finding for proprioceptive adaptation. An ANOVA with a within subject repeated measure of field strength and between-subject factor of group resulted in a significant effect of group ( $F(1,38)=4.7, p=0.035$ ) and field ( $F(2,37)=4.72, p=0.015$ ). There was no significant group by field interaction ( $F(2,37)=.29, p=0.75$ ). Thus, we find that when perturbed proprioceptively, children with ASD exhibit greater sensitivity than normal.

### 3.3.3 Learning from visual error

Individuals with ASD are less able to imitate (Williams et al., 2004) or to recognize biological motion (Cook et al., 2009), suggesting impairments in their visuomotor abilities. We therefore hypothesized that they would also show a decreased sensitivity to visual error, as part of their deficit in processing visual information as it relates to movement. To explore this question, we focused on our conditions in which there was both visual and proprioceptive error present. The learning that occurs, labeled as  $\lambda(e_v, e_p)$ , is plotted as a function of visual error,  $e_v$  in Fig. 3.2B: the left panel shows adaptation for visual errors that occurred with medium proprioceptive error ( $b = 13$ ), and the right panel shows adaptation in response to visual error with the small



proprioceptive perturbation ( $b = 6.5$ ). While it is difficult to discern visual sensitivity from conditions with visual and proprioceptive error together, the TD group appears to have a more dynamic response to changing visual error, which would suggest greater visual sensitivity. In fact, this was verified by a significant interaction. Additionally, we found a significant effect of field and gain on adaptation: ANOVA with a within subject effect of field and gain and a between-subject factor group found a significant effect of field ( $F(1,38)=5.1, p=0.29$ ), a significant effect of gain ( $F(2,37)=20.9, p<.001$ ), and a significant gain by group interaction ( $F(2,37)=3.53, p=0.039$ ). All other effects were not significant ( $p>0.05$ ). Given that there are both proprioceptive and visual errors driving this measure of adaptation, we have no specific hypothesis regarding a group effect.

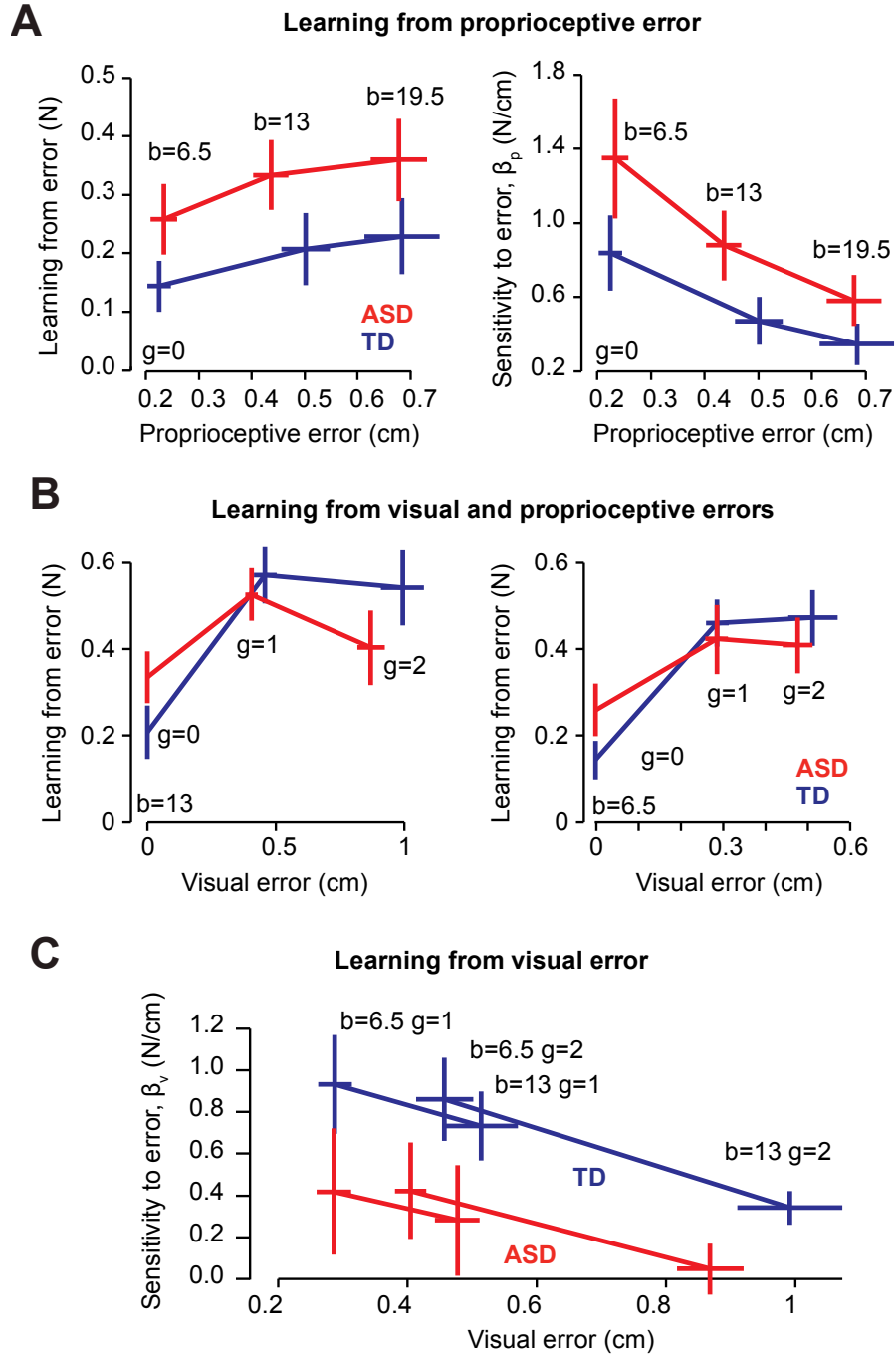
In Fig 3.2B, the middle data point for each plot shows the adaptation in the  $g = 1$  condition, or the condition in which visual and proprioceptive errors are consistent. This is a “normal” adaptation condition, for which prior studies have found no difference in the amount of adaptation between groups (Gidley Larson et al., 2008; Haswell et al., 2009). Likewise, we found no group difference in adaptation in response to a consistent visual and proprioceptive error: ANOVA with a within subject repeated measure of field strength and between subject factor of group found no significant effect of group ( $F(1,38)=0.28, p=0.61$ ), a significant effect of field ( $F(1,38)=4.45, p=0.042$ ) and no significant group by field interaction ( $F(1,38)=0.006, p=0.94$ ). Therefore, in “normal” conditions in which visual and proprioceptive feedback are consistent, the gross motor output of the ASD group appears normal.

