Multimodal Sensory Integration for Perception and Action in High Functioning Children with Autism Spectrum Disorder

Nicole Marie Gregor Salowitz
Marquette University

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MULTIMODAL SENSORY INTEGRATION FOR PERCEPTION AND ACTION IN HIGH FUNCTIONING CHILDREN WITH AUTISM SPECTRUM DISORDER

by

Nicole M. G. Salowitz, B.S.

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ABSTRACT
MULTIMODAL SENSORY INTEGRATION FOR PERCEPTION AND ACTION IN HIGH FUNCTIONING CHILDREN WITH AUTISM SPECTRUM DISORDER

Nicole M. G. Salowitz, B.S.

Marquette University, 2015

Movement disorders are the earliest observed features of autism spectrum disorder (ASD) present in infancy. Yet we do not understand the neural basis for impaired goal-directed movements in this population. To reach for an object, it is necessary to perceive the state of the arm and the object using multiple sensory modalities (e.g. vision, proprioception), to integrate those sensations into a motor plan, to execute the plan, and to update the plan based on the sensory consequences of action. In this dissertation, I present three studies in which I recorded hand paths of children with ASD and typically developing (TD) controls as they grasped the handle of a robotic device to control a cursor displayed on a video screen. First, participants performed discrete and continuous movements to capture targets. Cursor feedback was perturbed from the hand's actual position to introduce visuo-spatial conflict between sensory and proprioceptive feedback. Relative to controls, children with ASD made greater errors, consistent with deficits of sensorimotor adaptive and strategic compensations. Second, participants performed a two-interval forced-choice discrimination task in which they perceived two movements of the visual cursor and/or the robot handle and then indicated which of the two movements was more curved. Children with ASD were impaired in their ability to discriminate movement kinematics when provided visual and proprioceptive information simultaneously, suggesting deficits of visuo-proprioceptive integration. Finally, participants made goal-directed reaching movements against a load while undergoing simultaneous functional magnetic resonance imaging (MRI). The load remained constant (predictable) within an initial block of trials and then varied randomly within four additional blocks. Children with ASD exhibited greater movement variability compared to controls during both constant and randomly-varying loads. MRI analysis identified marked differences in the extent and intensity of the neural activities supporting goal-directed reaching in children with ASD compared to TD children in both environmental conditions. Taken together, the three studies revealed deficits of multimodal sensory integration in children with ASD during perception and execution of goal-directed movements and ASD-related motor performance deficits have a telltale neural signature, as revealed by functional MR imaging.

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CHAPTER 1: RATIONALE AND SPECIFIC AIMS

Rationale and Hypothesis

Many everyday tasks require movements of the hand to acquire a physical goal. For example, we reach to a stationary target such as a glass of water when we are thirsty or we track a moving target such as a toddler's hand to prevent her from touching a hot surface. Goal-directed behaviors can be modeled by several stages: sensation of limb and target states, spatial calibration of limb state sensations, integration of those sensations into a motor plan, execution of that plan, and updating of that plan based on sensations of the consequences of the action.

Two complementary sensory modalities commonly used to estimate limb kinematic state are vision and proprioception and many recent research studies have explored how differences in the neural encoding of information from these two modalities are resolved to produce a consistent estimate of limb state (Ernst and Banks, 2002; van Beers et al., 1999, 2002; Reuschel et al., 2010). This state estimate is used to select and update a motor plan based on automatic sensorimotor adaptation and/or volitional strategic compensatory reactions. Automatic sensorimotor adaptation is a form of learning that evolves over a series of movements whereby some aspect of original task performance is restored in the presence of external mechanical perturbations and/or distortions of sensory feedback of that performance (Kagerer et al., 1997; Klassen et al., 2005). During automatic adaptation the state estimate is used subconsciously to update subsequent motor commands to minimize the consequence of perturbation or sensory distortion (Scheidt et al., 2001). Volitional strategic compensation is another form of learning wherein a compensation strategy is selected from several available motor plans in response to conscious perception of sensorimotor discord (Redding and Wallace, 1997; Sekiyama et al., 2000; Cunningham and Pavel, 1991; Kagerer et al., 1997; Klassen et al., 2005).

Clinical observation has found that some people with autism spectrum disorder (ASD) exhibit abnormalities related to sensory information processing. Such abnormalities include heightened and/or attenuated responses to sensory stimuli compared to controls (O'Neill and Jones, 1997; Lane et al., 2010;

Ben-Sasson et al., 2009; Dawson and Watling, 2000; Marco et al., 2011; Ornitz, 1974, 1983); temporary loss of perception (O'Neill and Jones, 1997; Ornitz, 1974); incorrect attribution of perceived sensation to another modality (i.e. synesthesia; O'Neill and Jones, 1997); or stereotyped behaviors such as head-banging or hand-flapping (Lane et al., 2010; Ben-Sasson et al., 2009; Dawson and Watling, 2000; Ornitz, 1974, 1983). Case studies have attempted to characterize sensory processing abnormalities in these children (O'Neill and Jones, 1997). However, findings have been inconsistent because abnormal behaviors are transient and they range in severity across the broad spectrum of autism.

The studies described in this Dissertation take a systems-level approach to characterize deficits in the model of goal-directed movement in children with ASD. Using computational modeling and functional neuroimaging techniques, three aspects of sensorimotor control will be characterized by comparing performance of children with ASD to performance of TD children. These include alignment and calibration of visual and proprioceptive spaces, integration of sensory contributions from the two modalities for the perception of hand path kinematics, and memory-based predictive updating of discrete movements. *I test the hypotheses that children with ASD differ from TD children in how they use sensory information to guide limb movements and that deficits in sensorimotor information processing give rise to deficits in compensation for unpredictable environmental change during goal-directed movement in these children.*

Aim 1: Characterize the role of volitional strategic compensations and automatic sensorimotor adaptation to visuo-proprioceptive reference frame calibration during reaching and tracking behaviors in typically developing children and children with autism spectrum disorder

Because proprioceptive information from muscle spindles is encoded in a muscle-based coordinate frame and visual information is encoded in two different retinotopic coordinate frames, a transformation (or mapping) is required to align the spatial coordinates of afferent sensory information of limb and target state with that expected to arise from efferent motor commands (Ghahramani et al., 1996). For example, a transformation occurs between the coordinates of the retina and those of the muscles during visually-guided reaching such that the movement goal is represented in some reference frame intermediate to eye- and muscle-based frames (Pouget and Snyder, 2000; Andersen et al, 1993). The transformation must be amenable to change via volitional strategies (e.g. to observe and imitate the actions of another person viewed in a mirror or on a video screen or when large visuomotor distortions are imposed suddenly) or via automatic sensorimotor adaptation (e.g. to cope with changes in limb length during growth or when small visuomotor distortions are imposed gradually).

People with ASD exhibit clumsiness (Ghaziuddin and Butler, 1998) as well as specific motor impairments related to movement planning (Rinehart et al., 2001; Rinehart et al., 2006; Glazebrook et al., 2008; Schmitz et al., 2003), task sequencing (Hill, 2004) and postural control (Molloy et al., 2003; Minshew et al., 2004). However, there is conflicting evidence supporting a general coordination deficit in ASD (Ghaziuddin et al., 1994; Rinehart et al., 2001, 2006; Gidley Larson et al., 2008; Mostofsky et al., 2004). Here, in a series of two experiments, I characterized sensation of limb state, spatial calibration of limb state sensations, and motor plan updating during volitional strategic compensation and automatic sensorimotor adaptation for sensorimotor discord during goal-directed reaching and tracking.

In the first experiment, participants moved a robot handle out-and-back to targets presented on a video screen. Participants completed two versions of the experiment which differed in the way cursor feedback was perturbed. In one version of the task, cursor feedback was reflected about the participant's midline to assess his/her ability to select strategies to compensate for the known distortion. In the other version of the task, cursor feedback was incrementally rotated about hand position to assess children's ability to automatically use sensorimotor adaptive compensation. Hand path errors during the beginning of the trajectory were used to assess motor command updating. ***I tested the hypotheses that relative to TD children, children with ASD exhibit an impaired ability to compensate for novel visuomotor transformations during goal-directed reaching, and that the behavioral deficits have both a volitional strategic and automatic adaptive component.*** In the second experiment, participants moved the handle of a horizontal planar robot to continuously track the position of a target as it moved at one of two constant speeds within the space of a video screen. In some trials, the target appeared as a single dot on the screen. In others, it also included advanced spatiotemporal information about where the cursor would be some time in the future. After a period of baseline practice, the relationship between hand motion and cursor motion was reflected about the participant's midline. The task was repeated four times, once with each combination of target speed and configuration. We quantified the pattern of spatial errors between the hand and target during tracking to characterize the ability of children with ASD to integrate anticipatory visual information into their ongoing movements and to characterize their ability to apply strategic spatial transformations to that anticipatory information when needed to update their motor plan. ***I tested the hypothesis that relative to TD children, children with ASD exhibit deficits in the performance of manual tracking movements consistent with impaired ability to apply a strategic, compensatory, spatial transformation to the visual cues used to plan and execute ongoing manual tracking movements.***

Aim 2: Quantify visual and proprioceptive contributions to the estimation of limb kinematic state in typically developing children and children with autism spectrum disorder

ASD-related deficits in visuomotor compensation could be due to deficits in sensory perception, deficits in motor plan formation, or deficits in the transformation of the motor plan into action. The experiments described above (Aim 1) were designed to identify whether motor plan formation and/or execution are impaired in ASD. In the current experiment (Aim 2), I characterize sensory integration for perception and response selection in ASD. Vision and proprioception provide complementary information related to limb position. As a result, we retain the ability to perceive the environment when one of these modalities becomes unreliable (due to aging, disease, or environmental effects) by increasing the contribution of the other intact modality. We can assign priority rankings (weights) to each sensory source based on the relative uncertainty of the signals (Ernst and Banks, 2002). The contributions of both modalities are combined to produce a single estimate of limb state.

Some have reported that during sensorimotor integration tasks, children with ASD as a group prefer haptic modalities over visual modalities to a greater extent than TD children who favor vision (Frith and Hermelin, 1969; Masterton and Biederman, 1983; Haswell et al., 2009). However, these conclusions were derived from measures of motor performance which may have been influenced by deficits in the formation of a motor plan and deficits in the execution of that plan. Here, I quantified the extent to which the relative contributions of vision and proprioception for perception are updated in response to increasing levels of visual uncertainty.

Participants completed a two-interval forced choice discrimination task, in which they grasped the handle of a robotic device and/or watched a cursor displayed on a computer screen. They observed a series of two movements in which the curvatures of the hand and/or cursor paths were selected from a set of several distinct values. Participants indicated whether the second movement was more or less curved than the first movement by pressing one of two response buttons. The reliability of visual information was systematically manipulated by varying the width of the cursor's Gaussian spatial distribution on different trials. Psychometric analysis was used to measure the relative contributions of vision and proprioception to the perception of hand movement kinematics. ***I tested the hypotheses that relative to TD children, the neural processes underlying multisensory integration and the re-distribution of sensory weights in response to increased amounts of visual uncertainty are compromised in children with ASD.***

Aim 3: Identify neural correlates of goal-directed reaching during compensation for unpredictable loads in typically developing children and children with autism spectrum disorder

The experiments described above were designed to determine the extent to which ASD-related deficits in visuomotor compensation were due to sensation of limb and target states (Aims 1 and 2), spatial calibration of limb state sensations (Aim 1), integration of those sensations into a motor plan (Aim 1), and/or execution of that plan (Aim 1). The final experiment (Aim 3) was designed to characterize motor plan updating based on sensations of the consequences of the movement and to identify neural correlates of goal-directed reaching in children with ASD relative to TD children.

Sensorimotor adaptation allows us to restore some aspect of motor performance in the presence of an ever-changing environment. To respond to environmental changes, we must perceive the environment through sensory inputs (vision and proprioception, see Aims 1 and 2) and estimate outcomes of our actions. Previously we have shown that memories of prior experiences can be used to form predictions of future motor outcomes in a sample of healthy adults (Scheidt et al., 2012). Furthermore, we found neural correlates of memory and prediction within a distributed network of cortical and subcortical brain regions.

Children with ASD exhibit deficits in the formation of a motor plan (Rinehart et al., 2001, 2006; Hughes, 1996; Hill, 2004; Fabbri-Destro et al., 2009). However, it is unknown if these deficits are due to systematic updating of the motor plan based on sensations of movement outcomes. Here, I characterized kinematic performance measures and identified neural correlates of goal-directed reaching.

Participants grasped the handle of a pneumatic robot while they made goal-directed wrist flexion movements against forces applied to the hand that were either constant across trials or randomly-varying across trials. Magnetic resonance imaging data were simultaneously collected to later correlate brain activity with movement onset. By identifying neural correlates of motor execution and sensorimotor prediction, I was able to identify networks of brain regions that supported goal-directed reaching in each group. ***I tested the hypotheses that relative to TD children, children with ASD have a diminished capacity for prediction and a deficit in motor execution and that these performance characteristics engaged an alternate network of neural correlates.***

The experiments described in this Dissertation characterized differences in sensorimotor adaptation and corresponding brain activity between children with ASD and TD children. Such differences arose from quantifiable sensory information processing deficits in children with ASD. My findings have clinical significance because new therapies may be developed to improve motor performance of children with ASD by addressing specific deficits in their learning process (e.g. multimodal sensory integration, sensorimotor memory formation, environmental load prediction, etc). Finally, by identifying differences in brain activity correlated with behavioral learning signals in autistic (relative to TD) children I can identify ASD-related differences in how the brain responds to dynamically changing environments, thereby advancing our knowledge of autistic symptoms and their underlying neural sources and/or compensations.

CHAPTER 2: BACKGROUND

Limb Position Estimation

Limb position control can be modeled such that a visuo-proprioceptive estimate of limb position, S_{vp}, is subtracted from the desired limb state, P_d, to produce an error signal, ε, which modulates the motor plan (Figure 2-1; cf. Poladia, 2009; Wolpert et al., 1998; M. Heenan, personal communication, September 2, 2010; S. Beardsley, personal communication, December 1, 2010). There are at least two ways that we estimate limb position: by viewing the limb directly (vision) and by using muscle spindle proprioceptors to sense limb position in a muscle-based reference frame (proprioception). As shown in the feedback path of Figure 2-1, actual limb position, P_a, is sensed by cells (transducers) such as photoreceptor cells in the retina (vision) or receptors in the muscles, tendons, joints, and skin (proprioception). Sensory receptor cells are not perfect and they add noise and delays to the signal during transduction. However, a neural network may act as a filter for receptor noise as multiple sensors converge to a single modality-specific representation of limb position.

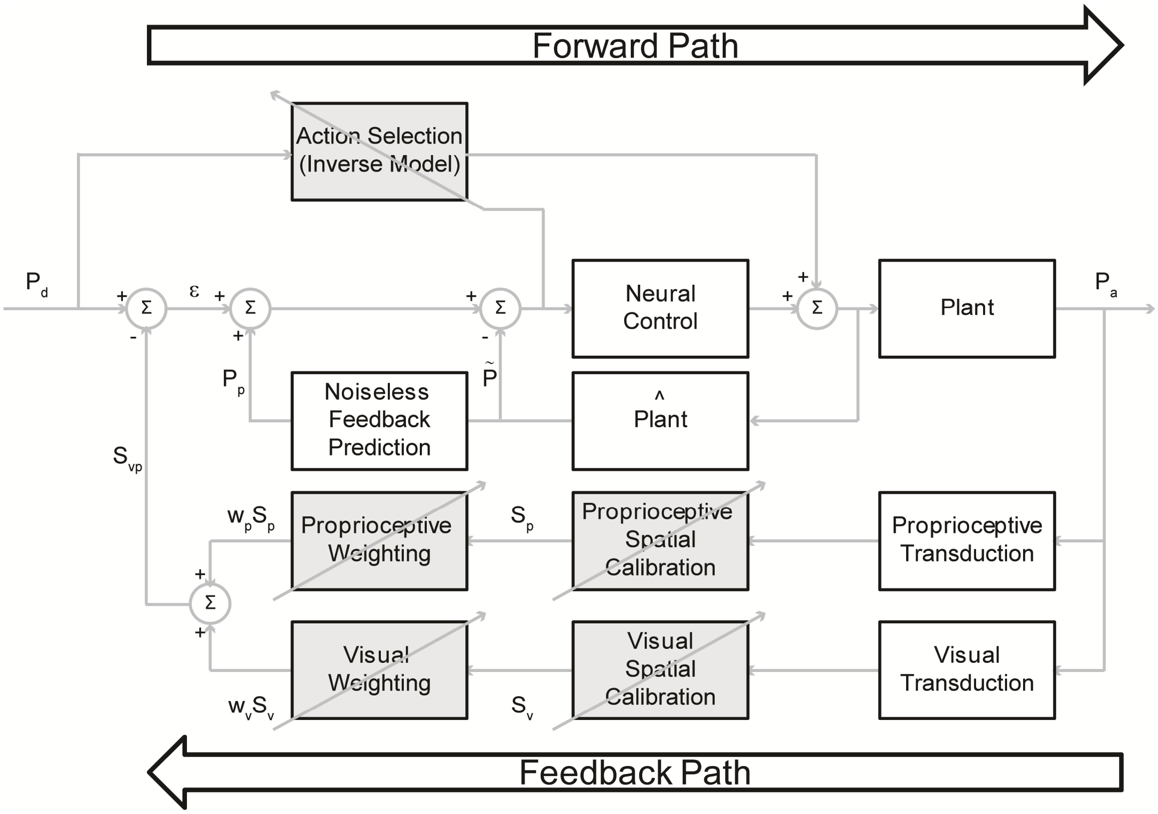

Figure 2-1: Block diagram of limb position control. In the forward path [top] motor commands are updated to produce limb movement in relation to predicted performance while in the feedback path [bottom] sensory signals from vision and proprioception are spatially processed and integrated to estimate actual limb position. Gray boxes illustrate Aims 1-3.

