
VISUOMOTOR LEARNING AND PROPRIOCEPTION ACROSS DEVELOPMENT

HOLLY ANN CLAYTON

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Abstract

Being able to adapt our motor repertoire to novel contexts is crucial for completing even the simplest daily tasks. This can be examined in visuomotor adaptation paradigms where the motor system is challenged to compensate for changes in vision, such as learning to reach to targets on a screen with a misaligned hand-cursor, which our brains do through trial-and-error. A motor command is sent to the arm and a prediction of the outcome is sent back into the brain. This prediction is compared with sensory feedback from proprioceptors and is thought to generate one of the error signals that drives motor learning. This begs the question of whether adaptation processes might differ across development if proprioception is less reliable, as proprioceptive impairments have been found to occur alongside normal aging (children and older adults differ from young adults) and in several neurological disorders. Proprioception is suspected to be impaired in Ehlers-Danlos syndrome (EDS), a group of inherited connective tissue diseases where the most common symptoms are joint hypermobility and chronic pain. In Chapter 2 I explored sensitivity of hand proprioception in EDS as a function of disease severity. In Chapter 3 I further explored proprioceptive sensitivity in EDS by comparing patients' estimates of hand position to those of controls, and changes in their estimates after participants underwent visuomotor adaptation. Finally, in Chapter 4, I examined whether visuomotor adaptation differs across the lifespan, by looking at several characteristics of learning and comparing them across groups of children, young adults, and older adults that I tested in familiar settings. Together, these findings provide further insight into how the sensorimotor system functions under special developmental circumstances, such as with connective tissue disease, or during early/late stages of life.

Keywords: Ehlers-Danlos syndrome, hypermobility, proprioception, visuomotor adaptation, aging.

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“In a dark place we find ourselves and a little more knowledge lights our way.” - Yoda

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Chapter 1: General Introduction

Movement is an integral feature of our daily lives; it is the main way we interact with each other, and with our environment. Many organisms possess primitive, innate motor behaviors that allow them to interact with the environment. One example of such behaviour is phototaxis in algae, which is the tendency for algae to move towards a light source. Many species also have inherited behaviours which are encoded in their genomes such as instincts, autonomic motor outputs and reflexes. For example, when babies are born, they can grasp, swallow, and suckle without being taught. However, these basic abilities are not enough to ensure organism survival in a continuously changing environment. To survive, organisms must always be expanding their motor abilities, while at the same time adapting familiar movements to novel circumstances. However, this can become challenging if the organism has trouble in accurately sensing current limb position.

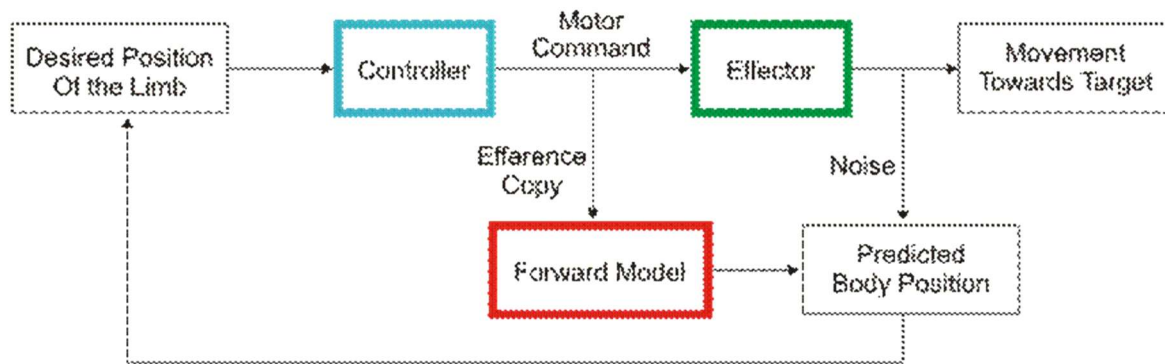
Motor Learning

In this context, learning is when an organism acquires new knowledge, because of interactions with its environment, which can be retrieved from memory again in the future. There are two main types of motor learning: skill acquisition and skill adaptation. Skill acquisition is the learning of an entirely new motor behaviour, which is stored in memory and broadens the repertoire of learned movements (Hallett et al., 1996). Several motor commands that humans possess have been learned through skill acquisition. For example, learning to write is a skill that most humans acquire during their lifetimes. However, changes in the environment might lead to one performing learned actions less effectively, and in such cases, we need to be

able to adapt our movements. For example, having to write on a vertical surface, such as a chalkboard, would require modification of the same motor plans used when writing on a horizontal surface, such as a desk. First attempts to interact with the new environment, or context, will likely contain errors (i.e., the letters may not be the same size), but after many attempts the individual learns to adjust their motor commands accordingly. Motor adaptation does not expand the motor repertoire the same way skill acquisition does. Rather, it provides an opportunity for the motor system to achieve comparable levels of performance across a variety of contexts.

Motor learning is thought to occur after the brain develops an internal model, which associates sensory and motor aspects of a particular action. An internal model is formed when the motor system simulates a response to predict the motor command's outcome. In other words, the internal model estimates what the motor command will do to the body. The brain sends a motor command to the end-effector (i.e., the arm), resulting in joint motion and muscle activation that move the arm to the desired location (Kawato, 1999). There are thought to be two types of internal models: Forward models and inverse models. Forward models predict the future state of the limb based on the chosen motor command and current state information, while inverse models predict which motor commands are required to produce a particular change in state (Figure 1.1).

Forward Model



Inverse Model



Figure 1.1. Internal models of motor control. The Forward Model and the Inverse Model.

In the forward model, desired limb position is sent to the brain, which creates a motor command (moving the limb into desired position) and the movement's efference copy (which is sent to the forward model). The efference copy is used to predict what the future position of the limb will be, and this prediction is compared with the actual final limb position. If there is a difference between the actual and predicted limb position (such as with motor adaptation), this information is fed back into the brain, which adjusts the motor plan to make future movements more accurate. In the inverse model, the actual and desired positions of the limb are sent to the brain, which predicts the motor commands needed to attain the desired position. The brain is thought to use both the forward and inverse models when guiding goal-directed movements, during movement execution as well as before movement initiation. It is possible to use efferent output (sensory feedback) from the inverse model as input to a forward model, to estimate which motor command will be most useful in achieving the desired goal (Wolpert et al., 1995;

Wolpert & Kawato, 1998). Results from several behavioural studies suggest the existence of internal models. When participants reach to targets when visual feedback of their hand is misaligned (i.e., the hand is represented by a visual cursor, which is misaligned with the actual hand's position), their movement path will also deviate from its normal trajectory. Rather than reaching in a straight trajectory, participants' movements might resemble Ss or Cs, depending on the type of cursor distortion. Furthermore, end-point error may be present if the hand's final position is significantly further from the target. However, over several trials, movement paths become straighter, and participants reduce their end-point error, reaching more accurately (Buch et al., 2003; Krakauer, 2009; Krakauer et al., 2000; Sainburg & Wang, 2002). Moreover, if the misaligned cursor is removed, movement trajectories become less straight and end-point errors are observed in the opposite direction of the cursor misalignment. These persistent movement errors are called aftereffects and provide evidence for the existence of internal models. In a well-known environment, the inverse model can easily predict the motor commands necessary to achieve a desired state. However, in a novel context (such as hand-cursor misalignment) the inverse model will not be able to compensate for the misaligned visual feedback. With repeated practice, though, the brain can use the information pertaining to hand-cursor misalignment to adjust motor commands during movements. In other words, the motor plan has been adjusted to produce motor commands that account for the visual distortion (motor adaptation). Additionally, once this new association between vision of the hand and motor output is fully formed, it can be used to plan movements that are accurate on the first trial. Upon removal of the distortion, the inverse model continually generates the adjusted

motor commands, attempting to compensate for the distortion, resulting in aftereffects (Kawato, 1999).

Visually Guided Movements

Goal directed movements are essential for many types of human activity. Although it seems easy to reach to objects in our environment, the underlying motor commands that control these movements are created by complex neural processes. To reach a target or object, the central nervous system (CNS) first estimates hand position at movement onset, and throughout movement duration. A difference vector is computed (the difference between the current desired hand location) and is sent back to the CNS, which determines what motor commands are needed to position the hand correctly. Proprioceptive information about arm configuration and position are also used in these calculations. We will now briefly discuss the roles of each sensory signal.

Vision and Action

It is generally thought that the visual system contains two separate, discrete, processing streams: the dorsal (action; where) and ventral (perception; what) streams (Faillenot et al., 1997; Milner & Goodale, 1993, 1995; Ungerleider & Mishkin, 1982). The dorsal stream localizes objects in space and controls actions on these objects. Its neurons project from V1 to areas in the parietal lobe (ie. V5 and MT). The ventral stream identifies objects and object features. Its neurons project from V1, through V2 and V4 to areas of the inferotemporal lobe.

The two-stream model is supported by evidence of dissociation between action and perception in those with focal lesions in certain cortical areas. Those with a lesion in the

parietal-occipital junction, or superior parietal cortex, had significant difficulties reaching to targets, while feature recognition and object identification remained intact. Alternatively, those with lesions in the inferior temporal lobe displayed difficulties identifying objects that they could accurately reach to (Adler, 1944; Milner & Goodale, 1995). It is well known that the dorsal stream is involved in visually-guided reaching. Specifically, the posterior parietal cortex (PPC) is known to code target location, maintain attention towards targets, and control movement planning and execution (Corbetta et al., 2000; Culham & Kanwisher, 2001; Milner & Goodale, 1993; Mountcastle et al., 1975; Snyder et al., 1998).

Early visual experiences are known to be critical for the brain to be able to accurately plan and execute movements. In an early study, monkeys were prevented from viewing their limbs for their first month of life. Compared to controls, who could see their limbs, the visually deprived monkeys displayed poorer performance during a reach task, suggesting that visual exposure to the limbs early in life is needed to properly control movements towards targets (Walk & Bond, 1971). Similar results were found when infant monkeys spent their first month in the dark, without any visual stimulation (Held & Bauer, 1974). These deprived monkeys performed significantly worse in a reaching task compared to those with normal vision. The influence of vision upon movement has also been shown in reaching studies where the hand's location is visually misrepresented via a cursor (i.e., Visuomotor adaptation studies; described in detail below). Over several trials participants alter their movements such that the visual hand-cursor attains a visual target on a screen. When participants reach to targets with no visual information about the hand (open-looped reaches) they tend to make greater errors (Westwood et al., 2001). Accuracy can be improved when participants receive visual feedback of

the hand's initial location (Prablanc, Echallier, Jeannerod, et al., 1979; Prablanc, Echallier, Komilis, et al., 1979). Moreover, pointing accuracy further increased when participants could see the hand for the entire movement duration. Similarly, participant's reaches to remembered targets are more accurate when vision of the hand is available (Admiraal et al., 2003). Pointing movements are also more accurate when the target itself is continually visible, rather than briefly flashed (Westwood et al., 2001). Overall, these results support the notion that visual information has a strong influence upon goal-directed movements.

Proprioception and Action

There are other types of sensory information available to the CNS when planning and executing movements. Various receptors in the muscles, skin, tendons, and joints relay sensory information about the positions of our limbs in space; proprioception is the general term used to describe these sensations (Konczak et al., 2009; McCloskey, 1978; van Beers et al., 2002). Aside from vision, proprioception also conveys important information that is necessary to plan goal-directed movements. For example, those with sensory neuropathy, who have impaired proprioception, show impairments in accuracy when reaching to visual targets without vision of the reaching hand (Ghez et al., 1995). It is suggested that this impairment is due to an inability to correct errors based on proprioceptive information. Proprioception is also suspected to be impaired in another patient group, Ehlers-Danlos Syndrome (described in detail later), but this area of knowledge is severely limited.

Proprioceptors

The peripheral neural units that convey proprioceptive information to the CNS are the muscle spindles and Golgi tendon organs. Muscle spindles convey information about muscle kinematics, or joint angles, and collagen is present in their outer capsules. Sensory axons wrap around the intrafusal fibers, sensing shifts in spindle length (Hulliger, 1984). The Golgi tendon organ conveys information about muscle dynamics, or tension. They are innervated by a single Ib axon which weaves around a netting of collagen fibers. Stretching of the tendon pulls on the collagen, which compresses the axon and causes it to fire (Schoultz & Swett, 1972). Cutaneous receptors may convey proprioceptive information via skin strain as joints are moved. Ruffini endings within joints are known to be slow adapting and may contribute to the sense of static position. Pacinian corpuscles, located much deeper within the connective tissues of joints, are faster to adapt and are likely more sensitive to changes in velocity (Hillier et al., 2015).

Proprioceptive Localization in Healthy Controls

For the most part, healthy individuals are quite good at localizing their unseen hand using proprioception (and efferent signals) (Baud-Bovy & Viviani, 1998; Haggard et al., 2000; Lovelace, 1989; Sarlegna & Sainburg, 2007). Haggard et al. (2000) and Lovelace (1989) found that when participants reached to the unseen location of their left index finger using a pen, they made localization errors of 1.74 and 1.77 cm, respectively. Results for proprioceptive-guided reaching from our lab (Jones, Byrne, et al., 2012; Jones et al., 2010) also show that participants are quite accurate in localizing their hidden hand-target. Average errors usually fell within 2 cm of the target site, for both the left and the right hands (Jones et al., 2010). When we tested a

smaller number of proprioceptive target sites, at a similar distance, but located 5 cm left and right of the midline (including the midline), we found similar sized errors (Jones, Byrne, et al., 2012). Again, the reach errors varied with the hand tested, (showed a hand-dependent bias) falling a couple centimeters on either side of the target site, consistent with the findings reported here.

Visuomotor Adaptation

Visuomotor adaptation has been measured in a variety of experimental situations and it involves introducing a misalignment between the seen and actual location, or motion, of the hand, while the hand is reaching to, or following, a target. In other words, movements one normally would produce no longer result in acquiring the target, nor produce the expected visual output. Early work on visuomotor adaptation used prism goggles to produce a visual-proprioceptive conflict, by shifting the view of the entire visual field, including the target and end-effector (Hay & Pick, 1966; Redding & Wallace, 1978, 1988, 1996, 1997, 2001, 2002). Yet, a majority of more recent studies on visuomotor adaptation utilize a virtual environment, where they only alter the visual location of the hand, usually by using a cursor to represent the unseen hand (Cunningham, 1989; Krakauer et al., 2000, 2005; Sainburg & Wang, 2002); these studies are more versatile, since only visual feedback of the hand is altered, rather than the whole workspace. Typically, this is done by deviating the direction by which the hand-cursor moves relative to the unseen hand, as illustrated in Figure 1.2. In Figure 1.2, the cursor path (in red) is deviated 30° clockwise (CW), relative to the hidden hand (whose path is depicted by the dashed white line). This type of altered visual feedback is sometimes known as a visuomotor, or cursor, rotation. Many studies have shown that people can quickly adapt their unseen hand

movements to move the cursor straight to the target (Krakauer, 2009; Krakauer et al., 2000, 2005, 2006). Complete, or near-complete, compensation for the visuomotor rotation can occur within around 20 trials, in the case when there is only one target, although about 60 trials are needed to achieve equivalent compensation when reaching to multiple targets with the misaligned cursor.

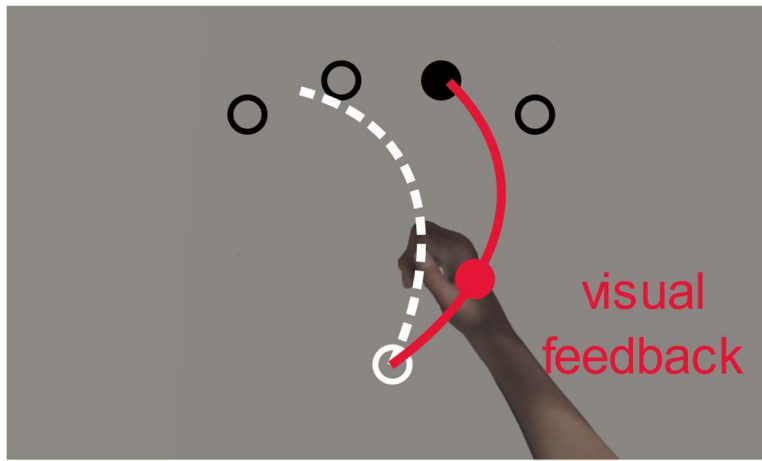


Figure 1.2. A depiction of a visuomotor rotation task. The actual hand path is shown with a white dashed line. The cursor, rotated from the hand's movement by 30° CW, is shown with a red dot and is the only visual feedback of hand position available to the participant; it's path is shown with a solid red line. The solid black circle represents the target the participant is currently reaching to, while hollow black circles represent other possible target locations.

If the perturbation is salient enough, then some of the adaptation will be due to consciously redirecting the hand movement to compensate for the altered visual feedback, that is, participants will use an explicit strategy (Heuer & Hegele, 2008; Taylor et al., 2014). Other times, changes in hand direction that compensate for the visual perturbation are implicit, that is, participants deviate their unseen hand without being aware that they are doing so. In the case where the perturbation is not salient, such that participants are not aware of the visual misalignment, adaptation is wholly implicit. This implicit contribution of adaptation can be seen

when reaches continue to deviate even after the perturbation is removed, either by removing the cursor or aligning the cursor with the hand movement. That is, once people learn to direct their hand movement to the left (counterclockwise; CCW) to compensate a rightward (CW) moving cursor, even after the cursor is removed, these unseen reaches will continue to be deviated partially to the left. These persistent reach deviations are referred to as aftereffects and are considered evidence of implicit learning. Such aftereffects suggests that a new internal model, or sensorimotor mapping, has been formed (Baraduc & Wolpert, 2002; Brown, 2003; Ghahramani et al., 1996; Krakauer et al., 1999, 2000, 2005; Simani et al., 2007). Adaptation to altered visual feedback of the hand is not restricted to only the trained targets, but generalizes to nearby novel targets, although to a lesser extent, for targets that are farther away from the trained direction (Krakauer et al., 2000). Once consolidated, adaptation can also be partially retained across time such that when people are exposed to the same visuomotor distortion the next day, they adapt more quickly the second time. This faster re-learning is known as savings (Krakauer et al., 2005)

Visuomotor Adaptation in Children

There have been a limited number of studies measuring how well children can adapt to visuomotor perturbations. Some of these studies suggest that younger children cannot adapt as quickly, or to the same extent, as older children, or adults. In one early study, Ferrel et al. (2001) found that, while children of all ages were able to adapt, or compensate, for a visuomotor rotation, children younger than eight adapted to a lesser extent than older children and adults. However, this was only the case when the cursor misalignment was large, specifically those

deviating by 135° & 180°. This suggests that younger children can adapt to altered visual feedback of their hand, so long as the perturbation is not so great.

Since then, others have shown that, like adults, young children adapt to smaller visuomotor perturbations, but do not always show aftereffects. Contreras-Vidal et al. (2005) found that 4, 6 & 8-year-old children were all able to adapt their reaches to a 45° cursor rotation. Age did not affect the extent to which they adapted to this cursor rotation, but age did affect the rate of adaptation in the early trials following initial exposure to the rotation; 8-year-olds adapted the most, followed by 6-year-olds. Interestingly, when the children reached with an aligned cursor (no rotation) following training with a rotated cursor, 8-year-olds continued to produce reach aftereffects, which are indicative of learning. However, 4 and 6-year-olds did not show any reach aftereffects (Contreras-Vidal et al., 2005). Another study using a 45° rotation found that 8-year-old children produced significant reach aftereffects following training to both gradual (slow incrementing increases in perturbation up to the desired magnitude) and abrupt (immediate) cursor-rotations (Kagerer et al., 2006; King et al., 2009). This is supported by another study that found 5-year-olds produced significant aftereffects after adaptation, but found they took longer to decay in these youngest children (Kagerer & Clark, 2014). However, because the cursor was invisible, and not simply re-aligned with the hand's actual position, it is also possible that this contributed to the size/rate of decay of aftereffects (5-year-olds took longer to de-adapt). Indeed, while children aged 5-8 were found to show similar sized aftereffects as older children and adults, their rate of de-adaptation was slower than the older groups (i.e., they took longer to return to baseline). This is like another study which found

slower aftereffect decay in children, compared to adults, following prism adaptation (Gómez-Moya et al., 2016).

In summary, it seems that both children and adults can adapt their reaching movements to a visually rotated hand-cursor. Children, even as young as 4, can adapt (i.e., compensate) to the misaligned hand-cursor (Ferrel et al., 2001). While some work suggests that rate of adaptation may be slower for the youngest children, this finding is not conclusive. The same is true regarding the ability to measure aftereffects in very young children (aged 4-6); some studies claim to have measured them (King et al., 2009), but others show inconsistencies across participants and conditions (Contreras-Vidal et al., 2005). However, children older than 8 typically show aftereffects, indicative of implicit learning, and some work suggests that they decay slower in children compared to adults.

Proprioceptive Recalibration

In addition to changes in movements, our sense of felt hand position (proprioception) is also thought to shift following visuomotor adaptation (Simani et al., 2007; van Beers et al., 2002). To measure proprioceptive sense of hand position in our lab (Barkley et al., 2014; Clayton et al., 2013; Cressman & Henriques, 2009, 2010; Jones et al., 2010; Mostafa et al., 2014; Nourouzpour et al., 2014; Salomonczyk et al., 2011, 2012), we use a robotic manipulandum (see Figure 1.3) to either passively place participants' hands or provide a guided path for participants to actively move their hand to various locations in the horizontal workspace. This method of hand placement has been utilized in two different tasks we commonly use that largely produce the same results (Clayton et al., 2014; Jones et al., 2010). The method used for measuring

proprioceptive recalibration in this dissertation will be reviewed later in this section, but we will begin by reviewing earlier studies from our lab that used the proprioceptive estimation task to measure changes in felt hand position, following visuomotor adaptation. This method asked people to judge the felt location of their hand, relative to a reference marker, and hand placement was determined by a 2-alternative-forced-choice (2-AFC) algorithm (Kesten, 1958; Treutwein, 1995). Since this algorithm involved an adaptive staircase, in which hand placement was calculated separately for each reference marker location, such that the hand was placed closer/farther from the marker on the next trial (depending on the accuracy of the current judgement), this required around 50 trials per reference marker to effectively calculate proprioceptive bias for each location and led to very long experiments.

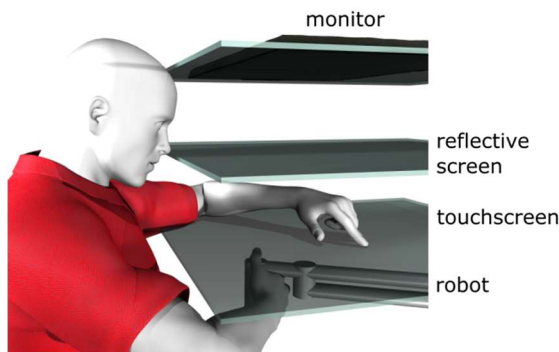


Figure 1.3. General robotic manipulandum set up.

To test whether visuomotor adaptation leads to changes in hand proprioception, we compared estimates of hand position before and after visuomotor adaptation training. In the original study by Cressman and Henriques (2009), similar changes in felt hand position were observed regardless of whether these estimates were made when the hand was actively moved into position along a robot generated grooved path, or when the hand was passively placed into

position. Specifically, they found that the change in estimates of felt hand position were shifted about 6° in the direction of the visual feedback provided, following training to a 30° CW cursor rotation, or about 0.8 cm following exposure to a 4 cm lateral cursor translation (Cressman & Henriques, 2009). In both cases, this change in felt position was about 20% of the magnitude of the cursor deviation introduced, which suggests that the magnitude of changes in perceptual estimates is the same following adaptation to the two different distortions. Furthermore, while the visual distortion in this original study was gradually introduced, we found the same results when the distortion was abruptly introduced (Salomonczyk et al., 2012), that it was specific to the trained hand, whether it be the dominant or non-dominant hand, and this recalibrated sense of hand position could still be observed 24 hours later (Nourouzpour et al., 2014). We also found that these visually driven changes in estimates of felt hand position became larger with increases in the magnitude of cursor rotation introduced during reach training (30° , 50° and 70°). Regardless of the amount of cursor rotation, however, shifts in felt hand position were always about 20% of the magnitude of the cursor rotation (Salomonczyk et al., 2011).

The studies described above focused on measuring visually-driven changes in hand proprioception, thus the hand was always either passively moved by, or constrained by, a robot manipulandum. However, other labs were interested in whether visuomotor adaptation also leads to changes in efferent-based estimates of hand position, or what is sometimes called the predictive consequences of movement, following visuomotor adaptation (Izawa et al., 2012; Synofzik, 2006; Synofzik et al., 2008). It is predictive because it is assumed that when a movement is generated, a copy of the motor command, or efference copy, is sent to other brain areas which use these efferent signals to simulate or predict (using an internal model) the

consequence of the resulting movement before sensory feedback is available. To study this question, Synofzik et al., (2008) and Izawa et al. (2012) both had participants make self-generated movements with their unseen hand before estimating its position. In this way, estimates of the hand position were based not only on proprioception, but also on the efferent-based estimates of the hand movement. This meant that the unseen hand location would vary across trials and, instead of having people report the perceived location relative to a reference marker with a 2-AFC task, participants used their opposite hand (either directly or by moving a cursor) to indicate the location of the unseen trained hand. They also found that, after adapting to altered visual feedback of their hand, people's estimates of hand location were shifted in the direction of the visuomotor distortion. Here, the authors attributed this shift to updating of sensory predictions (efference signals) in the forward model of motor control (as their task required active, self-generated movements which should make use of efference copies). Their conclusions were partly based on finding that cerebellar patient groups, in both studies, showed significantly smaller shifts in their estimate of hand positions. The cerebellum is believed to house the internal models used to simulate the predictive consequences of movement, and changes in hand estimate for these patients following adaptation were smaller than healthy controls because of deficits in predicting the (visual) sensory consequences of their movements. Nonetheless, cerebellar patients in both studies did show significant shifts in hand-localizations (but to a smaller magnitude than those of controls) following visuomotor adaptation, despite cerebellar damage. It could be that cerebellar damage only partially impacts the brain's ability to generate sensory predictions needed for efference signals. However, it is also possible that

the shifts observed in cerebellar patients were due to changes in proprioception, which would likely occur outside of the cerebellum.