To quantify sensitivity to visual error alone, we focused on the change in motor output when proprioceptive error was held constant and visual error was varied. As

shown in Fig. 3.1E, this occurs across visual gains within the small ( $b = 6.5$ ) and medium ( $b = 13$ ) perturbation conditions. As in Chapter 2, for a given field size, we can measure  $\lambda(0, e_p)$  in the  $g = 0$  condition, and substitute this into Eq. (3.2). We can then find sensitivity to visual error as:

$$\beta_v(e_v) = \frac{\lambda(e_v, e_p) - \lambda(0, e_p)}{e_v} \quad (3.5)$$

The result of this analysis is plotted in Fig. 3.2C. We again found that sensitivity to visual error was smallest for large errors, echoing our findings in adults (Chapter 2). We also found that sensitivity to visual error was smaller for children with ASD than TD controls: ANOVA with a within-subject repeated measure of perturbation size and between-subject factor of group resulted in a significant effect of group ( $F(1,38)=6.4$ ,  $p=0.016$ ), and a significant effect of perturbation size ( $F(3,36)=5.4$ ,  $p=0.004$ ), but no significant interaction ( $F(3,36)=0.21$ ,  $p=0.89$ ). In other words, children with ASD show less sensitivity to visual error, as compared to TD controls.



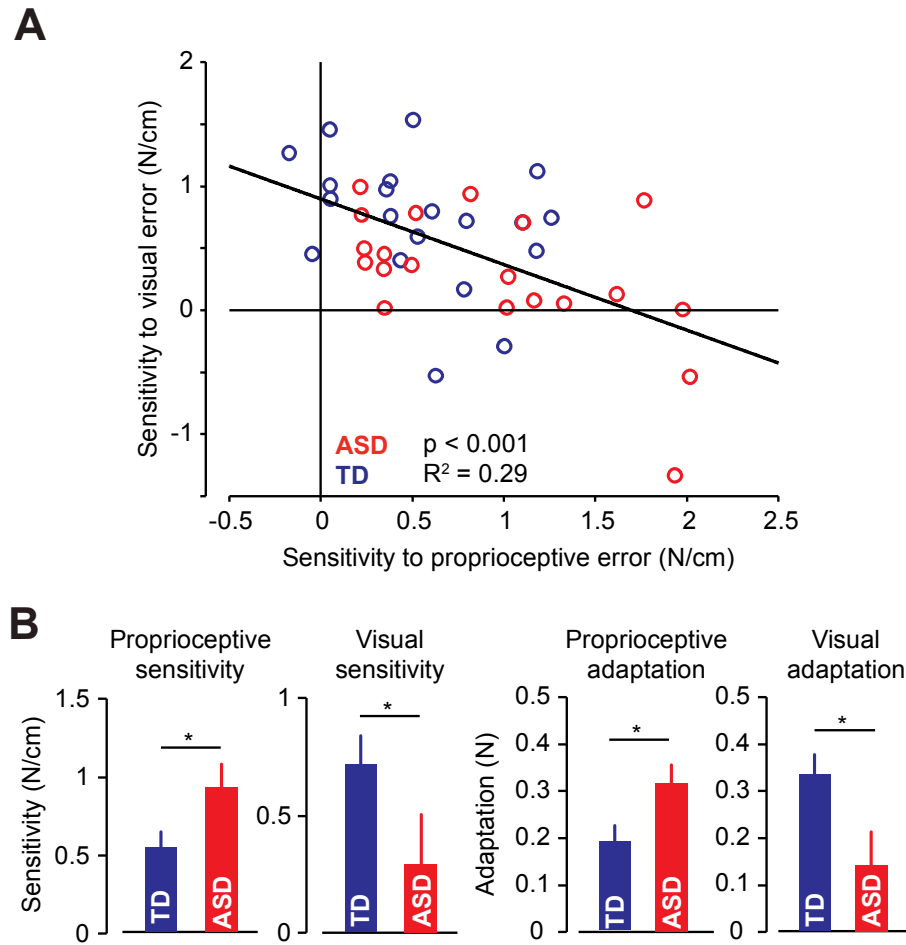
**Figure 3.2: Response to motor error in children with ASD.** **A.** Adaptation (left) and sensitivity (right) to proprioceptive error in children with ASD is greater than normal. **B.** Adaptation in response to visual and proprioceptive errors suggests that children with ASD are less responsive to changes in visual error. **C.** Sensitivity to visual error is lower than normal in children with ASD.