Visual information is transduced in retinotopic coordinates, while proprioceptive information is transduced in body-centered coordinates. To obtain a unified estimate of limb state that integrates information from both senses, contributions from both sources must be mapped to a common reference frame. A disturbance may cause the baseline spatial alignment of vision and proprioception to be inadequate. Recalibration of visual and proprioceptive alignment is necessary to restore motor function during environmental distortion and has been observed in adults (Kagerer et al., 1997; Klassen et al., 2005) and children (King et al., 2009). Two independent research groups (Kagerer et al., 1997; Klassen et al., 2005) characterized sensorimotor compensation in college students when visual feedback was rotated from the hand’s position by small amounts (0.125 and 10°) over many trials (240 and 600) and when visual feedback was rotated suddenly (within one trial) by a large amount (30 and 90°). When visuomotor rotations were applied gradually, performance errors remained small throughout the testing session.

However, when visuomotor rotations were applied suddenly, participants produced large errors at the onset of applied distortion, and then performance errors gradually decreased during the testing session. Researchers have found more complete adaptation following gradual visual rotations (Kagerer et al., 1997; Klassen et al., 2005), thus large performance errors are not necessary for spatial adaptation to occur (Klassen et al., 2005). Compensations for visuomotor rotations that were presented suddenly resulted in larger error, reduced aftereffects (Kagerer et al., 1997) and worse retention (Klassen et al., 2005) as compared to compensation for rotations that were presented gradually. Smeets and colleagues (2006) observed the stability of visuo-proprioceptive alignment during goal-directed reaching. Participants reached to targets during alternating periods in which visual feedback was absent or present. When visual feedback was removed, movements (relying exclusively on proprioception) drifted to a repeatable bias location approximately 5 cm from visuo-proprioceptive reaches. We confirmed this observation with healthy adult volunteers (Salowitz, neé Gregor et al., 2008).

The integration of visual and proprioceptive information can improve motor performance compared to information from a single sensory modality (Smeets et al., 2006). Prior studies have shown that healthy adults are biased to rely on visual information to a greater extent than other sensory modalities such as haptics (Ernst and Banks, 2002) and hearing (Battaglia et al., 2003). Furthermore, Helms Tillery and colleagues (1991) have shown that kinesthetic cues alone are insufficient to yield a reliable estimate of hand position. However, if visual feedback becomes unreliable, adults will re-distribute the relative sensory weighting of vision and haptics such that the relative influence of haptics will increase (Ernst and Banks, 2002). Ernst and Banks (2002) estimated relative visual and haptic weights during a two-interval forced choice task in which participants perceived the size of a cube by looking at it (vision) and/or feeling it (haptics). If vision, v, and proprioception, p, are used to estimate hand path kinematics then the bimodal state estimate (S_{vp}, cf. Figure 2-1) is determined from a weighted combination of the visual and proprioceptive state estimates, S_v and S_p, respectively, as follows:

$$S_{vp} = w_v S_v + w_p S_p$$

Ernst and Banks (2002) estimated the relative weights, w, of each sensory modality from their respective variances as follows:

$$w_v = \frac{\sigma_p^2}{\sigma_v^2 + \sigma_p^2} \text{ and } w_p = \frac{\sigma_v^2}{\sigma_v^2 + \sigma_p^2} \qquad [2\text{-}1]$$

such that $w_v + w_p = 1$. Furthermore, the variances of each sensory modality can be combined to estimate the variance of the bimodal estimate, σ_{vp}^2, as follows:

$$\sigma_{vp}^2 = \frac{\sigma_v^2 \sigma_p^2}{\sigma_v^2 + \sigma_p^2} \qquad [2\text{-}2]$$

By definition (*Eq 2-2*), the variance of the bimodal estimate is smaller than the variance of either sensory modality (Ernst and Banks, 2002). If the ability to perceive hand path kinematics is impaired, then the variance in the single modality estimates would increase and the overall response uncertainty would also increase as shown in Figure 2-2.

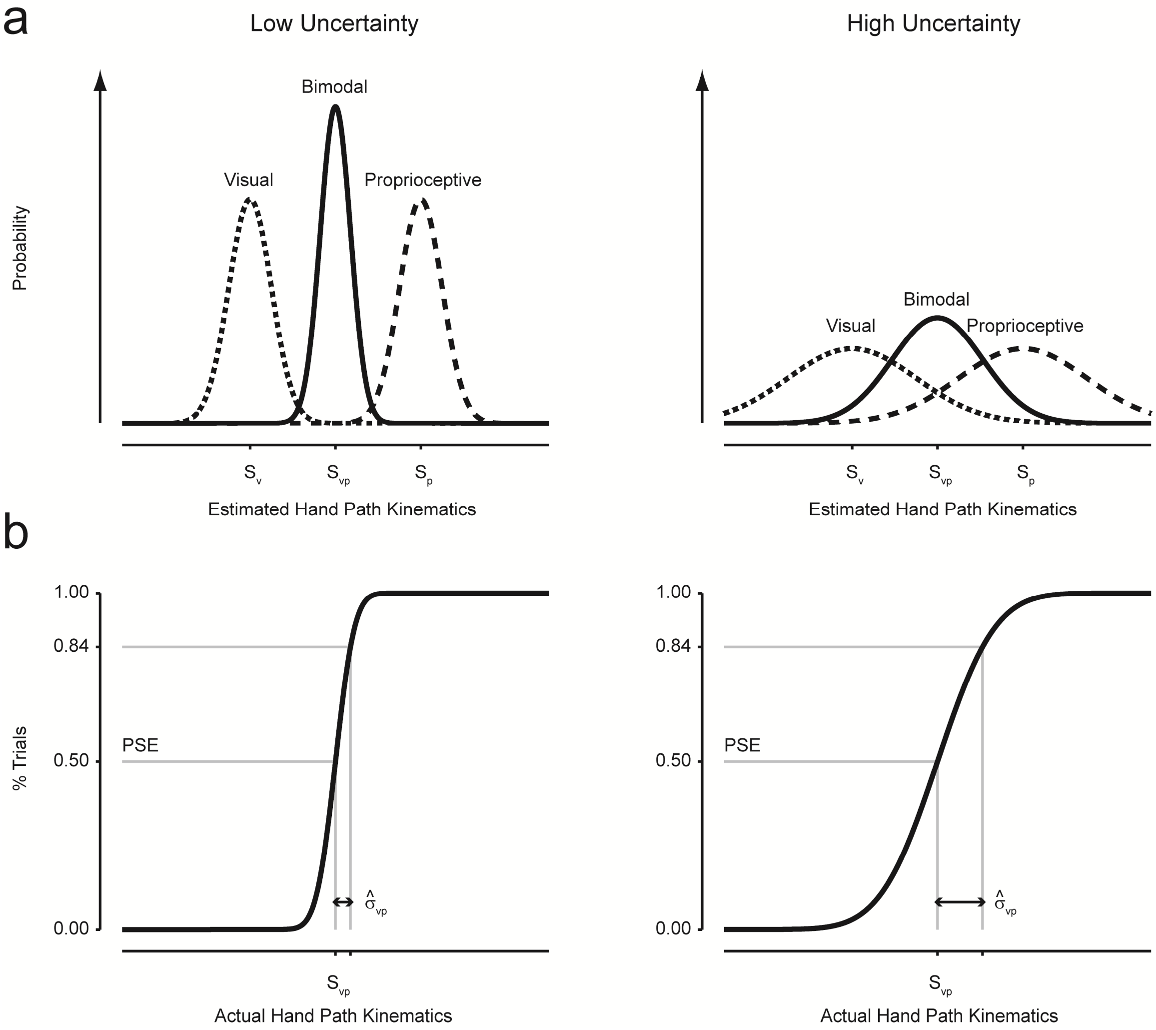

Figure 2-2: Multisensory integration with uncertainty in sensory estimates. (a) Probability density functions and (b) psychometric functions of perception of hand path kinematics. When uncertainty in the sensory estimates is low [left], sensory estimates are more variable and the discrimination threshold is smaller compared to the condition in which uncertainty in the sensory estimates is high [right].

Formation, Execution, and Updating of Motor Plans

We compare our body's estimate of limb state, S_{vp}, with the desired position, P_d, to form a motor plan, we execute the plan, and then we evaluate the consequences of our action to update subsequent motor plans. Following the forward path in Figure 2-1, the comparison of estimated and target positions yields a difference vector, ε. The difference vector is used to update motor commands in the form of torques by way of a neural controller which acts similarly to a proportional, integral, derivative (PID) controller (Poladia, 2009). Finally, the motor commands yield the actual position state, P_a, through the plant or controlled object (i.e. the body). Poladia (2009) showed that a forward model Smith predictor improves the estimate of current position by subtracting the effects of the plant and adding noiseless sensory feedback prediction to the error signal to temporally align the feedback signal with the desired state, thus accounting for delays in the transduction process. Without Smith predictor correction, participants could not reach the target because current desired position would be compared against actual position that occurred earlier in time.

During reaching, participants use a feedforward ballistic phase to quickly bring the hand close to the target (cf. “Action Selection” shown in Figure 2-1) followed by a fine-tuning phase (driven by sensory feedback) to improve accuracy. The brain uses separate mechanisms to plan the initial trajectory and final positioning phases (Scheidt and Ghez, 2007) each represented in a different coordinate frame (Ghez et al., 2007). During development children’s movements are primarily ballistic up to age 7 (Hay, 1978). At that time, performance errors increase as children learn how to use online feedback control (given by proprioception) and approach adult levels at age 11 (Hay, 1978). With practice and development, performance shifts to feedforward modes of control as an internal model of the environment is developed with experience (Seidler et al., 2004). Feedforward control occurs faster, yet accuracy depends on sensory information obtained through feedback control (speed-accuracy tradeoff; Seidler et al., 2004). Motor updating can be observed by discrete corrections during tracking or postural stabilization. The occurrence of discrete corrections might be related to retinal updating and/or an error threshold (Miall et al., 1993).

We have previously shown that goal-directed reaching is supported by memory-based predictive updating of motor commands (Scheidt et al., 2012). In our study, participants grasped the handle of a robot with their dominant hand and made wrist flexion movements against a random sequence of loads. Knowledge of results (KR) related to end position and movement duration were displayed upon movement completion. We found that movement error was linearly related to load. Unsupervised learning was represented by the statistics of state estimates. For example, in our experiment unsupervised learning was represented by two prior loads (determined by systems identification). We also analyzed a prediction signal derived from two prior memories of force perturbation. This signal was based on subject-specific behavioral data and a systems identification technique developed by Scheidt and colleagues (2001).

We found that adults adapted to random force perturbations using minimal effort with a time constant of 31 trials. Systems identification showed that error, ε_i, was estimated as a linear sum of current trial perturbation, K_i, and perturbations applied in the prior two trials, K_{i-1} and K_{i-2}, as follows:

$$\varepsilon_i = b_0 K_i + b_1 K_{i-1} + b_2 K_{i-2} \qquad [2\text{-}3]$$

From this equation, we found that the prediction of upcoming load, $\hat{K}_i$, was related to the prior two memories of loads as follows:

$$\hat{K}_i = -\frac{b_1}{b_0} K_{i-1} - \frac{b_2}{b_0} K_{i-2} \qquad [2\text{-}4]$$

Memory-based prediction occurs in the forward path illustrated in Figure 2-1 where $\hat{K}$ is given in units of torque. The memories of actual position state, P_a, were multiplied by the spring constant of the trial and a subject-specific weighting factor ($-b_1/b_0$,$-b_2/b_0$ see *Eq 2-4*) to produce a torque command. This prediction can modulate the limb's response to upcoming perturbations.

Sensorimotor Deficits in Autism Spectrum Disorder

Symptoms of autism spectrum disorder (ASD) include social deficits as well as stereotyped behaviors (American Psychiatric Association, 2013; for reviews, see Gerlai and Gerlai, 2003; Rapin, 1997). Sensory information processing is also impaired (Lane et al., 2010; Ornitz, 1974, 1983; O'Neill and Jones, 1997; Wiggins et al., 2009; Gerrard and Rugg, 2009; Hermelin and O'Connor, 1970; for reviews see Ben-Sasson et al., 2009; Baranek, 2002; Dawson and Watling, 2000) and sensory dysfunction is correlated with the severity of ASD in children but not adults (Kern et al., 2007). Sensorimotor learning might be altered in children with ASD to preserve aspects of motor function despite abnormal sensory processing. Other symptoms of ASD (poor imitative, language, and social skills) could be caused by impairments of sensory processing.

The ability to imitate another person requires compensation for the transformation between visual feedback of the observed demonstrator and proprioceptive feedback of one's own body. Imitation is impaired in children (Salowitz et al., 2013, Rogers et al., 2003; Stone et al., 1997; Haswell et al., 2009; Ohta, 1987; Bernabei et al., 2003) and adults (Leighton et al., 2008) with ASD (for a review, see Williams et al., 2001). Deficits in imitation might be due to improper spatial alignment between observation in visual coordinates and movement in proprioceptive coordinates. We conducted a pilot study (Salowitz et al., 2013) to determine whether deficits in imitation could be predicted by deficits in a task requiring compensation for a large, noticeable conflict between sensory feedback and motor command updating (i.e. mirror-drawing). We found that children with ASD made more errors related to hand orientation and we found a negative relationship between the percentage of trials with accurate hand orientation during imitation and the error magnitude during mirror-drawing. These findings suggest that the ability to imitate another's actions was related to the ability to compensate for large, noticeable sensorimotor transformations. However, the ability to imitate another's actions could also be due to deficits in visuospatial attention, sensorimotor memory, and the ability to understand and comply with task instructions.

Individuals with ASD exhibit impairments during tasks requiring visual spatial attention compared to controls (Townsend et al., 1996, 1999; Singer Harris et al., 1999; Wainwright and Bryson, 1996; Haist et al., 2005; Steele et al., 2007, for a review see Allen and Courchesne, 2001). These impairments include delayed responding (Townsend et al., 1996, 1999; Singer Harris et al., 1999; Wainwright and Bryson, 1996), reduced accuracy (Townsend et al., 1996, 1999; Haist et al., 2005) and deficits in spatial working memory (Steele et al., 2007). If children with ASD are impaired in their ability to attend to visual and/or proprioceptive stimuli, then we would anticipate deficits in tasks requiring re-calibration of visual and proprioceptive feedback signals when baseline alignment is perturbed.

Some studies have reported a preference for proximal (somatosensory, olfactory, and gustatory) over distal (visual and auditory) senses among children with ASD under normal conditions while the reverse preference may be true of typically developing (TD) children (Frith and Hermelin, 1969; Masterton and Biederman, 1983; Haswell et al., 2009). However, these studies characterized motor performance rather than measuring sensory perception directly. Proprioceptive accuracy and precision are comparable between individuals with ASD and TD participants (Fuentes et al., 2011) and children with ASD exhibit superior visual acuity than TD children (Ashwin et al., 2009). However, the integration of visual and proprioceptive information might be impaired in individuals with ASD during limb position estimation.