To measure the extent that changes in estimates of actively-displaced hand movements, following visuomotor adaptation, were due to changes in efferent-based estimates compared to proprioceptive-based estimates, our lab (t Hart & Henriques, 2016) ran a study to measure both types of changes. Specifically, we compared changes in hand localization, following visuomotor adaptation, after self-generated (active) hand placements (like the localization task in Izawa et al.) to changes in localizations when the trained hand was guided passively by a robotic manipulandum to the originally self-chosen locations. When localizing hand movements that were self-generated (active hand localization), any learning-induced changes could reflect both an updated predicted estimate of the hand movement, as well as recalibrated proprioception. But when localizing robot-displaced hand movements (passive hand localization), any changes should only reflect proprioceptive recalibration. While shifts in hand localization were found to be slightly larger following self-generated (active) placement, hand localizations following robot-generated (passive) placement also shifted significantly. This suggests that shifts in hand localization typically observed following visuomotor adaptation are not entirely due to updating predicted sensory consequences, but mostly depict changes in proprioception (t Hart & Henriques, 2016).

What is driving these changes in proprioception? A series of experiments from our lab has suggested that making self-generated movements during training may not be necessary; it is the discrepancy between vision and proprioception that appears to drive proprioceptive recalibration. This was originally found by Cressman and Henriques (2010), where they

introduced a new learning paradigm that allowed the separation of the visual-proprioceptive discrepancy from the typical visuomotor discrepancy. In this study, participants were exposed to a visual and proprioceptive misalignment of their felt hand position but were not permitted to make any voluntary, goal-directed movements using the altered feedback. Specifically, the robotic manipulandum either passively moved or actively guided their unseen hand in the direction of a briefly shown target. Participants always saw the cursor, representing their hand, move directly to the target, but the hand path was gradually rotated 30° CCW from the direct path to the target. This allowed researchers to explore if merely experiencing a discrepancy between vision and proprioception was enough to result in proprioceptive recalibration since this training paradigm did not include any volitional movement, nor motor performance errors seen in the typical visuomotor adaptation paradigm. It was found that shifts in proprioceptive estimates of felt hand position were like those found in all the above-mentioned studies from Henriques and colleagues in that they shifted by a similar magnitude to those observed following adaptation to a visuomotor rotation of 30° CW (Cressman & Henriques, 2009, 2010). Given the similarity in felt hand position found across both paradigms, this suggests that a motor task may not be required to induce this type of proprioceptive recalibration. However, when participants performed open loop reach trials without visual feedback, they still produced aftereffects (deviated reaching movements) although these aftereffects were only about 1/3 of the size that has been commonly found in typical visuomotor adaptation paradigms. In fact, these aftereffects were the same size and highly correlated with the changes in hand proprioception, i.e., also 6° CW. This suggests that the aftereffects following typical visuomotor adaptation may partly be due to a change in proprioception (around 1/3). Yet the additional

deviation in aftereffects following typical visuomotor adaptation (closer to 15-18° in our lab) may reflect the motor adaptation per se, which occurs on top of this common proprioceptive recalibration.

Not only does visuomotor learning lead to shifts in estimates of hand position, but it also leads to changes in proprioceptive acuity (better precision by which we feel the hand is in one location rather than the other). Wong et al. (2011) showed that visuomotor learning which involved reaching to visual targets with an aligned hand-cursor leads to improvements in proprioceptive acuity. Participants who underwent this training, in comparison to those that did not, showed significant improvements in proprioceptive acuity afterwards, as suggested by 11% reductions in their acuity scores (Wong et al., 2011), but only in the location where they trained to reach.

Proprioceptive Recalibration in Older Adults

To explore the influence of age on proprioceptive recalibration, Cressman et al. (2010) had both young and older participants adapt to a gradually introduced 30° CW cursor rotation to measure the resulting change in proprioception. They found older participants recalibrated their estimates of felt hand position to a similar extent as younger individuals. These shifts in felt hand position were like other results from this lab in that they were about 20% of the magnitude of the cursor rotation. However, results from Cressman et al. (2010) did reveal some differences between younger and older participants during proprioceptive recalibration. Even though older individuals were able to recalibrate their felt hand position to a similar extent, they found that older people had significantly larger uncertainty ranges, at all reference marker

locations (Cressman et al., 2010); in other words, they found that older adults were less precise than younger adults in estimating hand position. These results are consistent with others who suggest proprioception is less precise in older adults compared to young (Goble et al., 2009). Moreover, these results suggest that precision in hand proprioception does not influence the effect of proprioceptive recalibration. In other words, although poorer proprioceptive estimates may lead to greater weighting of more reliable visual estimates of hand position (van Beers et al., 1999), it does not necessarily lead to greater visual recalibration of proprioception.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of genetic connective tissue disorders that can afflict up to 2% of individuals (Castori, 2012). EDS was recently re-classified into thirteen sub-types (Classical EDS, Classic-like EDS, Cardiac-valvular EDS, Vascular EDS, Hypermobile EDS, Arthrochalasia EDS, Dermatosparaxis EDS, Kyphoscoliotic EDS, Brittle Cornea Syndrome, Spondylodysplastic EDS, Musculocontractural EDS, Myopathic EDS and Periodontal EDS) (Malfait et al., 2017), with the Classical and Hypermobile sub-types being the most common (Beighton et al., 1998). Most forms of EDS affect collagen throughout the body; some directly impact its structure (such as with Classical EDS), while others alter proteins that interact with collagen. However, the genetic etiology for the most common type of EDS, Hypermobile sub-type, is still unknown (Castori, 2012; Malfait et al., 2017). Although symptomatology can vary across, or sometimes within, each of the sub-types, the most common variants (classical and hypermobile) often present with hypermobile joints, atypical skin (possibly doughy, stretchy, saggy, atrophic, thin, translucent, and/or fragile), chronic pain, chronic fatigue, dysautonomia, developmental delays, poor wound healing, and may bruise easily (Beighton et al., 1998;

Castori, 2012; De Paepe & Malfait, 2004; Gazit et al., 2003; Rombaut, Malfait, et al., 2010; Sacheti et al., 1997). Clinicians also report that these patients are generally clumsy in nature, substantiating the suggestion that EDS patients may have proprioceptive impairments (Rombaut, De Paepe, et al., 2010). However, little is known about the exact nature of these sensory impairments; there are only a few studies that have attempted to explore proprioceptive abilities in EDS patients, or those with Hypermobility Syndrome (HMS) (Hall et al., 1995; Rombaut, De Paepe, et al., 2010; Sahin et al., 2008). Because the genetic etiology of HMS is still unknown, in addition to it having a virtually indistinguishable presentation from Hypermobility EDS (Castori et al., 2013; Tinkle et al., 2009), we will consider results obtained from HMS studies to be applicable to Hypermobility EDS.

Proprioception in EDS/HMS

Hall et al. (1995) was among the first to study proprioception in HMS patients by examining the knee joint. Using a threshold-detection paradigm in which participants indicated when they could feel movement in the knee joint and were asked to report the direction of the movement, the study revealed that hypermobile participants showed significantly higher threshold detection levels at knee flexion angles of 5° and 30° in comparison to age and gender-matched control participants. These findings are like those reported by Sahin et al. (2008) who found that HMS patients had significantly higher absolute angular errors than age and gender-matched control participants during a knee joint matching task. Rombaut, De Paepe, et al. (2010) later compared proprioceptive abilities and vibratory perception sense in EDS hypermobility type patients to those of age and gender-matched controls. Exploring proprioception in the knee and shoulder using both an active and passive joint matching

paradigm, they found that EDS patients showed significantly larger angular errors in joint matching at the knee joint, but not at the shoulder. However, they also found that EDS patients could detect tactile stimuli just as well as controls (using vibratory perception threshold at these same joints), suggesting that cutaneous receptors in the skin may not be contributing to the observed proprioceptive deficit in EDS; it could be that tendon and joint receptors are the most likely contributors to the proprioceptive impairment found in EDS (Hall et al., 1995; Rombaut, De Paepe, et al., 2010; Sahin et al., 2008).

More recently, a study in our lab explored proprioceptive localization of the hand in the two most common variants of EDS, classic and hypermobility types (Clayton et al., 2013). We found that, although EDS patients were just as accurate as controls in estimating the location of their unseen hand, they were less precise when tested in the peripheral workspace compared to healthy controls. Specifically, they showed greater just-noticeable differences compared to healthy controls, in that their unseen hand had to be further left or further right before they were as certain of its position relative to a visual reference as the controls. Moreover, we found a significant correlation between the magnitude of joint hypermobility (Beighton scores) and the magnitude of this proprioceptive deficit, such that those who were the least precise were those who had the highest Beighton scores. We were not able to detect any significant differences between the two types of EDS (Classical and Hypermobile) that participated in this study.

[Motor Adaptation and Proprioceptive Recalibration in EDS](#)

In our previous study (Clayton et al., 2013), we found that EDS patients adapted their reaches to a similar extent as healthy controls after training with a misaligned cursor, suggesting that proprioceptive deficits do not interfere with motor adaptation. These results are consistent with studies on deafferented participants, who lack proprioceptive input, yet can adapt to a novel visuomotor rotation and show aftereffects of a similar magnitude as healthy controls (Bernier et al., 2006; Ingram et al., 2000). Similarly, older adults, who also show poorer proprioceptive sensitivity, have also been shown to adapt just as well as younger controls, especially when the visuomotor rotation is introduced gradually (Buch et al., 2003; Cressman et al., 2010), although some studies have shown reduced motor adaptation (Anguera et al., 2009; Bock, 2005; Bock & Girgenrath, 2006; Seidler, 2006), typically when the rotation is large and introduced abruptly. Similar levels of visuomotor adaptation between controls and EDS patients allowed us to measure the effect of this adaptation on hand proprioception.

It is possible that people with poor proprioception may be more vulnerable to proprioceptive recalibration (as they might rely more on visual information), but this is not what we found. Although patients showed changes in felt hand position (i.e., leftward shifts) that were almost double those of controls, these results were still not statistically significant (Clayton et al., 2013). This is likely due to increased variability found in the patient group but could also be because results from our controls do not show changes of the same magnitude as those found in previous studies from our lab (Cressman et al., 2010; Cressman & Henriques, 2009; Salomonczyk et al., 2011); the changes of patients were similar to those of healthy controls in these other studies. Specifically, our controls showed a change in felt hand position of only about 10% of the size of the visuomotor distortion, while healthy participants in our previous

studies have shown a change closer to 20%, which is what we found in the EDS patients. Thus, one of the purposes of this dissertation is to re-examine proprioceptive recalibration in EDS, using a slightly different paradigm.

Overview of the Dissertation

In this series of experiments, I explored the sensorimotor capabilities of three special populations (EDS patients, children, and older adults) who are all thought to lack the same proprioceptive sensitivity as healthy young adults. I further examined proprioceptive abilities of EDS patients under a variety of contexts and explored whether their performance was related to the most common symptoms of EDS. I also wanted to replicate findings from my master's thesis where we found that visuomotor adaptation, and the subsequent proprioceptive shifts that follow, are no different between these patients and healthy controls, using a different method of assessing hand localization than in our first EDS study, that allowed us to measure efferent contributions to estimates of hand position. Additionally, I examined a variety of features indicative of visuomotor learning in a large sample of healthy individuals ranging from 5 to 78 years, in a short, gamified visuomotor rotation task that we hoped would better engage participants of all ages and permit comparison of all features, for all age groups, within the same study. To answer these questions, I used three different paradigms that required participants to reach to targets (visual or proprioceptive) in a virtual environment, which are briefly outlined below and, in more detail, in the chapters that follow. This dissertation presents novel findings regarding the sensorimotor capabilities of these special populations, who are more challenging to collect data from, and for whom research is lacking.

In the first study (Chapter 2), I implemented a proprioceptive localization paradigm (Jones, Byrne, et al., 2012) to further explore sensitivity of hand proprioception in EDS, by testing patients at a greater number of workspace locations than in my first master's study (Clayton et al., 2013). I also examined the relationships between proprioceptive sensitivity in EDS and two of the most common EDS symptoms (chronic pain and joint hypermobility) (Clayton et al., 2015). Since my master's EDS study only found differences in the uncertainty of estimates of hand position between patients and controls at the two lateral workspace locations, I hypothesized that patients' localizations would, overall, be less precise than controls, but that patients' localizations would be the least precise at more lateral workspace locations. Given this prediction, there should be significant differences in scatter of proprioceptive localizations (defined by the area of 95% ellipses) between patients and controls when collapsing across all workspace locations, and, only for the patients, there should be significant differences in this measurement at certain workspace locations. Additionally, I hypothesize that proprioceptive precision in patients will be related to their levels of chronic pain, as well as their joint hypermobility. This was expected to manifest in two separate, positive correlations, between elliptical area and scores from two common symptom severity scales (the McGill Pain Questionnaire and the Beighton Scale, respectively).

Motivated by findings from both of our previous EDS studies (Clayton et al., 2015; 2013), in the second study (Chapter 3), I compared hand localizations of EDS patients, to those of controls, using two different methods of hand placement (when their hand was passively displaced by a robotic manipulandum and when their hand was actively placed at a location chosen by the participant) to see if the presence of efferent information, generated by

voluntary movement, might attenuate the proprioceptive differences we have seen in EDS so far (Clayton et al., 2021). I also sought to replicate findings from my master's study, where we found that patients were no different from controls in how they adapted their reaches to a visuomotor rotation, nor in how their estimates of hand localization shifted following adaptation, even though patients' estimates were less precise and correlated with their Beighton scores. I hypothesized that EDS patients' proprioceptive localizations would be similar in accuracy to those of controls, but that patients' localizations would be significantly less precise. I also hypothesized that the availability of efferent information would reduce the expected imprecision in EDS. Furthermore, I hypothesized that EDS patients would adapt their reaches to a similar extent as healthy controls, that their estimates of hand location would shift similarly and that we would find a significant correlation between our measures of hand proprioception and Beighton scores, like in our first study (Clayton et al., 2013).

In the final experiment (Chapter 4), I examined whether several characteristics of visuomotor learning differ across the lifespan, by comparing performance of groups of children, and groups of older adults, to that of young adults, as well as each other, within a single visuomotor rotation paradigm. I wanted to approach the problem with a more ecologically valid lens, by testing all groups in a familiar setting, and utilizing a shorter, more gamified task to keep participants, of all ages, fully engaged. I included more child-friendly stimuli so that we could present the experiment as a game where participants helped aliens travel to planets; instead of coloured circles, the hand-cursor was represented by an alien, while the reach targets were represented by planets, and on each trial a random alien/planet pairing was chosen from a large set of cursor/target images. By limiting the number of trials in each phase

of the experiment, we were able to capture more characteristics of visuomotor learning within a much shorter experiment that only lasted about 5 minutes. By making the experiment more fun, I hypothesized that we would find no differences between any of our groups, for any of our measures of learning, revealing that visuomotor learning abilities remain stable throughout the lifespan, at least in the context of shorter bouts of gamified learning. If this is true, then it will suggest that some of the inconsistencies across studies involving children, or older adults, may simply be due to their participants not being fully engaged (perhaps they were bored, fatigued, or distracted by an unfamiliar lab environment).

In the final chapter (5), I summarize the findings of my research. Is proprioceptive localization of the hand less precise, or more variable, in EDS, and are these differences in sensitivity related to the most common symptoms of the disorder? Do people with EDS also show deficits in visuomotor learning, or proprioceptive recalibration? Can a shorter, more gamified visuomotor rotation paradigm reveal that visuomotor learning processes remain stable throughout the lifespan? My research shows that hand proprioception is less precise in EDS, that the magnitude of imprecision is partially related to joint hypermobility and suggests that differences in proprioceptive sensitivity may be attenuated by the presence of efferent information. This could explain why we see no differences between EDS patients and controls (or even between young adults and groups of children/older adults, two other special groups known to lack proprioceptive sensitivity, in our lifespan study) in how they adapt to a visuomotor rotation, since the adaptation process involves voluntary reaching movements.

Chapter 2: Proprioceptive precision is impaired in Ehlers-Danlos Syndrome

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Abstract

It has been suggested that people with Ehlers-Danlos Syndrome (EDS), or other similar connective tissue disorders, may have proprioceptive impairments, the reason for which is still unknown. We recently found that EDS patients were less precise than healthy controls when estimating their felt hand's position relative to visible peripheral reference locations, and that this deficit was positively correlated with the severity of joint hypermobility. We further explore proprioceptive abilities in EDS by having patients localize their non-dominant left hand at a greater number of workspace locations than in our previous study. Additionally, we explore the relationship between chronic pain and proprioceptive sensitivity. We found that, although patients were just as accurate as controls, they were not as precise. Patients showed twice as much scatter than controls at all locations, but the degree of scatter did not positively correlate with chronic pain scores. This further supports the idea that a proprioceptive impairment pertaining to precision is present in EDS but may not relate to the magnitude of chronic pain.

Introduction

Ehlers-Danlos syndrome (EDS) is a group of genetic connective tissue disorders that can afflict up to 2% of individuals (Castori, 2012). EDS is currently classified into six major types (classic, hypermobility, vascular, kyphoscoliosis, arthrochalasia and dermatosparaxis), with the classic and hypermobility types being the most common (Beighton et al., 1998). Most forms of EDS affect collagen throughout the body; some directly impact its structure (such as with classic type), while others alter proteins that interact with collagen. However, the genetic etiology for the most common type of EDS - hypermobility type - is still unknown (Castori, 2012). Although symptomatology can vary across, or sometimes within, each of the subtypes, the most common variants (classic and hypermobility) often present with hypermobile joints, atypical skin (possibly doughy, stretchy, saggy, atrophic, thin, translucent, and/or fragile), chronic pain, chronic fatigue, dysautonomia, developmental delays, poor wound healing, and may bruise easily (Beighton et al., 1998; Castori, 2012; De Paepe & Malfait, 2004; Gazit et al., 2003; Rombaut, Malfait, et al., 2010; Sacheti et al., 1997). Clinicians also report that these patients are generally clumsy in nature, substantiating the suggestion that EDS patients may have proprioceptive impairments (Rombaut, De Paepe, et al., 2010). However, little is known about the exact nature of these sensory impairments; there are only a few studies that have attempted to explore proprioceptive abilities in EDS patients, or those with Hypermobility Syndrome (HMS) (Hall et al., 1995; Rombaut, De Paepe, et al., 2010; Sahin et al., 2008). Because the genetic etiology of HMS is still unknown, in addition to it having a virtually indistinguishable presentation from EDS hypermobility type (Tinkle et al., 2009), we will consider results obtained from HMS studies to be applicable to EDS hypermobility type.

Hall et al. (1995) was among the first to study proprioception in HMS patients by examining the knee joint. Using a threshold-detection paradigm in which participants indicated when they could feel movement in the knee joint and were asked to report the direction of the movement, the study revealed that hypermobile participants showed significantly higher threshold detection levels at knee flexion angles of 5° and 30° in comparison to age and gender-matched control participants. These findings are similar to those reported by Sahin et al. (2008) who found that HMS patients had significantly higher absolute angular errors than age and gender-matched control participants during a knee joint matching task. Rombaut, De Paepe, et al. (2010) later compared proprioceptive abilities and vibratory perception sense in EDS hypermobility type patients to those of age and gender-matched controls. Exploring proprioception in the knee and shoulder using both an active and passive joint matching paradigm, they found that EDS patients showed significantly larger angular errors in joint matching at the knee joint, but not at the shoulder. However, they also found that EDS patients could detect tactile stimuli just as well as controls (using vibratory perception threshold at these same joints), suggesting that cutaneous receptors in the skin may not be contributing to the observed proprioceptive deficit in EDS; it could be that tendon and joint receptors are the most likely contributors to the proprioceptive impairment found in EDS (Hall et al., 1995; Rombaut, De Paepe, et al., 2010; Sahin et al., 2008).

Since then, a study in our lab explored proprioceptive localization of the hand in the two most common variants of EDS, classic and hypermobility types (Clayton et al., 2013). We found that, although EDS patients were just as accurate as controls in estimating the location of their unseen hand, they were less precise when tested in the peripheral workspace compared to

healthy controls. Specifically, they showed a greater just-noticeable difference compared to healthy controls, in that their unseen hand had to be further left or further right before they were as certain of its position relative to a visual reference as the controls. Moreover, we found a significant correlation between the magnitude of joint hypermobility (Beighton scores) and the magnitude of this proprioceptive deficit, such that those who were the least precise were those who had the highest Beighton scores. We were not able to detect any significant differences between the two types of EDS.

Given that EDS patients, who exhibit joint hypermobility, seem to have some proprioceptive impairments that vary across the workspace (Clayton et al., 2013), our goal was to further examine proprioceptive sensitivity in EDS across a greater number of workspace locations, and to see how they differ compared to healthy controls. Again, we wanted to examine proprioceptive localization of the hand, a body part in which movements need to be monitored with precision to interact with the environment. While joint matching tasks, or motion threshold detection paradigms, are commonly used to examine proprioception in patients exhibiting joint hypermobility (Hall et al., 1995; Rombaut, De Paepe, et al., 2010; Sahin et al., 2008; Smith et al., 2013), we used a paradigm which allowed us to precisely place the hand at a greater number of workplace locations in order to obtain very sensitive measures of hand proprioception (Jones, Byrne, et al., 2012). Here, we assess proprioceptive localization of the non-dominant left hand by having participants reach to its unseen location with their visible right hand. Since many EDS patients suffer from chronic pain (Sacheti et al., 1997; Voermans et al., 2010), and proprioceptive deficits have been observed in other chronic pain populations (Gill & Callaghan, 1998; Knox et al., 2006; Lewis et al., 2010; Tsay et al., 2015), we considered

the possibility that pain might be influencing our results, as well. Therefore, we quantified each patient's chronic pain to explore whether those with the most pain also have the worst proprioception.

Methods

Participants

Thirteen healthy age-matched control participants (mean age 27 years, range 16- 49, 5 females) and nine participants with EDS (mean age 31 years, range 26-43, 8 females), all of whom were right-handed, participated in the experiment described below. Control participants were laboratory volunteers or recruited from the Undergraduate Research Participant Pool at York University (and given course credit for their participation). Participants in the patient group were recruited through EDS Canada's GTA (General Toronto Area) Support Group. Patient clinical demographics are provided in Table 2.1. Four of the EDS patients were classic type (mean age 32 years, range 27-43, 3 females), while all the others were hypermobility type (mean age 31, range 26-43, 5 females). All participants provided informed consent, and the study was conducted in accordance with the ethical guidelines set by the York Human Participants Review Sub-committee. All participants had normal or corrected to normal vision. None of the EDS patients were on any medication known to affect their cognitive abilities during the experiment. Only patients with confirmed clinical diagnoses were admitted into the study. Joint hypermobility was measured using the Beighton criteria which rates patients' hypermobility on a 9-point scale after performing 9 movements. Patients' Beighton scores were obtained from genetic reports and, in all cases, were confirmed by the experimenter prior to testing. Chronic pain was measured using the McGill Pain Questionnaire, and a Pain Response

Index (PRI-R) score was calculated for each participant by summing the rank value of each word chosen, as described in Melzack (1975). Patients read 20 sets of words and were instructed to select the word that best described their pain (the least intense word is ranked 1) for each of the 20 dimensions, totaling a maximum of 78 points. If none of the words in a set applied, they made no selection (Melzack, 1975).

<i>Participant</i>	<i>Age</i>	<i>Sex</i>	<i>Type</i>	<i>Beighton Score</i>	<i>PRI-R</i>
CM1	26	F	hypermobility	6	11
CM2	27	F	classic	7	61
CO	26	F	hypermobility	8	57
RO	30	F	hypermobility	6	3
MR	28	F	hypermobility	7	23
BS	43	F	classic	5	19
TS1	30	F	classic	8	37
TS2	43	F	hypermobility	8	43
TW	27	M	classic	3	28

Table 2.1. EDS clinical demographics.

General Experimental Setup

A view of the experimental setup is provided in Figure 2.1. Participants sat on a height-adjustable chair in front of a 90-cm-high table. They were positioned so that they could comfortably reach to all areas of a transparent 43 cm (length) X 33 cm (width), 3-mm-thick horizontal touch screen panel (resolution of 4,096 X 4,096 pixels; Keytec, Garland, TX) placed

on top of an occluding platform (Figure 2.1A). The touch screen was used to record all reach endpoints. A complete description of the methodology is reported elsewhere (Jones, Byrne, et al., 2012).

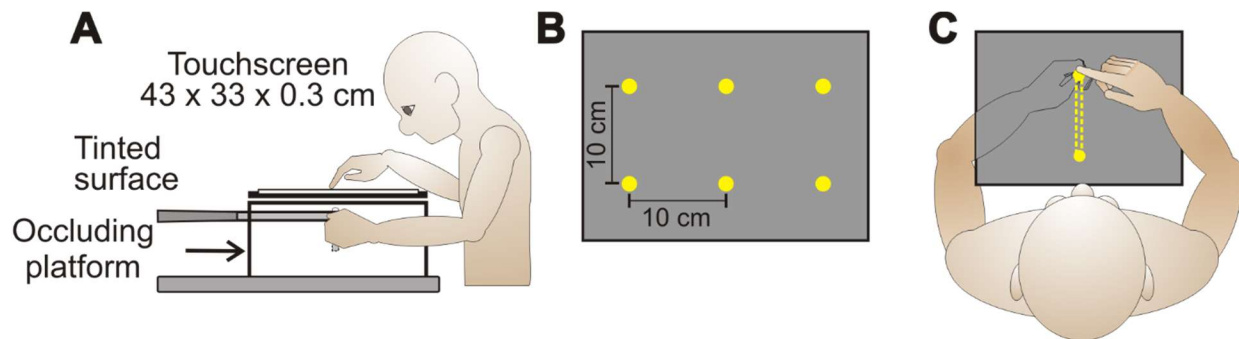


Figure 2.1. Experimental setup and tasks. **A:** Side view of the general experimental set-up. **B:** Six locations served as start and final target sites for the non-dominant left hand. **C:** The robotic manipulandum restricted active movement of the left target-hand along a straight path from one target site (start) to another target site (target position). Participants reached with their seen right hand to the felt location of the unseen left target-hand.