### 3.3.4 Relationship between sensory modalities

Children with ASD show increased proprioceptive sensitivity and decreased visual sensitivity, but a normal response when visual and proprioceptive errors are consistent. Therefore, we wondered if there was a tradeoff between the two modalities, balancing out the overall amount of learning. For each child, we averaged the three measurements of proprioceptive sensitivity (Fig. 3.2A, right) and the four measurements of visual sensitivity (Fig. 3.2C). The results are plotted for each subject in Fig. 3.3A. We saw that children who demonstrated greater proprioceptive sensitivity exhibited less visual sensitivity, and vice versa, as demonstrated by a significant correlation across the population: ( $r=-0.54$ ,  $p<0.001$ ). There was also a significant relationship within the ASD group alone, ( $r=-0.57$ ,  $p=0.0089$ ), and a trend towards significance in the TD group ( $r=-0.35$ ,  $p=0.13$ ). As it follows from the results in Fig. 3.2, the average proprioceptive sensitivity (x-axis) was significantly larger in the ASD group ( $t(38)=-2.1$ ,  $p=0.035$ ) and the average visual sensitivity (y-axis) was smaller ( $t(38)=2.5$ ,  $p=0.016$ ), (Fig 3.3B). We will use these parameters for our brain-behavior correlations in Chapter 4.

Finally, to ensure these results were not the product of our sensitivity analysis or due to the process of normalizing by error, we looked at the average proprioceptive adaptation,  $\lambda_p$ , and average visual adaptation,  $\lambda_v$ , for each child (Fig. 3.3B). We again found that children with ASD show greater adaptation in response to proprioceptive error ( $t(38)=2.4$ ,  $p=0.022$ ) and less adaptation in response to visual error ( $t(38)=-2.6$ ,  $p=0.013$ ), as compared to TD controls. Corresponding to our results with sensitivity to error, there was a negative correlation between the amount of adaptation in response to visual and

proprioceptive errors ( $r=-0.32$ ,  $p=0.044$ ). Therefore, our findings are robust to our methods of calculating sensitivity to error.



**Figure 3.3: Relationship between sensitivity to error in children.** **A.** The relationship between visual and proprioceptive sensitivity to error suggests that sensitivity is a trade-off across modalities. **B.** Consistent with our findings in Fig. 3.2, children with ASD show greater proprioceptive sensitivity and learning, and less visual sensitivity and learning, as compared to TD controls.

## 3.4 Discussion

Prior to being able to successfully execute complex motor behaviors, one must be able to learn to generate accurate motor commands. From infancy, these motor abilities must adapt and develop as our bodies change in size and strength, and we move through a lifetime of different environments. Present from infancy (Provost et al., 2007;Teitelbaum et al., 1998), motor impairments in autism spectrum disorder are potentially rooted in an inability to appropriately adapt their movements. In the present study, we examined how children with ASD respond to visual and proprioceptive errors. Though we found no clear differences in their within movement response to a perturbation, when measuring the trial-to-trial response to error, we found that children with ASD are more sensitive to proprioceptive errors and less sensitive to visual errors.

### 3.4.1 Proprioceptive sensitivity in ASD

A particularly interesting aspect of studying autism spectrum disorder is that in certain tasks, individuals with autism can outperform their typically developing peers. For instance, in a pair of creative tasks by Nakano and colleagues (Nakano et al., 2010;Nakano et al., 2012), adults with autism were tested in their ability to identify a common object or shape, by integrating sensory information about the object. In the first study, subjects were shown a line drawing of a common object as it passed behind an occluding screen with a small slit, allowing only a sliver of the image to be available at a time. When asked to identify the object, individuals with ASD made more errors than controls. The authors attributed their findings to the “weak central coherence” theory,

indicating that the impaired performance was due to an impairment in integrating sensory information to form a mental representation of “the big picture.” In the second study, the haptic equivalent to the original study, adults with ASD had to identify the shape of a wooden block by tracing it with their finger. Surprisingly, though the authors hypothesized that the ASD group would again show worse performance due to weak central coherence, the ASD group made fewer errors. In light of our findings, these studies seem to be consistent with a bias towards proprioceptive feedback and against visual feedback, and not due to weak central coherence. Alternatively, the proprioceptive integration task involved active movements to explore the block. This may tap into the increased proprioceptive sensitivity during movement we found to be present in ASD.

In another example of improved performance in autism, and our inspiration for our current study, we found that children with ASD showed increased generalization of force field adaptation in intrinsic, or proprioceptive, coordinates (Haswell et al., 2009; Izawa et al., 2012b). We believed this reflected an increased reliance on proprioceptive error during motor learning, but were unable to directly measure proprioceptive sensitivity. By using our single trial adaptation task, with a mix of visual and proprioceptive errors, we were able to measure adaptation and sensitivity to proprioceptive error alone and found support for our original hypothesis. Inevitably, one may wonder if this heightened proprioceptive sensitivity, allowing for “improved” performance, reflects a compensatory mechanism. If so, it presents a greater question at hand: does the ability to compensate for a visual deficit reflect an increased impairment due to autism, or are those who are less able to compensate more impaired? Given the complex developmental nature of ASD, this would require examining the developmental

time course of sensitivity to error in both healthy children and children with ASD. Though undoubtedly interesting, such a question is beyond the scope of this thesis.