Haswell and colleagues (2009) compared visual and proprioceptive contributions to motor command updating during adaptation of goal-directed reaching movements to a force field. They found increased transfer of sensorimotor adaptation between regions of the workspace requiring identical joint motion in children with ASD compared to controls and they concluded that children with ASD have a greater reliance on proprioception. Within the ASD group, those who showed the most reliance on proprioception also exhibited greatest impairment in motor function, social interaction, and imitation, three main symptoms of the disorder that contribute to delayed development (American Psychiatric Association, 2013; Salowitz et al., 2013, Rogers et al., 2003; Stone et al., 1997; Haswell et al., 2009; Ohta, 1987; Bernabei et al., 2003).

Some (Gidley Larson et al., 2008; Mostofsky et al., 2004) reported that children with ASD were able to adapt movements of the arm and hand to an environmental disturbance at a rate comparable to that of TD children, leading them to conclude that the ability to form an internal model is intact. However, motor abilities differ between children with ASD and TD children (Minshew et al., 1997). In fact, movement disorders are the earliest observed features of ASD present in infancy (Teitelbaum et al., 1998). Even though the rate of adaptation may be comparable between participant groups, children with ASD are likely to compensate for their sensory differences by forming altered internal models which lead to greater movement error.

Specifically, the feedforward mode of control used in movement planning may be impaired in ASD. Schmitz and colleagues (2003) have reported a preference for feedback over feedforward modes of control in children with ASD which could explain the slowness of anticipatory movements (Rinehart et al., 2001; Minshew et al., 1997; Schmitz et al., 2003), speech (Fulkerson and Freeman, 1980) and the ability to shift attention between sensory modalities (Townsend et al., 2001). In a study by Schmitz et al. (2003), a load was placed on a platform which was affixed to the left forearms of children with and without ASD. Children were asked to remove the load with their right hand while elbow angle, force, and electrical activity of *B. brachii* were measured with a potentiometer, strain gauge, and electromyography (EMG), respectively. There was no difference between groups in the maximum elbow angle during the unloading reflex; however, children with ASD exhibited longer duration of unloading as measured by the duration of increased force. Furthermore, the latency of the unloading reflex was much longer in children with ASD such that EMG recordings revealed that TD children reduced muscle activity 15 ms *prior* to the onset of unloading, whereas children with ASD reduced muscle activity 51 ms *after* the onset of unloading. Thus, children with ASD have a deficit of anticipatory postural adjustments as recorded by EMG which leads them to depend primarily on feedback modes of control to stabilize forearm position. Others (Rinehart et al., 2001, 2006; Hughes, 1996; Hill, 2004; Fabbri-Destro et al., 2009) also reported planning problems in ASD which could impair feedforward control even though movement execution is intact (Rinehart et al., 2001).

Memory impairments in ASD (Minshew et al., 1997) may also contribute to problems in feedforward control. Children with ASD and children with moderate to profound cognitive deficits exhibited less preference for vision in a visuomotor task; however, in a strictly motor task (in which vision was unavailable), children with ASD completed the task faster than TD children and those with cognitive deficits (Frith and Hermelin, 1969) which implies that they performed faster using kinesthetic feedback rather than feedforward control mechanisms and that they exhibited an adaptive strategy to improve performance despite their sensory limitations, unlike the children with cognitive deficits who had the slowest performance.

Abnormal Brain Anatomy and Function in Autism Spectrum Disorder

Many researchers have sought to identify brain regions associated with the symptoms of ASD. They considered anatomical volumes, cell density, connectivity and function and used a variety of imaging and post-mortem techniques. At times, their conclusions were conflicting, but a review of the literature suggests that the following brain regions may contribute to the symptoms of ASD: frontal, parietal and temporal lobes; cingulate gyrus; hippocampus; corpus callosum; caudate; amygdala; cerebellum; cerebellar vermis and brainstem (for reviews see Verhoeven et al., 2010; Brambilla et al., 2003; Cody et al., 2002).

Early studies considered head circumference as an indicator of brain volume and found that in ASD head circumference is in the 25th percentile at birth, rapidly increases to the 84th percentile at two years of age (Courchesne et al., 2003) and is followed by a period of abnormally slow or arrested growth in which brain volumes (measured by magnetic resonance imaging) of TD children “catch up” to those of children with ASD (Courchesne et al., 2001, for a review see Courchesne, 2004). However, there is some debate as to whether head size remains enlarged in ASD during adolescence and adulthood (Piven et al., 1995).

People with ASD exhibit communication deficits and suspended attention similar to patients with frontal lobe lesions (Damasio and Maurer, 1978). Courchesne and Pierce showed that during the period of rapid brain overgrowth, the frontal lobe in particular exhibited the greatest growth compared to other brain regions (2005a). They also found that local circuitry was overdeveloped and disorganized within the frontal lobe and long-distance connections with other brain regions were underdeveloped (2005b). These differences in frontal lobe circuitry may cause poor high-level processing such as integrating information to provide feedback to low-level processes (Courchesne and Pierce, 2005b). Similar patterns of underconnectivity were observed in ASD between frontal and parietal regions and in the corpus callosum which is important for interhemispheric communication suggesting poor integration of information (Just et al., 2007). Our recent electroencephalogram study (Carson et al., 2014) found reduced interhemispheric coherence between the frontal lobes and between the temporal-parietal lobes in children with ASD compared to TD children. Müller and colleagues (1998) recorded brain activation using positron emission tomography as men with ASD and controls listened to, repeated, and generated sentences. Men with ASD exhibited less activation compared to controls in Brodmann area (BA) 46 of the frontal lobe during tasks of receptive and expressive language; however, they exhibited greater positive blood flow changes in BA 46 during motor speech functions.

Sensorimotor cortices are regions of interest in ASD research because children and adults with ASD exhibit a variety of sensory- and motor-related deficits. In a simple finger-tapping task, adults typically exhibit activation in primary motor, premotor and supplementary motor cortex. Müller and colleagues (2001) found that out of seven participants with ASD, three demonstrated no activation in contralateral precentral gyrus and three demonstrated activation in the supplementary motor area. However, participants with ASD exhibited activation in posterior regions such as superior parietal lobe and precuneus which were not identified in typical adults suggesting that individuals with ASD use alternative neural correlates for motor control. This study was especially well-controlled because individual participant data was analyzed without warping to Talairach space, thus accounting for the observation that autistic brain structure volumes are different from those of healthy controls. In a follow-up study of sequenced six-digit finger-tapping (Müller et al., 2003), participants with ASD and typical controls demonstrated parietal activations related to the task; however activations of participants with ASD were located inferior and posterior to those of TD participants.

Differences in brain function between people with ASD and controls may be due to abnormal neural organization within regions of the brain. Coskun and colleagues (2009) used magnetoencephalography to identify regions of sensory cortex that respond to pneumatically-driven taps of the index finger, thumb, and lip. Within the sensory cortex, the distance between cortical representations of thumb-taps and lip-taps were larger in people with ASD compared to controls. Cortical representations of thumb-taps and finger-taps were equidistant from those of lip-taps in people with ASD; however the distance between cortical representations of finger-taps and lip-taps was shorter than the distance between representations of thumb-taps and lip-taps in controls. The period in which somatotopic organization develops in children coincides with the period of brain overgrowth in ASD. Nebel and colleagues (2014) used parcellation of functional resting-state magnetic resonance imaging data to identify differences in the organization of the primary motor cortex between children with ASD and controls. They found that the dorsomedial region of the primary motor cortex was larger in children with ASD compared to controls suggesting that cortical representations of the leg/trunk and upper limb/hand were less distinct in ASD. Interestingly, parcellation of the primary motor cortex was similar between children with ASD and the younger sample of TD children suggesting that the development of the primary motor cortex may be delayed in ASD.

Abnormal organization within the sensorimotor cortex could be related to differences in cell size between groups. Post-mortem brain samples showed increased neuron density and smaller cell size in autistic samples compared to control samples in areas of primary motor, primary visual, and primary sensory cortices and frontal association cortex (Casanova et al., 2006). Furthermore, Mostofsky and colleagues (2007) found that increased white matter volume in primary motor cortex was correlated with poor motor skill in participants with ASD, but improved motor skill in TD participants, thus anatomical differences may contribute to functional abnormalities in ASD.

The temporal lobes are involved in sensory integration (Allison et al., 2000 cf. Boddaert et al., 2004), social perceptual skills (Iacoboni, 2005, Allison et al., 2000 cf. Boddaert et al., 2004), language (Bigler et al., 2007), and imitation (Iacoboni, 2005) which are impaired in ASD (Lane et al., 2010, Salowitz et al., 2013). Children with ASD exhibit connectivity problems (Lee et al., 2007) and hypoperfusion (Zilbovicius et al., 2000) in temporal lobe regions which is correlated with the severity of autistic symptoms (Gendry Meresse et al., 2005). Hypoperfusion in the temporal lobes in ASD might be attributed to decreased gray matter and white matter volume within the temporal lobes of children with ASD (Boddaert, 2004). However some (Bigler et al., 2003) have found no difference in anatomical morphometry between individuals with ASD and controls within the temporal lobe when older participants (up to 31 years) are also included.

The thalamus relays sensory and motor signals from subcortical regions to cerebral cortex. Studies of thalamic volume and composition yield conflicting results in ASD. Thalamic volumes typically scale with total brain volume in neurologically-intact individuals. However, two studies (Tsatsanis et al., 2003; Hardan et al., 2006) found no relationship between thalamic volume and total brain volume in individuals with ASD, but one follow-on study (Hardan et al., 2008) reported positive scaling of thalamic volume and total brain volume in ASD which was similar to that of controls. One study (Hardan et al., 2006) found no relationship between the volume of the thalamus and clinical features of ASD. Another study (Hardan et al., 2008) found a trend between metabolite concentrations within the thalamus measured with magnetic resonance spectroscopy and sensory abnormalities in ASD.

The cerebellum is particularly important in ASD research because over 90% of autistic autopsies revealed cerebellar abnormalities (Kemper and Bauman, 1998; cf. Allen and Courchesne, 2003) such as fewer Purkinje cells (Bauman and Kemper, 1994), and smaller cerebellum and brainstem volume (Hashimoto et al., 1995; Courchesne et al., 2001) even though cerebellar white matter is larger in ASD compared to controls (Courchesne et al., 2001). In addition, the pons and cerebellar vermis develop at a faster rate in ASD compared to typical controls (Hashimoto et al., 1995). Based on a survey of the literature, it is clear that the symptoms of ASD are not caused by a single brain region, but likely result from abnormalities of several brain regions and the interactions between them and it is likely that neural deficits vary widely across the broad spectrum of ASD.

CHAPTER 3: VISUO-SPATIAL GUIDANCE OF MOVEMENT DURING GESTURE IMITATION AND MIRROR DRAWING IN CHILDREN WITH AUTISM SPECTRUM DISORDER

Thirteen autistic and 14 typically developing (TD) children (controls) imitated hand/arm gestures and performed mirror drawing; both tasks assessed ability to reorganize the relationship between spatial goals and the motor commands needed to acquire them. During imitation, children with autism spectrum disorder (ASD) were less accurate than controls in replicating hand shape, hand orientation, and number of constituent limb movements. During shape tracing, children with ASD performed accurately with direct visual feedback, but when viewing their hand in a mirror, some children with ASD generated fewer errors than controls whereas others performed much worse. Large mirror drawing errors correlated with hand orientation and hand shape errors in imitation, suggesting that visuospatial information processing deficits may contribute importantly to functional motor coordination deficits in ASD. With kind permission from Springer Science+Business Media: Journal of Autism and Developmental Disorders, Brief Report: Visuo-spatial Guidance of Movement during Gesture Imitation and Mirror Drawing in Children with Autism Spectrum Disorders, 43, 2013, 985-995, Nicole M. G. Salowitz, Petra Eccarius, Jeffrey Karst, Audrey Carson, Kirsten Schohl, Sheryl Stevens, Amy Vaughan Van Hecke, Robert A. Scheidt.

Introduction

Most people easily modify hand movements to compensate for computer mousing errors caused by holding the mouse at an angle. Compensation depends on the brain's ability to adjust the relationship or “mapping” between an intended movement and the motor commands (muscle activities, joint torques) needed to perform it. Most actions are *sensorimotor* in nature in that ongoing task performance is adjusted using sensory information to shape the motor commands needed to compensate for deviations from the intended action. In this way, behavior depends on the integrity of neural mechanisms that process sensory information, those that process motor information and those that bridge the two information sources to generate coordinated action. Children with ASD often exhibit clumsiness (Ghaziuddin and Butler, 1998) as well as abnormalities in sensory information processing (American Psychiatric Association, 2013; Lane et al., 2010; O’Neill and Jones, 1997; Wiggins et al., 2009). While there is conflicting evidence supporting a general coordination deficit in ASD (Ghaziuddin et al., 1994; Rinehart et al., 2001; Rinehart et al., 2006; Gidley Larson et al., 2008; Mostofsky et al., 2004), people with ASD often exhibit specific motor impairments related to movement planning (Rinehart et al., 2001, 2006; Glazebrook et al., 2008; Schmitz et al., 2003), task sequencing (Hill, 2004) and postural control (Molloy et al., 2003; Minshew et al., 2004). We hypothesize that sensory and motor deficits are causally linked in this population, i.e. that abnormal sensory information processing is a direct cause of quantifiable motor coordination deficits.

We used gesture imitation and mirror drawing tasks to compare how autistic and TD children transform visuospatial goals into arm and hand motions. Imitation is a real-life behavior important for social interaction and the development of language skills (Iacoboni, 2005) – two domains that show impairment in ASD (American Psychiatric Association, 2013; Hermelin and O’Connor, 1970). Imitation requires participants to direct visual attention to relevant aspects of a demonstrated movement (i.e. “encoding” see Vivanti et al., 2008), to commit the demonstrated movements and the visuospatial goals they represent to working memory and then to transform such representations into action. It is known that the ability to imitate is impaired in children (Rogers et al., 2003; Stone et al., 1997; Haswell et al., 2009; Ohta, 1987; Bernabei et al., 2003) and adults (Leighton et al., 2008) with ASD (for review see Williams et al., 2001). Because deferred imitation tasks have yielded conflicting results (Rogers et al., 2008; Dawson et al., 1998), the contribution of working memory deficits to impaired imitation is unclear in this population and indeed, imitation tasks alone cannot discriminate between deficits in working memory, sensory information processing, and/or motor execution. In contrast, mirror drawing - when compared to drawing with direct view of the hand - can differentiate deficits in motor execution from deficits in visuospatial information processing underlying the transformation of goals into action. Although mirror-drawing has been studied in adults with ASD including savants and non-savants (Hermelin et al., 1994), this task has not been studied in non-savant autistic children, who constitute the overwhelming majority of children diagnosed with ASD nor has it been used to compare performance of individuals with ASD compared to those without ASD. We hypothesize that children with ASD differ from TD children in how they process sensory information to transform visuospatial goals into action. Moreover, if deficits in visuospatial information processing contribute to performance deficits in imitation, then mirror drawing performance should correlate with performance in imitation.

Methods

Participants

Twenty-seven children participated in this pilot study. Thirteen had diagnoses of ASD [2 female; aged 14.5 ± 1.6 years, mean ± standard deviation (here and elsewhere)] and 14 were TD [3 female; aged 13.1 ± 1.3 years]. Children were recruited using online advertisements and by word-of-mouth within the Marquette University community. All children participated after informed assent and informed parental consent. All procedures were approved by Marquette University's institutional review board in compliance with the Declaration of Helsinki.

Social status was assessed with the Barratt Simplified Measure of Social Status (Barratt, 2006). The ASD and TD subject groups overlapped substantially in age and social status. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971): right-handed ($LI > 40$), ambidextrous ($-40 \leq LI \leq 40$) and left-handed ($LI < -40$). Intelligence quotients (IQ) were measured with the Kaufman Brief Intelligence Test, second edition (KBIT2; Kaufman and Kaufman, 2004). On average, the ASD and TD groups had average intelligence quotients (IQ: 85 to 115) with no difference between groups in verbal ($t_{(24)} = -1.27$; $p = 0.216$), nonverbal ($t_{(25)} = -1.09$; $p = 0.284$) or total ($t_{(24)} = -1.24$; $p = 0.227$) scores. (One TD child was a non-native speaker of English, so his verbal/total KBIT2 scores were dropped). ASD diagnoses were confirmed with the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1994): a total score ≥ 7 confirmed presence of an ASD. Group statistics for age, sex, handedness, social status, KBIT2, ADOS, and medication are presented in Table 3-1.