Six sites served as the proprioceptive target locations (Figure 2.1B). These sites were spaced 10 cm apart and arranged in two lines (3 sites/line and 10 cm between the two lines). The closest three target sites were 23 cm from participants (bottom line of targets in Figure 2.1B). Participants were instructed to grasp the vertical handle of a modified two-joint robotic manipulandum (Interactive Motion Technologies, Cambridge, MA) with their left target-hand in such a way that their thumb rested on top of the robot handle (1.4 cm in diameter); the handle was just above waist level (Figure 2.1A). On each trial, the robotic manipulandum was programmed to restrict participants' active movement of their left hand along a straight path from one of the six target-hand locations to one of the five remaining target-hand locations (dashed lines in Figure 2.1C; see Cressman & Henriques, 2009 for details about active placement of the target-hand). On each trial, participants were asked to reach to the felt

location of their left thumb located at one of the six sites (Figure 2.1C). For convenience, the term target-hand will be used in place of target-thumb.

The manipulandum was occluded by a tinted translucent Plexiglas platform (on which the transparent touch screen panel was fixed), which was located 2cm above the height of the target-hand (Figure 2.1A). Once the room lights were turned off, participants were not able to see their left target-hand or forearm. A cloak was used to cover the participant's left upper arm and shoulder to ensure that no additional visual information concerning hand or arm position could be used at any point throughout the testing sessions (cloak not shown in Figure 2.1A). Participants could see their right reaching-hand.

Participants reached with their right (dominant) hand to their unseen left target-hand (Figure 2.1C). Each session began with the left target-hand at the bottom-center target-hand location (Figure 2.1B). Participants first reached with their right hand/index finger to the felt location of the left target-hand in this initial location. A tone indicated to participants' that they made contact with the touch screen. Participants then returned their right reaching-hand to the right of their body and actively pushed the robotic manipulandum using their left target-hand (guided along the robot-constrained pathway, illustrated as a yellow rectangle in Figure 2.1C) from this starting location to one of the five remaining target sites. Once the left target-hand arrived at its final location, a tone prompted participants to reach to the left target-hand once again at this new target site, making contact with the touch screen with the index finger of their right hand (Figure 2.1C). Participants then returned their right reaching-hand to the right of their body, and the left target-hand was actively guided to the next final target-hand location. Therefore, the final position of the left-target hand for each reach trial served as the starting

position of the left target-hand for the subsequent trial. To limit proprioceptive drift, the left target-hand began in the bottom-center start location twice as many times as in any other starting position. On 50% of these trials, the left target-hand was illuminated using three white light emitting diodes (LEDs), and was therefore visible, for 1s (Brown, 2003; Desmurget et al., 2000; Wann & Ibrahim, 1992). The illumination of the target-hand in this bottom-center location occurred prior to reach onset of the right hand. The left target-hand was not illuminated in any other location in this task. Trials in which the left target-hand was visible in the bottom-center location were not included in the analysis.

Each participant made 52 reaches to the left target-hand for each of the 35 start and final target position combinations (including those combinations when the target-hand was illuminated in the bottom-center start position) for a grand total of 1820 trials. Two sessions were used to collect 6 blocks of data across two days of testing. Each participant also completed a baseline reaching task at the end of each experimental block. The baseline task consisted of five reaches to the continuously visible left target-hand for each start and final target position combination. Horizontal and sagittal reach errors were calculated by taking the reach endpoint, as recorded by the touch screen, for each reaching trial and subtracting this baseline average reach endpoint for each start and target position pairing. Precision (or variability) of the proprioceptive-guided reaches was examined by fitting 95% error ellipses around reach endpoints for each final target position, for each participant. The area of the ellipses, as well as the sum of the major and minor axes, was used to compare precision of locating the unseen left hand across groups and proprioceptive target positions. While area of

the ellipses provides a common and intuitive assessment of variance, using the length of the axes provide a robust measure, which is less sensitive to outliers.

Data Analysis

To assess proprioceptive accuracy in EDS patients and healthy controls, we compared horizontal and sagittal errors using a mixed ANOVA that included group (EDS vs. healthy) as a between-groups factor and proprioceptive target location (target-hand positions that were near-left, near-centre, near-right, far-left, far-centre and far-right) as a within-groups factor. To assess differences in precision of hand localization between the two groups, we ran similar 2 X 6 mixed ANOVAs on elliptical error and the individual and sum of elliptical axes. All ANOVA results are reported with Greenhouse-Geisser corrected p values to compensate for violations of sphericity. Differences with a probability of $p \leq 0.05$ were considered significant. Bayesian statistics are also reported with BF_{10} , which estimates the likelihood of the alternative hypothesis being true given our data, for each corresponding frequentist test. However, post-hoc tests were only conducted with frequentist analyses. Pairwise comparisons with Bonferroni correction were used to determine the locus of these differences. Finally, we ran regression analyses to explore the relationship between chronic pain and proprioceptive precision, as well as that of joint hypermobility and proprioceptive precision.

Results

Accuracy

The bars in Figure 2.2A show that for both the EDS and control groups, participants' reach endpoints were quite accurate; reaches fell within 2cm of the actual target-hand

locations. Errors in proprioceptive localization for both groups are also depicted in Figure 2.2B as circles (mean endpoints) within the ellipses, relative to the “X” representing the location of the proprioceptive target. Horizontal errors were no different, for both EDS (striped bars in Figure 2.2A; dashed circles in Figure 2.2B) and control participants (solid bars and circles) ($F(1, 20) = 2.50$, $p = 0.13$, $\eta^2 = 0.111$, $BF_{10} = 1.027$), as were errors along the sagittal direction ($F(1, 20) = 1.41$, $p = 0.25$, $\eta^2 = 0.066$, $BF_{10} = 0.75$), and absolute displacement errors ($F(1, 20) = 1.61$, $p = 0.22$, $\eta^2 = 0.075$, $BF_{10} = 0.71$). An interaction between group and (horizontal) target location revealed that leftward errors for left targets, and rightward errors for right targets, were larger for controls than EDS participants (whose reaches were shifted to the left for all targets) ($F(1.15, 22.92) = 5.71$, $p = 0.022$, $\eta^2 = 0.223$, $BF_{10} = 7.539$). For sagittal errors, both groups tended to underestimate the distance of far proprioceptive targets, but not closer targets ($F(1, 20) = 28.61$, $p < 0.001$, $\eta^2 = 0.589$, $BF_{10} > 100$). These results can be seen by comparing the circles in each ellipse to the “X”s in Figure 2.2B.

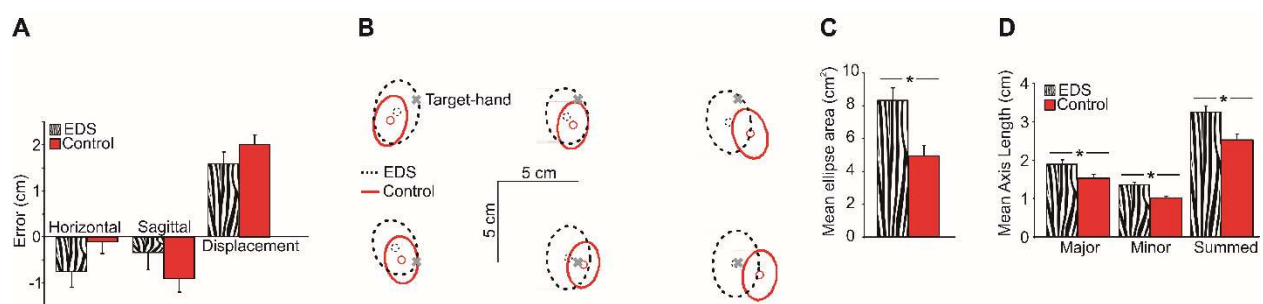


Figure 2.2. Proprioceptive localization results. **A:** Average horizontal and sagittal reach endpoint errors. Error bars reflect standard error of the mean. **B:** Average two-dimensional errors (centre of ellipses, represented by circles) and precision of reach endpoints (95% error ellipses) at each target-hand position (X’s), for EDS patients (dashed) and healthy controls (solid). **C:** Mean elliptical areas (cm²) collapsed across all hand-target locations. Error bars reflect standard error of the mean. **D:** Mean axis length (cm) for the major, minor, and summed axes. Error bars reflect standard error of the mean.

Precision

While EDS patients were as accurate as healthy controls, the larger dotted ellipses in Figure 2.2B suggest that they were not as precise at localizing their unseen left hand. EDS patients (dashed ellipses) showed greater scatter when localizing proprioceptive targets than healthy controls (solid ellipses). Specifically, the areas of the elliptic fits (Figure 2.2C) were significantly larger for EDS (striped bar; on average 8.33 cm²) than healthy controls (solid bar; on average 4.90 cm²) ($F(1, 20) = 11.40, p < 0.001, \eta^2 = 0.363, BF_{10} = 9.743$). Likewise, the sum of the major and minor axes (shown in Figure 2.2D) was significantly larger for EDS patients than controls ($F(1, 20) = 9.60, p < 0.001, \eta^2 = 0.324, BF_{10} = 6.551$). This increase in the sum of the axes reflected a significant increase in size of both axes (larger major ($F(1, 20) = 5.28, p = 0.03, \eta^2 = 0.209, BF_{10} = 2.153$), and minor axes ($F(1, 20) = 18.82, p < 0.001, \eta^2 = 0.485, BF_{10} = 65.531$) for patients compared to healthy controls. This suggests that the increase in variance was not skewed in a particular direction. Although precision (both measured by elliptical area and sum-of-axes) was compromised at more peripheral target locations compared to the middle target location ($F(1.17, 23.45) = 7.29, p = 0.001, \eta^2 = 0.267, BF_{10} = 13.061$; $F(1.24, 24.82) = 6.52, p = 0.013, \eta^2 = 0.245, BF_{10} = 11.81$), this did not significantly vary with Group ($F(1.17, 23.45) = 0.69, p = 0.51, \eta^2 = 0.033, BF_{10} = 0.577$; $F(1.24, 24.82) = 0.44, p = 0.553, \eta^2 = 0.022, BF_{10} = 0.337$).

Chronic pain and proprioception

All EDS patients reported chronic pain, but at varying levels of severity. The mean PRI-R (pain rating index; ranked) for patients was found to be 31.33 and ranged from 3 to 61. Although some patients indicated they experienced more pain than others, we did not find a significant relationship between chronic pain scores and proprioceptive precision ($F(1, 7) =$

0.08, $p = 0.79$). In other words, those with the largest elliptical areas did not have the highest PRI-R scores. This suggests that chronic pain is likely not contributing to the observed proprioceptive deficit shown in this study.

Discussion

The goal of the present study was to explore proprioceptive sensitivity of the hand in EDS patients across space, and to see how their proprioceptive sensitivity compared to that of healthy controls. We used a robotic manipulandum to precisely place the non-dominant left hand at 6 different target-hand positions (near and far as well as left, center and right) and measured participants' ability to localize the left-hand using reaches with the seen right hand. Although EDS patients were as accurate as healthy controls, as shown by the similar horizontal and sagittal endpoint errors in Figures 2.2A (bars) and 2.2B (circles inside ellipses), patients were much less precise than healthy controls. Specifically, the magnitude of 2D scatter for proprioceptive localization errors (measured by 95% confidence ellipses (across 52 trials per target) for the patients were significantly larger (almost double) than those of the healthy controls. Overall, these results suggest EDS patients are impaired in their proprioceptive sensitivity.

For the most part, healthy individuals are quite good at localizing their unseen hand using proprioception (and efferent signals) (Haggard et al., 2000; Jones, Byrne, et al., 2012; Jones et al., 2010; Lovelace, 1989). While there are many ways to measure hand proprioception, one of the main methods involves participants reaching to the current location of an unseen body part, usually the hand (Baud-Bovy & Viviani, 1998; Haggard et al., 2000;

Lovelace, 1989; Sarlegna & Sainburg, 2007). Haggard et al. (2000) and Lovelace (1989) found that when participants reached to the unseen location of their left index finger using a pen, they made localization errors of 1.74 and 1.77 cm, respectively. Results for proprioceptive-guided reaching from our lab (Jones, Byrne, et al., 2012; Jones et al., 2010) also show that participants are quite accurate in localizing their hand-target. When these hand-targets were radially displaced about 12 cm from the start position, from -30° to 120° (ranging horizontally by 20 cm), errors tended to systematically vary with the target angle. Nonetheless, average errors usually fell within 2 cm of the target site, for both the left and the right hands (Jones et al., 2010). When we tested a smaller number of proprioceptive target sites, at a similar distance, but located 5 cm left and right of the midline (including the midline), we found similar sized errors (Jones, Byrne, et al., 2012). Again, the reach errors varied with the hand tested, (showed a hand-dependent bias) falling a couple centimeters on either side of the target site, consistent with the findings reported here. In the current study, and in Clayton et al., (2013) we find similar accuracy for both controls and EDS patients when localizing their unseen left hand. What differed between patients and controls was the precision of localizing the unseen hand: 95% error ellipses were about 4 cm^2 for controls and double that for EDS patients.

While some studies have found that how well healthy people localize their unseen hand varies with the location in space (Jones et al., 2010; Wilson et al., 2010), in the current study, we found only small target-dependent effects for both accuracy and precision. For accuracy, the target-dependent pattern between groups was the same for sagittal errors or only mildly different for horizontal errors. For precision, both groups were slightly more variable when localizing their unseen hand at more peripheral locations compared to central localizations.

However, as consistent with the overall effect, EDS patients showed almost twice the amount of scatter in both central and peripheral location as those of controls.

The larger variance that EDS patients show when localizing their felt hand, compared to controls, may reflect some impairments in their ability to reach. In our previous study (Clayton et al., 2013) we had EDS patients (half of them participated in both studies) reach to visual targets without visual feedback of their hand. Additional analyses from this earlier study revealed that EDS patients were just as accurate but trended towards being less precise than controls when reaching to visual targets [$F(1, 32) = 2.68, p = 0.11$; $F(1, 32) = 3.36, p = 0.08$], by about 20%. Thus, the twofold increase in variance when reaching to the unseen hand in the current study compared to the 20% increase in variance when reaching (with the unseen hand) to a visual target in our previous study, suggests that most of the variability we find in this study reflects poorer hand proprioception. Nonetheless, it is possible that this impairment in hand proprioception could be what is driving the slightly larger variability in reaches to visual targets in the previous study where the reaching hand was not visible.

The current study shows that EDS patients were less precise (almost twice as variable) than controls at all target sites in the workspace. Specifically, they were just as variable at locating their unseen hand both when the hand was located along the body midline and when it fell 10 cm left and right of the midline (peripheral). This is somewhat different than our previous results where we found differences in precision (relative to controls) only at the peripheral locations. In that study, patients were twice as unsure of their hand's position compared to controls, but only at more peripheral reference markers located 7.5 cm left and right of their body midline. The more global impairment in the current study may reflect a

difference in the task; the current study involves participants reaching to the proprioceptive target, while the previous study had them judge the felt location of the proprioceptive target relative to visual references. It could be that the way this sensory information is processed differs across task goals (Jones, Fiehler, et al., 2012) - we used a more perceptual task in Clayton et al. (2013), but a more goal-directed task in the current study. Alternatively, the difference across studies could be because this study involves localizing the non-dominant left hand, while Clayton et al. (2013) involved localizing the dominant right hand. People are usually poorer at perceiving the position of their non-dominant hand compared to their dominant (Haggard et al., 2000). Previous work in our lab (Jones et al., 2010) found that healthy controls were slightly less precise (about 20%) at reaching to the left-target hand compared to the right-target hand but found no difference in precision (the uncertainty range) between the two hands in a perceptual task similar to what was used in Clayton et al (2013). Thus, if we used the right hand as a target in the current study, it is possible that overall, precision may have been slightly better for both controls and patients, but likely the patients would have still shown an impairment. In fact, we chose the non-dominant hand in this experiment to make the task slightly more challenging.

Another difference between our previous perceptual study and the current reach study was the relationship between joint hypermobility and proprioceptive impairment. In the previous study, we found a correlation between joint hypermobility, as measured by the Beighton scores, and the magnitude of the uncertainty ranges when perceptually judging the location of the dominant hand (in the peripheral locations). However, unlike our previous study, here the size of the deficit (variance in localization error) did not correlate with our

measure of joint hypermobility ($r^2 = 0.21$, $p = 0.22$). In other words, patients with lower Beighton scores were just as imprecise at proprioceptive localization as patients with higher Beighton scores. It can be argued that Beighton scores, which measure hypermobility at 9 specific locales, are not the most ideal way to measure the magnitude of joint hypermobility (Fairbank et al., 1984). It is possible that we would have found different results had we measured hypermobility another way. Additionally, it could be that reaching to (rather than perceptually judging) the felt location of the non-dominant hand is challenging enough for even the least hypermobile patients to show deficits.

EDS patients are not the only special group that have shown impairments in proprioception. According to a review (Goble et al., 2009), several studies have shown that proprioceptive acuity decreases with age. These paradigms typically employ joint matching tasks where participants are required to reproduce the perceived position of one joint with that of the other (Adamo et al., 2007; Barrack et al., 1983), or are asked to reproduce a joint angle from memory using the same or opposite arm (Adamo et al., 2007; Kaplan et al., 1985).

It is plausible that our observed deficit is being influenced by chronic pain, which is common in both EDS subtypes we studied (Sacheti et al., 1997; Voermans et al., 2010). Proprioceptive deficits have been observed in other chronic pain populations that do not exhibit joint hypermobility. For example, those with chronic low-back pain are found to have impaired lumbar proprioception (Gill & Callaghan, 1998). However, pain does not need to be restricted to the body part being examined to reveal proprioceptive impairments. For example, those with neck pain are not able to reproduce elbow joint positions when their head is turned as well as healthy controls can (Knox et al., 2006). Thus, even though the patients in this study

experienced pain in areas other than their left arm, it is possible that their pain could have influenced their proprioceptive judgements. However, this is not what we found; we found no correlation between chronic pain and proprioceptive precision. In other words, those with the worst proprioception (largest elliptical areas) were not those with the most chronic pain (highest PRI-R scores). It is possible that, had we examined more patients, such a relationship would reveal itself. Therefore, we recommend gathering a much larger patient group to properly explore this relationship in the future.

It is unlikely that the proprioceptive deficits observed in EDS patients are due to sub-cortical impairments, like in the case of Parkinson's disease (Lee et al., 2013). It is possible that these deficits are a result of probable abnormal collagen present in proprioceptors but could also be due to repetitive stress-inducing injuries. It could be that these more downstream/peripheral components may be more related to the peripheral deterioration that is likely leading to proprioceptive impairments in the aged.

Conclusion

In conclusion, although we found that EDS patients were just as accurate as controls when localizing their unseen, non-dominant left hand, they were not as precise. Specifically, patients showed twice as much scatter as controls when localizing this hand when it was placed at a variety of locations. However, we found no relationship between proprioceptive precision and chronic pain. These results suggest that EDS patients may experience different levels of proprioceptive sensitivity than healthy controls. Future work should explore how to improve

proprioceptive sensitivity in the EDS population, which could reduce the frequency of accidental injuries in this group.

Chapter 3: Sensing Hand Position in Ehlers-Danlos Syndrome

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Abstract

Purpose: To explore the effect of joint hypermobility on acuity, and precision, of hand proprioception.

Materials and Methods: We compared proprioceptive acuity, and precision, between EDS patients and controls. We then measured any changes in their estimates of hand position after participants adapted their reaches in response to altered visual feedback of their hand. The Beighton Scale was used to quantify the magnitude of joint hypermobility.

Results: There were no differences between the groups in the accuracy of estimates of hand location, nor in the visually-induced changes in hand location. However, EDS patients' estimates were less precise when based purely on proprioception and could be partially predicted by Beighton score.

Conclusions: EDS patients are less precise at estimating their hand's location when only afferent information is available, but the presence of efferent signalling may reduce this imprecision. Those who are more hypermobile are more likely to be imprecise.

Introduction

Ehlers-Danlos syndrome (EDS) is a group of genetic connective tissue disorders that can afflict up to 2% of individuals. Most forms of EDS affect collagen throughout the body; some directly impact its structure (such as with Classical EDS), while others alter proteins that interact with collagen (Castori, 2012). Although symptoms can vary across, or sometimes within, each of the sub-types, the feature that most EDS patients have in common is joint hypermobility (Malfait et al., 2017) for a more detailed review of variations in genetics, and symptomology, across the thirteen subtypes).

Motor control requires knowledge of where our limbs are in space. An impaired sense of proprioception can sometimes lead to movements that appear 'clumsy'. EDS patients are frequently described as exhibiting clumsy movements, for which impaired proprioception is offered as an explanation (Ferrell et al., 2004). Indeed, a limited number of studies have suggested that EDS patients, or other groups exhibiting joint hypermobility, may have proprioceptive impairments (Clayton et al., 2013, 2015; Hall et al., 1995; Rombaut, De Paepe, et al., 2010; Sahin et al., 2008), but the exact nature of this impairment is still unclear. Specifically, we are not sure whether this impairment only emerges during passive proprioception (which should only rely on afferent information), or whether it also occurs during active proprioception (which should rely on both afferent and efferent information). In addition to furthering our understanding of proprioceptive acuity in EDS, we also test the extent to which proprioception is affected by visual misalignment of the hand during reaching movements. The goal of this study is to understand how joint hypermobility, which is typically seen in those with EDS,

affects both the accuracy (average) and precision (variability) of estimates of hand position both before and after sensorimotor adaptation.

Previous research from our lab suggests that EDS patients do show differences in proprioceptive sensitivity. Most recently we found that, although patients were just as accurate as controls, they were significantly less precise when indicating the felt position of their left hand at 6 different locations in a horizontal workspace. Specifically, patients showed twice as much scatter in these judgements compared to controls at all locations (Clayton et al., 2015); this suggests proprioception is less precise in EDS. The greater amount of scatter did not correlate with the magnitude of chronic pain, suggesting that pain was not contributing to the proprioceptive deficit here. In another study of ours (Clayton et al., 2013), we again found that EDS patients showed proprioceptive estimates that were no different than controls, and the precision of these estimates was significantly worse (around half of that of controls), but only at locations lateral to the body midline. The precision of these estimates at peripheral locations was significantly correlated with Beighton scores, which are commonly used to measure the magnitude of joint hypermobility. In other words, we found that those who were the most hypermobile were also the least precise when estimating their hand at peripheral locations. This suggests that hypermobility could be related to the proprioceptive deficit that seems to occur in EDS.

However, in both studies mentioned above, for proprioceptive assessment, participants moved their own unseen hand along robot-generated slots to their final location. Thus, the estimates of their unseen hand may not have been purely based on proprioceptive information since the participant had to push their hand to the final site. Yet their hand path was

constrained, and its direction and final location varied across trials, so they also could not benefit from the extra information contained in efferent signals that would have been fully available if the hand direction had been entirely generated by the participant themselves. It is possible that proprioceptive differences would have been even larger in EDS participants if their hand had been passively carried to its final location. Therefore, we want to know the extent that additional efferent information (produced during self-generated movements) can attenuate these proprioceptive deficits. To test for this, we measured both (1) estimates of hand location after the hand was passively displaced, using a robotic manipulandum and (2) estimates of hand location after the hand was actively displaced, by the person themselves, at a self-chosen location. We compared proprioceptive acuity in both tasks between EDS patients and controls. Based on our past research (Clayton et al., 2013, 2015), we hypothesized that EDS patients' proprioceptive localizations would be similar in accuracy to those of healthy controls, but that patients' localizations would be significantly less precise. We also anticipated that having efferent information available would reduce the expected imprecision in EDS.

Our second goal was to measure proprioceptive plasticity in EDS. For this goal, we altered visual feedback of the hand during a reach-training task, and afterwards measured how training with this visual distortion shifted estimates of hand location. Again, we compared the extent of the visually-induced changes between EDS patients and controls, and further, whether Beighton scores were related with proprioceptive acuity or plasticity. We hypothesized that EDS patients would adapt their reaches to a similar extent as healthy controls, that their estimates of hand location would shift similarly and that we would find a significant correlation between our measures of hand proprioception and Beighton scores, like in our first study

(Clayton et al., 2013). Our results confirm that proprioceptive information is less precise in EDS, but may be slightly attenuated by efferent information, and that proprioceptive precision is partially related to the magnitude of joint hypermobility. Our results provide a more comprehensive understanding of the proprioceptive sensitivity in EDS.

Methods

Participants

Sixteen healthy controls (mean age 34 years, range 18-54, 13 females) and fourteen EDS patients (mean age 34 years, range 25-37, 11 females; 3 Classical EDS, 9 Hypermobile EDS, 1 Arthrochalasia EDS and 1 Spondylodysplastic EDS) voluntarily took part in the experiment outlined below. All participants had corrected-to-normal vision and were right-handed. Controls were laboratory volunteers or recruited from the Undergraduate Research Participant Pool at York University (and given course credit for their participation). Participants in the patient group were recruited through EDS Canada's General Toronto Area Support Group. All participants provided informed consent, and the study was conducted in accordance with the ethical guidelines set by the York Human Participants Review Sub-committee.

EDS was recently re-classified into thirteen sub-types (Malfait et al., 2017), after identifying the genetic mutations responsible for twelve of the sub-types (genetics responsible for Hypermobility type are still unknown). Only patients with confirmed diagnoses (confirmed clinical diagnoses for Hypermobility type; confirmed molecular diagnoses for all other types) were admitted into the study. Joint hypermobility was measured using the Beighton criterion, which rates patients' hypermobility on a 9-point scale after performing 9 movements. Patients'

Beighton scores were obtained from genetic reports and were confirmed by the experimenter prior to testing with a goniometer. None of the EDS patients were on any medication known to affect their cognitive abilities during the experiment.