### 3.4.2 Visual sensitivity in ASD

With this study, we found that children with ASD learn less from visual feedback about their movements, using a very basic, single trial adaptation task. The ability of individuals with ASD to imitate, likely a much more complex and higher order form of visual learning, has long been a focal point of autism research (Dowell et al., 2009; Vanvuchelen et al., 2007; Stieglitz et al., 2008; Williams et al., 2004). Often, it is attributed to a deficit in theory of mind, or the rather ability to mentally assume another's perspective (Baron-Cohen et al., 1985). Likewise, additional tasks have found deficits in recognition and understanding of biological motion (Cook et al., 2009). For instance, a study by Cattaneo et al. (2007) found that when TD children observe someone bring a piece of food to their mouth, relative to watching a person bring an object to a cup on their shoulder (a very similar series of movements), children experience muscle activation in their neck as though they themselves were preparing to eat (Cattaneo et al., 2007). This activation was absent in children with ASD. However, children with ASD show impairments in imitation of meaningless gestures as well as meaningful gestures, suggesting that the deficit lies in the visuomotor requirements of such tasks (Dziuk et al., 2007; MacNeil and Mostofsky, 2012). If the ability to learn from visual feedback regarding one's own movements is impaired, it could potentially underlie the ability to learn and understand a complex series of movements performed by others, or to imitate.



It is important to note, however, that our measure of visual sensitivity is not an absolute quantity. Certainly, sensitivity to error changes with task parameters (Burge et al., 2008; Wei and Kording, 2009; Marko et al., 2012). For instance, in a force field adaptation task in which visual feedback was removed, adaptation occurred normally compared to adaptation with cursor feedback available (Scheidt et al., 2005). Additionally, task structure can alter sensitivity to error, such that subjects up-regulate learning in the presence of consistent errors (Smith and Shadmehr, 2004). Perhaps this can explain our previous findings: when children with ASD were asked to make reaching movements in the presence of a visual rotation, a perturbation in which the cursor feedback is rotated relative to the reach direction, and causing a visual error but no proprioceptive error, children with ASD were able to adapt at normal speeds (Gidley Larson et al., 2008). Given the flexible nature of sensitivity to error, it is possible that consistent, repeated visual errors up regulate sensitivity to visual error in the ASD group.

# Chapter 4

## Cerebellar abnormalities in children with autism

### 4.1 Introduction

When exposed to a force field, individuals with acquired cerebellar damage are unable to adapt to the suddenly experienced, large errors that result from the perturbation (Smith and Shadmehr, 2005; Criscimagna-Hemminger et al., 2010). Specifically, cerebellar deficits reduce the ability to learn to predict the sensory consequences of motor commands (Izawa et al., 2012a). This implicates the cerebellum as the most likely location for the acquisition and storage of internal models of action. In fact, temporary disruption of the cerebellum through transcranial magnetic stimulation (TMS) delays proper planning and execution of movement, indicating that it is responsible for the feedforward component of adaptation (Miall et al., 2007).

Interestingly, the cerebellum has been a key focus for autism pathology. In post-mortem studies of individuals with ASD, reduced Purkinje cell numbers are the most consistent neuropathological finding (Ritvo et al., 1986; Bailey et al., 1998; Whitney et al.,

2008;Kemper and Bauman, 1998). Furthermore, imaging studies find a decrease in the size of the cerebellar vermis (Murakami et al., 1989;Hashimoto et al., 1995;Courchesne et al., 2001;Scott et al., 2009), while reports of overall cerebellar volume are more mixed but tend to show an overall increased volume (Courchesne et al., 2001;Sparks et al., 2002;Murakami et al., 1989;Stanfield et al., 2008). Functionally, MRI activation during motor activity is abnormal in ASD as well (Mostofsky et al., 2009;Allen and Courchesne, 2003). If the cerebellum is the site of pathological disruption in ASD, then this would likely interfere with the ability to appropriately form internal models and lead to the array of motor impairments found in ASD. Here, we examined the region of the cerebellum that exhibits resting state functional connectivity with the motor and somatosensory cortices, as described by Buckner et al. (2011). We hypothesized that the volume of this region would relate to the anomalous patterns of motor learning found in children with ASD, presented in Chapter 3.

## **4.2 Methods**

We wanted to focus our analysis on the specific region of the cerebellum that is most likely related to motor adaptation, and determine if these regions are related to performance in the psychophysical task. To do so, we utilized the cerebellar mappings described by Buckner et al. (2011). These maps defined distinct regions on the basis of differential functional connectivity with the cerebral cortex. This produced two atlases of the cerebellum, mapping its functional relationship to the cortex on a voxel-by-voxel basis. One atlas labeled each cerebellar voxel as communicating with one network

within a 7 network cerebral cortex. The other atlas labeled each cerebellar voxel as communicating with one network within a 17 network cerebral cortex (each cortical map covered the entire cortex). For the 7 network atlas, Buckner and colleagues found a region of the cerebellum that exhibited resting state functional connectivity to the motor and somatosensory cortices, which we will refer to as the sensorimotor cerebellum. The connectivity between the cortex and this region of the cerebellum was validated using a movement task of the tongue, hand and foot. For the 17 network atlas, the cortical sensorimotor area was split, separating the tongue from the hand and foot representations. In the cerebellum, the sensorimotor region was more finely resolved into two corresponding networks. We focused on the network that contained the hand representation, which we will term the hand and foot sensorimotor region of the cerebellum. Both the 7 and the 17 network atlases were recently published as a standardized atlas with the Spatially Unbiased Infra-Tentorial (SUIT) toolbox (Diedrichsen, 2006), allowing us to isolate and examine these sensorimotor regions of the cerebellum in our healthy children as well as children with autism.