Table 3-1 Participant Characteristics

Group	Participant	Age	Sex	Laterality	SS	KBIT2 T (V, N)	ADOS T (C, S)	Medication
ASD	1	12.6	M	90	48	87 (84, 93)	10 (4, 6)	-
	2	13.0	M	-54	60	127 (129, 117)	8 (1, 7)	AD, AH
	3	14.7	M	-100	59	104 (87, 119)	14 (5, 9)	S
	4	13.8	M	100	38	81 (89, 78)	17 (6, 11)	AD
	5	11.4	M	100	21	107 (117, 95)	20 (6, 14)	-
	6	15.5	M	30	34	106 (100, 110)	7 (1, 6)	AD
	7	16.4	F	0	45	101 (92, 109)	18 (6, 12)	-
	8	15.8	M	89	42	102 (106, 96)	9 (3, 6)	AC, AP, AD
	9	15.9	M	-18	51	110 (116, 100)	10 (3, 7)	S
	10	15.4	F	100	64	114 (97, 126)	11 (3, 8)	AD
	11	16.1	M	50	61	101 (102, 100)	12 (4, 8)	S
	12	15.1	M	50	22	99 (112, 85)	11 (3, 8)	AD
	13	12.7	M	26	31	115 (117, 108)	7 (2, 5)	AD
	M ± SD	**14.5 ± 1.6**	**-**	**36 ± 64**	**44 ± 14**	**104 ± 12**	**12 ± 4**	**-**
TD	1	13.8	M	0	62	120 (120, 114)	-	-
	2	11.0	F	100	48	94 (95, 95)	-	-
	3	11.6	M	90	62	* (*, 117)	-	-
	4	11.2	F	88	66	139 (130, 139)	-	-
	5	14.5	M	58	66	116 (122, 105)	-	-
	6	13.8	M	79	39	109 (101, 117)	-	-
	7	14.7	M	100	53	104 (101, 105)	-	-
	8	15.3	F	53	42	106 (108, 104)	-	-
	9	12.7	M	88	66	117 (121, 108)	-	-
	10	14.4	M	89	66	109 (111, 104)	-	-
	11	12.5	M	80	18	125 (124, 118)	-	-
	12	12.9	M	79	66	82 (94, 75)	-	-
	13	12.6	M	100	46	116 (105, 122)	-	-
	14	12.8	M	100	32	100 (100, 100)	-	-
	M ± SD	**13.1 ± 1.3**	**-**	**79 ± 27**	**52 ± 15**	**111 ± 14**	**-**	**-**

* indicates non-native English speaking participant

Abbreviations: ASD autism spectrum disorder, TD typically developing, SS social status, KBIT2 Kaufman Brief Intelligence Test, 2nd Edition, ADOS Autism Diagnostic Observation Schedule, V verbal, N nonverbal, T total, C communication, S social, M male, F female, AD anti-depressant, AH anti-hypertensive, S stimulant, AC anti-convulsant, AP anti-psychotic, **M** mean, **SD** standard deviation

Experimental Procedures

Each participant performed two experiments testing visually-guided, goal-directed motor performance in a single session lasting ~30 min. The experiments were designed to evaluate whether motor coordination deficits in ASD arise from deficits in the formation of visuospatial representations of movement goals and/or in the utilization of these representations to guide ongoing movement.

Experiment 1: Gesture imitation

Participants stood and watched a 12-min “interactive” video of a demonstrator who faced the camera and performed a set of 52 different discrete non-meaningful gesture sequences with the hands and arms. Gestures were presented one at a time in video form so that the demonstrated "target" gestures were the same for all participants. Target gestures were comprised of primitive elements including hand shape and sequences of movements with one or both arms. Hand shapes were derived from American Sign Language ("1", "5", "8", "S", "V" and "W") and movements involved one ($n = 38$) or both ($n = 14$) arms. Single-handed movements were made with the demonstrator’s right hand. On average, each gesture’s video clip lasted 5 s. After each clip, the word ‘Copy’ appeared on a black background for 8 s, instructing participants to imitate the gesture they had just observed. Thus, participants were required to commit the demonstrator’s gesture to memory and then use that memory to guide production of their own hand and arm movements. No guidance was provided as to how participants should imitate the gestures, only that they should “do exactly what the demonstrator did” and thus the task was "goal-directed" because the participants' goal was to replicate the demonstrated movement. After imitating each gesture, participants were encouraged to resume a neutral position with arms at their sides. Each participant's movements were videotaped for later analysis of movement kinematics, as described below.

Experiment 2: Shape tracing with direct and mirrored feedback

Participants sat at a desk upon which six sheets of white paper were placed in succession. Each sheet was imprinted with a black outline of a 13 x 13 cm^2 geometric shape (circle, square or 5-point star). The paper was centered along the subject’s midline, with the bottom edge located 10 to 20 cm from his or her torso. Participants were to trace the shape with a blue pen using their dominant hand while the arm rested in a lightweight, low-friction, chair-mounted arm support that minimized tactile feedback within the arm (MASF friction controlled mobile arm support, Jaeco Orthopedic, Inc.). Participants were instructed to start and stop their traces within a gray circle (5 mm diameter) printed on the perimeter of the shape. Each shape was traced twice, once with *direct visual feedback* and once with *mirror feedback*. During direct visual feedback, participants traced with direct view of their hand. During mirror feedback, an opaque shield hovered above the pen, blocking direct view of the hand; participants viewed their hand in a vertical mirror situated opposite their dominant hand, causing leftward motions to appear as moving to the right, and *vice versa*. The order of shapes and viewing conditions was randomized across participants. If participants could not return to the starting position or if they did not comply with task instructions, they were allowed to repeat the drawing. Time to complete each drawing was recorded with a stopwatch. Data from three participants (ASD5, TD2, and TD11) were discarded due to inability or unwillingness to comply with task instructions.

Data Analysis

For gesture imitation, the children's ability to spatially align their limb segments and the motions of these segments with remembered target gestures was analyzed. The demonstrator was viewed from the front (i.e. facing the camera) and thus, target gestures were observed within a spatial reference frame rotated 180º from the subject's body-image reference frame. As such, participants might adopt one of two viable imitation strategies. Participants could assume the demonstrator's perspective (an *anatomical* strategy requiring rotation of the target gestures into the subject's own body-image reference frame) or they could copy the movements as if in a mirror (a *specular* strategy requiring left-right reflection). Each child's videotaped trials were scored for quality in up to five performance categories (not all categories were appropriate for each demonstrated trial; see Table 3-2): 1) *limb selection* (anatomical, specular or unclear); 2) *hand path/sequencing direction* (accurate or inaccurate in accord with limb selection); 3) *number of path strokes* (accurate, greater than or less than demonstrated); 4) *hand shape* (accurate or inaccurate with respect to that demonstrated); and 5) *hand orientation* (accurate or inaccurate). We assumed that hand path/sequencing direction followed the strategy established by limb selection (Medendorp et al., 2005); therefore, path direction accuracy was defined with respect to the limb chosen by the subject for each individual trial. Three raters (first author and two raters who were blind to the study hypotheses and subject groups) evaluated each child's performance in each category. Inter-rater reliability was assessed with Fleiss' kappa and a majority vote of the three raters' scores produced a single score for each trial of each subject. For limb selection, we report the number of children in each group who chose the anatomical limb for the majority of trials. For the remaining four measures, we report the percentage of accurate trials out of the total number of trials per category. Performance measures were compared across groups using Analysis of Covariance (ANCOVA) with age, sex, and medication status (ON- or OFF-meds) as cofactors. Multiple correlation analysis was used to determine if total KBIT2 or ADOS scores correlated with any performance measure for either group.

Table 3-2 Categories of Gesture Imitation

Movement Description			**Scoring Categories**				
	Movement Type	# of Trials *(n)*	Limb Selection *(46)*	Path Direction *(26)*	Path Stroke *(32)*	Hand Shape *(52)*	Hand orientation *(52)*
Unimanual	Raise the hand by bending at the elbow	12	X			X	X
	Push the hand forward	2	X			X	X
	Raise the hand, then open/close the fingers	4	X			X	X
	Abduct/Adduct the fingers	2	X			X	X
	Move the hand about an arc by rotating at the elbow	2	X	X	X	X	X
	Pronate/Supinate the forearm	4	X	X	X	X	X
	Sequentially flex/extend the fingers	2	X	X	X	X	X
	Trace an invisible shape	10	X	X	X	X	X
Bimanual	Alternate rotation of the hands	6			X	X	X
	Move right hand up/down over the stationary left hand	4	X	X	X	X	X
	Move left and right hands in opposing paths	4	X	X	X	X	X

For shape tracing, the children’s ability to minimize error between their drawing and the printed template was analyzed. Drawings were scanned to color JPEG files (200 x 200 dpi) and processed within the MATLAB computing environment (The Mathworks Inc., Natick, MA). Shape templates were separated from pen drawings with a color threshold. Shape templates were low-pass filtered and both images were converted to binary format (`imfilter` and `imcomplement` functions). The lines of each image were thickened (`imdilate` function) using a 9 x 9 square structure element (`strel` function). The centroid of the shape template was identified (`bwlabel` and `regionprops` functions) and 360 equally spaced "sample points" were placed around the template's perimeter. The minimum distance between each sample point and any pixel in the pen drawing was computed and these distances were summed to yield a conservative measure of path error. Movement time and path error were averaged across shapes within participants for each viewing condition.

We analyzed performance separately for the direct viewing and mirror viewing conditions. During direct viewing, movement time and error from both subject groups were normally distributed. Therefore, performance measures were compared across groups using ANCOVA with age, sex, and medication as cofactors. During mirror viewing, data from the TD group were normally distributed whereas data from the ASD group were non-Gaussian with error concentrating on either side of mean ± one standard deviation of the TD distribution. We failed to find an explanation for the multiple modes despite testing whether movement errors were correlated with ADOS and KBIT2 scores. Therefore, to assess whether ASD children differ from TD children in how they transform visuospatial goals into action, we transformed path error and movement time data into |z|-scores (a Mahalanobis distance) on the TD distribution for both subject groups:

$$|z_{ASD}| = \left| \frac{x_{ASD} - \bar{x}_{TD}}{\sigma_{TD}} \right| \qquad [3\text{-}1]$$

$$|z_{TD}| = \left| \frac{x_{TD} - \bar{x}_{TD}}{\sigma_{TD}} \right| \qquad [3\text{-}2]$$

In each case, x corresponds to the independent variable of interest (path error or movement time), subscripts indicate the subject group, whereas $\bar{x}_{TYP}$ and σ_{TYP} are the mean and standard deviation of the TD distribution, respectively. The |z|-scores represent how far movement errors in each group differ from the group average defined by the TD group without considering direction (i.e. lower-than-typical or higher-than-typical). Because Mahalanobis distance is strictly non-negative, the |z|-scores of movement time and path error were normalized prior to statistical testing using a Box-Cox transformation [$\lambda = 0$; BC = ln(|z|)] (Box and Cox 1964). ANCOVA was used to compare group performance in the mirror viewing condition with age, sex, and medication as cofactors. Multiple correlation analysis determined whether total KBIT2 or ADOS scores were correlated with raw performance measures during direct viewing or with normalized

|z|-score measures during mirror viewing. Linear regression evaluated the relationship between the un-normalized tracing error and duration data within each subject group. Finally, linear regression determined whether mirror drawing error could predict un-normalized performance in any of the imitation measures within each group. Statistical tests were performed using Minitab (Minitab, Inc., State College, PA) and SPSS 21 (IBM, Armonk, NY) software. As this was a pilot study, we did not correct for multiple comparisons (i.e. effects were considered statistically significant at a $p = 0.05$ threshold).

Results

Gesture Imitation

Each child responded to each demonstrated gesture. The three raters achieved significant inter-rater reliability ($p < 0.001$) for each of the performance categories: limb selection [98% agreement; $\kappa = 0.97$], path direction [83% agreement; $\kappa = 0.75$], number of path strokes [78% agreement; $\kappa = 0.69$], hand shape [86% agreement; $\kappa = 0.63$], and hand orientation [81% agreement; $\kappa = 0.54$]. Nine out of 13 children in the ASD group and 12 of 14 TD children chose the anatomical limb in at least half of the movements. Compared to the TD group, the ASD group had fewer accurate movements as quantified by: hand shape (52 trials per subject) [TD = 89 ± 7% accurate, ASD = 83 ± 8% accurate; ANCOVA: $F_{(1,22)} = 10.55$, $p = 0.004$], hand orientation (52 trials per subject) [TD = 93 ± 5% accurate, ASD = 77 ± 16% accurate; ANCOVA: $F_{(1,22)} = 29.64$, $p < 0.001$] and correct number of path strokes (32 trials per subject) [TD = 80 ± 7% accurate, ASD = 61 ± 21% accurate; ANCOVA: $F_{(1,22)} = 17.05$, $p < 0.001$] (Figure 3-1). Children in the ASD group were as likely to produce more path strokes than needed as they were to produce fewer path strokes than needed [MORE = 22 ± 23%, FEWER = 17 ± 12%, $t_{(24)} = 0.77$, $p = 0.449$]. Age was a significant cofactor for hand shape accuracy ($F_{(1,22)} = 5.18$, $p = 0.033$) and medication status was significant for hand orientation ($F_{(1,22)} = 9.63$, $p = 0.005$) and number of path strokes ($F_{(1,22)} = 5.14$, $p = 0.033$). Limb selection scores revealed that children did not frequently switch between anatomical and specular strategies when transforming visual goals into motor actions (Figure 3-1a). There was no difference between groups in the choice of hand path direction as defined by the selected limb [TD = 68 ± 11%, ASD = 65 ± 17%;

ANCOVA: $F_{(1,22)} = 0.09$, $p = 0.766$]. Total KBIT2 scores were positively correlated with hand shape performance in the ASD group (Pearson's $r = 0.516$, $p = 0.046$) and positively correlated with hand orientation in the TD group (Pearson's $r = 0.742$, $p = 0.004$).

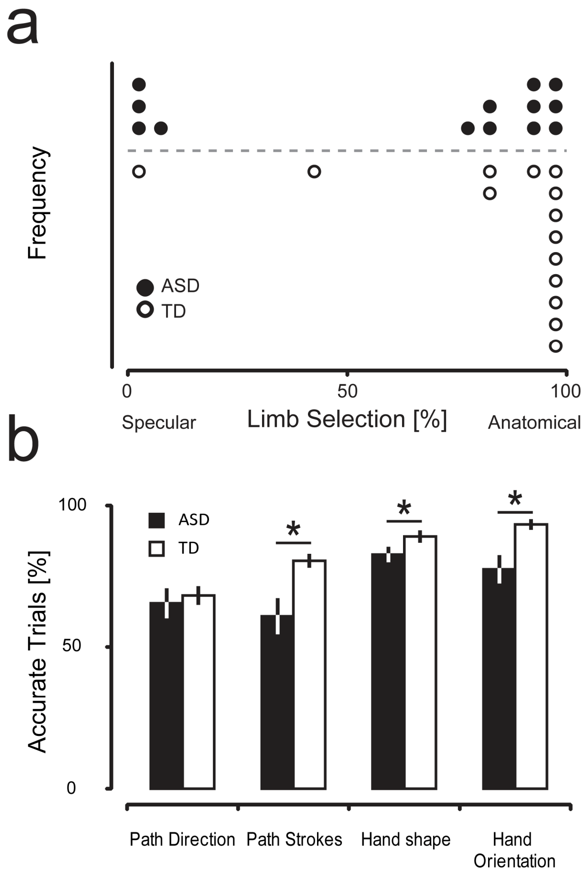

Figure 3-1: Gesture imitation. (a) Dot plot histograms of percent limb selection for ASD participants (filled) and TD participants (open) and (b) mean percentage of accurate movements for children with ASD [filled] and TD children [open] during imitation for each scoring category. Dotted lines indicate separation between groups here and elsewhere. Vertical error bars: ± 1 SEM. * $p < 0.005$.

Five children with ASD but none of the TD children exhibited perseveration in at least one of the movements (i.e. they moved their hand repeatedly along an erratic path). Even though all the demonstration gestures incorporated simultaneous hand shape formation and limb movement, many children in both groups performed gestures using separate postural adjustment and movement phases. That is, they copied the demonstrator's hand shape prior to limb movement while directly looking at their own hand, then they completed the arm movements in a second, distinct phase. For the unimanual gestures, one child in the ASD group repeatedly copied the demonstrator's hand shape with his left hand while watching the demonstration, then made the movement during the 'Copy' screen using his right hand and arm.