General Experimental Setup

Participants sat on a height and distance adjustable chair in front of the experimental set-up. With their right hand, participants held onto the vertical handle of a two-joint robot manipulandum (Interactive Motion Technologies Inc., Cambridge, MA, USA) such that their thumb rested on top of the handle. A black cloth was draped over their shoulder, and right arm, to occlude visual feedback of the reaching limb. Visual stimuli were projected from a downward facing monitor (Samsung 510 N, 60 Hz) located 28 cm above the robotic arm. A reflective surface was mounted on a horizontal plane 14 cm above the two-joint robotic arm, midway between the manipulandum and the monitor, such that images displayed on the monitor appeared to lie in the same horizontal plane as that of the robotic arm (Figure 3.1A).

Underneath the reflective surface, ~2 cm above the position of the thumb, as it rested on the modified handle of the manipulandum, a touch screen was mounted so participants could indicate unseen right-hand locations (specifically the unseen thumb) with their left hand, for some tasks. The left hand was illuminated by a small lamp during these tasks, and therefore was visible when reaching to the touch screen panel. For each task, the home position of the right hand was located ~20 cm in front of the participants, along the participants' body midline.

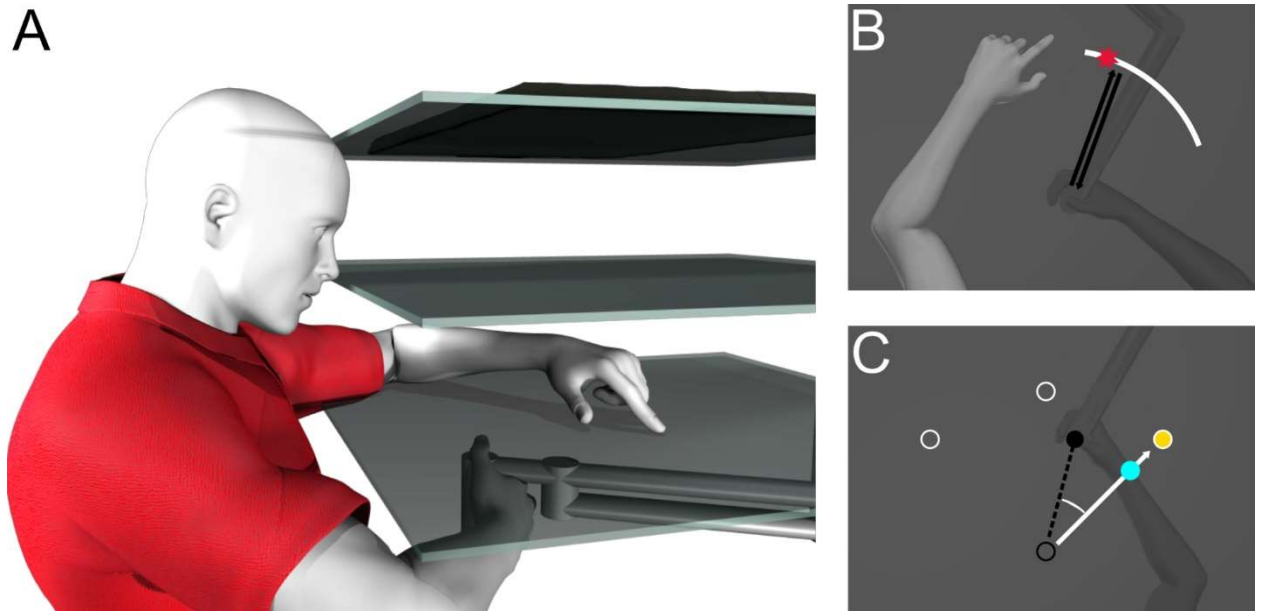


Figure 3.1. Setup and experimental design. **A:** Participants moved their right hand which was hidden by a mirror (middle surface) half-way between their hand and the monitor (top surface). A touchscreen located just above the right hand was used to collect responses from the left hand (bottom surface). **B:** Active and Passive Localization Trials. One of three white arcs, spanning 60° , located 12 cm away from the home position and centred at 50° , 90° or 130° would appear. Only the 50° arc is shown as an example. The participants' invisible, right hand first moves to the arc and back to the home position, either by their own voluntary movement ("active localization") or by the robot ("passive localization"), indicated by the black pathway. Then they use their visible, left hand to indicate on the touch screen where their right hand crossed the arc, indicated by the red star. The home position is not shown to prevent it from being used as a reference point (the hand is at the home position in the illustration and is at the same position as the open black circle in panel C). **C:** Reach training task and No-Cursor reach trials. The targets were located 12 cm away from the home position (shown by the hollow black circle) at 45° (shown here by the yellow circle), 90° , and 135° (shown by the hollow white circles) and were presented one at a time in a pseudorandom order. In the rotated training tasks, the hand-cursor (blue circle) was rotated 30° relative to the home position. In the aligned training task, the cursor was green and aligned with the hand's position (not depicted here). In the No-Cursor trials, the cursor was not visible, thus no visual feedback of the hand's position was available.

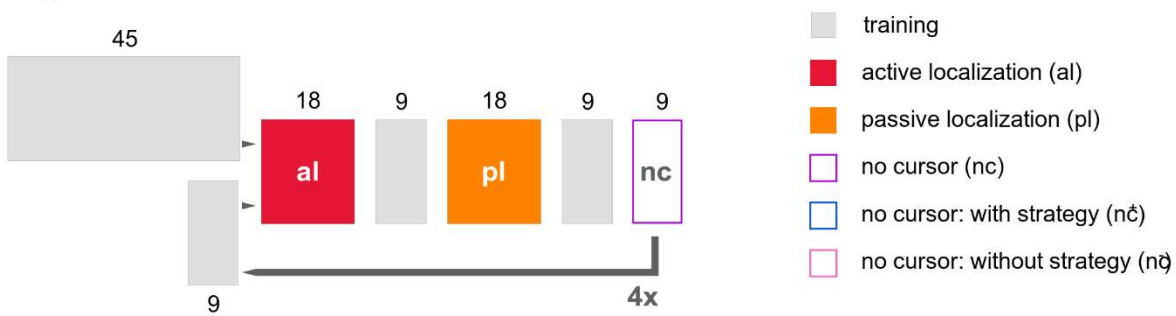
Procedure

All participants completed the set of tasks in a specified order in two sessions performed one after the other (see Figure 3.2). Each session started with a reach training task, followed by several localization tasks, as detailed below. In between the localization tasks there were blocks of no-cursor reaches and additional training.

The aligned session consisted of four blocks of reach training, hand localization and no-cursor trials; this served as baseline data (Aligned session; Figure 3.2). The session began with 45 aligned (green) cursor training trials, followed by blocks of 18 active localization trials, 18 passive localization trials, and 9 no-cursor trials. Shorter blocks of 9 cursor training trials, referred to as 'top-up' cursor training trials, were interleaved between localization and no-cursor blocks.

Following the aligned session, participants were told that the cursor would be moving differently, and that they would have to compensate for the difference, but they were not explicitly informed that the cursor's trajectory would be rotated 30° CW from their actual hand's movement. During the rotated session, the cursor was blue, and its motion was rotated 30° CW relative to the home position. To perfectly compensate for this visuomotor rotation, the unseen hand would have to move in a direction 30° CCW from any displayed target relative to the home position. The rotated session (Figure 3.2) began with a longer training session of 90 rotated training trials and each top-up block contained 30 trials, to reduce learning decay of the visuomotor rotation. Each block of rotated reach training trials was followed by 18 trials of active localization, 18 trials of passive localization and 18 no-cursor trials. Each block of no-cursor trials was done twice, although only one set (those where participants were asked not to employ a strategy during reaching, see task description below) was used for this analysis.

Aligned Session



Rotated Session

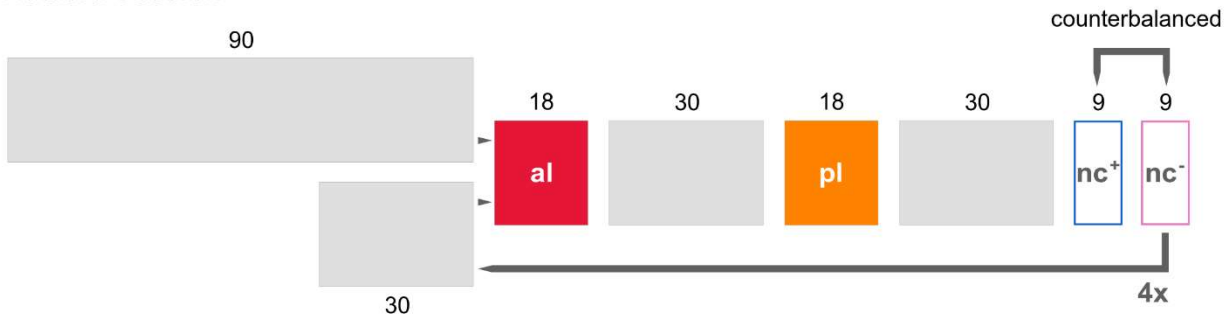


Figure 3.2. Experiment paradigm detailing the order of tasks, and number of trials, across aligned and rotated sessions. **Top:** For the first session the cursor was aligned with the position of the right hand. Participants began with 45 cursor training trials that were then followed by blocks of active localization (red, 18 trials each), passive localization (orange, 18 trials each) and no-cursor trials (hollow, 9 trials each). Nine ‘top up’ aligned-cursor training blocks were interleaved in between localization and no-cursor blocks for four more repeats. **Bottom:** During the second session the cursor was rotated 30° CW relative to the position of the right hand. Participants began with 90 cursor training trials that were then followed by blocks of active localization (18 trials each), passive localization (18 trials each) and two variations of blocks of no-cursor trials (with or without strategy; 9 trials each). Each block was followed by 30 ‘Top up’ rotated-cursor training blocks for four more repeats. In both the aligned and rotated sessions, passive localization always occurred after active localization, since endpoint locations of the robot-generated movements in passive localizations were based on locations that participants voluntarily moved towards during active localization.

Hand Localization

The hand localization tasks (Figure 3.1B) were used to measure acuity of unseen hand localization and have been established as a reliable measure of proprioceptive abilities (Gastrock et al., 2020; Izawa et al., 2012; Modchalingam et al., 2019; Mostafa et al., 2019; Hart & Henriques, 2016; Vachon et al., 2020). In the active hand localization tasks, participants

moved their own hand to a self-chosen position on the arc, and thus both afferent and efferent information was available. In the passive hand localization task, the robot displaced their passive hand, such that only afferent information on hand location was available. The robot displaced the hand to the same endpoints that were recorded in the preceding 'active' task (to ensure no differences in hand-target locations across conditions), but in a shuffled order, which required the active hand localization task to always be performed first.

Each hand localization trial began with a white arc (0.5 cm thick, located 12 cm away from the home position, which was not visible to participants because it could provide a reference point) appearing on the screen (Figure 3.1B; home position is at the same location as the right invisible hand). The arc spanned 60° and was centered on either the 50°, 90° or 130° location in polar coordinates, and the target-hand was moved 12 cm out (either by the participant or by the robot) until the hand hit a force cushion. With the arc still displayed, participants used their visible left hand to indicate, on the touch screen mounted above the manipulandum, the location where the movement of their unseen right hand had crossed the arc (comparable to Mostafa et al., 2019; participants were to point with the left hand to 'where they believed their right hand crossed the circle'). After each touchscreen response participants were instructed to place their left hand under their chin to prevent unintended contact with the touchscreen.

Training

Besides measuring estimates of hand location, we also wanted to measure how these estimated locations change with visuomotor training (Cressman & Henriques, 2009).

Visuomotor adaptation is when people reach to targets with a misaligned cursor, representing

their unseen hand, and is considered a reliable method for studying visuomotor learning (Krakauer, 2009). Visuomotor training involved reaches to a single, visual target (a yellow disc with a diameter of 1 cm), 12 cm away at 45°, 90° or 135° relative to the home position (Figure 3.1C). Participants were instructed to reach to the target as quickly and as accurately as possible using a green (aligned session) or blue (rotated session) circular cursor, 1 cm in diameter, representing their unseen hand. A reach trial was complete when the centre of the hand cursor overlapped with the target (i.e., the hand was within 0.5 cm of the target's centre). Upon completion of the reach, both the cursor and target vanished, and the participants moved their hand back toward the home position, along a constrained, straight path. That is, if participants tried to move outside of the path, a resistance force (a stiffness of 2 N/(mm/s) and a viscous damping of 5 N/(mm/s) was generated perpendicular to the path. During aligned-cursor training the cursor was aligned with movement of the unseen hand. During rotated-cursor training the motion of the cursor was abruptly rotated 30° clockwise relative to the home position where it remained for all subsequent trials and blocks.

No-Cursor Reaches

Reach aftereffects are measured by having participants reach to targets in the absence of the hand-cursor and are considered a reliable measure of implicit learning (Krakauer, 2009). Participants reached to each of 3 targets: 45°, 90°, and 135°, three times each, pseudo-randomly, for a total of 9 reaches per block (Figure 3.2). After the hand moved out and was held in the same position for 300 ms, the target disappeared which indicated that the trial was over. Participants then returned their hand to the home position along a constrained pathway, like in training.

During the rotated session, we used two variations of No-Cursor trials (including and excluding a strategy; Figure 3.2). Participants completed these two variations in succession and the order was counterbalanced across, and within, participants. Participants were instructed to either include or exclude any strategy that they may have developed to counter the visuomotor rotation during rotated cursor training trials, even though they were not explicitly told how to counter it. These tasks were inherited from other studies in our lab, involving healthy participants, which measured explicit and implicit processes of visuomotor adaptation (Gastrock et al., 2020; Modchalingam et al., 2019; Mostafa et al., 2019; Vachon et al., 2020). Out of convenience we used the same set of programmed tasks for the current study, but since our goal here was to measure proprioceptive acuity in EDS (and we did not think implicit/explicit contributions would be relevant here) we planned a priori to exclude the “with-strategy” trials from analysis.

Data Analysis

The main goal of this experiment was to determine the effect of EDS on the accuracy and precision of both active and passive hand localizations. To put any such effect in the proper context, we first tested if there were any differences in performance in visuomotor learning (Table 3.1; first two tasks). Finally, we investigated the relation between hypermobility and hand localization. For all statistical tests, the alpha level was set to 0.05 and, when appropriate, Greenhouse-Geisser corrections were used. A summary of the measures derived from each task are presented in Table 3.1 and are described further below. All data pre-processing and analyses were done in R version 3.6.0 (R Core Team, 2019). All data and analysis scripts are available on OSF (<https://doi.org/10.17605/OSF.IO/TF8KC>).

Task	Accuracy Measure (Aligned or Rotated)	Accuracy Difference Measure (Rotated - Aligned)	Precision Measure (Aligned or Rotated)
Training	Mean angle of movement at maximum velocity; not shown in figures.	Reach deviations; Figure 3.3 (A-C).	Standard deviation of angle at maximum velocity; Figure 3.3D.
No-cursor Reaching	Mean angle at movement endpoint; Figure 3.4A.	Aftereffects; Figure 3.4B	Standard deviation of angle at movement endpoint; Figure 3.4 (C-D).
Active Localization	Smoothed-spline interpolation through the angular differences between the location where the participant's unseen, self-generated, right-hand movement ended and the perceived hand location, where participants indicated on the touchscreen with their left hand; Figure 3.5A (aligned only; rotated not shown).	Active shifts; Figure 3.5C	Mean squared error between the angular location of the perceived hand position and a smoothed-spline interpolated reference. This assumes the smoothed-spline as equivalent to a mean, to approximate the standard deviations in the other tasks; Figure 3.6.
Passive Localization	Smoothed-spline interpolation through the angular differences between the location where the participant's unseen, robot-generated, right-hand movement ended and the perceived hand location, where participants indicated on the touchscreen with their left hand; Figure 3.5B (aligned only; rotated not shown).	Passive shifts; Figure 3.5D	Mean squared error between the angular location of the perceived hand position and a smoothed-spline interpolated reference. This assumes the smoothed-spline as equivalent to a mean, to approximate the standard deviations in the other tasks; Figure 3.6.

Table 3.1. A summary of the measures that were used to analyze results from each of the experimental tasks.

Rate of Adaptation

First, we analyzed group differences in rates of learning for reaches during cursor training trials (Table 3.1; first task row). All cursor, and no-cursor reaches, included in both sessions (aligned and rotated) were manually inspected to ensure participants performed the task as requested. For example, a trial would be removed if a participant did not attempt to reach directly towards the target. The very small number of trials (less than 5% in each group) that were found to have violated the instructions were removed from further analyses. For the remaining trials, we calculated angular reach deviation at the point of maximum velocity. We corrected for individual baseline biases, by calculating the average reach deviation for each target separately within each participant, during the last 30 out of the first 45 aligned-cursor training trials. The first set consisted of the first 3 trials (trials 1-3), the second consisted of the next 3 trials (trials 4-6), and the third consisted of the last 15 trials of training (trials 76 to 90). We then compared measures of angular reach deviation, for each of these three trial sets across patients and controls using a 3 X 2 mixed design ANOVA (with block as the within-subjects factor and group as the between-subjects factor); this allowed us to confirm whether both groups learned to counter the perturbation and to explore any differences across both groups.

We also computed the standard deviation of both cursor and no-cursor reaches, for both the aligned and rotated sessions, as a measure of precision which we compared across both groups by using two separate 2 X 2 mixed design ANOVAs.

Reach Aftereffects

Then we explored possible group differences in reaching movements when cursor feedback was absent (Table 3.1; second task row). We took the angular reach deviations at movement endpoints for these no-cursor, open-loop, reaches. For all no-cursor trials, we calculated the angular difference between a straight line from the home position to the point where the participant's hand movement ended, and a line from the home position to the target. Using the endpoint of the reach, rather than the point of maximum velocity, makes data more comparable to those obtained in localization trials (see below).

To measure implicit learning following training with a rotated cursor, angular reach deviations from aligned no-cursor trials were subtracted from without strategy no-cursor trials. Since we were only interested in implicit motor adaptation, we only looked at the reach aftereffects without strategy. We compared implicit learning across both groups by using a 2 X 2 mixed design ANOVA.

Hand Localization

To answer our main questions, we explored the effect of EDS on hand location estimates. To do so, we analysed hand location estimates (both after active and passive hand displacement) before and after visuomotor adaptation (Table 3.1; last two task rows). We computed the angular difference between a line connecting the home position to the location where the participant's unseen right-hand movement ended, and a line connecting the home position to perceived hand location (where participants indicated on the touchscreen with their left hand). To account for possible differences in performance of these localization tasks, we ensured that arc responses were centred where we expected the arc to be displayed, 12 cm

from the home position, by using the same circle-fitting procedure as another study from our lab (Mostafa et al., 2019). This helped to ensure that any localization shifts detected in analyses were not due to unwanted response biases or technical issues. Furthermore, all localizations included in both sessions were manually inspected to ensure participants performed the task as requested, just like we did for our reaching tasks, and only a few trials were excluded from analysis. Since participants chose the locations on the arc that they moved towards in the Active Localization task, their movements did not always encompass all possible arc locations. Thus, as we did in our other studies which used the same tasks (Gastrock et al., 2020; Modchalingam et al., 2019; Mostafa et al., 2019; Vachon et al., 2020), we interpolated changes in hand localization across the workspace (using kernel-smoothing with a gaussian width of 15°) for every participant. In order to confirm that baseline hand localizations were no different between the groups we calculated 95% confidence intervals, based on sample t-distributions, and plotted them for both groups, across the workspace, separately for each of the localization tasks (active and passive), as a way of testing for significant differences; this is equivalent to running a t-test but has the advantage of showing how the effect varies with reach direction, which occurs similarly for both groups. Then we used the mean of these values, at each of the three points, to estimate the accuracy of hand localization errors in active and passive movements for both the aligned and rotated sessions, which we compared across both groups using a 2 X 2 X 2 mixed design ANOVA (with task as a within-subjects factor, session as a within-subjects factor and group as the between-subjects factor).

To measure the effect of visuomotor adaptation on hand localization, we first confirmed that hand localization after rotated-cursor training significantly differed from localizations after

aligned-cursor training, as in our previous studies. Then, we calculated the difference of localization errors between the two sessions to represent visually-induced shifts in hand localization (3rd column of the last two tasks in Table 3.1). These shifts were compared across groups, separately for active and passive hand localization, using two separate 2 X 2 mixed-design ANOVAs.

We also computed the standard deviation of the hand location estimates, for both afferent-based estimates and efferent-based estimates in both the aligned and rotated sessions, as a measure of proprioceptive precision which we compared across both groups using a 2 X 2 X 2 mixed design ANOVA. Given the low power in our study, along with the a priori hypotheses we set out to explore, which were based on our previous findings showing poorer proprioceptive sensitivity in EDS, we opted to follow up our significant main effect of group for localization precision, but absence of a significant interaction between group and localization type, for each of the four localization conditions, using a series of 1-sided Welch t-tests. Thus, we used less conservative follow-up tests to verify a non-significant interaction that would normally be interpreted to mean that the group difference applied to all the conditions. Nonetheless, we encourage readers to interpret the results more cautiously, given the low power, but our main reason for choosing these analyses was to reduce the likelihood of false negatives.

Results

Learning Rate

Before investigating how EDS affects changes in hand localization, we first confirmed that both groups appropriately countered the perturbation by the end of 90 training trials (Figures 3.3 A-C). We tested for group differences in reach deviations at different time points during adaptation training (three blocks: trials 1-3, 4-6, 76-90) using a 3 X 2 mixed design ANOVA, with block as a within-subject factor (blocks 1, 2 and 3) and group as a between-subject factor (control and EDS). We found a statistically significant effect of block ($F(1.63, 45.72) = 41.117, p < .001, \eta^2 = 0.459$) and Tukey post-hoc analyses revealed that there were significant differences between all three of the blocks (Figure 3.3B). However, we found no statistically significant differences between the two groups ($F(1, 28) = 0.271, p = .777, \eta^2 = 0.001$), nor an interaction between group and block ($F(2, 56) = 0.114, p = .892, \eta^2 = 0.002$). This suggests that, as expected, both groups learned and that there is no discernible difference in their rate, or asymptotic level, of learning.

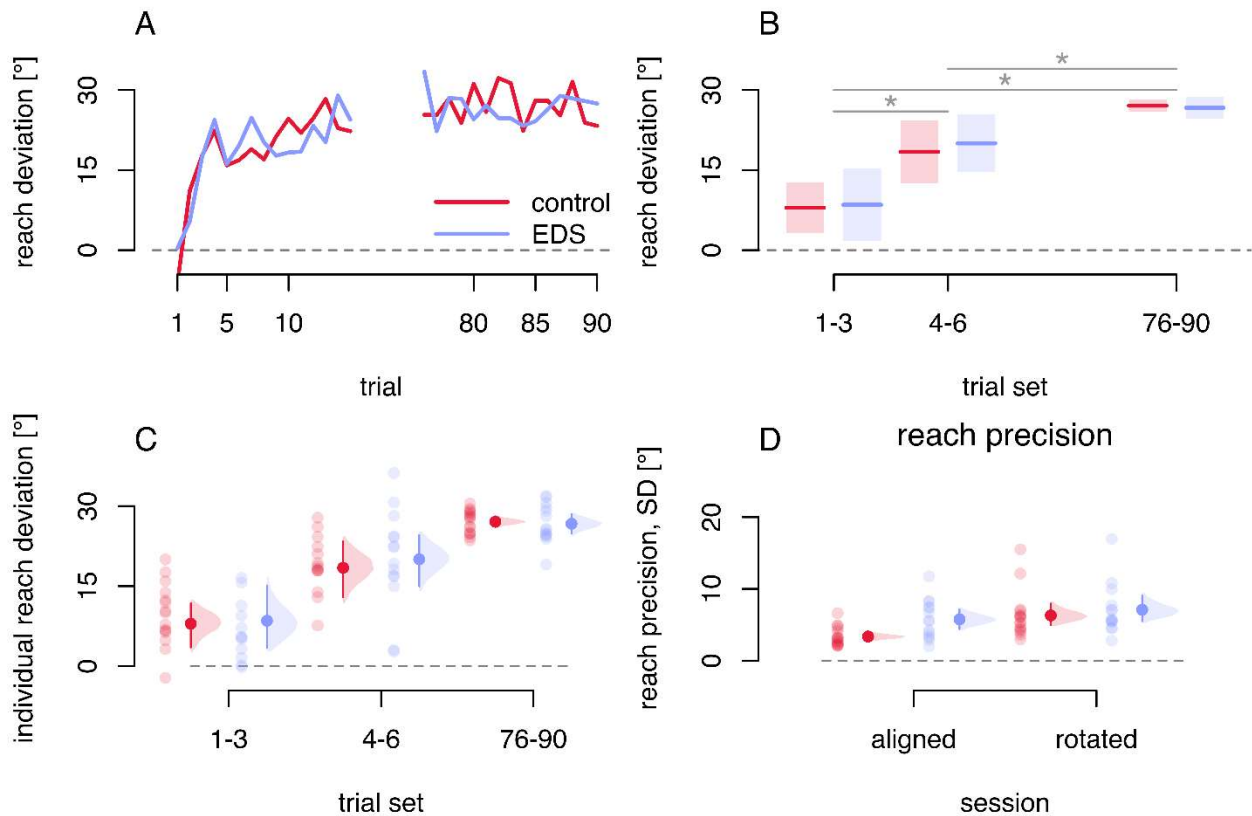


Figure 3.3. Rate of learning during adaptation. Controls are shown in red and EDS participants are shown in blue. Significant differences are indicated with an asterisk. Grey dashed line at the 0° mark indicates where aligned reaches are directed. **A-C:** The first and last 15 trials of rotated-cursor training are shown (A) across trials and (B-C) averaged for 3 sets of trials. Reaches directed towards 30° would mean that the hand had fully deviated to counter the perturbation. Solid lines are means and shaded regions are showing 95% confidence intervals (A-B), while individual data are shown as lighter-coloured dots. **D:** The standard deviation of target-normalized reach errors, for the last 15 trials of training in both the aligned and rotated sessions for each participant in each group (lighter dots). **C-D:** Dark dots and error bars correspond to the group mean and bootstrapped 95% confidence intervals.