For each child who participated in the reaching task described in Chapter 3 (see Table 3.1), we acquired a 1 mm<sup>3</sup> isotropic T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) on a Philips 3T (Achieva, Philips Healthcare, Best, The Netherlands). The MP-RAGE scans were acquired using the following parameters: TR = 7.99 ms, TE = 3.76 ms, Flip angle = 8°, 200 coronal slices. Two children were excluded from the analysis due to poor image quality: one due to severe motion artifact, and one for poor gray/white matter segmentation. The cerebellum was isolated and the resulting image was then registered to the SUIT template (Diedrichsen, 2006). This produced a

deformation matrix, which morphed the native image to the standardized template of the cerebellum. To find the volume of the sensorimotor regions of the cerebellum, we used the deformation matrix for each child, produced by SUI, to invert the atlas of the 7 and 17 network cerebellar parcellation into each child's native space. This produced a native space, labeled atlas of the whole cerebellum.

In particular, we chose to focus on the brain tissue (excluding CSF). To do so, we segmented the cropped native image, which resulted from the isolation step, into gray matter, white matter and CSF, using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). We thresholded the resulting tissue probability maps by 0.5 to produce binary tissue maps. For each child, we multiplied their grey and white matter binary maps by the labeled, native space atlas of the cerebellum. From this, we calculated the regional gray and white matter volume of the sensorimotor cerebellum (or the hand and foot sensorimotor cerebellum), and summed the resulting volumes to get total brain tissue for the specific region of the cerebellum.

## 4.3 Results

### 4.3.1 Volume of the sensorimotor region

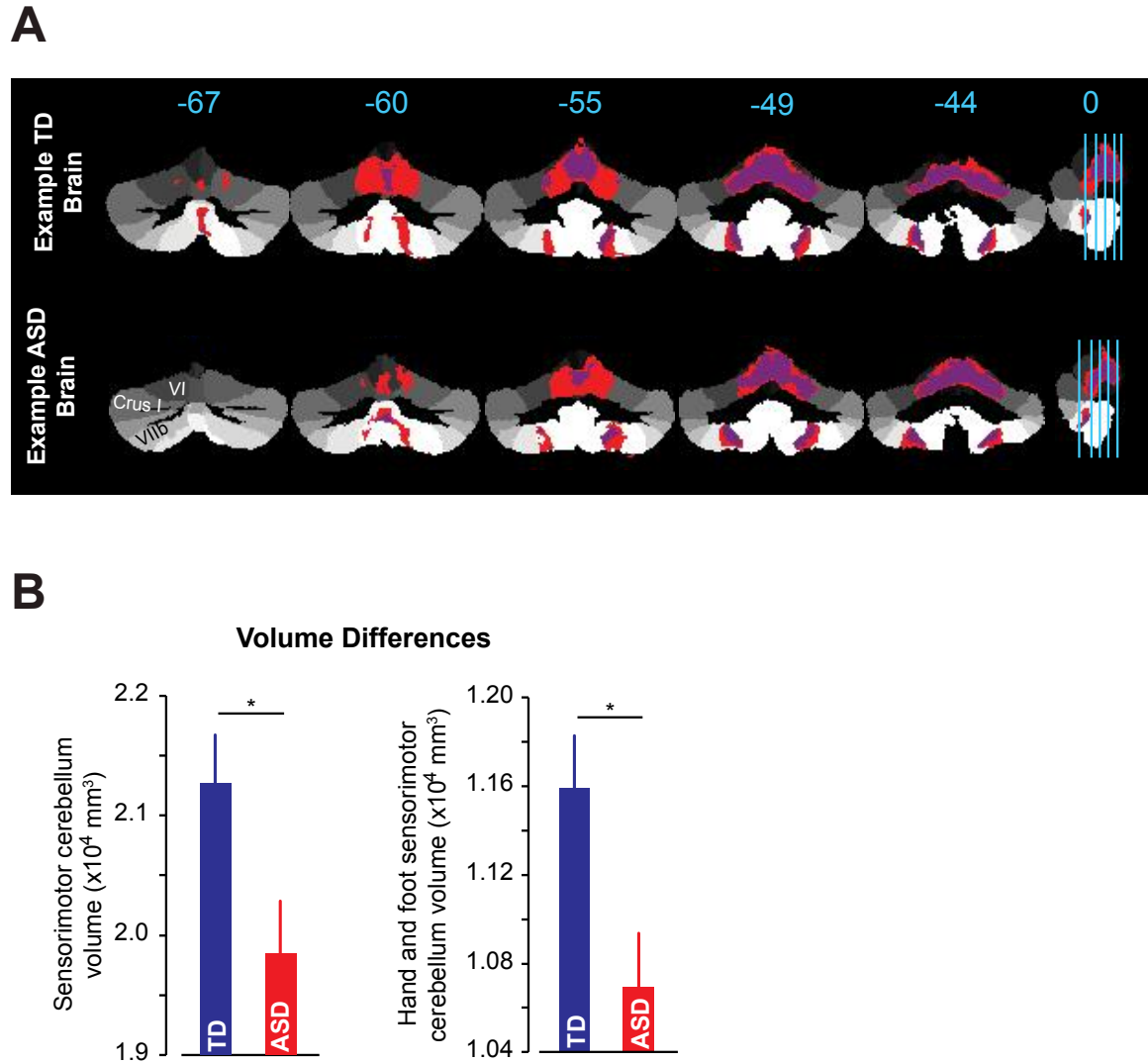
The reach adaptation task studied in chapters 2 and 3 depends on the integrity of the cerebellum (Smith and Shadmehr, 2005; Criscimagna-Hemminger et al., 2010; Miall et al., 2007; Donchin et al., 2012). Thus, we hypothesized that the behavioral differences we found from our reaching task would be reflected in anatomical differences in the volume