Shape Tracing

To address the question of whether the ASD group differed from the TD group in their ability to execute shape-tracing tasks, we assessed group differences in path error (TYP = 985 ± 558 mm, ASD = 819 ± 547 mm) and movement time (TD = 16.1 ± 8.9 s, ASD = 23.1 ± 9.9 s) in the direct viewing condition. We found that when the hand was viewed directly, performance of shape tracing was similar across groups (Figure 3-2) for both path error [ANCOVA: $F_{(1,19)} = 0.97$, $p = 0.337$] and movement time [ANCOVA: $F_{(1,19)} = 2.26$, $p = 0.150$]. No cofactor exerted significant influence over movement time or error.

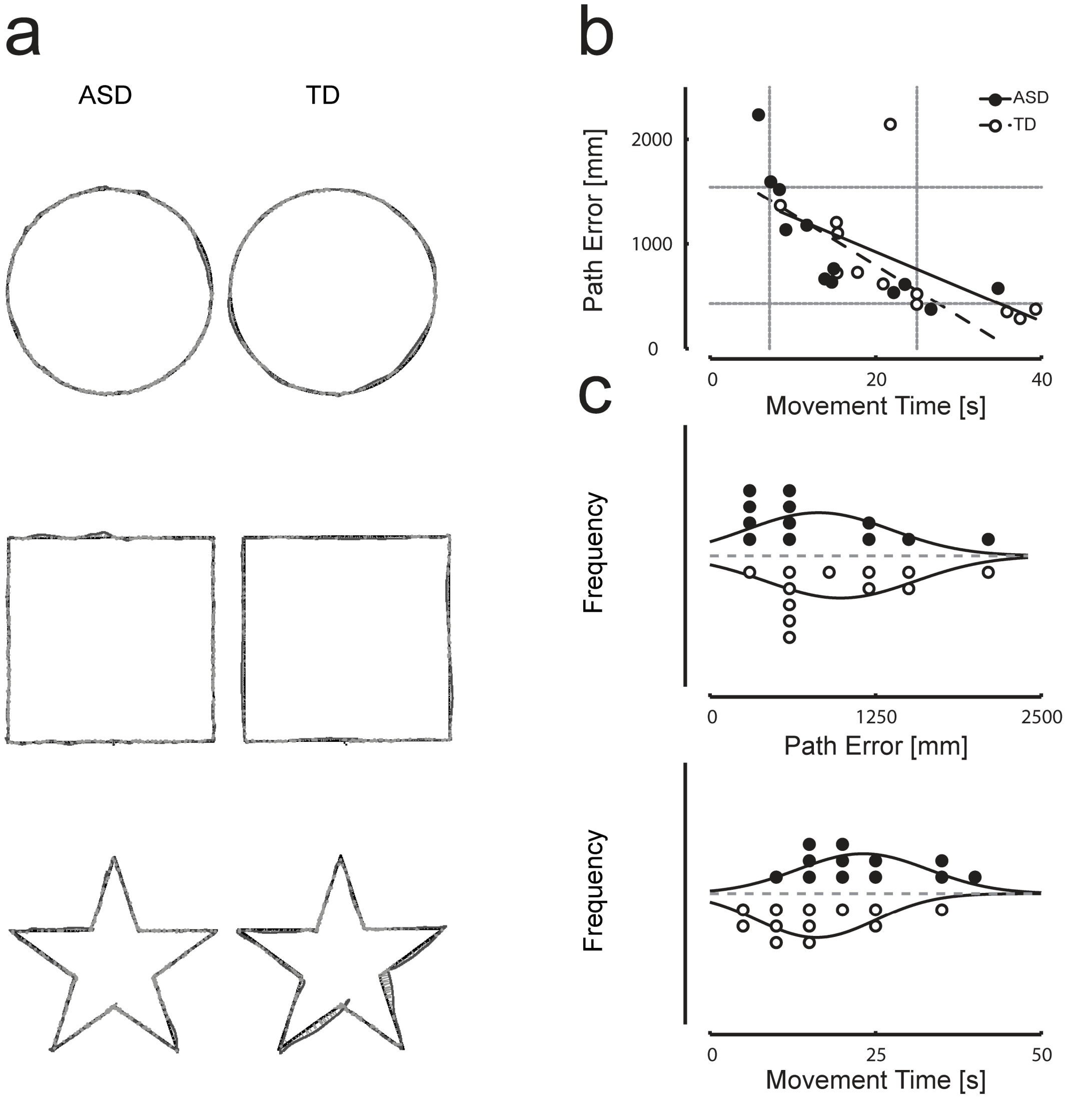

Figure 3-2: Shape tracing (direct view). (a) Drawings [thick, gray lines] and shape templates [thick, black lines] from a representative child with autism (ASD1) and a TD child (TD1). Path error was computed as the sum of deviations [thin, gray lines] from 360 equally-spaced sample points along the template path. (b) Linear regressions of path error as a function of movement time for ASD (filled, solid line) and TD (open, dashed line) groups. Grey dotted lines represent $\bar{x}_{TD} \pm \sigma_{TD}$. (c) Dot plot histograms of path error and movement time.

To determine whether the ASD group deviated from the TD group in their capacity for visuospatial information processing during shape-tracing, we assessed group differences in path error and movement time in the mirror viewing condition. Here, hand path errors and movement times were generally greater than those obtained during direct viewing (Figure 3-3). But whereas path errors were normally distributed in the TD group (3831 ± 2025 mm), the distribution of errors deviated from normality in the ASD group. Only 5 out of 12 ASD participants had path errors within ± 1 standard deviation (SD) of the TD group: 5 were above and 2 were below that range. A similar group-wise difference in the distributions of movement times was also observed. Altogether, 8 of 13 ASD participants had mirror drawing errors and/or movement times outside the range established by the TD group mean ± 1 SD (Fig 3-3B, top).

To quantify how much the ASD group deviated from average TD performance, we converted movement time and path error to |z|-scores in each group and then used a standard Box-Cox transformation [ln(|z|)] to normalize each distribution (see Methods). ANCOVA found that ASD participants generated path errors that were outside the distribution of the TD group during mirror drawing [|z|-scores: TD = -0.51 ± 0.84, ASD = 0.43 ± 1.77; ANCOVA: $F_{(1,19)} = 4.59$, $p = 0.045$]. This outcome lends preliminary support to the hypothesis that children with ASD differ from TD children in how they process sensory information to transform visuospatial goals into action. A separate ANCOVA found no effect of group on movement time. Age, sex, and medication status were not significant cofactors for any |z|-score performance measure.

Path error was correlated with total KBIT2 scores in the ASD group during direct viewing (Pearson's $r = -0.603$, $p = 0.038$) but there was no such correlation between path error and total ADOS scores nor was there a relationship between path error and KBIT2 in the TD group. Movement time was uncorrelated with total KBIT2 scores in both groups and movement time was uncorrelated with total ADOS scores in the ASD group. Path error |z|-scores were correlated with total KBIT2 scores in the TD group (Pearson's $r = -0.761$, $p = 0.007$) but neither KBIT2 nor ADOS scores were correlated with path error |z|-scores in the ASD group during mirror viewing. Movement time |z|-scores were not correlated with total KBIT2 scores in either group and were uncorrelated with ADOS scores in the ASD group. We found an inverse relationship between error and movement time in both groups during direct viewing [TD: $F_{(1,11)} = 16.44$, $t_{(11)} = -4.05$, $p = 0.002$; ASD: $F_{(1,11)} = 6.13$, $t_{(11)} = -2.48$, $p = 0.031$], but not during mirror viewing.

One child with ASD (ASD1) exhibited 'perseverative' movements in which the pen was moved repeatedly in quasi-random motions (Figure 3-3, arrows). Another child with ASD (ASD3) incrementally pivoted the pen and hand while correcting for errors (a motion resembling that of an inchworm); this data was discarded and he repeated the task (without pivoting the hand) on a second day's visit to the lab. In addition, six children with ASD and four children in the TD group periodically 'jittered' the pen during mirror drawing. The three ASD children who had been using stimulants achieved errors within one SD of the mean of the TD group.

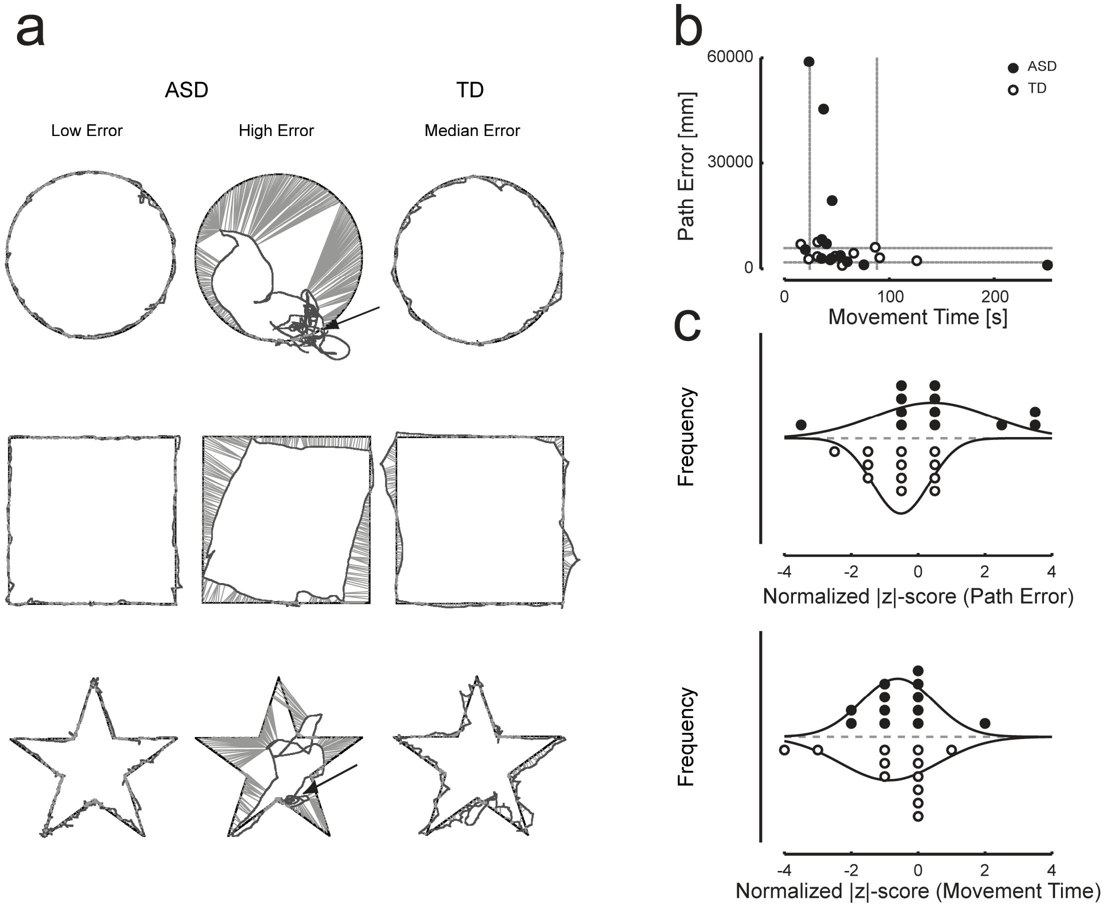

Figure 3-3: Shape tracing (mirror view). (a) Drawings, shape templates and path deviation measures from a representative child with ASD who had low error [left; ASD6], a child with ASD who had high error [middle; ASD1] and a TD child with a median level of error [right; TD1]. Path errors were computed as described in Figure 2. Regions of perseveration are highlighted with arrows. (b) Path error as a function of movement time for ASD and TD groups. Grey dotted lines represent $\bar{x}_{TYP} \pm \sigma_{TYP}$. (c) Dot plot histograms of Box-Cox normalized |z|-scores related to path error and movement time.

We tested the hypothesis that deficits in visuospatial information processing predict imitation performance deficits by evaluating the relationship between mirror drawing error and each imitation sub-score using linear regression for each subject group. Mirror drawing error was correlated with hand orientation during imitation in the TD group (R^2 = 72%, t = 5.13, p < 0.001; Figure 3-4a). A similar relationship was evident for the ASD participants (R^2 = 48%, t = 2.86, p = 0.019; Figure 3-4a) if we exclude the only ASD subject (ASD8) taking anti-psychotic and anti-convulsant medications at the time of the study. Known side-effects of anti-psychotic medications include “unusual movements of your face or body that you cannot control” (MedlinePlus, 2014). We also found that mirror drawing error was correlated with deficits in hand shape formation in the ASD group ($R^2 = 67\%$, $t = 4.31$, $p = 0.002$; Figure 3-4b). Thus, children who produced large mirror drawing errors also made more hand orientation errors in the imitation task in both groups and children with ASD who made large mirror drawing errors also made large hand shape errors during imitation. No other imitation scores were correlated with mirror drawing error.

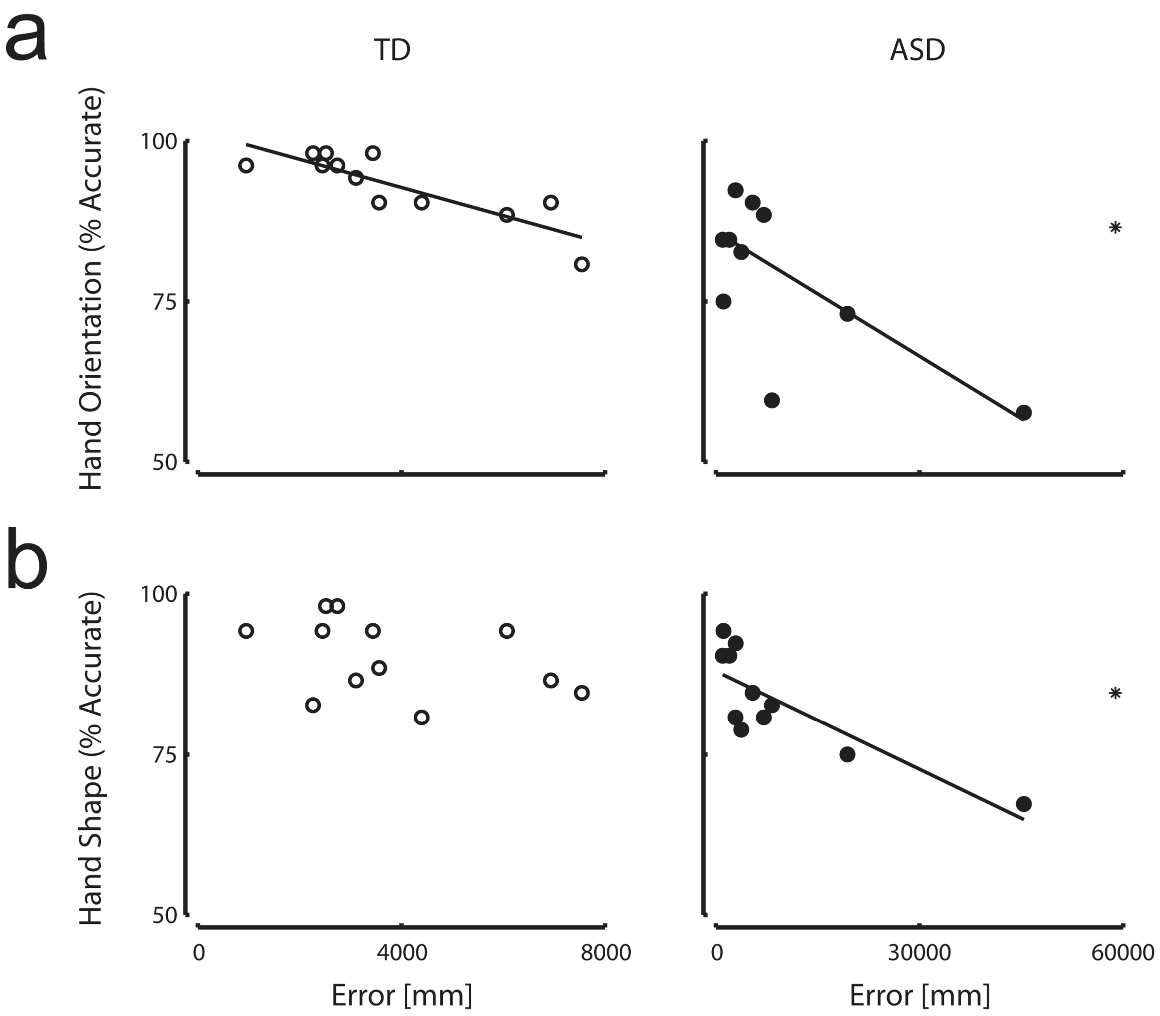

Figure 3-4: Mirror drawing errors correlate with gesture imitation performance. (a) Hand orientation was correlated with mirror drawing error in the TD group (left, open) and the ASD group (right, filled). One child who took three medications (including an anti-psychotic and an anti-convulsant) on the day of the study (ASD8, *) did not perform in a manner consistent with the trend between mirror drawing error and hand orientation established by the TD group and was dropped from the regression. (b) Hand shape was also correlated with mirror drawing error in the ASD group (right, filled).