Reach Aftereffects

To measure implicit learning, we compared no-cursor trials both before (aligned) and after (rotated) adaptation (Figures 3.4 A & B) using a 2 X 2 mixed design ANOVA with training (aligned or rotated) as a within-subject factor and group as a between-subject factor. We confirmed the presence of reach aftereffects with a statistically significant main effect of training ($F(1, 28) = 133.19, p < .001, \eta^2 = 0.607$). However, we did not find a statistically

significant main effect of group ($F(1, 28) = 0.271, p = .607, \eta^2 = 0.006$), nor a statistically significant interaction between group and training ($F(1, 28) = 0.030, p = .863, \eta^2 = 0.0003$). This suggests that, as expected, there is no difference between the groups in implicit learning.

Closer to our main questions, to measure the precision of reaching when people cannot see their hand, we compared the standard deviation of target-normalized open-loop reach errors both before (aligned) and after (rotated) adaptation (Figures 3.4 C & D). We conducted a 2 X 2 mixed design ANOVA with training (aligned or rotated) as a within-subject factor and group as a between-subject factor. We found a significant effect of training ($F(1, 28) = 10.747, p = .003, \eta^2 = 0.163$), such that reach scatter increased after rotated training. However, we found no significant effect of group ($F(1, 28) = 0.119, p = .733, \eta^2 = 0.002$) nor any significant interaction between training and group ($F(1, 28) = 0.303, p = .587, \eta^2 = 0.005$). A similar pattern was found for reaches made with a visible hand-cursor (Figure 3.3D; refer to OSF for analyses). This suggests that EDS does not lead to greater variance in reaches.

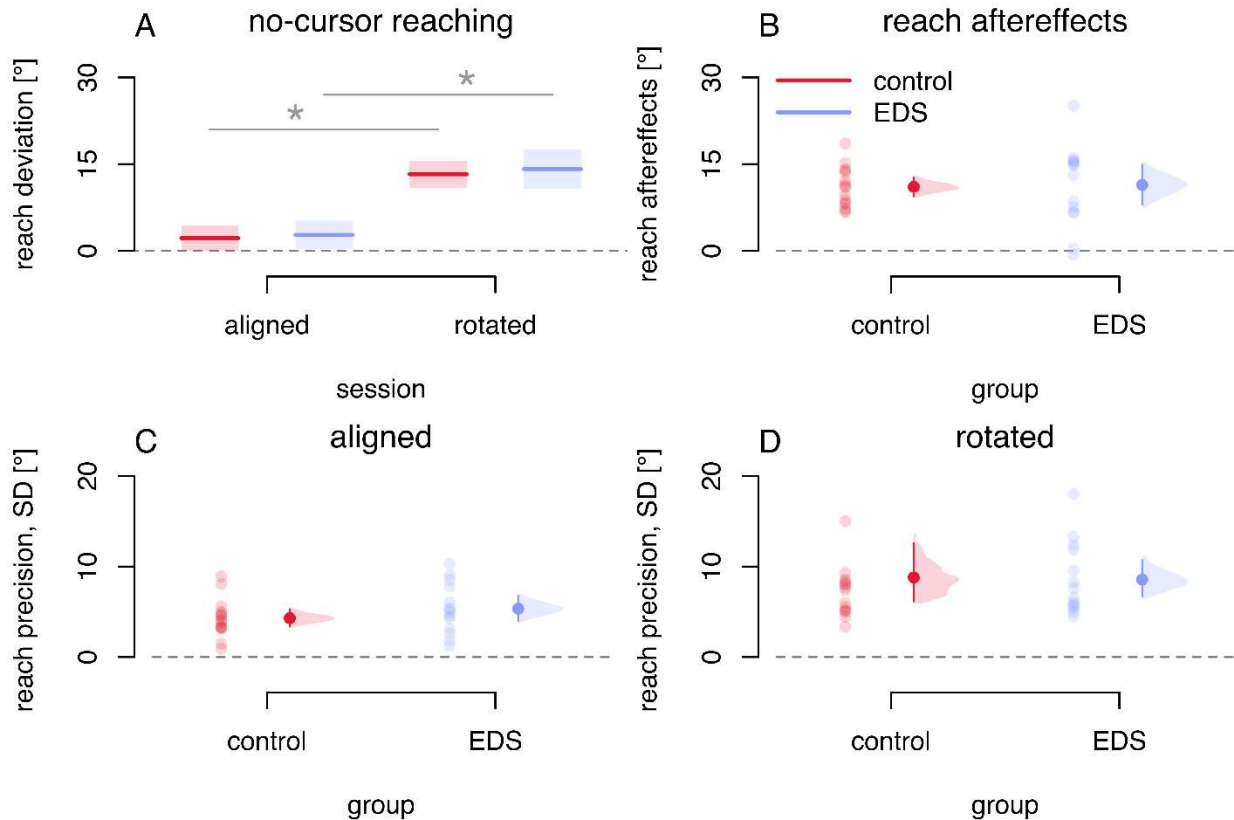


Figure 3.4. Measures of implicit learning. No-cursor reaches for controls are shown in red and those for EDS participants are shown in blue. Significant differences are indicated with an asterisk. The grey dashed line at the 0° mark indicates reaches that did not correct for the perturbation. **A:** Angular reach deviations of the hand per group before (aligned), or after (rotated), training. A reach deviation of 30° would indicate angular reach deviations equivalent to full compensation for the perturbation. Solid lines represent group means and shaded regions represent 95% confidence intervals. **B-D:** Individual participant data from each group are shown with transparent dots, while solid dots correspond to the group mean and bootstrapped 95% confidence intervals, respectively. **B:** Individual participant reach aftereffects (differences in reach deviations between the aligned and rotated sessions). **C-D:** Individual participant reach precision. The SD is calculated from all trials for each individual for the aligned session (**C**) and rotated session (**D**).

Hand Location Estimates

After confirming that EDS does not seem to affect baseline reaches, or adaptation, next we explored our main set of questions: whether EDS leads to differences in estimates of hand location, both before and after adaptation. Beginning with before adaptation (aligned session), to see if there are any differences in accuracy, or systematic errors, we plotted active

localization biases (Figure 3.5A; refer to OSF for analyses) and passive localization biases (Figure 3.5B; refer to OSF for analyses) for hand positions ranging from 30° to 150°. As we can see in each of these figures, there is no such evidence of significant differences between the groups given that the means of these biases (and their 95% confidence intervals) overlap.

Next, we investigated the effects of EDS on learning-induced 'shifts' in hand localization estimates (3rd column of the last two tasks in Table 3.1). We conducted a 2 X 2 X 2 ANOVA on localization error with group (EDS or control) as a between subject factor, as well as training (aligned or rotated) and localization type (active or passive) as within-subject factors. We found a significant main effect of training ($F(1, 28) = 58.85, p < .001, \eta^2 = 0.220$), a significant main effect of localization type ($F(1, 28) = 5.78, p = .023, \eta^2 = 0.005$) and a significant interaction between training and localization type ($F(1, 28) = 17.77, p < .001, \eta^2 = 0.014$). This suggests that estimates of unseen hand location shifted following reach training with a rotated cursor and that the size of these shifts were slightly larger for active localization compared to passive localization (illustrated in Figures 3.5 C & D), as found in previous studies from our lab (Gastrock et al., 2020; Modchalingam et al., 2019; Mostafa et al., 2019; Hart & Henriques, 2016; Vachon et al., 2020). Since the focus of the current study is concerned with exploring these patterns in EDS, we then investigated group differences in active and passive localization shifts (by subtracting aligned localizations from rotated localizations to create a measure of localization shift) and conducted a 2 X 2 mixed design ANOVA on localization shifts with localization type (active or passive) as a within-subjects factor and group (EDS or control) as a between-subjects factor. We again found a significant effect of localization type ($F(1, 28) = 17.769, p < .001, \eta^2 = 0.059$), that is active localization (Figure 3.5C) was slightly larger than passive localization

(Figure 3.5D), and this difference can be seen when comparing Figures 3.5 C & 3.5 D. However, we found no significant effect of group ($F(1, 28) = 0.064, p = .803, \eta^2 = 0.002$) nor any significant interaction between localization type and group ($F(1, 28) = 0.650, p = .427, \eta^2 = 0.002$). This suggests that there is no difference between the EDS and the control group in the magnitude of their localization shifts across either localization task.

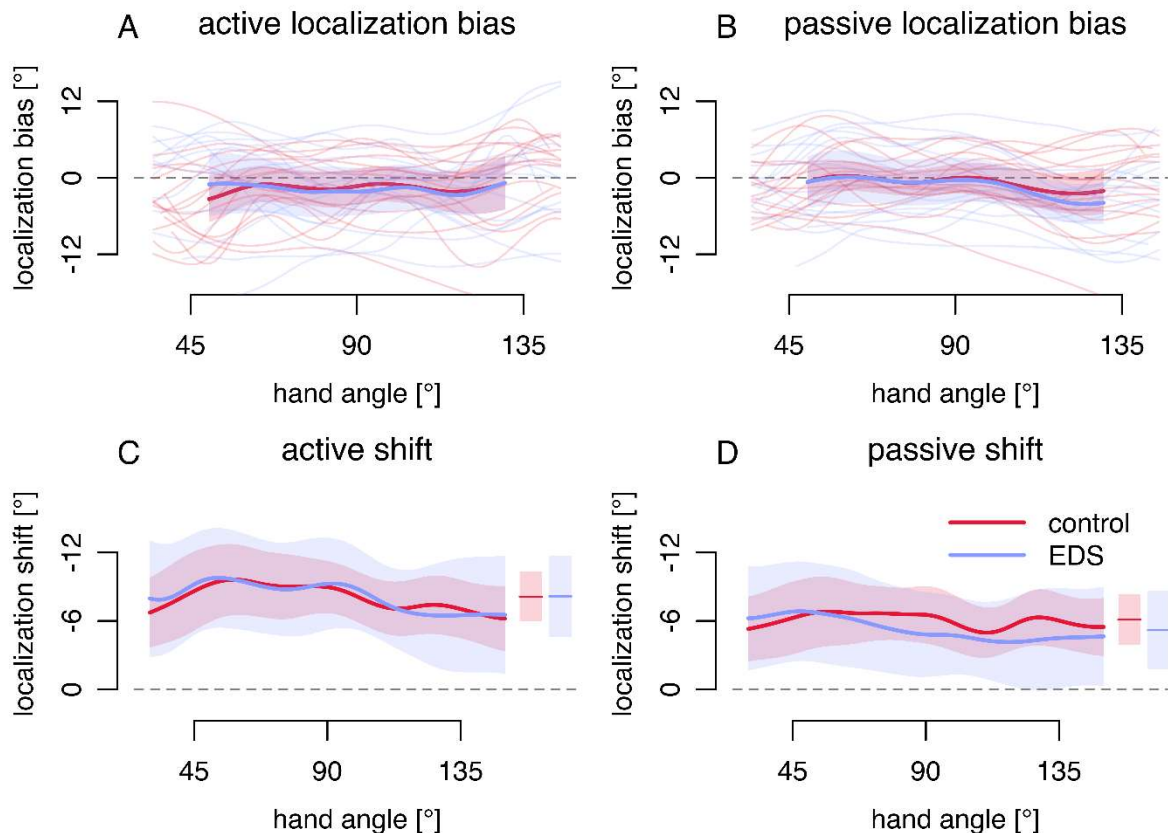


Figure 3.5. Hand localization estimates. Controls are shown in red and EDS participants are shown in blue. Active (A) and Passive (B) hand localization bias across the tested range during the aligned session. Bold, solid lines correspond to group means at each hand angle while shaded bars correspond to 95% confidence intervals for all panels. Individual participant data is shown with transparent lines. (C-D): Visually-induced changes in hand location estimates for Active (C) and Passive (D) localization. Grey dashed lines at the 0° mark indicate the absence of shifts, while negative values indicate the direction of shifts consistent with the visual distortion. Horizontal lines correspond to group means collapsed across hand angles while shaded bars represent the 95% confidence intervals of these means.

Localization Precision

Although, as expected, we did not find any group effects on any of the localization measures that reflect accuracy, we wanted to investigate the effect of EDS on precision of hand location estimates. We used standard deviations of hand localizations for each participant, then compared precision between groups (Figure 3.6). We conducted a 2 X 2 X 2 mixed ANOVA with training (aligned vs rotated) and localization type (active vs passive) as within-subjects factors and group (control vs EDS) as a between-subjects factor. We found a significant main effect of group ($F(1, 28) = 7.95, p = .009, \eta^2 = 0.143$), as well as a significant main effect of localization type ($F(1, 28) = 13.21, p = .001, \eta^2 = 0.050$). However, we found no significant interaction between group and localization type ($F(1, 28) = 0.92, p = .346, \eta^2 = 0.004$), which would suggest the significant group effect applies to all four conditions of hand localization. That is, the EDS group was less precise in all four conditions. However, in case the absence of a significant interaction was due to insufficient power, we decided to investigate this specifically using less conservative follow-up tests (one-tailed t-tests) to compare both groups across all 4 combinations of conditions (aligned active localizations, aligned passive localizations, rotated active localizations, and rotated passive localizations). We found no significant difference between groups for aligned active localizations (one-tailed $t(23.69) = -1.25, p = .112, \eta^2 = 0.055$) (Figures 3.6 A & C). However, we confirmed the significant difference between groups in the other three conditions (Aligned Passive: one-tailed $t(15.83) = -1.92, p = .037, \eta^2 = 0.128$; Rotated Active: one-tailed $t(17.34) = -2.64, p = .008, \eta^2 = 0.215$; Rotated Passive: one-tailed $t(26.02) = -2.48, p = .010, \eta^2 = 0.183$) (Figures 3.6 B & D). Consistent with the absence of a group & localization-type interaction, the results of these less-conservative, and uncorrected, t-tests

suggest that precision in passive hand-localization was poorer for EDS compared to controls, as we predicted. That is, sense of proprioception is more variable in the EDS group when only afferent information is available. But when efferent information was also available, like in the active localization tasks, the difference was not so consistent, with the EDS group showing poorer precision following rotated training but not aligned training.

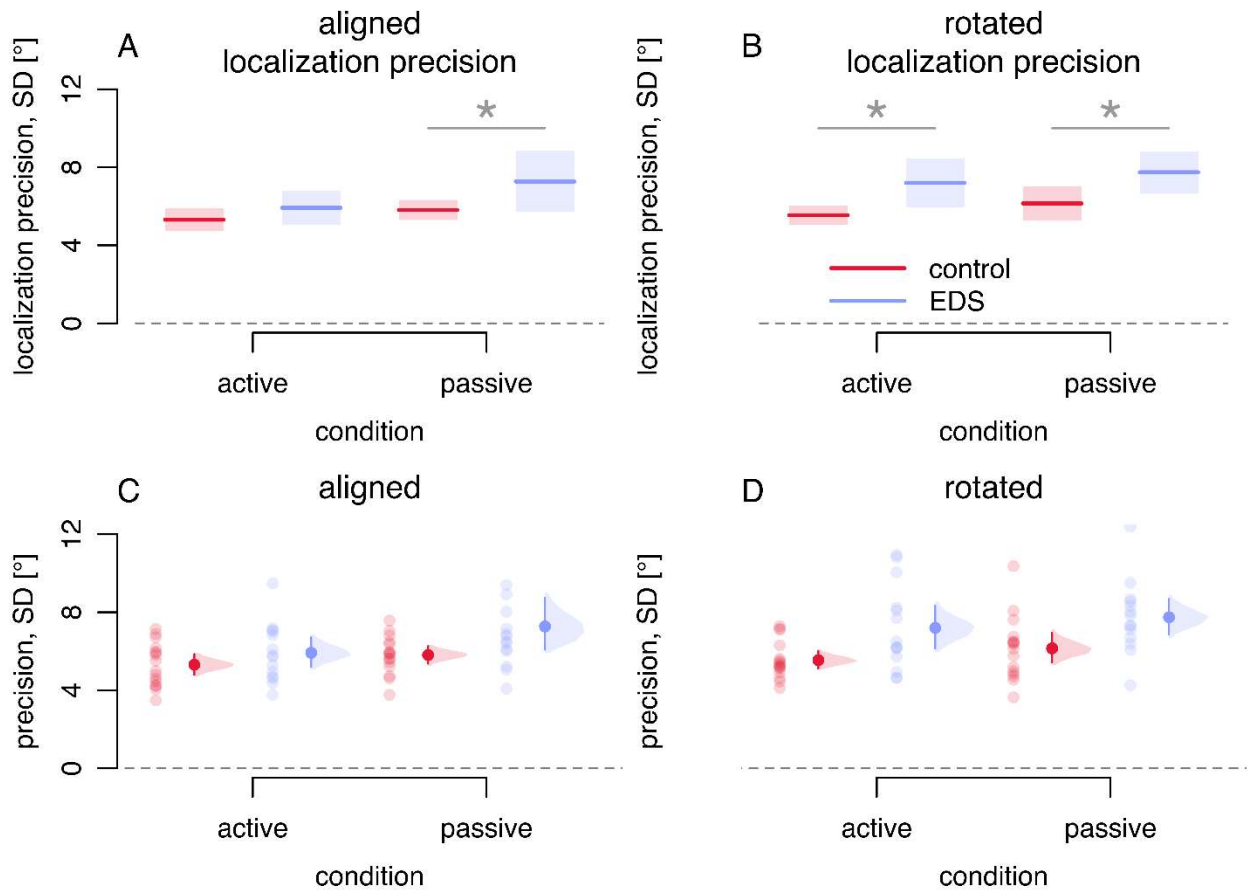


Figure 3.6. Localization precision. Controls are shown in red and EDS participants are shown in blue. Significant differences are indicated with asterisks. **A-B:** Solid lines represent group means and shaded regions correspond to 95% confidence intervals for hand localization precision (SD) in the aligned (**A**) and rotated (**B**) conditions, for both the active and passive hand localization tasks. **C-D:** Transparent dots indicate individual participant variability (SD) for hand localization in the aligned (**C**) and rotated (**D**) conditions for each group, and for both active and passive localization. Solid dots and error bars to the side of individual data correspond to group means and bootstrapped 95% confidence intervals.

Since variability in hand estimates is greater in the EDS group, then perhaps there is a relationship between joint hypermobility and the precision of limb localization. We used Beighton scores as a measure of joint hypermobility, measured in both groups, to investigate whether this is correlated with overall localization variance (variance was calculated across all 4 conditions for every participant to provide more power). Results of a Pearson correlation revealed that there was a significant relationship between joint hypermobility and measures of hand localization (Figure 3.7; $p = 0.036$, $r^2 = 0.117$). This suggests that those who are the most hypermobile tend to have the least precise (most variable) proprioceptive estimates of hand position.

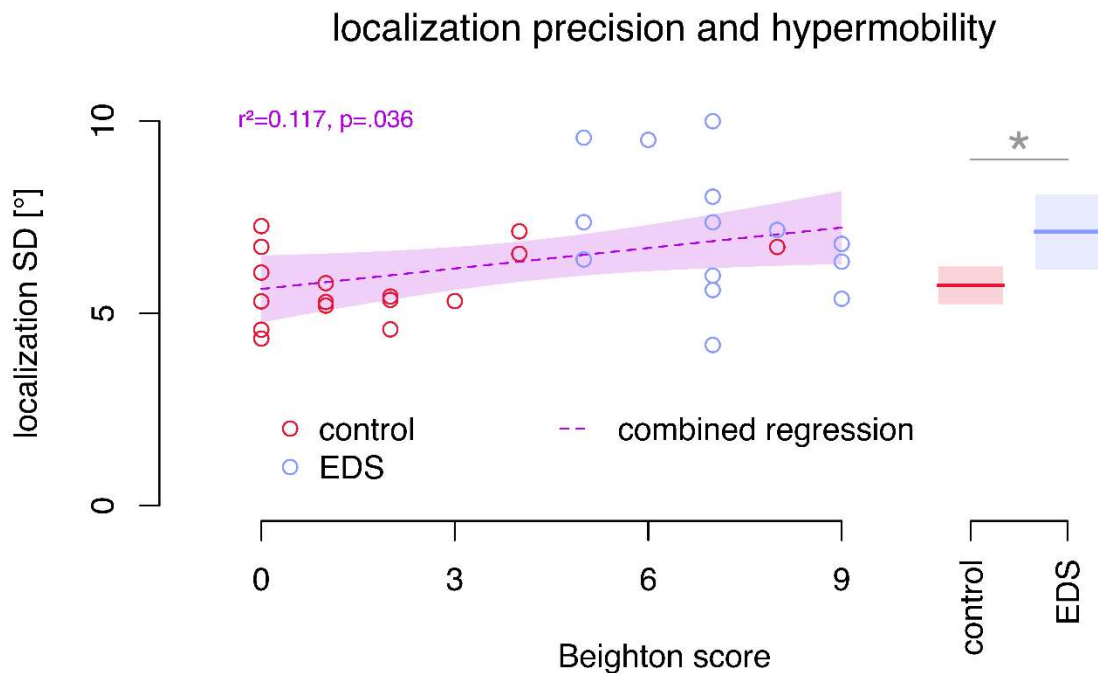


Figure 3.7. The relationship between localization precision and joint hypermobility. Localization standard deviations are plotted as a function of Beighton scores for EDS participants (blue) and controls (red). The dashed line corresponds to a regression line, while the purple shaded regions correspond to 95% confidence intervals. Solid lines represent group means, collapsed across all 4 localization

conditions, and shaded bars correspond to 95% confidence intervals. The significant difference between the groups is indicated with an asterisk.

Discussion

The goal of this study was to explore the effect of EDS on acuity and plasticity of hand proprioception. Specifically, our main goal was to quantify proprioceptive acuity of the hand, when only proprioceptive feedback was available (passive localization) or when afferent and efferent signals were both available (active localization). Our second goal was to better understand proprioceptive plasticity in EDS by having participants adapt their movements to a visual perturbation and then comparing shifts in both active and passive estimates of hand location across patients and controls. We found that people with EDS moved, and adapted their movements, just as well as controls. Accuracy and precision in reaching movements, and adaptation rates, did not differ between the two groups. Moreover, the accuracy by which the two groups estimated their unseen hand did not differ. The only aspect where people with EDS differed from controls was the precision of hand estimates, which was poorer for EDS patients when estimates were based on proprioception. When efferent information was also available, this difference disappeared. However, visuomotor adaptation disturbed estimates of hand position enough to produce poorer precision in estimates for EDS patients compared to controls for both types of hand localization. In summary, our results support the notion that proprioceptive sensitivity is different in EDS, and that poor proprioception can be overcome by additional efferent information.

There were no differences between patients and controls in any of our other measures in both the current study and in a previous study (Clayton et al., 2013). The absence of reliable

differences suggests that we have found an impairment that relates purely to proprioception. However, the current study suggests that efferent information may be sufficient to overcome poorer proprioceptive sensitivity. This would in turn explain why the poorer proprioceptive sensitivity did not lead to poorer reaches, or poorer reach adaptation, in this and our previous studies. Thus, arm-motor control and visuomotor integration processes in EDS are no different than in healthy controls. Given the pathophysiology of EDS, it is possible that the small deficit we have observed in this study could have both central and peripheral origins which are elaborated upon below.

Our current findings are in line with our past research, and the research of others, which suggests that proprioceptive precision of the upper limb is different in EDS. In our previous study (Clayton et al., 2015), we also found that people with EDS showed twice as much scatter, compared to controls, when indicating the felt position of their unseen left hand. In the current study, we again show EDS did not differ from controls in the accuracy of their proprioceptive estimates, but in precision. While Rombaut, De Paepe, et al., (2010) found that there were no significant differences between Hypermobility-EDS patients and controls in absolute angular errors during their shoulder joint reposition test (the target-hand was passively placed, but its position was indicated both actively, like in our study, but also passively at target angles of 45° and 75°), they did find larger variations in angular errors (standard deviations that were 27-65% higher) for the patients in 3 of their 4 conditions (all except the passive 75° reproduction). What is new in the current study is the finding that these differences disappeared when people actively displace their own target-hand. Visuomotor adaptation, however, increased the uncertainty of the unseen hand location in EDS patients such that both types of hand estimates

were less precise when compared to controls. Thus, proprioceptive variability was greater for patients in three of four hand localization conditions, which suggests some differences in proprioceptive sensitivity, and leads us to believe the phenomenon is likely afferent in nature, although central mechanisms cannot be ruled out.

Studies which measure proprioception of the knee in those with joint hypermobility tend to find more obvious impairments. Rombaut, De Paepe, et al. (2010) also measured proprioception of the knee at two different detection angles. While they found that patients showed larger absolute angular errors than controls, the standard deviations of these errors were also much larger for patients (around 30% greater for most conditions but were double for active reposition of the 30° angle). Their findings are like those of Sahin et al. (2008) where absolute angular errors were twice as large in EDS patients, compared to controls, for a knee joint reposition task. It is possible that we see greater differences in proprioceptive acuity at the knee joint since it is more of a weight-bearing joint; therefore, the knee may be more prone to repetitive stress-induced injury, which could have effects on proprioceptive acuity (Rombaut, De Paepe, et al., 2010). Another possibility is that the upper limbs, especially the hands, are more precisely represented in the somatosensory cortex, which could make people better able to compensate with varying sensory input when estimating the position of their hand (Penfield & Boldrey, 1937). Given that poorer proprioceptive precision is found for lower limbs and upper limbs in EDS patients, this suggests that proprioception may be compromised in those with hypermobility throughout the entire body.