of specific regions in the cerebellum. To test our hypothesis, we obtained anatomical MRIs for the children who participated in the task in Chapter 2. We isolated the cerebellum and measured the regional volume of the sensorimotor network, or the region of the cerebellum that exhibits the greatest amount of resting state connectivity with the somatosensory and motor cortices in the cerebrum (Buckner et al., 2011). This region stretches bilaterally over the anterior lobe of the cerebellum, extending into parts of lobule VI as well. It also includes the posterior proprioceptive representations in lobule VIIIb. This region is identified in red for a representative ASD and representative TD child in Fig. 4.1A. It appeared that the volume of this region was smaller for the ASD child. Indeed, as shown in Fig. 4.1B, we found that the volume of this region was significantly smaller for children with ASD than TD controls ( $t(36)=-2.39$ ,  $p=0.022$ ).

We then refined our analysis through use of the 17 network atlas. This allowed us to focus on the hand and foot sensorimotor region, which covered a smaller and more specific region of the cerebellum, as displayed in blue for the same example subjects in Fig. 4.1A. As this region is completely contained within the sensorimotor region of the cerebellum, it overlays onto the red labels as purple. Again, this region appeared smaller for children with ASD, which we verified across the group in Fig. 4.1B ( $t(36)=-2.59$ ,  $p=0.013$ ). This finding is entirely independent of our psychophysical results in Chapter 3, and finds that the anatomical region of the cerebellum involved in sensorimotor control is smaller in children with ASD than in TD controls.

To check the specificity of this result, we considered two additional volumes – the total cerebellar volume (TCV), found as the sum of the volumes of all of the cerebellar networks from the 7 network atlas, and the total brain volume (TBV), as measured by

FreeSurfer, which includes the grey matter and white matter for the whole cerebrum and cerebellum, and excludes the dura, CSF, and ventricles. We found no significant difference between groups, for both TCV ( $t(36)=-1.67$ ,  $p=0.10$ ) and TBV, ( $t(36)=-0.54$ ,  $p=0.59$ ).



**Figure 4.1: Volume differences of the sensorimotor cerebellum.** **A.** Representative cerebellum from a TD child and ASD child. Red labels indicate the sensorimotor cerebellum, blue labels (which overlay onto the red labels as purple) indicate the location of the hand and foot sensorimotor cerebellum. **B.** Group results for volume of each region show that children with ASD have significantly less volume for both the sensorimotor cerebellum and the hand and foot sensorimotor cerebellum.

### 4.3.2 Behavioral relationship to cerebellar anatomy

Does this volume relate to performance in the learning task? To understand the relationship between sensitivity to error and volume of the sensorimotor cerebellum, we used a generalized linear model (GLM). In the GLM, the volume of the sensorimotor cerebellum for each child was the dependent variable, and sensitivities to visual and proprioceptive error (found in Chapter 3) were the independent variables. As a result, the GLM included factors of group, sensitivity to proprioceptive error, sensitivity to visual error and group by sensitivity interactions. We found that the GLM was significant ( $p=0.008$ , Table 4.1), suggesting that these factors are robust predictors of cerebellar volume. The GLM identified a significant main effect of group, a significant main effect of visual sensitivity and a significant group by proprioceptive sensitivity interaction. The main effect of visual sensitivity indicates that as visual sensitivity increases, the volume of the sensorimotor cerebellum increases. The interaction suggests that there is a significantly more positive relationship between proprioceptive sensitivity and volume for the ASD group. We repeated this analysis using the restricted volume of the hand and foot sensorimotor cerebellum, and found our results to be consistent (Table 4.2). This confirms our finding that sensitivity to error is a significant predictor of volume in the regions of the cerebellum most likely related to motor adaptation.



	Likelihood Ratio Chi- Square	df	Sig.
<b>Omnibus Test</b>	15.650	5	.008
<b>Tests of Model Effects</b>			
	Type III		
Source	Wald Chi- Square	df	Sig.
(Intercept)	901.142	1	<0.001
Group	10.482	1	.001
Proprioceptive Sensitivity	1.593	1	.207
Visual Sensitivity	4.799	1	.028
Group * Proprioceptive Sensitivity	6.705	1	.010
Group * Visual Sensitivity	1.988	1	.159

**Table 4.1: GLM results for the sensorimotor cerebellum.** We found a significant relationship between the volume of the sensorimotor cerebellum to the learning task (Chapter 3).

	Likelihood Ratio Chi- Square	df	Sig.
<b>Omnibus Test</b>	16.953	5	.005
<b>Tests of Model Effects</b>			
	Type III		
Source	Wald Chi- Square	df	Sig.
(Intercept)	804.050	1	<0.001
Group	12.126	1	<.001
Proprioceptive Sensitivity	1.269	1	.260
Visual Sensitivity	4.605	1	.032
Group * Proprioceptive Sensitivity	7.585	1	.006
Group * Visual Sensitivity	2.323	1	.127

**Table 4.2: GLM results for the hand and foot sensorimotor cerebellum.** We repeated our analysis for the hand and foot sensorimotor cerebellum, and found our results to be consistent with the results presented in Table 4.1.