Discussion

Gesture imitation and mirror drawing revealed abnormalities in the way children with ASD transform visually-specified goals into motor actions. During imitation, children with ASD were less accurate than TD children in replicating hand shape, hand orientation, and number of constituent limb movements. These children likely did not suffer generally from problems with motor execution because they traced shapes with speed and accuracy comparable to that of TD children when viewing the hand directly. However, when viewing the hand in a mirror, the magnitudes of errors in the ASD group were largely outside the distribution of errors made by the TD group. Some ASD participants performed better than TD children whereas others performed much worse. Moreover, mirror drawing error was correlated with hand orientation and hand shape deficits in imitation, suggesting that the ability to adapt to a new sensorimotor transformation was abnormal in children with ASD in both tasks. These results suggest that abnormalities in visuospatial information processing may contribute to functional motor coordination deficits in ASD.

Imitation is an important skill for child development (Rogers et al., 2003) and ability to perform imitation tasks is correlated with social responsivity (Rogers et al., 2003) and expressive language skills (Stone et al., 1997) in children with ASD. Imitation deficits distinguish children with ASD from those with other developmental disorders (Rogers et al., 2003; Stone et al., 1997). Imitation, as studied here, is a complex behavior that requires directed attention and the ability to identify, remember, and execute movements toward visuospatial goals. The deficits we observed during imitation were not likely due to an inability to attend to the instructed task, because each child attempted to imitate every instructed gesture during the cued "copy" interval. During hand shape formation and orienting, the children had to transform a two-dimensional representation of the demonstrator's hand into the three-dimensional configuration of their own hand, and ASD children made more errors than TD children. These aspects of task performance require (but cannot differentiate between) the identification, memorization, and recall of visuospatial goals, as well as execution of actions appropriate to acquire those goals. Reproducing the correct number of hand path strokes during imitation also requires the encoding, recall, and execution of a *sequence* of movements between a *set* of desired spatial goals; ASD children underperformed the TD cohort in this respect as well. In contrast, limb selection was a cognitive choice with no clear "right" or "wrong" classification. Most children (ASD and TD) chose the anatomical limb to perform the instructed gesture in most trials, and given that choice, ASD and TD children were equally consistent in directing limb movements commensurate with their selected strategy. In contrast, Hamilton, et al. (2007) found that young children (ASD and TD) were more likely to use the specular limb in a task that followed an earlier experiment in which mirror imitation was required. Therefore, limb selection may be influenced by prior instructions and practice.

Imitation is also impaired in ASD when visual feedback is unavailable (oral-facial imitation, Rogers et al., 2003). A potential limitation of our imitation task is that we did not evaluate performance without ongoing visual feedback of limb movement and hand shape formation. As such, we cannot determine conclusively whether the imitation deficits we observed were due to deficits in the ability to adapt the visuospatial sensorimotor map needed to transform intended movements into motor commands or whether they were due to deficits in the moment-by-moment visual feedback guidance of an ongoing movement, which relies on that transformation. Future studies should include a condition in which ongoing visual feedback is unavailable.

Mirror drawing is neither typically encountered in daily life nor ecologically relevant, but it can differentiate deficits of attention and motor execution from those of visuospatial representation, particularly when contrasted with shape tracing performance during direct viewing. Group differences in error compensation during mirror viewing were not likely due to general deficits in either attention and/or the ongoing visual feedback guidance of movement (i.e. motor execution) because we found no group differences in shape tracing with direct view of limb movement. However, the pattern of mirror drawing errors we observed suggests differences in how the TD and ASD groups form the sensorimotor maps needed to transform visuospatial goals into motor commands. Participants in both groups periodically “jittered” the pen, presumably in an attempt to identify the novel visuospatial transformation imposed by the mirror. Jittering the pen effectively injects noise into the limb/pen system (Miall et al., 1993) and by monitoring the (visual) consequence of that action, the subject can identify motor commands that achieve the goal under the new visuospatial transformation [i.e. by learning an inverse of the mapping from motor commands onto their kinematic consequences (cf. Liu et al., 2011)].

Viewing the hand in a mirror establishes unusual conflict between how vision and proprioception (muscle-based limb position sense) report the direction of hand movement in response to descending motor commands. Thus another possible strategy to compensate for sensorimotor transformation is to modify the relative contributions of vision and proprioception for motor command updating. During mirror drawing, if proprioception is blocked transiently (transcranial magnetic stimulation: Balslev et al., 2004) or chronically (deafferentation: Lajoie et al., 1992) adults perform with less error than when proprioception is available. Previous research (Hermelin and O'Connor, 1970) has shown that sensory dominance and integration are abnormal in children with ASD. Thus, a plausible explanation for differences in mirror drawing seen here is that some children with ASD favored visual cues and were thus better able to reduce errors (Figure 3-3a, 'Low Error') while others ignored visual errors in favor of proprioceptive cues, thereby producing large errors during mirror drawing (Figure 3-3a, 'High Error'). Future studies of visuospatial learning in ASD should include assessment of visuo-proprioceptive bias, which might help explain the elevated motor performance variability observed in this participant group.

Importantly, abnormalities in mirror tracing in ASD predicted deficits of hand orientation and hand shape during imitation, raising the possibility of a common etiology of errors in the two tasks. Imitation and mirror drawing engage the frontal lobes [Brodmann area 45 (Iacoboni, 2005) and dorsolateral prefrontal cortex (Imamura et al., 1996)], which are important for executive function and which exhibit anatomical and functional abnormalities in children with ASD (Courchesne and Pierce, 2005b). It is likely that physiological abnormalities of the frontal lobes contribute importantly to visuospatial performance deficits in ASD. Rumiati, et al. (2004) propose that imitation, specifically, involves distinct neural processes involved in the recall and execution of over-learned "meaningful" actions and the transformation of novel but "meaningless" visuospatial targets into actions. Our study only involved reproduction of "meaningless" actions and so we feel our findings can only speak to possible impairment of the dorsal processing stream identified by Rumiati, et al. (2004), which includes brain regions thought to be involved in the representation of visual goals in proprioceptive coordinate frames (i.e. parietal association areas; cf. Grefkes et al., 2004) as well as areas more directly involved in goal-directed action (PMv and primary motor cortex).

In summary, the results of this pilot study support the hypothesis that impaired visuospatial information processing is a cause of functional coordination deficits in children with ASD. Future studies should be conducted to test these preliminary findings in a larger cohort of ASD participants using experimental approaches specifically designed to quantify the ability to process visuospatial information during goal-directed movement while controlling for abnormalities (and/or bias) in multimodal sensory integration.

CHAPTER 4: SENSORIMOTOR ADAPTIVE AND VOLITIONAL STRATEGIC COMPENSATION FOR SENSORIMOTOR DISCORD DURING GOAL-DIRECTED MOVEMENTS IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND TYPICALLY DEVELOPING CHILDREN

Eleven children with autism spectrum disorder (ASD) and nine typically developing (TD) children performed goal-directed reaching and tracking tasks with sensorimotor distortion. Both tasks assessed participants' abilities to reorganize the relationship between spatial goals and the motor commands needed to acquire them. Children grasped the handle of a robotic device as it recorded hand position, and they watched a screen which displayed visual feedback and task instructions. Two versions of the reaching task were performed, which differed in the type of distortion between visual feedback and motor commands: during *incremental rotation*, cursor feedback was gradually rotated up to a maximum value of 30° over many trials and required automatic sensorimotor adaptation; whereas during *sudden reflection*, cursor feedback was immediately reflected about the participant's midline and required volitional strategic compensation. Children also tracked a moving target, which varied in the amount of temporal and spatial information available for planning, and which was subjected to the *sudden reflection* feedback condition. During the reaching task with small, incrementally-imposed rotations, we found subtle differences in initial hand path errors between groups, suggesting ASD-related deficits in automatic sensorimotor adaptation. During the reaching and tracking tasks with suddenly-imposed reflection, we found significant differences in hand path errors between groups, suggesting ASD-related deficits in volitional strategic compensation. We found no difference across groups in movement kinematics for reaching or tracking experiments, suggesting that deficits in feedforward planning were unrelated to movement execution in general. These findings suggest that children with ASD are impaired in their ability to use feedforward control to update their motor commands in response to novel sensorimotor transformations.

Introduction

Many everyday tasks require movements of the hand to acquire a physical goal. For example, we reach to a stationary target such as a tissue, or we track a moving target such as a toddler's hand to prevent her from touching a hot surface. Most people easily modify hand movements to compensate for sensorimotor disturbances, such as a gust of wind, which moves the tissue, or a change in the direction of the toddler's hand. Compensation depends on the brain's ability to adjust the relationship or "mapping" between an intended movement and the motor commands (muscle activities, joint torques) needed to perform it. The transformation must be amenable to change via volitional strategies (e.g. to observe and imitate the actions of another person, or when large visuomotor distortions are imposed suddenly) or via automatic sensorimotor adaptation (e.g. to cope with changes in limb length during growth or when small visuomotor distortions are imposed incrementally). Imitation, for example, requires compensation for the transformation between the intended movement represented in the demonstrator's coordinate system and the motor commands represented in one's own body-centered coordinate system. Imitation is impaired in children (Salowitz et al., 2013, Rogers et al., 2003; Stone et al., 1997; Haswell et al., 2009; Ohta, 1987; Bernabei et al., 2003) and adults (Leighton et al., 2008) with ASD (for a review, see Williams et al., 2001). Imitation deficits might be the result of deficits in the ability to compensate for sensorimotor transformations requiring reflections or other large visuomotor distortions.

Redding and Wallace (1997) have identified two mechanisms which are used to compensate for sensorimotor discord. Volitional strategic compensation or "controlled processing" (cf. Redding and Wallace, 1997) is a high-level process which requires attention to select a single strategy from several available movement plans. In contrast, automatic sensorimotor adaptation or "automatic processing" (cf. Redding and Wallace, 1997) is invoked in response to predictable movements, such that feedforward control is used to maintain accurate performance during subtle sensorimotor discord. Systematically perturbing the relationship between sensory feedback and motor command updating allows us to measure the ability to compensate for sensorimotor discord. For example, if visual feedback is incrementally rotated about a central home position during reaching movements of the hand (Kagerer et al., 1997; Klassen et al., 2005), errors would be subtle, such that participants would automatically adapt their movements to compensate for small sensorimotor discord. However, if visual feedback is reflected about the person's midline during reaching (Cunningham and Pavel, 1991) or pursuit tracking (Grigorova and Bock, 2006), errors would be large and noticeable and would require a different strategy for each movement direction, thus volitional strategic compensation would be required to perform the movement.

Two independent research groups (Kagerer et al., 1997; Klassen et al., 2005) have characterized visuospatial compensation during two types of reaching experiments, which differed in the way visual feedback rotations were presented (incrementally over many trials or suddenly). Participants made reaching movements while moving a pen on a digitizing tablet (Kagerer et al., 1997) or while moving a robotic manipulandum (Klassen et al., 2005), such that hand paths were recorded. One group of participants was exposed to a visuospatial rotation that was applied incrementally over many trials and the other group of participants was exposed to a visuospatial rotation that was applied suddenly. When visual feedback was rotated incrementally, reaching errors were small, even at the end of training when the rotation reached its maximum (Kagerer et al., 1997; Klassen et al., 2005). When visual feedback was rotated suddenly, large obvious reaching errors were generated at the start of visuospatial distortion, then decreased with training (Kagerer et al., 1997; Klassen et al., 2005); however, reaching errors at the end of training remained higher than those produced when rotations were applied incrementally (Kagerer et al., 1997). Following both types of visuospatial distortion, Kagerer and colleagues (1997) also included trials in which visual feedback suddenly returned to veridical coordinates. They found that reaching errors during this post-exposure phase (i.e. aftereffects) were larger for the group exposed to incrementally-imposed rotation compared to the group exposed to sudden rotation. The presence of large and persistent aftereffects suggested that automatic sensorimotor adaptation was used to compensate for rotations that were applied incrementally (Redding and Wallace, 1997). In contrast, aftereffects which quickly decreased upon removal of visuospatial conflict suggested that volitional strategies were used to compensate for a rotation that was applied suddenly (Redding and Wallace, 1997). In another study, Sekiyama and colleagues (2000) examined hand movements after participants wore left-right reversing spectacles for more than a month. They found that healthy adults learned to compensate for the reflection of visual feedback within two weeks, such that error and latency returned to pre-exposure levels. Interestingly, the error and latency of hand movements quickly returned to pre-exposure levels one day after the spectacles were removed. Thus, aftereffects quickly returned to baseline levels, suggesting that volitional control strategies were also used to compensate for sudden application of visuospatial reflection.

Not only can we characterize volitional strategic compensation during reaching movements of the hand, but we can also identify volitional strategies during continuous tracking movements in which the target is represented by a single cursor, which moves about an unpredictable path. Tracking tasks can be used to characterize on-line corrections or submovements which are required to bring the hand into alignment with the moving target (Miall et al., 1993; Roitman et al., 2004; Pasalar et al., 2005; Miall and Jackson, 2006). During simple tracing, the entire goal path is provided to allow motor plan updating of future goal states (cf. Salowitz et al., 2013), however, the exact positional goal of the current time step is ambiguous. Tracking and simple tracing can be combined such that the exact positional goal of the current time step is indicated by a single cursor, but future goal states are also provided with additional cursors. We hypothesize that variations in the amount of spatial information related to current and future target positions will influence motor planning. Furthermore, by introducing variations in the speed of the moving target, we can examine the effect of temporal information on movement planning.

Here, in a series of three experiments, we recorded hand paths while children with ASD and TD children moved the handle of a horizontal planar robot to capture stationary or moving visual targets in tasks we will refer to as reaching and tracking, respectively. We manipulated the correspondence between the hand's actual spatial location and that of a cursor representing the hand using sudden visuomotor reflections or gradual visuomotor rotations to quantify the contributions of volitional strategic compensations and automatic sensorimotor adaptation to visuo-proprioceptive reference frame recalibration. In two sets of experiments, the children made out-and-back reaching movements to eight spatial targets that were distributed evenly around a central starting location. After a period of initial practice, wherein the children acquired proficiency capturing the targets with an honest cursor, visual perturbations were small and incrementally-imposed (requiring automatic sensorimotor adaptation) or large and suddenly imposed (requiring volitional strategies). In the third experiment, children tracked fast- and slow-moving targets that were designed to provide controlled amounts of information about the target's future trajectory. After an initial period of practice, visual feedback was reflected about the participant's midline. We compared hand path errors from each of these three experiments across participant groups to test the hypotheses that children with ASD exhibit an impaired ability to automatically adapt to sensorimotor distortions (reaching task with incrementally-imposed rotations) and to select strategies for compensation (reaching and tracking tasks with suddenly-imposed reflection). We compared movement characteristics from each of these experiments across groups to test the hypothesis that children with ASD exhibit deficits in movement execution. Taken together, these experiments determine the extent to which children with ASD are impaired in their ability to use ongoing visual feedback to adjust movement plans to compensate for novel sensorimotor coordinate transformations.

Methods

Participants

Eleven children with ASD [aged 15.7 ± 1.3 years (mean ± standard deviation); one female] and 9 TD children [aged 14.3 ± 1.6 years; two female] participated in this study, which received institutional approval from Marquette University in compliance with the Declaration of Helsinki. All children participated after giving informed assent and after obtaining informed parental consent. Upon enrollment, parents of children in both groups were asked to complete the Child Behavior Checklist for ages 6-18 (CBCL; Achenbach and Rescorla, 2001). Parents were also asked to complete a questionnaire to report their child’s medication use and to report parents’ or caregivers’ occupations and highest educational degrees [which were used to determine social status with the Barratt Simplified Measure of Social Status (Barratt, 2006)]. Additionally, parents of children who did not have a prior diagnosis of ASD were asked to complete the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers et al., 1999); children receiving a total score > 13 on the ASSQ exhibited behaviors characteristic of ASD and were therefore excluded from the study. Prior diagnoses of children in the ASD group were confirmed using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1994): a total score ≥ 7 confirmed presence of ASD. Children in both groups were administered the Kaufman Brief Intelligence Test, second edition (KBIT2; Kaufman and Kaufman, 2004) to measure intelligence quotients (IQ). Only high-functioning children (verbal IQ > 70) were included in the study. Each child's handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), which yielded a laterality index (LI) score to determine whether participants were predominately right-handed (LI > 40), left-handed (LI < -40) or ambidextrous (-40 ≤ LI ≤ 40). Participant characteristics are shown in Table 4-1.