An important finding from our current study is that the magnitude of joint hypermobility, as measured by Beighton Scores, is significantly related to our measures of

proprioceptive precision; those who were the most hypermobile tended to also be those who were the least precise. This is like what we found in our first study, where joint hypermobility was found to be significantly related to uncertainty of proprioceptive estimates, but only at locations lateral to the body midline (Clayton et al., 2013). However, we did not find a relationship between joint hypermobility and precision of hand location estimates in our other previous study, where participants had to reach to the felt location of their left hand, even though the precision of these estimates was double that of controls. We assumed that was due to the challenging nature of the task used, such that even those with mild levels of joint hypermobility would be likely to show proprioceptive impairments (Clayton et al., 2015). Regardless, we have found evidence (in the current study, and in the first) which suggests that proprioceptive variability is, at least partially, related to a person's magnitude of joint hypermobility.

Why proprioception may be less precise in EDS is not clear, although some explanations have been proposed. Many types of EDS are known to be due to mutations in the genes that code for collagen, which could ultimately interfere with structural, and functional, aspects of the Extracellular Matrix (ECM) of connective tissues (Syx et al., 2017). There are various neuroreceptors which are thought to contribute to our sense of proprioception (see Hillier et al., 2015 for a review) and these are all surrounded by connective tissues in our joints, muscular tissue, or skin, which may be affected by EDS; it is possible that activation of these proprioceptors is altered due to the interactions they would ultimately have with the ECM, but this possibility has never been explored. It is also possible that proprioceptive sensitivity in EDS is due to peripheral nerve damage, as small fibre neuropathy (Cazzato et al., 2016) and ulnar

nerve subluxation/luxation (Granata et al., 2013) were found in those with EDS. Unfortunately, no studies to date have directly linked peripheral nerve damage to deficits in proprioception in this population. Recently, it was suggested that the proprioceptive differences commonly seen in adolescents with Hypermobile EDS could be due to physical deconditioning, because of kinesiophobia, since those with joint hypermobility are more prone to injuries and experience pain more intensely than the general population (van Meulenbroek et al., 2020). Unfortunately, there have been no EDS proprioceptive studies to date which have included a measure of physical activity in their protocol, although a few studies have already found various forms of exercise to be effective in relieving pain, and sometimes proprioceptive deficits, in those with joint hypermobility (Ferrell et al., 2004; Palmer et al., 2014; Sahin et al., 2008). Wearing compressive garments was also found to somewhat improve postural deficits in EDS (Dupuy et al., 2017), which researchers attributed to altered cortical representations of body schema that could be reorganized by enhancing cutaneous sensation. Given that many types of EDS often present with cutaneous abnormalities (Malfait et al., 2017) and cutaneous receptors contribute to our sense of proprioception (Hillier et al., 2015), it is possible that these are factors in the current study as well. It has been found that people with chronic low-back pain were significantly less accurate in their judgements of trunk rotations during a motor imagery task (Bray & Moseley, 2011), although the possibility of disrupted, cortically held, representations of body schema in EDS has never been directly tested. It is our impression that proprioceptive deficits can arise for multiple reasons, but further studies need to be done to fully understand the impact of each of these potential causes on proprioceptive sensitivity in EDS.

Limitations

We recognize that this study was likely underpowered. We determined that we would need 36 participants in each group in order to achieve 80% power. Unfortunately, we were not able to recruit as many participants as we hoped since EDS patients are rare and some people who were recruited were unable to attend due to health reasons. Then the COVID-19 pandemic occurred, which made it impossible to collect any more data. While our findings need replication, they should still be relevant to researchers in various fields.

Although we did have some a priori hypotheses, we did not pre-register our research protocol, or analysis online. However, all our data and analysis scripts are available on our OSF repository (see link in Data Analysis subsection of the Methods).

Chapter 4: Visuomotor Adaptation Across the Lifespan

Clayton, H. A., Abbas, S., 't Hart, B. M., & Henriques D. Y. P. (Unpublished manuscript).

Abstract

It is unclear whether visuomotor learning abilities are fully developed in young children and, if so, whether they remain stable in the elderly, since these groups sometimes exhibit less learning than young adults in visuomotor adaptation experiments. Variations in cursor rotation size or number of training trials may explain some inconsistencies across studies; however, no study has ever compared visuomotor adaptation performance of both children and the elderly to that of young adults, or to each other, within the same paradigm. Our goal was to do just that, by implementing a shorter, gamified experimental task, that we assumed would be more engaging for people of all ages, to show that visuomotor learning processes remain stable as we age. Young children (n = 18), older children (n = 40), young adults (n = 20), middle adults (n = 36) and older adults (n = 17) adapted to a 45° visuomotor rotation, at a single training target, in a centre-out reaching task. Then we compared the magnitude of aftereffects across groups, after realigning the cursor with hand movement, compared the rate of unlearning, and compared generalization to novel target locations. We also compared rate of relearning (i.e., savings) across groups when the rotation was re-introduced. We found that all groups performed similarly for each of these measures, suggesting that visuomotor learning processes are relatively stable across the lifespan. That is, at least for short bouts of gamified learning, children and older adults perform just as well as young adults.

Introduction

Being able to adapt our motor repertoire to changes in the environment can easily be taken for granted. Visuomotor learning allows us to become self-sufficient adults; without it we might struggle with the simplest daily tasks, such as feeding ourselves or brushing our teeth. In the laboratory, motor learning can be examined via visuomotor adaptation paradigms, where participants reach to targets on a screen with a cursor. Adaptation is required when the mapping between the hand and cursor is perturbed. The most common perturbation is known as a visuomotor rotation, where the cursor movement is deviated from the expected direction, relative to the home position, usually by 30 or 45°. To move the cursor directly to the target, the required movement must compensate for this rotation, which young adults usually adapt to quickly and completely (Krakauer, 2009). While visuomotor adaptation has been extensively studied in young adults, there are far fewer studies that have examined visuomotor adaptation in children, or older adults, and many of the findings are inconsistent across experiments.

Following rotated training, young adults show aftereffects (i.e., when they continue to compensate for the cursor rotation even when it is no longer present), which implies that internal models have been updated (Krakauer, 2009). Aftereffects are usually no larger than 15°, regardless of the size of the abruptly introduced rotation (Bond & Taylor, 2015) and will decay rapidly as participants revert to baseline performance (Kitago et al., 2013). When young adults train to reach with a rotated cursor at a single target location, their learning has been shown to partially generalize to novel target locations that are close in proximity to the trained target (Krakauer et al., 2000; Wang & Sainburg, 2005). Young adults also exhibit savings, often

evidenced as a quicker rate of relearning, when re-adapting to the same cursor rotation encountered up to a week prior (Krakauer et al., 2005).

Studies involving children have indicated that they may have difficulty adapting to cursor rotations. Some studies show that younger children do not compensate for cursor rotations as much as older children (Contreras-Vidal et al., 2005; King et al., 2009), or young adults (Ferrel et al., 2001). However, one study found that even young children compensated for a 60° rotation just as well as both older children and young adults (Kagerer & Clark, 2014). To our knowledge, no study has measured rate of learning in children since these earlier studies, at most, merely reported how participants compensated for the rotation across averaged sets of several trials that occurred early or late in training; in our study we only included 3 trials in each block of trials to better capture potential group differences in learning rate. Like compensation, children younger than 8 do not always show significant reach aftereffects (Contreras-Vidal et al., 2005). However, others have found significant aftereffects, that were comparable in magnitude, in children of all ages (King et al., 2009) and young adults (Kagerer & Clark, 2014) by using a slightly larger rotation (60°) and including more training trials. It is not known whether children show similar generalization patterns as adults. The only study that explored savings in children did not find evidence of a quicker relearning rate when children re-adapted to the same 60° cursor rotation they encountered 10 hours earlier (Urbain et al., 2014), although there was no adult control group to compare the children's performance to. Therefore, it is unclear whether children, especially those younger than 8, possess fully mature visuomotor learning abilities, like those of young adults.

Studies involving older adults have also indicated that, like children, they may have difficulty adapting to cursor rotations. Some studies found no differences in compensation for a rotated cursor between older and younger adults (Heuer & Hegele, 2008; Noohi et al., 2016; Vachon et al., 2020), while others found that older adults adapted at a slower rate (Lei & Wang, 2018), or to a lesser extent (Anguera et al., 2011; Bock & Girgenrath, 2006; Buch et al., 2003; Heuer et al., 2011; Heuer & Hegele, 2008; Seidler, 2006), than young adults. Differences in compensation tend to emerge when training with larger cursor rotations and are attributed to deficits in cognitive components of learning in older adults (Heuer & Hegele, 2008; Vandevorde & Orban de Xivry, 2019). Even when their adaptation performance differed from young adults, older adults still show comparable aftereffects to young adults (Heuer & Hegele, 2008; Vachon et al., 2020), which decay at a similar rate (Noohi et al., 2016; Seidler, 2006). Of these studies, only one measured generalization patterns to nearby, untrained target locations; Heuer and Hegale (2008) found older adults showed similar generalization patterns, that were of a similar magnitude, as young adults. A final aspect that has been explored to a lesser extent in older adults is savings, with a few studies (Anguera et al., 2011; Seidler, 2007a; Vandevorde & Orban de Xivry, 2019) that have found that they exhibited savings, that was of a similar magnitude as young adults, and only one finding greater savings in older adults (Bock & Schneider, 2001). Thus, it is unclear whether the visuomotor learning capabilities of younger adults persist into old age.

The main goal of this study was to compare various properties of visuomotor learning performance across the lifespan. Given the conflicting evidence regarding visuomotor learning abilities in older or younger groups, we aimed to create a short, gamified experiment, that

could be utilized in a familiar environment (such as at a library or camp), to better motivate participants of all ages to maintain focus on the task. Although the study was short, we tried to capture a variety of performance measures of adaptation, such as rate of learning, generalization, and savings, which have been largely unexplored in children or older adults. Furthermore, we are unaware of any other studies that have compared visuomotor adaptation abilities of all age groups within the same paradigm, like we did here. We first measured the rate, and extent, of visuomotor adaptation when a 45° CCW cursor was abruptly introduced. To do this, we first had to determine levels of baseline accuracy, and variability, when reaching with an aligned cursor, so that we could see how performance changed across adaptation training. We measured aftereffects, after the cursor was realigned with hand movement, to compare the sizes of aftereffects, to compare the rate of unlearning, and to examine generalization of learning to untrained targets, all of which we compared across the age groups. We also examined the rate of re-learning, when the cursor rotation was introduced a second time, and to compare levels of savings across the age groups. We hypothesized that the gamified nature of the short task would prevent boredom, and fatigue, in our participants, revealing that visuomotor adaptation performance is no different across the lifespan, at least in short, gamified situations.

Methods

Participants

One hundred and thirty-one participants voluntarily took part in the experiment outlined below. There were 18 young kids (mean age 7 years, range 5-8, 9 females), 40 older

kids (mean age 11 years, range 9-13, 15 females), 20 young adults (mean age 20 years, range 19-22, 10 females), 36 middle-aged adults (mean age 40 years, range 27-51, 28 females) and 17 older adults (mean age 67 years, range 59-78, 11 females). All participants had corrected-to-normal vision, were pre-screened for neurological dysfunction, and most were right-handed. An a-priori power analysis was conducted and indicated that we would need at least 40 participants per group for this study (at least 200 participants in total) to be adequately powered; this study is likely underpowered, but due to the COVID-19 pandemic we were unable to recruit additional participants.

All young children, and some older children, were recruited through the Innisfil Public Library. The remaining older children were recruited through the York Science Camp program. The guardian of each child indicated the child's experience using a computer mouse (not at all, very little, some, a lot, or every day). The adults of all ages were recruited through the York Circle lecture series event, while some were recruited through word of mouth. Adults only indicated whether they used a mouse when they used a computer. No monetary rewards were provided to any individual for their participation in the study. All participants, or their guardians, provided written informed-consent, and all minors provided an additional verbal assent, to participate in the study. The study was conducted in accordance with the ethical guidelines set by the York Human Participants Review Sub-committee.

General Experimental Setup

Participants sat on a chair in front of a 14" Dell laptop and held a wired computer mouse with their right hand. A miniature mouse was used when testing the children, to accommodate

their smaller hands. The chair was positioned so that they could comfortably see images, as they appeared on the laptop, and reach with their right hand, represented by the mouse's cursor, from a starting home position on the screen to one of three possible target locations. The experiment was designed to resemble a children's game (about 5 minutes long), to help motivate children's participation, in which the targets were images of planets, about 1 cm wide, while the cursor was an image of an alien. The home position is a 0.5 cm wide circle located at the bottom-centre of the screen (Figure 4.1).

The targets were displayed at approximately 10 cm distance from the home position at 45°, 90° & 135° angles. Target and cursor images were randomized across trials from a set of 30 different planets and 45 different aliens. The programming language Python was used to display cursor movements/target positions and measure cursor movements, at roughly 20 Hz.

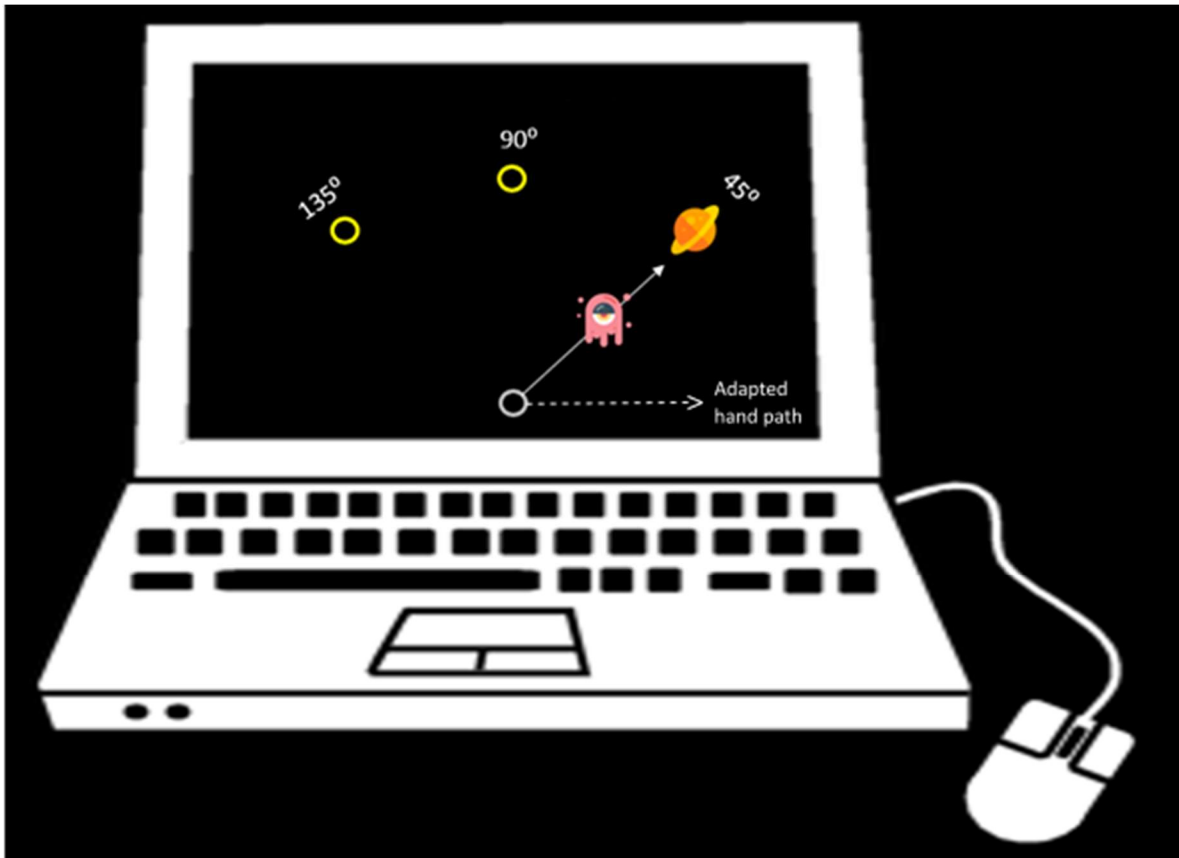


Figure 4.1: A depiction of the laptop and screen setup used throughout the experiment. Participants use the mouse to place the cursor (alien) on the target (planet). There was one target visible per reach. Once the reach was complete the participant returned to the home position (open grey circle) and a new target appeared. The open yellow circles represent additional target locations that were part of the baseline and washout phases. The solid arrow represents a hand movement path during the aligned phase towards the 45° target. The dashed arrow represents the hand movement path needed during the training phase, when the cursor is rotated, to land the cursor on the 45° target.

Procedure

The experiment comprised of 4 phases: baseline, learning, washout, and relearning. All participants completed the four phases, in the described order, during one continuous session. Participants were instructed to move the alien (mouse cursor) directly from a common home position, with their right hand, as smoothly and as accurately as possible towards the planet (target). A reach trial was complete when the centre of the mouse cursor overlapped with the

target. Upon completion of the reach, the target vanished, and participants were required to return the mouse cursor to the home position before a new target appeared.

Reaches were made with either an aligned cursor or a rotated cursor. When reaching with the aligned cursor, the mouse-cursor movement was aligned with the movement of the participant's hand. During the rotated cursor blocks, the movement of the mouse-cursor was abruptly rotated 45° counter-clockwise (CCW) relative to the home position. To compensate for this rotation, a participant would have to reach 45° clockwise (CW) to acquire the target with the cursor (dashed arrow in Figure 4.1). Participants were not informed of the cursor rotation at any point throughout the experiment.

The initial baseline phase consisted of 15 reach trials with the aligned cursor. During this phase, all 3 of the target locations (45°, 90° and 135°) were used, with 5 reaches per location. Each of the 3 locations were presented in a pseudorandom order. During the learning phase the cursor was abruptly rotated 45° CCW, and this phase consisted of 45 reaches towards the 45° target location only. The washout phase was a repeat of the baseline phase, wherein participants again reached 15 times with the aligned cursor towards all 3 of the targets. Finally, during the relearning phase, participants reached 15 times with the 45° abruptly rotated cursor towards the target located at 45°. There were no time limits imposed on any task, but the experiment was designed to take only 5-10 min to keep children, and members of the public, engaged.

Data Analysis

The main goal of this experiment was to determine the effect of age on visuomotor learning processes, as well as upon general motor control. First, we tested if there were any

differences in baseline motor control. Then, we explored if there were any differences in visuomotor learning abilities across various phases of the experiment. Our measurement unit was “hand angle”, which is the angular difference between the hand movement path, at 1/3 of the total distance to the target, and a straight trajectory towards the target. We selected this distance to better capture the ballistic movement to the target, rather than corrective movements. Outliers were removed via pre-processing scripts in Python, when errors were larger than $\pm 30^\circ$ for the baseline and $\pm 60^\circ$ for the washout phase. For training and relearning phases, the window was asymmetrical, to incorporate the rotation, spanning from -30° to $+75^\circ$. Errors of this size would imply the participant did not attempt to reach directly towards the target as instructed. One middle-aged participant was removed from the data set for not showing any evidence of learning throughout the experiment.

All analyses were done in JASP version 0.16.3 (JASP Team, 2022). For all statistical tests the alpha level was set to 0.05 and Greenhouse-Geisser corrections were applied when appropriate. Bayesian statistics are also reported with BF_{10} , which estimates the likelihood of the alternative hypothesis being true given our data, for each corresponding frequentist test. However, post-hoc tests were only conducted with frequentist analyses. A summary of the measures derived from each task, and the analyses conducted, are described further below. All data and analysis scripts will be available on the OSF prior to submitting for publication.

Baseline Motor Control

First, we analysed group differences in reach directions during the baseline phase. We calculated means, and standard deviations, for each participant, based on the last 9 trials in the

phase (trials 7-15). Then we compared mean reaching errors (as a measure of accuracy) and mean standard deviations of the reaching errors (as a measure of variability), across the five groups using two separate 1-way ANOVAs. For all further analyses described below, these baseline averages were subtracted from the reaching blocks (average of three consecutive trials) of interest and are called “reach deviations”.

Finally, we explored whether children’s baseline motor control could be influenced by their mouse experience. First, we converted guardian’s ratings of the children’s mouse experience to a Likert scale (not at all, 0; very little, 1; some, 2; a lot, 3; or everyday, 4). Then, we compared mean mouse experience across the two groups of children (young vs older) using a Welch T-test. Lastly, we explored whether the standard deviations of the reaching errors (our measure of variability) were related to mouse experience in children using a Pearson correlation.

Learning Rate

Then, to begin answering our main questions, we wanted to confirm that all groups learned to counter the cursor rotation by the end of the 45 training trials. We calculated average reach deviations for block 1, block 2, block 5 and block 15 (trials 16-18, 19-21, 28-30, and 58-60, respectively). Then we compared these means using a 4 X 5 mixed ANOVA with block as the within-subjects factor and group as the between-subjects factor; this allowed us to explore whether the rate, and extent, of learning was different across the age groups.

Aftereffects, Washout Rate and Generalization

Then we wanted to confirm that each group showed aftereffects, which are considered evidence of implicit learning, by performing 5 separate single-sample t-tests, for each of the groups, to see if their reach deviation for the first block of washout was significantly different from 0. Then, to see if there were any group differences in aftereffects, we conducted a 1-way ANOVA. Next, we wanted to compare group performance in block 1, block 2 and block 5 of the washout phase (trials 61-63, 64-66 and 73-75, respectively). We conducted a 3 X 5 mixed ANOVA with block as the within-subjects factor and group as the between-subjects factor; this allowed us to explore group differences in the rate at which their learning decayed. We also wanted to confirm that all groups returned to baseline performance by the end of the 15 washout trials. We performed 5 separate single-sample t-tests, for each of the groups, to see if their reach deviation for the last block of washout was significantly different from 0. Then we compared group performance in this last block of washout using a 1-way ANOVA.

Lastly, we wanted to see if age influenced how learning generalizes from the trained target (45°) to untrained targets (90° and 135°) during the washout phase. We calculated average reach deviations for each of the target locations, collapsing across all trials in the washout phase. We conducted a 3 X 5 mixed ANOVA with target as the within-subjects factor and group as the between-subjects factor; this allowed us to explore group differences in generalization patterns.

Relearning Rate and Savings

Finally, we wanted to compare group differences in the rate of re-learning, and savings, during the last phase of the experiment. We calculated reach deviations, for each group, for block 1, block 2 and block 5 of re-learning (trials 76-78, 79-81, and 88-90, respectively). Then we compared these measures using a 3 X 5 mixed ANOVA with block as the within-subjects factor and group as the between-subjects factor; this allowed us to explore group differences in rates of learning when the cursor rotation was introduced a second time.

To test for group differences in savings, we compared the percentage of the final learning extent attained in block 1 of training (dividing each participant's reach deviation in block 1 by the average total learning extent achieved by all groups in block 15, which was 41.68°) with the percentage of learning extent attained in block 1 of relearning (using the same calculation). Since none of the groups returned to baseline by the end of the washout block, we had to re-correct their reach deviations in block 1 of relearning to account for this (Yin & Wei, 2020); instead of subtracting their original baseline average from their actual hand angle in block 1 of relearning, the average reach deviation from block 5 of washout was subtracted and these new reach deviations were used to calculate the percentage of learning extent in block 1 of relearning. We conducted a 2 X 5 mixed ANOVA with phase (percentage of learning extent achieved in block 1 of training or relearning) as the within-subjects factor and group as the between-subjects factor; this allowed us to test for savings in relearning when the cursor rotation was introduced a second time and to see if all groups showed comparable levels of savings.

Results

Baseline Motor Control

Before investigating how age affects visuomotor adaptation processes, we first explored how age affects baseline motor control (Figure 4.2). We tested for group differences in average reach errors and found no significant differences between the groups (Figure 4.2A), with moderate support for the null hypothesis ($F(4, 126) = 1.792$, $p = 0.134$, $\eta^2 = 0.054$, $BF_{10} = 0.293$). However, we found a significant effect of group on reach variability ($F(4, 126) = 6.735$, $p < 0.001$, $\eta^2 = 0.176$, $BF_{10} > 100$), and extreme evidence in support of the alternative hypothesis (Figure 4.2B). Tukey post-hoc tests revealed that this difference was only between the young children and all other groups. Taken together, these findings suggest that motor accuracy remains stable as we age, but that young kids are almost 50% more variable in their baseline motor performance when operating a mouse.

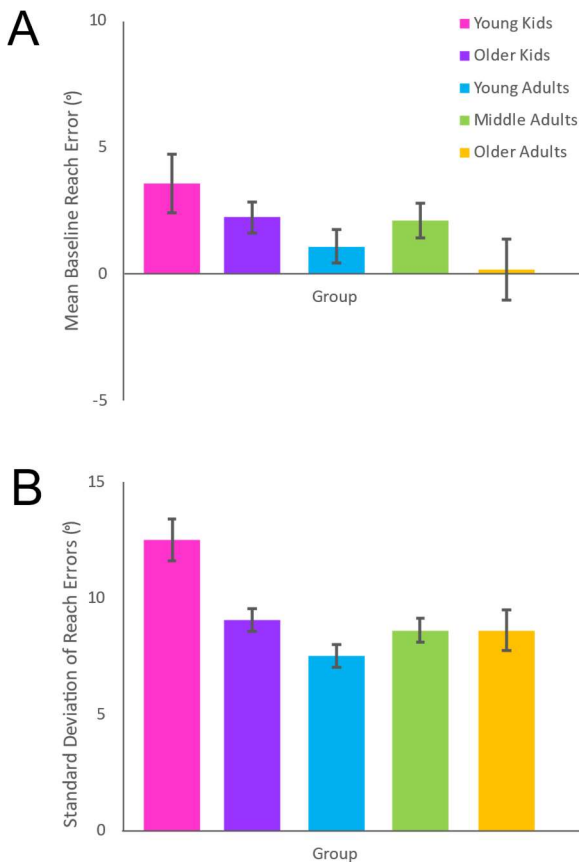


Figure 4.2. Baseline motor performance. Young kids are shown in pink, older kids are shown in purple, young adults are shown in blue, middle adults are shown in green and older adults are shown in yellow. **A:** The mean reach error, taken from the last 9 trials of baseline, is shown for each group with bars. Error bars represent standard error of the mean. The solid line at the 0° mark indicates where baseline reaches were directed. **B:** The standard deviation of reach errors, taken from the last 9 trials of baseline, are shown for each group. Error bars represent standard error of the mean.