## 4.4 Discussion

### 4.4.1 Autism and the cerebellum

Despite the range of potential upstream physiological causes of autism, there are still key diagnostic features present in all patients that define the disorder – deficits in social and communication skills, and repetitive and stereotyped patterns of interest and behavior. How might the cerebellum relate to these features? It is important to note that the cerebellum is not simply a motor structure, and is reciprocally connected to the frontal cortex (Middleton and Strick, 2001) and the basal ganglia (Middleton and Strick, 2000). Children with congenital or early cerebellar insults show a range of autistic symptoms (Tavano et al., 2007), while adults with acquired cerebellar disease experience a host of non-motor symptoms, termed the Cerebellar Cognitive Affective Syndrome, that impacts executive function, visual spatial abilities, language and affect (Schmahmann and Sherman, 1998). Certainly, damage to the cerebellum can have effects far outside of the motor domain.

Importantly, the cerebellum has been the location of a number of physiological abnormalities for individuals with autism. In fact, lower Purkinje cell numbers are the most consistent post mortem finding (Ritvo et al., 1986; Bailey et al., 1998; Kemper and Bauman, 1998; Whitney et al., 2008). Imaging studies with targeted measurements of the vermis find it to be smaller in size, as well (Murakami et al., 1989; Hashimoto et al., 1995; Courchesne et al., 2001; Scott et al., 2009). However, the results are not always clear, and reports of overall cerebellar volume are mixed, tending to find an overall larger

volume compared to controls (Courchesne et al., 2001; Sparks et al., 2002; Murakami et al., 1989; Stanfield et al., 2008). Likewise, functional imaging studies have found children with ASD to have both reduced (Mostofsky et al., 2009) and increased (Allen and Courchesne, 2003) cerebellar activation during a simple movement task. Indeed, a greater understanding of the role of the cerebellum in autism may offer a greater understanding of the diverse autism phenotype.

#### 4.4.2 The sensorimotor cerebellum and motor learning

Dating back to the 1940's, recordings during proprioceptive and tactile stimulation found two sets of sensory maps in the cerebellum: an inverted homunculus stretching primarily over the anterior lobe, and two smaller fully body representations in the hemispheres of lobule VIII. This sensory information reaches the cerebellum through both spinocerebellar projections and neocortical afferents projected through the pontine nuclei (Manni and Petrosini, 2004). It came as no surprise, therefore, that Buckner and colleagues (Buckner et al., 2011) chose to validate the findings of their resting state connectivity maps with a motor task, and found corresponding functional activation for simple hand, foot and tongue movements (see Fig. 5 in Buckner et al. 2005). But do these sensorimotor maps relate to motor adaptation? In a study of cerebellar patients using voxel based morphometry, or a voxel-by-voxel quantification relating the density of grey matter to performance in a reaching task, Donchin et al. (2012) found that anterior regions from lobules IV-VI were related to the ability to adapt in a force field or visual motor rotation paradigm. Performance in the two tasks was not correlated and was dependent on largely separate regions within the cerebellum, supporting our claim that

learning occurs from independently from visual and proprioceptive errors. Importantly, the region of the cerebellum most relevant to adaptation appears to correspond with that sensorimotor cerebellum described by Buckner et al. (2011).

Given the anatomical and functional relationship between the cerebellum and adaptation, how can we understand our findings? Independent of our psychophysical results, we find that the volume of the sensorimotor region of the cerebellum is smaller in children with ASD. When relating this volume to sensitivity to error, we found a main effect of visual sensitivity and a group by proprioceptive sensitivity interaction. The main effect of visual sensitivity on volume echoes that which is described in Donchin et al. (2012): that visual motor adaptation depends on integrity of this general region, and greater volume will allow for improved performance. For our task, higher visual sensitivity can be considered comparable to improved visual performance, which correlates with higher volume. Potentially, reduced cerebellar Purkinje cell density in ASD (Ritvo et al., 1986; Bailey et al., 1998; Kemper and Bauman, 1998; Whitney et al., 2008) may cause this reduced volume, and may subsequently reduce one's ability to learn from visual error.

The significant group by proprioceptive interaction is a bit more difficult to interpret. We found that there is a more positive relationship between volume and proprioceptive sensitivity in the ASD group than in the TD group. A popular theory explaining the underlying basis of ASD claims that there is a bias towards short range connections in the brain, and against long range connections (Frith and Happe, 1994). With no direct connections between the visual cortex and the cerebellum, visual information must travel from through the parietal cortex before it is relayed to the

cerebellum through the pons (Glickstein, 2000). Proprioceptive information, however, is relayed both through the pons from the cortex, and through the spinocerebellar tract, directly from the body (Manni and Petrosini, 2004). Therefore proprioceptive feedback may have an advantage, relative to visual feedback, in that it can be received both from the shorter path through the somatosensory cortex as well as directly through the spinocerebellar tract.