Each child participant completed three separate reaching and tracking experiments within two separate testing sessions, which were spaced >5 days apart. Two of the experiments required participants to perform discrete reaching movements; one of these required compensation for a suddenly-imposed visuomotor reflection, whereas the other required compensation for the slow incremental imposition of a visuomotor rotation. The third experiment required participants to perform a pursuit tracking task, which also required compensation for a suddenly-imposed visuomotor reflection. All participants performed the reaching task with reflection in one experimental session and all performed the reaching task with incremental rotation and the tracking task with sudden reflection in the other session. The order of experimental sessions was counterbalanced across participants. Each participant also completed a brief control test wherein we measured simple and choice reaction times. This test was always performed at the beginning of the first day of testing.

Table 4-1 Participant Characteristics

Group	Participant	Sex	Age (years)	Laterality	SS	KBIT2 T (V, N)	*ADOS/ASSQ T (C, S) / T	Medication
ASD	A1	M	13.1	26	31	115 (117, 108)	7 (2, 5)	AD
	A2	M	16.7	89	32	102 (106, 96)	9 (3, 6)	AC, AP, AD
	A3	F	17.3	0	45	101 (92, 109)	18 (6, 12)	BC, AH, AD
	A4	M	17.0	50	61	101 (102, 100)	12 (4, 8)	AD
	A5	M	14.0	88	48	131 (135, 118)	10 (4, 6)	ST, AD
	A6	M	16.4	78	53	96 (100, 92)	7 (2, 5)	ST, AP, AH, AC, CD
	A7	M	15.3	-100	59	104 (87, 119)	14 (5, 9)	AD, AP
	A8	M	15.6	53	47	117 (107, 122)	7 (3, 4)	-
	A9	M	16.2	71	47	122 (112, 125)	13 (3, 10)	ST, AH
	A10	M	14.6	41	53	121 (132, 104)	7 (3, 4)	-
	A11	M	16.7	100	43	102 (104, 98)	8 (2, 6)	-
	M ± SD		**15.7 ± 1.3**	**45 ± 57**	**47 ± 10**	**110 ± 11**	**10 ± 4**	
TD	T1	F	16.0	53	42	106 (108, 104)	0	-
	T2	M	15.5	0	62	120 (120, 114)	0	-
	T3	M	13.1	80	63	125 (124, 118)	4	-
	T4	M	13.5	79	66	82 (94, 75)	2	-
	T5	M	13.3	100	32	100 (100, 100)	0	-
	T6	M	13.2	100	46	116 (105, 122)	1	-
	T7	M	15.5	58	66	116 (122, 105)	0	-
	T8	M	16.5	70	43	119 (118, 114)	0	-
	T9	F	12.2	88	66	139 (130, 139)	0	-
	M ± SD		**14.5 ± 1.6**	**71 ± 29**	**53 ± 13**	**114 ± 15**	**0.7 ± 1.3**	

Abbreviations: ASD autism spectrum disorder, TD typically developing, SS social status, KBIT2 Kaufman Brief Intelligence Test, 2nd Edition, ADOS Autism Diagnostic Observation Schedule, ASSQ Autism Spectrum Screening Questionnaire, T total, V verbal, N nonverbal, C communication, S social, M male, F female, AD anti-depressant, AC anti-convulsant, AP anti-psychotic, BC birth control, AH anti-hypertensive, ST stimulant, CD central nervous system depressant, **M** mean, **SD** standard deviation
* ADOS reported for ASD; ASSQ reported for TD

Experimental Setup

Seated participants made goal-directed reaching and tracking movements while holding the handle of a custom two-joint robotic manipulandum with their dominant hand (Figure 4-1a). The arm was supported against gravity using a light-weight chair-mounted support (Jaeco Orthopedic, Hot Springs, AR). Task instructions, visual stimuli, and performance feedback were projected onto a horizontal screen located above the plane of movement. Direct view of the arm was blocked by the video display screen and by a smock draped over the arm and shoulders. Robot handle position was recorded by two encoders (A25SB17P180C06E1CN, Gurley Precision Instruments; Troy, NY) at a rate of 200 Hz and mapped onto a cursor (0.5 cm diameter white circle) on the screen. The visual display was updated at a rate of 40 Hz.

Robot control and post-processing of data were performed within the MATLAB computing environment (The Mathworks Inc., Natick, MA).

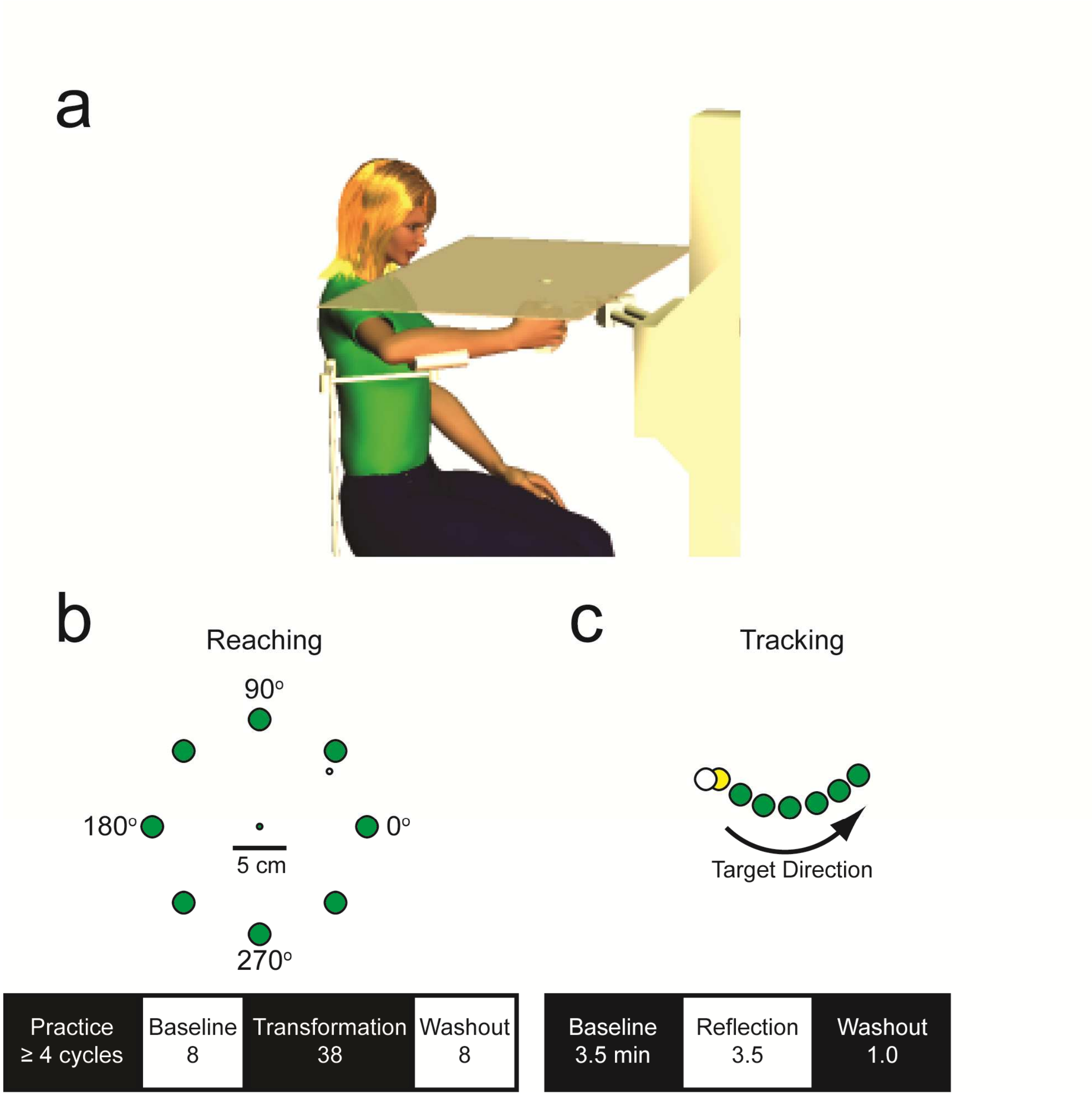

Figure 4-1: Experimental apparatus and procedure. (a) Participants moved the handle of a robotic manipulandum to control a cursor on a screen (b) Following practice, children completed four blocks [bottom] of reaches to one of eight targets [large circles] from a central ‘home’ position [small circle] (c) Children completed 3 trials [bottom] of tracking a single target [yellow circle] or a single target with leading indicators [green circles] along a pseudo-random path at two different goal speeds.

Procedures

Goal-Directed Reaching Experiments

We designed two experiments that sought to quantify the ability of TD children and children with ASD to invoke strategic compensatory strategies and sensorimotor adaptive compensations during a reaching task that required visuo-proprioceptive reference frame recalibration. “Out-and-back” reaching movements began and ended within a central home target (0.5 cm diameter green circle) that was visible during the entire experiment and was centered along the participant’s midline. For each movement (trial), participants were to capture one of eight goal targets (2 cm diameter green circle) at the moment they reversed movement direction. Goal targets were distributed evenly around the perimeter of a circle (10 cm radius) concentric with the home target (Figure 4-1b). The sequence of goals was pseudo-randomly ordered such that each goal was presented once per cycle of 8 trials. We required the hand (and cursor) to be held within the home target for 100 ms prior to the generation of a “GO” signal that was subject to an additional delay (pseudo-randomly selected from a uniform distribution with a mean of 2.1 s and a range of 1.0 s to 3.3 s). The “GO” cue consisted of the simultaneous presentation of one of the visual targets and a 100 ms audio tone. Participants were to “move the cursor to the target and return home in one smooth motion”.

Prior to data collection, participants completed at least 4 practice cycles to gain familiarity with the robotic device and the task requirements. Participants then completed 432 trials in a series of three blocks that lasted approximately 45 minutes: 8 cycles of *baseline* with veridical cursor feedback; 38 cycles of *transformation* with one of two distortions applied to the cursor (see below); and 8 cycles of *washout* trials with veridical feedback. The two reaching task experiments differed in the way visual distortions were applied to the cursor during the transformation block. In the *incremental rotation* experiment, motion of the cursor was rotated slowly in the counter-clockwise direction about the home target with respect to the actual motion of the hand. The rate of rotation was 1° per cycle during the first 30 cycles of the transformation block (30° maximum rotation). The visuomotor distortion was then held constant at 30° counter-clockwise rotation for the remaining 8 cycles, which allowed us to assess steady-state performance in response to the rotation. The applied rotation was the same across target locations; therefore, we anticipated that compensation strategies would be similar across all eight target directions. Importantly, the incremental rotation was designed to be small and imperceptible such that the participants’ compensatory response would favor automatic sensorimotor adaptation over voluntary (cognitive) strategic compensations (Kagerer et al., 1997; Redding and Wallace, 1997)[1]. In the *sudden reflection* experiment, the x-coordinate of the cursor was reflected across the participant's midline during the transformation block, whereas the cursor's y-direction motion remained veridical throughout the entire experiment (cf. Grigorova and Bock, 2006). Reflection is a novel, conspicuous transformation that requires participants to develop different compensation strategies for four different types of targets: vertical targets required no transformation of the movements performed in baseline testing; horizontal targets required a 180° reversal; and diagonal targets required 90° rotations in the clockwise direction for the lower right and upper left targets and in the counter-clockwise direction for the upper right and lower left targets. We were interested in how participants would use volitional (cognitive) strategies to compensate for large, observable direction-dependent distortions; thus, participants were informed: "Sometimes the cursor will move to the left when you move your hand to the right and *vice versa*".

In both reaching experiments, we removed visual feedback entirely during some baseline and transformation block trials. These 'blind' trials were randomly interspersed at a rate of 1 per cycle and were used to evaluate the influence of visual feedback on hand position early in the movement trajectory. Similarly, we applied a single-trial impulse of the visual distortion (30° rotation or x-coordinate reflection) at a rate of 1 per cycle during the baseline block. These 'catch' trials were used to measure kinematic performance characteristics during initial exposure to the full visuomotor perturbations to be experienced later in that experiment.

Trials were considered successful if the end-of-movement cursor position was within 1.25 cm of the goal and if the maximum speed during the outward movement was between 30 and 70 cm/s. Successful trials were rewarded with a high-pitched tone and the goal turned white. Unsuccessful trials were punished with a low-pitched tone and the goal turned yellow. Participants were encouraged to return to the home

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[1] The rate of rotational increment during *incremental rotation* was designed to be imperceptible to participants. During a pilot study, we tested increments that were less than the standard deviation of initial direction error (IDE) averaged across baseline cycles (SD = 9°) of a healthy adult. For increments of 2° per cycle of 8 movements, initial direction error decreased during the constant 30° rotation cycles suggesting that adaptation was incomplete at the end of the transformation block; however an increment of 1° per cycle of 8 movements was imperceptible to the participant and led to stable performance during the constant 30° rotation phase.

position within 1.25 s of movement onset. Failure to do so resulted in a “Too Slow” warning above the home target.

Pursuit Tracking Experiment

We anticipated that the reaching task described above might reveal deficits in voluntary strategic control in children with ASD. This experiment therefore sought to challenge the ability of TD children and children with ASD to integrate visual information of upcoming target motions into the ongoing sensorimotor control of a tracking task that required strategic compensation for a sudden reflection of the visuo-proprioceptive reference frame. We recorded hand paths while participants used a cursor to track a moving target, which followed an unpredictable and unseen path. Participants completed four blocks of three trials each: 3.5 minutes of *baseline* tracking with veridical cursor feedback to allow participants to learn the task; 3.5 minutes of *reflected* cursor feedback to evaluate strategic compensation as a function of movement direction; and 1 minute of *washout* with veridical cursor feedback to allow the visuospatial mapping to return to normal before proceeding with the next block. Participants were encouraged to rest after each block. To encourage voluntary strategic compensation, participants were told “the cursor will move to the left when you move your hand to the right and vice versa” prior to trials in which the reflection was applied.

At the start of each trial, the target (0.5 cm diameter yellow circle) appeared at the center of the screen (the ‘home’ position) and remained stationary until the participant moved the cursor within 0.5 cm of the home position for 500 ms. Once alignment was achieved, the target began to move at one of two constant speeds along a predefined pseudo-random path and participants were to maintain alignment between cursor and target by moving the robot handle. The target path was constructed such that the target returned to the home position at the end of each trial, whereupon the participant was given a 5 s break. The target path was the same in baseline and reflection trials and was computed as a sum of sinusoids with frequencies of 0.06, 0.11, and 0.13 rad/s for x and y with amplitudes ranging between -0.5 cm and 0.5 cm and phase shifts of 0 or $\pi/2$ rad (cf. Miall and Jackson, 2006).The target path during the washout trial was computed similarly as a sum of sinusoids with frequencies of 0.08 and 0.10 rad/s for x and y with the same range of amplitudes and phase shifts as in baseline and reflection.

The four trial blocks differed in the amount of spatial information that was available for planning and in the amount of time participants had to capitalize on that information. The target had one of two possible configurations: a *single* yellow cursor (0.5 cm diameter) or a yellow cursor with 7 equally-spaced green *leading indicators* (each 0.5 cm diameter) placed in front of the target on the path. The leading indicators provided a controlled amount of spatial information that participants could use to guide ongoing tracking movements (Figure 4-1c). The visual effect of adding the leading indicators was to transform the cursor into a caterpillar that marched about the screen. Participants were instructed to “follow the caterpillar’s tail by keeping the cursor over the yellow goal target”. Because the path of the target was random, the leading indicators showed the direction in which the caterpillar was going to move, thus providing information about future goal states. That is, the leading indicators provided spatial information that could be used to strategically plan upcoming compensatory movements based on the direction of future cursor movements. The target could also move at two possible speeds: *slow* (2.5 cm/s) or *fast* (5 cm/s). In both cases, the length of the caterpillar at each speed was designed to be at least twice the participant’s choice reaction time (determined from the control experiment described below). The four trial blocks included all combinations of movement speed and cursor configuration: slow/single cursor; slow/leading indicators; fast/single cursor; and fast/leading indicators. Trial block order was counterbalanced across participants. The tracking experiment was performed within the same session as the reaching experiment with incremental rotation so as to reduce the likelihood of interaction with the reaching experiment involving sudden reflection, which was performed in the other session. The order of experimental sessions was counterbalanced across participants.