Learning Rate

Figure 4.3 shows the reaching performance across all trials for the five groups, while Figure 4.4 shows boxplots for the blocks of trials we used for analyses across the last 3 phases of the experiment. When investigating the learning rate during initial training (training blocks 1, 2, 5 and 15 in Figure 4.4), as expected, we found a statistically significant effect of block reflecting the usual learning pattern ($F(2.77, 348.93) = 490.74, p < .001, \eta^2 = 0.610, BF_{10} > 100$). More importantly, we found no clear effect of age across the five age groups ($F(4, 126) = 2.15,$

$p = 0.078$, $\eta^2 = 0.014$, $BF_{10} = 0.559$) and only a small, but significant, 5 X 4 interaction between group and block ($F(11.08, 348.93) = 1.877$, $p = 0.041$, $\eta^2 = 0.009$, $BF_{10} = 0.423$) which, in both cases, only suggests anecdotal support for the null hypothesis. For completeness, we conducted a Bonferroni post-hoc analysis on the significant interaction, which revealed that, although there was a significant difference between block 1 and block 2 of learning for the young kids, there was no further significant differences found in this group between block 2, block 5 and block 15 of learning. In contrast, significant differences were found between all these blocks for all other age groups (training blocks in Figure 4.4). Taken together, this suggests that young kids might be reaching asymptotic levels slightly faster than older age groups.

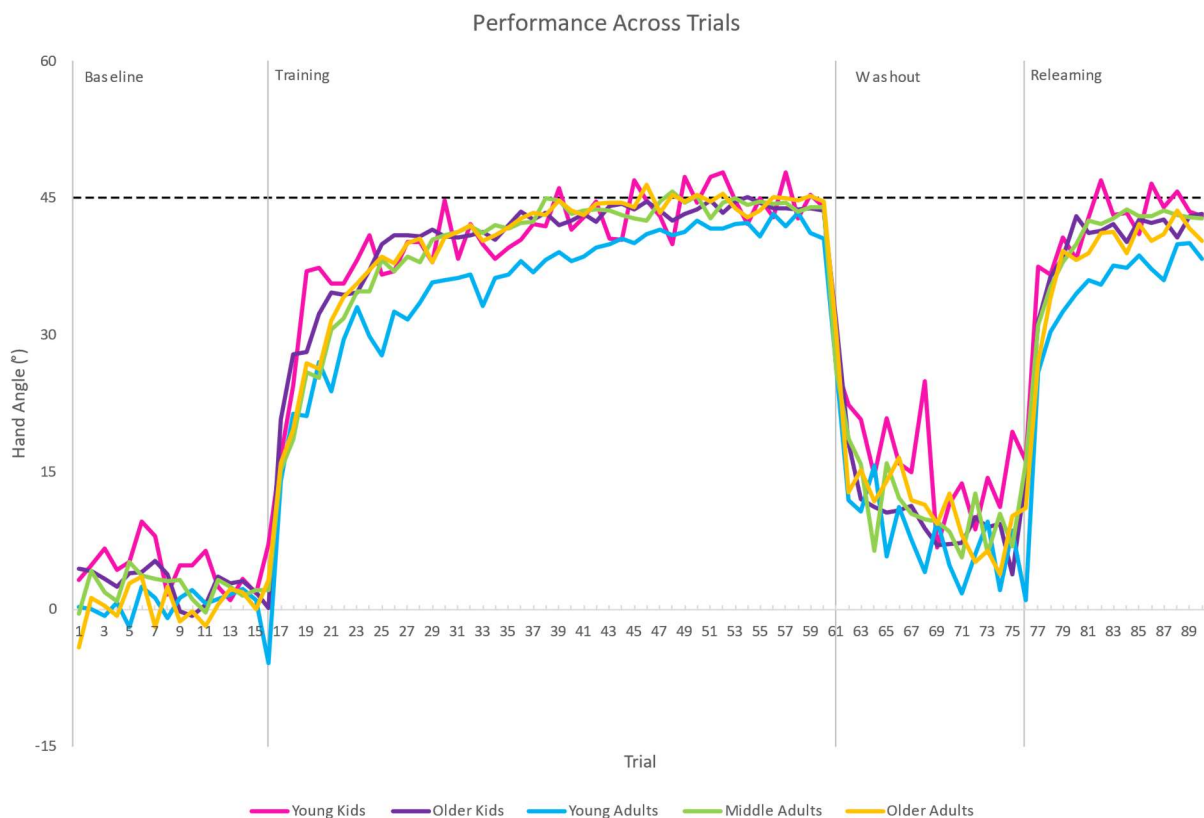


Figure 4.3. Performance across trials. Solid lines represent group means. Young kids are shown in pink, older kids are shown in purple, young adults are shown in blue, middle adults are shown in green and older adults are shown in yellow. The dashed black link at the 45° mark indicates angular reach

deviations equivalent to full compensation for the perturbation and the solid grey line at the 0° mark indicates reaches that did not correct for the perturbation.

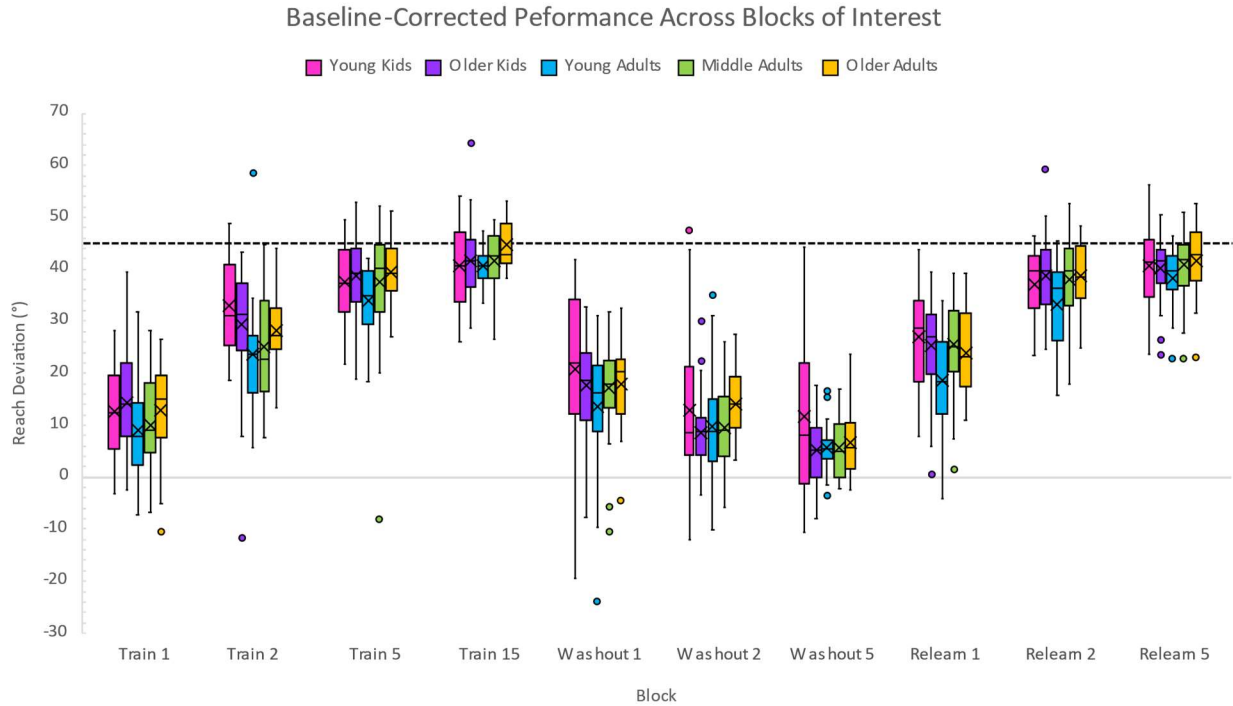


Figure 4.4. Group performance across blocks, and phases, used for analysis, shown with boxplots. Young kids are shown in pink, older kids are shown in purple, young adults are shown in blue, middle adults are shown in green and older adults are shown in yellow. Blocks 1, 2, 5 and 15 are shown for the learning phase. Blocks 1, 2 and 5 are shown for both the washout and relearning phases. The dashed black link at the 45° mark indicates angular reach deviations equivalent to full compensation for the perturbation and the solid grey line at the 0° mark indicates reaches that did not correct for the perturbation.

Aftereffects and Unlearning

Then we wanted to confirm that people continued to make deviated hand movements, even after the cursor rotation was removed, during washout; these are known as reach aftereffects, and usually reflect implicit learning. We then compared the extent of these initial aftereffects, and rate of de-adaptation, when provided with the re-aligned cursor across the age groups. Aftereffects were confirmed by 5 separate single-sample t-tests, which all found

that each group's baseline-corrected mean during the first block of washout was significantly different from 0 (Young Kids: $t(17) = 5.673$, $p < 0.001$, $d = 1.337$, $BF_{10} > 100$; Older Kids: $t(39) = 12.438$, $p < 0.001$, $d = 1.967$, $BF_{10} > 100$; Young Adults: $t(19) = 4.685$, $p < 0.001$, $d = 1.048$, $BF_{10} > 100$; Middle Adults: $t(35) = 11.541$, $p < 0.001$, $d = 1.924$, $BF_{10} > 100$; Older Adults: $t(16) = 8.575$, $p < 0.001$, $d = 2.080$, $BF_{10} > 100$). More importantly, we found that these aftereffects in block 1 were not significantly different across the age groups ($F(4, 126) = 1.087$, $p = 0.366$, $\eta^2 = 0.033$, $BF_{10} = 0.120$), with moderate support for the null hypothesis (washout block 1 in Figure 4.4). This suggests that learning was quite similar across the age groups.

Next, we wanted to explore group differences in de-adaptation across the washout phase (washout blocks 1, 2 and 5 in Figure 4.4). Unsurprisingly, especially since the cursor was visible during this phase, we found that reach errors decreased across blocks ($F(1.95, 245.15) = 50.586$, $p < .001$, $\eta^2 = 0.153$, $BF_{10} > 100$). Again, we found no major differences (anecdotal support for the null hypothesis) between the groups ($F(4, 126) = 2.009$, $p = 0.097$, $\eta^2 = 0.027$, $BF_{10} = 0.339$) and, most importantly, we found no evidence of a significant interaction between group and block ($F(7.78, 245.15) = 0.838$, $p = 0.567$, $\eta^2 = 0.010$, $BF_{10} = 0.030$) with very strong support for this null hypothesis. Taken together, this suggests that all groups de-adapted at a similar rate.

As we can see in Figure 4.4, it appears that none of the groups returned to baseline performance by the end of the 15 washout trials (washout block 5 in Figure 4.4). If that were the case, then baseline-corrected reach errors in this block should have been close to 0. This was confirmed by 5 separate single-sample t-tests, which all found that each group's baseline-corrected mean during the last block of washout was significantly different from 0 (Young Kids:

$t(17) = 3.086, p = 0.007, d = 0.727, BF_{10} = 7$; Older Kids: $t(39) = 4.607, p < 0.001, d = 0.728, BF_{10} > 100$; Young Adults: $t(19) = 5.278, p < 0.001, d = 1.180, BF_{10} > 100$; Middle Adults: $t(35) = 6.048, p < 0.001, d = 1.008, BF_{10} > 100$; Older Adults: $t(16) = 4.272, p < 0.001, d = 1.036, BF_{10} = 60$). We confirmed that there were no differences between the groups in this last block of washout ($F(4, 126) = 2.146, p = 0.079, \eta^2 = 0.064, BF_{10} = 0.517$). Although Bayesian analysis only suggests anecdotal support for the groups being similar in this block, the purpose of these tests was just to confirm that none of the groups returned to baseline performance by the end of the washout phase; aftereffects were still present for all groups when they entered the relearning phase.

Generalization of Learning

Figure 4.5 shows the learning performance across all targets, collapsed across all trials, for the five groups during the washout phase. When investigating the amount of adaptation at different distances from the trained target (0° was the distance from the trained target, while 45° and 90° are the distances untrained targets were from the trained) we found a statistically significant effect of target distance, reflecting the usual generalization pattern ($F(1.18, 228.55) = 56.03, p < .001, \eta^2 = 0.184, BF_{10} > 100$). Bonferroni post-hoc analysis confirmed that these differences were between the trained target and both untrained targets but that learning at the untrained targets was no different from one another. More importantly, we found no differences between the age groups ($F(4, 126) = 1.77, p = 0.140, \eta^2 = 0.020, BF_{10} = 0.174$) with moderate support for the null hypothesis, nor any significant 5 X 3 interaction (but only anecdotal support for the null hypothesis) between group and target ($F(7.27, 228.55) = 1.99, p = 0.055, \eta^2 = 0.026, BF_{10} = 0.762$). Taken together, this suggests that generalization patterns are

no different across the lifespan; we can see in Figure 4.5 that all age groups show limited generalization to untrained target locations throughout the washout phase.

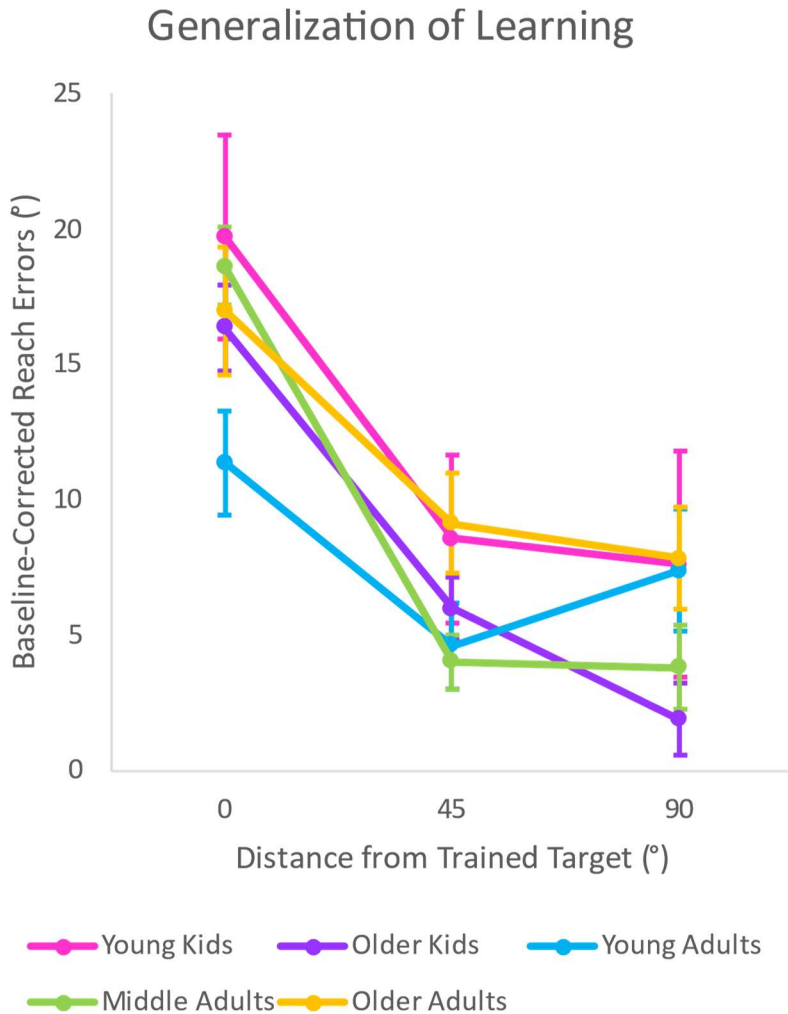


Figure 4.5. Generalization of learning to different distances of untrained targets (45° and 90°) targets, from the trained target (0° difference) during the washout phase. Young kids are shown in pink, older kids are shown in purple, young adults are shown in blue, middle adults are shown in green and older adults are shown in yellow. Group means are shown by dots and error bars represent standard error of the mean.

Relearning Rate and Savings

Lastly, we wanted to explore group differences in the rate of re-learning, and savings, during the last phase of the experiment. We tested for group differences in baseline-corrected

reach errors at different time points during re-learning (re-learning blocks 1, 2 and 5 in Figure 4.4). Again, we found no effect of age group, with only anecdotal support for the null hypothesis ($F(4, 126) = 2.109, p = 0.083, \eta^2 = 0.027, BF_{10} = 0.722$), nor a significant interaction (with moderate support for the null hypothesis) between group and block ($F(7.86, 247.66) = 1.658, p = 0.111, \eta^2 = 0.008, BF_{10} = 0.173$), but just the expected effect of block ($F(1.97, 247.66) = 353.393, p < .001, \eta^2 = 0.413, BF_{10} > 100$). Bayesian analysis suggested this difference was extreme and Bonferroni post-hoc tests revealed that there were significant differences between all three of the blocks. Taken together, this suggests that all groups re-learned to counter the cursor rotation at a similar rate. Then we compared the percentage of learning extent attained in block 1 of training to that attained in block 1 of relearning, using the re-corrected reach deviations for the relearning phase described earlier, and tested for possible group differences in savings (Figure 4.6). Here we found a significant effect of phase ($F(1, 126) = 36.64, p < 0.001, \eta^2 = 0.105, BF_{10} > 100$), a significant, but very weak (anecdotal evidence for), effect of group ($F(4, 126) = 3.15, p = 0.017, \eta^2 = 0.047, BF_{10} = 1.550$), but, more importantly, no significant interaction between phase and group ($F(4, 126) = 1.50, p = 0.205, \eta^2 = 0.017, BF_{10} = 0.329$). Results of a Bonferroni post-hoc test found that the group difference was only due to differences between the older children and young adults. We noticed that young adults in this study seemed to show poorer performance than other groups throughout most phases of the study (Figure 4.3), although none of our other analyses detected this until now. This group difference, for which Bayesian analyses only suggested anecdotal support for, merely highlights slight differences in learning extent collapsed across both blocks; since we did not find a

significant interaction, with moderate support for the null hypothesis, we can conclude that all groups showed similar patterns of savings.

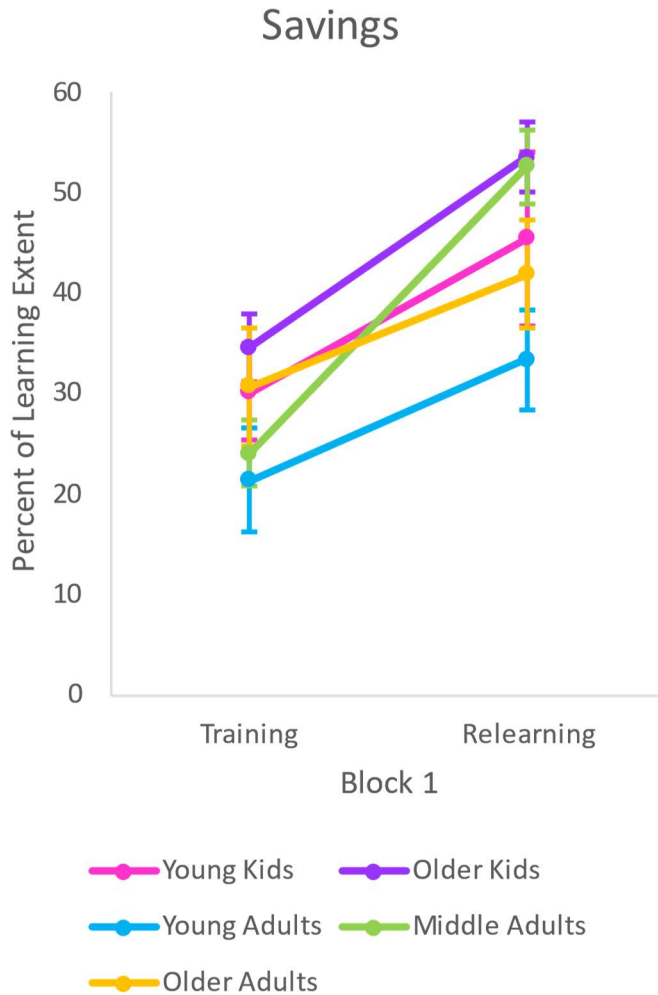


Figure 4.6. Savings during relearning. Percent of final learning extent achieved in block 1 of training is compared to percent of final learning extent achieved in block 1 of relearning. Young kids are shown in pink, older kids are shown in purple, young adults are shown in blue, middle adults are shown in green and older adults are shown in yellow. Group means are shown by dots and error bars represent standard error of the mean.

Discussion

The main goal of this study was to compare visuomotor learning performance, for various properties of learning, across the lifespan. Specifically, we quantified the rate, and

extent, of visuomotor adaptation when a 45° CCW cursor was abruptly introduced, as well as during washout, generalization, and rate of re-learning. Prior to comparing adaptation to this visuomotor distortion, we first confirmed that baseline accuracy, when reaching with an aligned cursor, was similar across the age groups. Only young children showed significantly more variability operating this mouse relative to the other age groups. All groups adapted quickly, and almost completely, in both phases where they were exposed to a 45° rotation in this short, gamified learning task. These learning curves closely overlapped across the age groups (Figures 4.3 and 4.4) with no evidence for differences in learning extent. At most, we found some evidence that young kids seemed to adapt their reaches at a slightly faster rate. All groups continued to deviate their cursor even when the 45° cursor-rotation was removed; that is, they showed significant aftereffects. These aftereffects, and subsequent rate of de-adaptation, were similar across age groups. As expected, reach aftereffects were present not only for the trained target, but also to a smaller extent to the untrained targets. Yet, this typical pattern of generalization did not differ as a function of age. Not only did all groups also relearn to counter the cursor rotation at a similar rate, but this re-learning (also known as savings) was significantly faster the second time participants were exposed to the rotation and, again, was independent of age. In summary, our results suggest that visuomotor learning performance, across multiple characteristics, does not differ across the lifespan.

Baseline Motor Control

Our finding that baseline accuracy is no different across the lifespan for simple cursor-to-target movements (Figure 4.2A) is supported by other literature. Studies that compare groups of children of various ages have found no significant differences in baseline accuracy

when reaching to visual targets with an aligned cursor (Contreras-Vidal et al., 2005; King et al., 2009). The same is true when a group of young adults are included for comparison with groups of children (Ferrel et al., 2001; Kagerer & Clark, 2014). Additionally, baseline accuracy of older adults is no different than younger adults (Bock & Girgenrath, 2006; Cressman et al., 2010; Lei & Wang, 2018; Noohi et al., 2016; Seidler, 2006). Thus, general visuomotor accuracy remains stable across the lifespan and cannot explain any of the differences found between groups in the studies we review below.

In our study, we found that young kids were significantly more variable (by almost 50% more than other age groups) in their baseline reaching performance (Figure 4.2B), which is also supported by other work. In a previous study, young children (aged 5-6) were found to be almost 30% more variable than older children (aged 7-8 and 9-10) at baseline (King et al., 2009). Ferrel et al., (2001) also found reaching performance of 6-year-olds to be almost 30% more variable than older children or young adults. However, in this simple task, we, along with others (Cressman et al., 2010; Fernández-Ruiz et al., 2000), found that older adults are no more variable than younger adults during these aligned-cursor reaches. Overall, the results suggest that variability in reaches made with an aligned is consistent across age, apart from young children.

Extent and Rate of Adaptation

Although we found young kids were more variable in their baseline reaching performance, this did not impact their rate, or extent, of visuomotor adaptation as we found no major differences between any of our groups for either aspect (Training Blocks in Figure 4.4).

Our study was designed to be short and engaging to ensure our young participants were motivated to do well and not become fatigued, or bored. Past work has indicated that children younger than 8 may have difficulties adapting their reaching movements to a rotated cursor, especially for rotations larger than 90°, but that 11-year-olds perform similarly to adults for rotations of all sizes, albeit with slower movement times (Ferrel et al., 2001). Given that their participants only completed 8 trials for each of the 5 rotations tested, this may not have been enough trials to sufficiently capture children’s visuomotor learning abilities. However, a study that imposed a 45° rotation (the same as in our current study), over 60 training trials, still found that 4-year-olds had some trouble adjusting their movements, as their initial movement plans suggested less compensation for the rotation compared to older children (6 or 8-years-old). They found that 8-year-old children compensated for it more than both younger groups, although all groups of children were able to increase their compensation by the end of the adaptation phase (Contreras-Vidal et al., 2005). Likewise, using a slightly larger (60°) rotation and over 100 training trials, King et al., (2009) found younger children compensated about 25-30% less than older children, although both groups doubled their amount of compensation in the last training block, compared to the first. Taken together, children can adapt to visuomotor rotations, although the youngest children may adapt less well than slightly older children, especially when visuomotor adaptation tasks are more challenging, or less fun.

A major difference between our results and those of previous studies involving children is how quickly, and the overall extent of which children (and even adult controls) compensated for the 45° cursor rotation. All groups compensated for the rotation by at least 90% by the end of our 45 training trials (Training Block 15 in Figure 4.4) and if we look at their performance

across all trials (Figure 4.3) it appears that this large compensation occurred early (within the first 25 trials). In most previous studies, nearly all of which had more training trials, participants compensated for the rotation at most by 80%. For example, Kagerer and Clark (2014) found that both adult controls and children only achieved 70% compensation of a 60° visuomotor rotation. This suggests that some of the poor performance in children (and perhaps adults) may be partly due to lack of motivation and fatigue. Given the protocol and lab setting of previous studies, it is possible that children were not fully attending to the task, since it only involved moving one dot to another. Therefore, we shortened and gamified our visuomotor learning task to make it more engaging for children. The children in our study also used a child-size mouse rather than a digitizing pen, so the movements would have been smaller and perhaps required less fine motor ability. Lastly, given that our task was portable, we ran children in a fun, familiar environment for them (at a library or camp). All these aspects should have made the entire experience less intimidating and less boring; this could be more motivating for children to learn and might explain the greater compensation that we observed early in training for all our age groups. The only group who showed any departure from this excellent performance (although non-significantly so) were our young adults, who were the only group that would have done this study in a lab setting, and for course credit, rather than purely out of interest. Our results suggest the quality of task, and environment, may play an important role in motor learning performance, especially for special groups like children.