#### 4.4.3 The relevance of the functional connectivity atlas

It is important to note that the atlas used for this analysis was developed through the analysis of 1000, healthy, adult subjects (Buckner et al., 2011). Our analysis is focused not only on children, but children with a developmental disorder, therefore it is unclear how appropriate the Buckner atlas is for our participants. Though the cerebellum does have a protracted development, reaching peak volume around age 15 (Tiemeier et al., 2010), the children in our study were restricted in age and are believed to be stable, developmentally speaking. It would be undoubtedly exciting to track the evolution of a functional cerebellar atlas through development, even more so within an autism population. Regardless, based on anatomy alone, the region that we can best assume to be related to motor control in the cerebellum is smaller in children with ASD. This anatomical finding is a promising potential contributor to the multitude of motor impairments that impact children with ASD.

# Chapter 5

## Conclusion

Whether you are a stumbling toddler learning to navigate the playroom, a professional baseball player perfecting your swing, or a student learning to type on a new keyboard, the ability to learn from motor error shapes all of our lives on a continuous basis. Any disruption to this process, especially in the developing mind of a child, will have far reaching consequences. In Chapter 2, we used computational principles to quantify how much one learns from motor error. We found that in healthy adults, adaptation to visual and proprioceptive feedback occurs independently. Sensitivity, or the relative amount one learns from an error, is greatest for small errors and declines as error size increases, a phenomenon we found to be true for both vision and proprioception. Critically, this led us to reexamine the neural basis of error based learning, where we found that complex spikes in the Purkinje cells of the cerebellum resembled sensitivity to error more than error itself. This changes our view of cerebellar learning, which previously was thought to depend on error signals delivered through climbing fiber input to the Purkinje cells, generating a complex spike (Marr, 1969; Albus, 1971; Ito, 1972). Instead, we now believe that error, which is rich and complex in nature, is delivered through high frequency simple spikes. This offers a deeper look into a critical mechanism by which we learn.

With the framework developed in Chapter 2, we could then ask a targeted question in Chapter 3 – how do children with autism spectrum disorder learn from motor error? We found that, as with adults, sensitivity to error declines with increasing error size. Importantly, we found that, as compared to their TD peers, children with ASD show an increased sensitivity to proprioceptive error and a decreased sensitivity to visual error. A diminished capacity for learning from the visual feedback of one's own motor error may offer a simple underlying cause for the difficulty that children with ASD show in performing more complex visual-motor tasks, such as identifying biological motion (Cook et al., 2009) and imitation (Williams et al., 2004). Imitation, in particular, plays a key role in the development of social cognition (Iacoboni, 2009), deficits of which are a defining feature of autism.

While the neurophysiology of social cognition is decidedly complex, the neural basis of motor learning is relatively well understood. Error based motor learning depends on the cerebellum (Smith and Shadmehr, 2005), therefore we hypothesized that sensitivity to error would relate to volume of the cerebellum, in particular, a region of the cerebellum that is functionally connected to the motor and somatosensory cortices. In Chapter 4, we found that children with ASD had a smaller volume of the sensorimotor cerebellum, and that sensitivity to error was a robust predictor of this volume. Interestingly, the cerebellum has been a known site for neurophysiological dysfunction in autism for decades (Ritvo et al., 1986), and with projections to the frontal cortex (Middleton and Strick, 2001), cerebellar damage can affect far more than motor abilities (Schmahmann and Sherman, 1998).

This work has brought to focus an interesting element of motor learning, shining a spotlight on error sensitivity. Simple in concept, sensitivity is often assumed to be a fixed parameter, fit to data telling a compelling story about another aspect of motor control. But when examined on its own, sensitivity to error had unique properties, its own neural representation, and may hold the key to deficits in a devastating developmental disorder. Naturally, with this further insight, comes further questions. If complex spikes encode error sensitivity, how is error represented during learning? Can we increase visual sensitivity for individuals with autism? What causes the sensorimotor cerebellum to be smaller in children with autism? Though this thesis ends without those answers, the body of work completed here offers insight towards a greater understanding of how the brain learns from error, and a small step towards an ultimate understanding of autism spectrum disorder.



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## REFEREED PUBLICATIONS

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MK Marko, AM Haith, MD Harran, and R Shadmehr (2012) Sensitivity to prediction error in reach adaptation. *Journal of Neurophysiology* 108:1752-1763.

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## ABSTRACTS

MK Marko, D Crocetti, T Hulst, O Donchin, R Shadmehr, SH Mostofsky (2014) Neural basis of anomalous motor learning in children with autism. *Society for Neuroscience Meeting*, Washington, DC

MK Marko, D Crocetti, R Shadmehr, SH Mostofsky (2014) Behavioral and neural basis of anomalous motor learning in autism. *International Meeting for Autism Research*, 155.034, Atlanta, Georgia.

MK Marko, SH Mostofsky, R Shadmehr (2012) Sensitivity to error during motor adaptation in children with autism. *Society for Neuroscience Meeting*, 275.08, New Orleans, LA.

MK Marko, SH Mostofsky, R Shadmehr (2012) Sensitivity to visual and proprioceptive error during motor adaptation in children with autism. *International Meeting for Autism Research*, 140.097, Toronto, Ontario, Canada.

MK Marko, A Haith, MD Harran, R Shadmehr (2010) Seeing is not always believing: sensitivity to visual and proprioceptive errors. *Society for Neuroscience Meeting*, 836.6, San Diego, CA. [Abstract was chosen for platform presentation and a conference Hot Topic.]

## **RESEARCH GRANTS**

- 2012 NIH Ruth L. Kirschstein National Research Service Award  
1F31NS079121-01, “Forward Models, the Cerebellum and Development”
- 2009 NIH Research Supplement to Promote Diversity in Health-Related Research  
5R01NS037422

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