The effect of aging on visuomotor rotations have been equally mixed for older adults. Generally, there is more consistent evidence that for larger rotations, i.e. 60° or larger, older adults adapt at a slower rate, and to a lesser extent than young adults (Anguera et al., 2011;

Bock & Girgenrath, 2006; Buch et al., 2003; Heuer et al., 2011; Heuer & Hegele, 2008; King et al., 2013), which has been attributed most to aging-related deficits in the explicit or cognitive component of learning (Heuer & Hegele, 2008; Vachon et al., 2020; Vandevoorde & Orban de Xivry, 2019). For smaller rotations, usually 30°, the impact of aging on visuomotor adaptation is less clear. Some studies find that older adults do not differ from younger adults in the rate or extent of their adaptation (Heuer & Hegele, 2008; Noohi et al., 2016; Vachon et al., 2020), but others have found that older adults adapt to a lesser extent (Lei & Wang, 2018; Seidler, 2006) and at a slower rate compared to young adults (Lei & Wang, 2018). Again, we found no difference in adaptation performance across age for a 45° rotation, which may suggest that in our short, gamified study, older adults did not find this moderate rotation size exceptionally challenging compared to younger adults. The shortness of the study also meant we didn't include additional tasks, or instructions, to be able to distinguish the extent by which implicit and explicit components contribute to the adaptation performance. Since we found no differences in adaptation performance between our groups, it is unlikely that the contributions of these components differed across groups. Since all our age groups adapted at the same rate, and to the same extent, we then investigated whether age affected other aspects of adaptation, such as aftereffects, de-adaptation, generalization, and relearning.

Aftereffects, Rate of Unlearning and Generalization

Following adaptation, our participants continued to deviate their mouse movements during washout, even though the hand-cursor was realigned once more; that is, they displayed significant aftereffects (Washout Block 1 in Figure 4.4). More interestingly, the magnitude of these reach aftereffects did not differ across the age groups. Although the aligned cursor was

visible in our study, the reach aftereffects for the first block of 3 trials (to the trained and untrained targets) were about 17°, which is typically the size of reach aftereffects elicited when the cursor is not visible in young adults (Bond & Taylor, 2015). Thus, our gamified study, with only a short bout of training, was able to elicit robust reach aftereffects across the lifespan.

One of the first studies to measure aftereffects in children, after adapting to a 45° rotation, found that the younger children (aged 4 and 6) did not produce these typical aftereffects, while 8-year-olds did (Contreras-Vidal et al., 2005). However, their results are possibly confounded since these two youngest groups also did not fully compensate for the 45° cursor rotation during training, compared to 8-year-olds. Subsequent studies by King et al., (2009) and Kagerer & Clark, (2014), have found that 5–6-year-old children showed a similar magnitude of reach aftereffects as older children and adults. Thus, consistent with our findings, young children who can adapt to a visuomotor rotation produce aftereffects that are comparable to older children and adults.

Not only did we investigate the initial trials during washout to gauge for reach aftereffects, but we also compared de-adaptation rates across the age groups. We found that rate of de-adaption to the cursor rotation did not differ across the age groups (Washout Block in Figure 4.4). Unsurprisingly, given that we only had 15 trials of washout, de-adaptation was not complete at the end, like in the study by Kagerer and Clark (2014), although they included 35 trials, and the cursor was not visible during these washout trials. Yet, Kagerer and Clark (2014) found that both the rate, and extent, of de-adaptation in young children (5-6) was smaller than that of older children (11-12), as well as young adults. This discrepancy, between their results and ours, could be due to different learning process when the aligned cursor is

visible, compared to invisible, during washout. Typically, aftereffects will decay faster when the hand-cursor is still visible, due to concurrent de-adaptation, compared to if the cursor is removed entirely during aftereffect trials (Kitago et al., 2013); having the cursor visible in our study may have helped our younger kids de-adapt quickly. However, the availability of visual feedback is unlikely to be the full explanation since a prism study by Gomez-Moya et al, (2016) found a significant interaction between age and trial number during de-adaptation. To test for aftereffects after prism adaptation, the prisms are removed during de-adaptation and, therefore, aligned visual feedback is available because they can see their own hand. Although they did not run post-hoc tests, it does seem that this significant interaction was due to slower rates of unlearning in the two youngest groups (4-5 and 7-8) compared to adults. This was despite finding no significant effect of age on rate, or extent, of adaptation to the displacing prism. Furthermore, there were no age differences in reach aftereffects captured during the first trial of their washout phase, yet they still found children deadapted slower than adults even though this aligned feedback was present. Therefore, whether young children de-adapt slower, and whether this depends on the availability of visual feedback during washout requires further investigation. In our study, to better engage all participants, we opted to make the cursor visible during washout, rather than invisible, since reaching with an invisible mouse cursor would have made the study much longer, and far less enjoyable, especially for the children. Thus, we can only conclude that for short bouts of gamified visuomotor learning, adaptation and de-adaptation may be equivalent across the lifespan.

Our finding that older adults show comparable aftereffects, as well as similar rates of unlearning, as younger participants is much more in line with previous work, even when

comparing our results to studies where older adults have showed reduced compensation for the rotation during the training phase (Buch et al., 2003; Seidler, 2006). Regardless of the size of the cursor rotation used during training, so long as participants were not cued, or instructed, to evoke a cognitive strategy, older adults have consistently been found to show significant aftereffects that are of a similar magnitude as young adults (Cressman et al., 2010; Heuer & Hegele, 2008; Vachon et al., 2020) which decays at a similar rate (Noohi et al., 2016; Seidler, 2006). It is only when explicit strategies are evoked, after adaptation to cursor rotations larger than 45°, that older adults produce smaller aftereffects than young adults (Heuer & Hegele, 2008). When the rotation is smaller, even when eliciting a cognitive strategy during aftereffect trials, older adults again show aftereffects that are a similar size as young adults (Heuer & Hegele, 2008; Vachon et al., 2020). Since aftereffects are often considered a measure of implicit learning (Krakauer, 2009), it is possible that preserved implicit processes in older adults can counteract deficits in explicit learning during aftereffect trials (Vandevoorde & Orban de Xivry, 2019), at least after adapting to smaller rotations. Although our study cannot distinguish between implicit and explicit processes, it is unlikely that explicit strategy contributed that much to either the adaptation or de-adaptation given the rotation size was not so large. Thus, our results are generally in line with most of the past recent literature showing comparable rates and extent of adaptation and de-adaptation for small visuomotor rotation for younger and older adults.

Finding comparable levels of aftereffects, as well as similar rates of unlearning, for all groups during the washout phase permitted us to explore possible group differences in generalization patterns towards untrained target locations. Despite having only 15 washout

trials in total, in addition to the cursor being visible during these trials, we found the typical generalization pattern (Cressman & Henriques, 2015; Krakauer et al., 2000; Taylor et al., 2013), whereby people showed the largest deviations at the trained target (45°) and significant, but reduced deviations when reaching towards nearby, untrained targets (90° and 135°) (Figure 4.5). Specifically, we found that reaches toward both untrained locations were almost 3 times smaller, on average for all groups, than those towards the trained location, but more importantly, this generalization pattern did not differ across any of our age groups. To our knowledge, our study is the first to examine generalization patterns in children following visuomotor adaptation. We are aware of one study that has investigated generalization in older adults; Heuer & Hegele (2008) found that older adults showed comparable generalization patterns as young adults, such that after adapting to a 75° rotation at a single trained target location, and having them reach with an invisible cursor during washout trials, aftereffects at nearby target locations were about half the size of those at the trained location, like in our study (where we provided vision of the realigned cursor). Overall, our results suggest that our ability to generalize visuomotor learning to new, nearby locations is present in early childhood and remains stable throughout the lifespan.

Relearning Rate and Savings

Finally, we found that all groups relearned to counter the cursor rotation at a similar rate, and that all groups showed evidence of savings, when the rotation was introduced a second time (Figure 4.6). Since none of our groups fully returned to baseline performance by the end of washout, we calculated new reach deviations for each participant, for the first block of the relearning phase, to account for the possibility that the reach deviations seen in Figure

4.4, for all groups in relearning blocks, may be achieving final extent sooner than in the training phase due to carryover effects from the washout block. To account for this, we subtracted the final block of washout from each participant's hand angle in the first block of relearning (instead of subtracting the original baseline means), like what was done in another similar study where they did not include a consolidation break before relearning and did not observe complete unlearning during their washout phase (Yin & Wei, 2020). By doing so, we were also able to confirm that all groups exhibited savings during the relearning phase. Although we did find an effect of group, such that the percentage of the total learning extent achieved in both first blocks of training and relearning was lower for young adults than older children, we assume that this is because our young adults seemed to compensate for the rotation slightly less than other groups throughout all training and relearning blocks (blue boxplots in Figure 4.4). However, this was not flagged as a significant difference in any of our other analyses. We attribute this minor difference to the fact that our young adults were university students who were required to participate in studies in exchange for course credit, whereas all other groups were recruited through the general community and chose to participate because they were genuinely interested in helping with the study. Since we found a significant effect of phase (training vs relearning), but no significant interaction between phase and group, we can conclude that savings was similar across all age groups.

Most of the previous work on savings has focused on young adults, but there have been a few studies that have examined savings in older adults; studies testing savings in children are incredibly scarce. The only study we found that tested for savings in children found no evidence of a quicker relearning rate, to the 60° cursor rotation they first trained with, in older children

(aged 10-12) after a break of at least 10 hours (Urbain et al., 2014). However, this study did not include a group of young adults for comparison, making it difficult to know if their null result was really an effect of age. Since Kitago et al. (2013) found that young adults produce greater savings after experiencing a washout phase, in which the cursor is visible but realigned with the hand's position, compared to unlearning over time alone (general forgetting), it is possible that the discrepancy between our results and those of Urbain et al. (2014) are simply due to differences in paradigm; 15 washout trials may not be an equivalent break in time compared to a 10-hour delay. The few studies which test savings in older adults are also inconsistent with our results; all we are aware of showed older adults exhibit similar savings as young adults, even though older adults adapted less overall during training (Seidler, 2007a, 2007b; Vandevorde & Orban de Xivry, 2019). The rarity of these studies, in addition to the discrepancies between their findings and ours, warrants future replication of our results. However, at least in the context of short, gamified situations, our study suggests that savings is no different across the lifespan.

Conclusion

In this study we found that visuomotor learning abilities are similar across the life span; we found no differences in performance between young kids, older kids, young adults, middle adults and older adults for adaptation extent, adaptation rate, aftereffects, de-adaptation rate, generalization, or savings. Our results differ from past studies, which sometimes, but not always, find an effect of age on visuomotor adaptation. Past findings are also confounded by the fact that these experiments can be rather long, boring, and may involve a special trip to an

unfamiliar laboratory. This is not the case for young adults who tend to be students at the university where the research is being conducted. By testing children and older adults in a more familiar setting, such as at a library or camp, we found that visuomotor adaptation performance was similar across the lifespan, at least for short bouts of gamified learning.

Limitations

It is possible that we did not find that younger children performed differently than other age groups because our youngest group included children aged 5-8. When significant differences were found in other childhood-focused studies we reviewed, these differences were mostly observed in 5–6-year-olds. Originally, we wanted to collect enough children to further separate our youngest group (to distinguish 5-6 from 7-8), like in these other studies, but due to the COVID-19 pandemic we had to stop data collection; we recognize that our study was likely underpowered. We determined that we would need at least 40 participants in each group to achieve 80% power. However, since we are one of the first studies to measure several aspects of learning across multiple age groups, our results should still be relevant to researchers in various fields. Although we did have some a priori hypotheses, we did not pre-register our research protocol, or analysis online. However, all our data and analysis scripts will be available on our OSF repository (before submitting for publication).

Chapter 5: General Discussion

The primary goal of my dissertation was to understand how human sensorimotor capabilities might differ under special developmental circumstances, such as with connective tissue disease, or during early/late stages of life. Throughout our lifespan our bodies undergo many changes, and we must continually adapt our motor repertoire to be able to navigate our environment. This can be examined in visuomotor adaptation paradigms where the motor system is challenged to compensate for changes in vision, such as learning to reach to targets on a screen with a rotated hand-cursor, and our brains do this through trial-and-error. A motor command is sent to the arm and a prediction of the outcome is generated by the brain. This prediction is compared with sensory feedback from proprioceptors and is thought to generate the error signal that drives motor learning. This process may be further complicated if one's sense of proprioception is less reliable, which is thought to be the case for those with EDS, young children, and older adults. While research of how these processes operate in young adults is quite extensive, it is not clear if they function differently across these unique developmental contexts, as studies involving these special groups are quite scarce.

Guided by findings from my master's thesis which showed that people with EDS had greater uncertainty than controls when judging the position of their felt hand compared to a visual reference marker, but only at peripheral locations, and that those who were the most hypermobile (having the largest Beighton scores) were also those with the greatest uncertainty ranges at these locations, in chapter 2 I further investigated proprioceptive abilities in EDS. Specifically, I examined patients' ability to localize their non-dominant hand, in a

proprioceptive-reaching paradigm, that tested participants at a greater number of workspace locations, in addition to exploring the relationship between patients' proprioceptive imprecision and two of the most common symptoms of EDS (chronic pain and joint hypermobility). In chapter 3, I followed up on findings from chapter 2 by comparing proprioceptive acuity, and precision, of estimates of hand position in EDS patients, to those of controls, using two variations of a new proprioceptive estimation task that would permit direct comparison of proprioceptive estimates derived solely from afferent information (when a robotic manipulandum guided their hand to a location) to those when efferent information was additionally present (when the participant moved their hand to a self-chosen location). I also followed up on findings from my master's thesis by seeing how these estimates changed following visuomotor adaptation and whether patients' estimates were related to their magnitude of joint hypermobility (Beighton scores). Finally, in chapter 4, in the pursuit of a more ecologically valid understanding of visuomotor adaptation across the lifespan, I designed a short, gamified visuomotor rotation task, that could be implemented in non-laboratory settings, to better engage participants of all ages. No study on the effect of age on visuomotor adaptation has compared children to young adults and older adults within the same paradigm. Furthermore, no other aging study has captured as many different visuomotor learning characteristics within the same experiment, whereas we compared rate/extent of adaptation, aftereffects, rate of de-adaptation, generalization, savings, and rate of relearning between each of our age groups.

By examining performance patterns of these special groups across these three different paradigms, this research furthered theoretical knowledge about how the sensorimotor system

functions under unique developmental circumstances. More specifically, we found that proprioception is more variable, or less precise, in people with EDS and that their proprioceptive sensitivity is related to the symptom of joint hypermobility, but not chronic pain. Yet this did not interfere with their ability to adapt their reaches to a visuomotor rotation, or recalibrate their sense of proprioception, suggesting that differences in proprioceptive precision do not impact visuomotor learning. This might also explain why we found children and older adults (two other populations thought to exhibit proprioceptive differences) performed similarly to young adults, as well as to each other, for each of the visuomotor learning characteristics we measured in our lifespan study, at least in the context of short bouts of gamified learning. This is profound because it suggests that the sensorimotor system can facilitate efficient visuomotor learning, even when proprioceptive sensitivity might be affected by connective tissue disease, or healthy aging. Lastly, I examine the practical implications stemming from my findings and provide areas of future research.

Proprioception in EDS

Results from my experiments revealed that only precision of hand proprioception, but not acuity, is impacted in EDS and that these deficits are most likely related to the magnitude of joint hypermobility. In the first experiment, I found that patients exhibited twice as much scatter than controls, when reaching to the felt location of their non-dominant hand, at all workspace locations, but the degree of scatter did not positively correlate with chronic pain scores, suggesting that chronic pain is not related to proprioceptive issues in EDS. Likewise, findings from the second experiment also showed that the only aspect where people with EDS

differed from controls was the precision of hand estimates, which was poorer for EDS patients when estimates were based purely on proprioception. When efferent information was also available, this difference disappeared. However, visuomotor adaptation disturbed estimates of hand proprioception enough to produce poorer precision in estimates for EDS patients, compared to controls, for both active and passive types of hand localization. Furthermore, we found that Beighton scores, a common measure of joint hypermobility in EDS, was a partial predictor of less precise proprioceptive estimates. Taken together, these findings support the idea that proprioception is less precise in EDS and is partially related to a person's magnitude of joint hypermobility.

A complete explanation as to why proprioception is impacted by EDS is currently lacking, as EDS is a rare disease with limited research interest. In fact, the genetic causes of 12 of the types were only discovered in 2017, and the cause of the 13th, most common type – Hypermobile EDS (hEDS) – is still unknown (Malfait et al., 2017). Thus, attempting to uncover other potential causes of these patients' proprioceptive differences is challenged by the issue that most EDS studies, to date, involved patients whose diagnoses were based primarily on clinical criteria, which became more strict for hEDS in 2017, and could not be confirmed via genetic testing; it is possible that the full range of symptom presentation is not completely understood and cannot truly be captured until the genes responsible for hEDS are found and many past studies have been replicated, but with the caveat of only recruiting patients with confirmed molecular diagnoses. However, based on what we know so far, we can speculate on what other factors might contribute to the lessened proprioceptive sensitivity we found in EDS patients in both studies from this dissertation, as well as in my master's thesis.

Proprioceptive impairments are more obvious in EDS when testing the lower limbs, where reduced acuity is often observed alongside reduced precision, when comparing patients' knee proprioception to that of controls (Rombaut, De Paepe, et al., 2010). It is not known whether differences in lower-limb proprioceptive acuity are related to measures of joint hypermobility (Beighton scores) as this has never been tested. In the discussion section of the second experiment in this dissertation (chapter 3), we already suggested other possible sources of proprioceptive differences in EDS, aside from the most common symptom of joint hypermobility, which could have both central, and peripheral, origins. Therefore, there are still many avenues that future research could explore, to better understand proprioceptive issues in EDS, but I would argue that there is more of a need for developing rehabilitative tools, since this population tends to suffer more after accidental injuries, which might be more preventable if we could find a way to improve proprioceptive sensitivity in EDS. For example, since compressive garments have been found to improve posture in EDS (Dupuy et al., 2017), it is possible that they could also improve proprioceptive sensitivity, via enhanced cutaneous sensation, and, if so, then we might also gain further insight into other sources of proprioceptive issues in EDS.

Proprioceptive Plasticity in EDS

Results from my second experiment revealed that proprioceptive plasticity is not impacted by EDS, as we found no differences between patients and controls regarding the magnitude of hand estimate shifts (active or passive) following visuomotor adaptation to an abruptly introduced cursor rotation. Furthermore, the adaptation process itself was also not

impacted by EDS, as we found no differences in rate, or extent, of visuomotor adaptation between patients and controls, nor any differences in the sizes of their aftereffects. Likewise, a similar pattern emerged in my master's EDS study, where we found that patients recalibrated their sense of felt hand position no differently than controls after adapting their reaches to a gradually introduced cursor rotation. Thus, even though proprioception appears to be less sensitive in EDS, as we discussed above, this does not interfere with their sensorimotor plasticity or general motor control.

This finding is not unique to EDS, as older adults, another group known to exhibit differences in proprioceptive sensitivity (Goble et al., 2009) have been found to recalibrate their sense of felt hand position just as much (Cressman et al., 2010), if not more (Vachon et al., 2020) than healthy controls following visuomotor adaptation. The study by Cressman et al. (2010) used an identical paradigm as my master's EDS study, and found almost the same results for their older adults as we did with EDS patients, such that older adults recalibrated their sense of felt hand position similarly to controls, but showed larger uncertainty ranges (both before and after adapting their reaches to a gradually introduced cursor rotation) at all locations, whereas we only found larger uncertainty ranges for EDS patients at peripheral reference marker locations. However, the study by Vachon et al. (2020), which used an identical paradigm (but expanded upon, to explore the factor of explicit instruction on adaptation) as the second study from this dissertation, found that older adults shifted their hand location estimates almost twice as much as healthy controls, following visuomotor adaptation to an abruptly introduced cursor rotation, although older adults in that study were not found to have less precise hand localizations, like our EDS patients showed. It is possible that the greater plasticity

measured in this more recent study from our lab reflects an effect of age, and that we would only see greater shifts in EDS if we had tested much older EDS patients. Regardless, results from both our EDS studies that measured proprioceptive plasticity (Clayton et al., 2013, 2021) suggest that sensorimotor plasticity is not impacted by EDS, even though their proprioception is generally less sensitive.

The Importance of Inclusion in Research Design

Sensorimotor processes are typically studied in a laboratory, on a university campus, using customized experimental set-ups that are intended to control for possible confounds. This is a convenient location to collect healthy control data from, since these recruits are most often undergraduate students who are familiar with the campus environment. However, studying special populations, like we did here with EDS patients, children, and older adults, requires that extra consideration be given to the research design; certain accommodations may be needed to better control for additional potential confounds, that are population-specific, to ensure validity of the findings.

None of the EDS patients who participated in our studies were students from York University and these paradigms required a visit to the campus because our proprioceptive set-up was not portable. Chronic fatigue is another common EDS symptom (Castori et al., 2012) and we were worried that traveling to the laboratory might exhaust patients, potentially confounding some of our results. Therefore, all patients were given the option to be chauffeured to/from their homes by myself and were not expected to have any lengthy walks on campus, unless they wanted some physical activity during a break. The extent to which this

occurred varied across participants, as some preferred to arrive in their own vehicles, but still requested transport to/from the visitor parking lots. Thus, we assessed each patient's needs well before planning their trip to our laboratory. Furthermore, we provided patients with a rest station that they could use during their visit, booked longer sessions in case rests were needed, and always had a research assistant present to ensure food/drinks were delivered more efficiently. It is unclear whether accommodations like these were implemented in any of the EDS studies we reviewed, but it is possible that this is another reason why the proprioceptive differences we observed were not as extreme as those from other studies. In the future, we would like to design a portable set-up that could test proprioception in EDS. With modern technologies becoming more affordable, such as the Raspberry Pi, 3D printing, touchscreen interfaces or VR headsets, it is entirely possible to customize a portable set-up that could collect proprioceptive data on a much larger scale; implementing this at the yearly EDS Society Patient Conference, or taking it directly to patients, in the comfort of their own homes, would likely increase sample sizes well beyond what is needed to sufficiently power these types of studies.

Since we did not measure proprioception in our lifespan study, a basic laptop was chosen for its convenience, allowing us to test participants, of all ages, in more accessible community locations. More importantly, a shorter, gamified experimental task was designed to better engage participants, especially the children, for whom we believe that inconsistencies in previous visuomotor adaptation studies are due to the experiments being rather long and boring. Instead of cursor/target stimuli being simple dots, we used very large sets of brightly coloured aliens/planets, respectively, to describe the experiment to children as a game where they were helping aliens travel back to their home planets. Because an alien was randomly

selected as the cursor (out of 45 different options) and paired with a randomly selected planet as the target (30 different options), the excitement of what stimuli might appear tended to keep most children engaged with the task without any reminders to maintain focus. For older adults, like our EDS patients, we were more concerned with fatigue being a confound for their results. Thus, having a short experiment, lasting only around 5-10 minutes, satisfied the needs of both special populations and it did not make sense to burden them with travelling to the university for such a short period. However, it is possible that some phases of this experiment were too short, such as the washout phase, as we did not observe complete return to baseline performance for any of our groups, making it more challenging to examine evidence of savings upon relearning. Future work examining visuomotor learning across the lifespan might consider including slightly more trials in certain phases of the experiment, so long as they gamify the experience to keep participants interested. This type of portable, fun design would also be a better choice for further studies on the effect of age on visuomotor adaptation in other special populations, such as children with Developmental Coordination Disorder (DCD), where there is some evidence of visuomotor learning impairment (Kagerer et al., 2004), but where research on this topic is scarce and often plagued by small sample sizes.

Conclusion

This dissertation enhanced our current understanding of how the sensorimotor system functions under special developmental circumstances, such as with connective tissue disease, or throughout healthy aging. Findings across two of these experiments provide a cohesive view that proprioception is less precise, or more variable, in EDS and is more likely related to joint

hypermobility, rather than chronic pain. The third experiment suggests that visuomotor learning abilities are fully mature in childhood and remain consistent throughout the lifespan in a healthy aging population. Lastly, this work further shows the importance of inclusive design when researching special populations, raising the possibility that some of the sensorimotor issues observed in various other unique groups might be found to be less extreme if they were tested under a more ecologically valid lens.

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Appendix A: Disclaimer for Co-Authored Chapters

Chapter 2 in this dissertation has been published in SpringerPlus with Stephanie A.H. Jones and my supervisor, Denise Y.P. Henriques as coauthors. Denise Y.P. Henriques, along with B. Marius `t Hart, are coauthors of Chapter 3, which is published in Somatosensory & Motor Research. Chapter 4 is currently being written up for publication, with coauthors Sahir Abbas, B. Marius `t Hart and Denise Y.P. Henriques.

Denise and I conceived and designed the experimental methodology. For Chapters 2-3, we used control data, stimuli and modified experimental methods from two previous studies from our lab. I created the stimuli for Chapter 5 and designed the experimental methods along with Denise and Marius `t Hart. Experiments were programmed by Errol Cheong (Chapter 2) and Marius `t Hart (Chapters 3-4). I performed the experiments and collected the data for all chapters, with assistance from undergraduate students Jennifer Ruttle (Chapter 2), Ayça Erdem (Chapter 3), Sahir Abbas (Chapter 4), Aqib Mannan (Chapter 4), and Safiya Erdogan (Chapter 4). I received assistance with scoring chronic pain questionnaires from undergraduate student Alyssa Romualdi (Chapter 2). I analyzed all the data and wrote the manuscripts.