Reaction Time Testing

Each child participated in a control experiment at the beginning of the first day of testing, to quantify two forms of reaction time (simple, choice) using variations on a button-press task. Participants held a computer mouse with their dominant hand while viewing a 19” computer monitor (viewing distance:

~60 cm), which displayed a visual stimulus (a 4 cm diameter red circle, centered along the vertical dimension of the screen). The visual stimulus could appear in the middle of the display during evaluation of *simple* reaction times, or 12 cm to either side of a thin, vertical, midline during evaluation of the *choice* reaction time. During evaluation of the *simple* reaction time, participants were instructed to “press the mouse button with your index finger as soon as you see the circle”. Right-handed participants pressed the left mouse button and left-handed participants pressed the right mouse button. During evaluation of the *choice* reaction time, participants were instructed to “press the left button as soon as possible if the stimulus appears to the left of midline or the right button if the stimulus appears to the right of the line”. The order of left/right stimuli presentations was pseudo-randomized such that half of the stimuli appeared on each side of the screen. In both tasks, reaction time was defined as the time between stimulus onset and button press. The interval between stimulus presentations was selected pseudo-randomly from a uniform distribution (with a mean of 4.5 s and a span of 3 to 6 s).The order of assessment of simple and choice reaction times was randomized across participants. Twenty-one trials were presented in each simple or choice reaction time task. We used the estimate of choice reaction time to customize the cursor with leading indicators for each individual participant in the Tracking Experiment.

Data Analysis

Instantaneous hand position was recorded at 200 samples/s using 17-bit rotational encoders mounted on the robot’s motors. Hand paths had a spatial resolution better than 0.2 mm and were low-pass filtered using a second-order zero-lag Butterworth filter with 10-Hz cutoff frequency before computing hand velocities. Velocities were filtered similarly before computing hand accelerations.

Reaching Experiments

Movement kinematics were plotted and visually-inspected; trials where the hand failed to move > 3 cm from the home target were removed from further analysis. Only the outward strokes of the out-and-back movements were analyzed.

We identified several kinematic features using an automated algorithm within the MATLAB programming environment. Each was verified visually and manually adjusted if necessary. *Movement onset* was identified as the moment when the hand velocity first exceeded 5 cm/s at the beginning of a trial. *Initial direction error (IDE)* was computed as the angular difference between an ideal movement vector (directed from the cursor's position at movement onset to the goal) and the initial direction vector directed from the cursor's position at movement onset to its position 80 ms later. Because ideal compensation for a reflection transformation depends on target location (cf. Cunningham and Pavel, 1991), we anticipated that the sign of initial direction errors (+: clockwise; -: counter-clockwise) would depend on target location. We therefore used the absolute magnitude of IDE for the reaching task with sudden reflection and we used the signed IDE for the reaching task with incremental rotation to characterize the feedforward reach plan prior to corrections made with visual feedback (Kagerer et al., 1997), which is delayed approximately 90 ms in primates (Andersen and Cui, 2009). *Movement offset* was identified as the moment when the hand reversed direction (i.e. returned toward home). We computed *aspect ratio (AR)*, as the ratio between the cursor's maximum deviation from a line drawn between its locations at movement onset and offset to the length of that line (i.e. deviation/extent).

We quantified *movement smoothness* during reaching movements using a method developed by Fishbach and colleagues (2005) to measure the temporal symmetry (SYM) of the velocity profile:

$$SYM = \frac{\sum_{i=1}^{T_v-1} V(T_v - i) - \sum_{i=1}^{T_v-1} V(T_v + i)}{\sum_{i=1}^{T_v-1} (V(T_v - i) + V(T_v + i))} \qquad [4\text{-}1]$$

where V is velocity and T_v is the time of peak velocity. A SYM value of zero indicates perfect symmetry of the velocity profile about its peak, whereas positive and negative values indicate velocity profiles skewed toward the acceleration or deceleration phase, respectively.

The time to select and prepare reaching movements was estimated by *reach reaction time (RRT)*, defined as the interval between GO Cue and movement onset. The time to execute movements was estimated by *reach movement time (RMT)*, defined as the interval between movement onset and movement offset. Prior to statistical hypothesis testing, we computed within-subject averages for each of the five performance measures (IDE or |IDE|, AR, SYM, RRT, and RMT) within three experiment phases: eight cycles of ***baseline*** movements (excluding each catch trial and the trial immediately following it in the trial sequence); the last eight cycles of transformation (***late training***); and the first cycle of washout (***post-exposure***). Only the first cycle was included in the post-exposure block because aftereffects are known to dissipate quickly following volitional strategic compensation (Contreras-Vidal et al., 2005; cf. Kagerer et al., 1997).

Pursuit Tracking Experiment

We filtered hand position data (10 Hz low-pass) prior to re-sampling at the visual display rate of 40 Hz to facilitate quantification of tracking performance. At each resulting time step, *Euclidean Error* was computed as the vector pointing from cursor to target. *Lag Error (LE)*, our primary performance measure in this experiment, was defined as the component of Euclidean Error along the direction of the target's instantaneous motion. We also computed *Orthogonal Error (OE)*, defined as the component of Euclidean Error perpendicular to the target's instantaneous direction of motion. Whereas LE provides a measure of tracking performance that is sensitive to sensory feedback delays and the ability to compensate for them using predictive control, OE provides a general measure of performance error that is independent of instantaneous target motion, due to the random nature of the target's path. We analyzed only baseline and reflection trials in detail (washout trials were not examined), and performance variables were computed using data from just the second half of each trial (after steady state performance had been achieved).

We next sought to quantify the occurrence and efficacy of discrete corrective submovements that may have occurred during tracking. We identified discrete corrective submovements using the method of Roitman and colleagues (2004). Hand paths were plotted and color-coded by speed. A *Submovement* was defined as a movement that occurred between consecutive local minima in the speed profile. *Submovement Count* was the total number of submovements that occurred within the trial. *Submovement Amplitude* was defined as the difference between the peak and the average of the two local minima that bounded the submovement. *Submovement Duration* was defined as the time period between bounding local minima. Submovements are often stereotyped such that the slope of submovement amplitude as a function of submovement duration scales in relation to task difficulty (Roitman et al., 2004, see also Milner, 1992). We sought to test whether the regression slope of submovement amplitude as a function of duration would scale in relation to the three design parameters: trial type (reflection or baseline), target speed (fast or slow), and target length (a single cursor or one with leading indicators). For each participant and each combination of design parameters, we grouped submovement duration into 7 equally-spaced bins with widths of 0.1 s, and we fit a line to submovement amplitude as a function of duration averaged within each bin to obtain the *Submovement Regression Slope* from the linear regression.

Reaction Time Experiment

For the reaction time experiments, we discarded the first trial of each trial block prior to estimating performance variables to avoid potential bias due to the novelty effects. *Simple Reaction Time (SRT)* and *Choice Reaction Time (CRT)* were computed for each participant by averaging the time interval between stimulus presentation and button press across all remaining trials wherein there were one or two possible responses, respectively.

Statistical Hypothesis Testing

We sought to discern whether subtle motor performance deficits in ASD reflect learning-related deficits of automatic sensorimotor adaptation and/or deficits of volitional strategic compensation, or whether they simply result from deficits in the ability to plan and execute actions. We reasoned that deficits of automatic sensorimotor adaptation and/or deficits of volitional strategic compensation (but not motor planning and execution) would present as deficits in the ability to capture and track visual targets during transformation trials (but not baseline trials). By contrast, we hypothesized that ASD-related deficits of motor execution would present as target capture deficits in every trial, although performance deficits might be exacerbated by the imposition of visuomotor distortions or by requiring faster tracking speeds. Statistical tests were performed using the SPSS 21 (IBM, Armonk, NY) software package. We performed post-hoc tests with Bonferroni correction to examine significant main effects and interactions. Effects were considered statistically significant at the α = 0.05 threshold. Specifically, we sought to test three hypotheses:

Hypothesis 1: Children with ASD exhibit deficits in automatic sensorimotor adaptations in response to a slowly-accumulating rotation of the visual-proprioceptive reference frame

We used signed initial direction error, IDE, as our primary performance measure of sensorimotor adaptation during the reaching experiment with incrementally-imposed visuomotor rotation. We employed a linear mixed model with compound symmetry covariance matrix (SPSS command: MIXED) and post-hoc t-tests (SPSS commands: EMMEANS, COMPARE, ADJ) to compare IDE across participant groups {ASD, TD}, using experimental phase {8 cycles of baseline practice, 8 cycles of late training, 1 cycle of post-exposure} as a repeated factor.

Importantly, failure to generate aftereffects of training (i.e. post-exposure trial movements without persistently large IDE values) would indicate a deficit of automatic (i.e. preconscious) sensorimotor adaptation. We therefore performed a follow-on analysis to determine when post-exposure trial cycle performance returned to baseline levels of IDE. Within each group, we used a 1-tail t-test to compare the average IDE from the last cycle of baseline trials (excluding the catch trial and the immediately subsequent trial) to IDE averaged within each cycle of post-exposure trials. We sought to identify the first post-exposure cycle in which IDE was not larger than the baseline value.

Hypothesis 2: Children with ASD exhibit deficits in their ability to plan and execute volitional strategic compensations in response to a spatially complex and suddenly-imposed distortion of the visuo-proprioceptive reference frame

We used a linear mixed model analysis and post-hoc t-tests with correction to evaluate the hypothesis that children with ASD exhibit deficits in their ability to develop and execute volitional strategic sensorimotor compensations in response to a spatially-complex and suddenly-imposed distortion of the visuo-proprioceptive reference frame.

Reaching

We used the unsigned initial direction error, |IDE|, as our primary performance measure of volitional strategic compensations during the reaching experiment with suddenly-imposed visuomotor reflection. We employed a linear mixed model and post-hoc t-tests to compare |IDE| across participant groups (ASD, TD), using experimental phase (8 cycles of baseline, 8 cycles of late training, 1 cycle of post-exposure) and target direction (horizontal, diagonal, vertical) as repeated factors.

In contrast to the reaching task with incrementally-imposed rotation, if aftereffects persisted throughout the post-exposure phase, then volitional strategic (i.e. cognitive) compensation would be impaired. Within each group, we used a 1-tail t-test to compare the average |IDE| from the last cycle of baseline trials (excluding the catch trial and the immediately subsequent trial) to |IDE| averaged within each cycle of post-exposure trials. We identified the first post-exposure cycle in which |IDE| was not larger than the baseline value.

Pursuit Tracking

We designed the tracking task to have discrete levels of difficulty: transformation between sensory feedback and motor commands (reflected feedback compared to veridical cursor feedback), temporal information to plan the movements (fast compared to slow target speed), and spatial information to plan the movements (a single cursor compared to one with leading indicators). This allowed us to test the hypotheses that performance variables varied with task difficulty. We used average lag error, LE, as our primary performance measure of volitional strategic compensation during the tracking experiment. We used a linear mixed model and post-hoc t-tests to compare lag error across participant groups (ASD, TD), using experimental phase (reflection, baseline), target speed (fast, slow), and target length (single cursor, leading indicators) as repeated factors.

LE was designed to characterize the ability to update motor commands in response to the target’s motion. We anticipated that children with ASD would exhibit increased LE due to deficits in feedforward planning (Rinehart et al. 2001, 2006; Glazebrook et al., 2008; Schmitz et al., 2003). However, increased LE could also be caused by deficits in movement production. Therefore, to distinguish deficits of movement production from deficits of feedforward planning, we compared average OE across groups (ASD, TD) using a linear mixed model with experimental phase (reflection, baseline), target speed (fast, slow), and target length (single cursor, leading indicators) as repeated factors. ASD-related deficits in LE, but small or no deficits in OE would indicate specific impairment of feedforward planning in ASD unrelated to movement production deficits.

Hypothesis 3: Children with ASD exhibit deficits in the execution of planned reaching and tracking movements

Each of the statistical tests described above included the baseline condition (in which visual feedback was veridical) in the experimental phase repeated factor. This allowed us to test whether children with ASD exhibit deficits in the execution of reaching and tracking movements when they were not required to update their motor commands in response to a novel visuospatial distortion. Additionally, we used repeated measures multivariate analysis of variance (RM-MANOVA) with post-hoc linear mixed models and post-hoc t-tests to compare movement characteristics across participant groups during baseline as well as visuospatial distortion phases. For the two reaching experiments, this entailed two separate RM-MANOVAs to compare movement characteristics (AR, SYM, RRT, and RMT) across participant groups (ASD, TD) with experimental phase (baseline, late training, post-exposure) as a repeated factor for both versions of the reaching task and target direction (vertical, horizontal, diagonal) as a repeated factor for the reaching task with sudden reflection. For the tracking experiment, this entailed a RM-MANOVA to compare movement characteristics (standard deviation of LE, standard deviation of OE, Submovement Count, and Submovement Regression Slope) across participant groups (ASD, TD) with experimental phase (reflection, baseline), target speed (fast, slow), and target length (single cursor, leading indicators) as repeated factors.

Results

One TD child and 4 children with ASD were dropped from the study because they were unable to follow task instructions. One additional participant in the TD group produced small errors in response to the initial 30° exposure trials during the reaching experiment with incremental rotation, suggesting that the measure of IDE may have been confounded by feedback control; therefore his data was discarded. The remaining 11 children with ASD and 9 TD children (Table 4-1) were attentive to the task on both days of testing. Participant groups were well matched for social status (t_{18} = 1.34, p = 0.197) and total IQ (t_{18} = 0.56, p = 0.580); however, there was a small difference in age (t_{18} = 2.17, p = 0.043) between the two groups. In the ASD group, eight children were right-handed, two were ambidextrous and one was left-handed, whereas in the TD group, eight children were right-handed and one was ambidextrous. All children in the ASD group met criteria for ASD measured by the ADOS. None of the children in the TD group exhibited behaviors characteristic of an ASD diagnosis as measured by the ASSQ and only 1 child in the TD group (participant T4) attained a score within the clinical range of the CBCL for the Obsessive-Compulsive Problems category. None of the other children in the TD group attained a score within the clinical range of the CBCL. Group statistics for age, social status, IQ, handedness, ADOS and ASSQ scores are presented in Table 4-1.

Reaction times from the control experiment in which participants pressed a button in response to visual stimuli were compared across participant groups using a linear mixed model with task type (simple, choice) as a repeated factor. We found a main effect of task type ($F_{1, 18}$ = 35.64, $p < 0.001$) such that reaction times were longer for the choice stimulus (CRT = 415 ± 63 ms) compared to the simple stimulus (SRT = 345 ± 40 ms). There was no main effect of group (p = 0.49) and no interaction between group and task type (p = 0.73). Thus, the lengths of the leading indicators in the continuous tracking experiment (computed as twice the CRT) did not differ between groups.

Automatic Sensorimotor Adaptation to Incremental Rotations

We sought to determine the extent to which children with ASD exhibit automatic sensorimotor adaptation to a visuo-proprioceptive rotation applied incrementally over many trials. One participant in the ASD group (participant A5) reported that he perceived the applied rotation and thus, his data from this experiment was not included in further analyses. The remaining participants were attentive to the task, failing to move on less than 1% of all trials (average number of botched trials in the ASD group: 3 ± 3 trials; TD group: 2 ± 2 trials).

Figure 4-2a plots the signed IDE as a function of trial, averaged across children with ASD (left) and TD children (right). Participants in both groups made straight and accurate movements with low IDE values during baseline training when visual feedback was veridical (top inset to Figure 4-2a - Baseline). Hand paths were markedly curved during baseline catch trials, wherein participants were exposed to the full 30° rotation (bottom inset to Figure 4-2a – Baseline). A two-sample t-test identified no group difference in IDE during initial exposure catch trials ($IDE_{ASD} = -29.58 \pm 1.62°$, $IDE_{TD} = -28.59 \pm 1.25°$; $t_{17} = 1.00$, $p = 0.329$), suggesting that uncompensated perturbations yielded errors of similar magnitude in both groups of children. By contrast, IDE values remained low and cursor trajectories were straight during early training (when visual feedback was incrementally rotated from 1 to 8°; inset to Figure 4-2a - Early) as well as during late training (when the rotation was held steady at its maximum of 30°; inset to Figure 4-2a – Late). When rotation was suddenly removed (i.e. post-exposure), movements curved in the counter-clockwise direction, consistent with the expression of a large aftereffect of sensorimotor adaptation that had accumulated slowly throughout the training phase (inset to Figure 4-2a – Post).

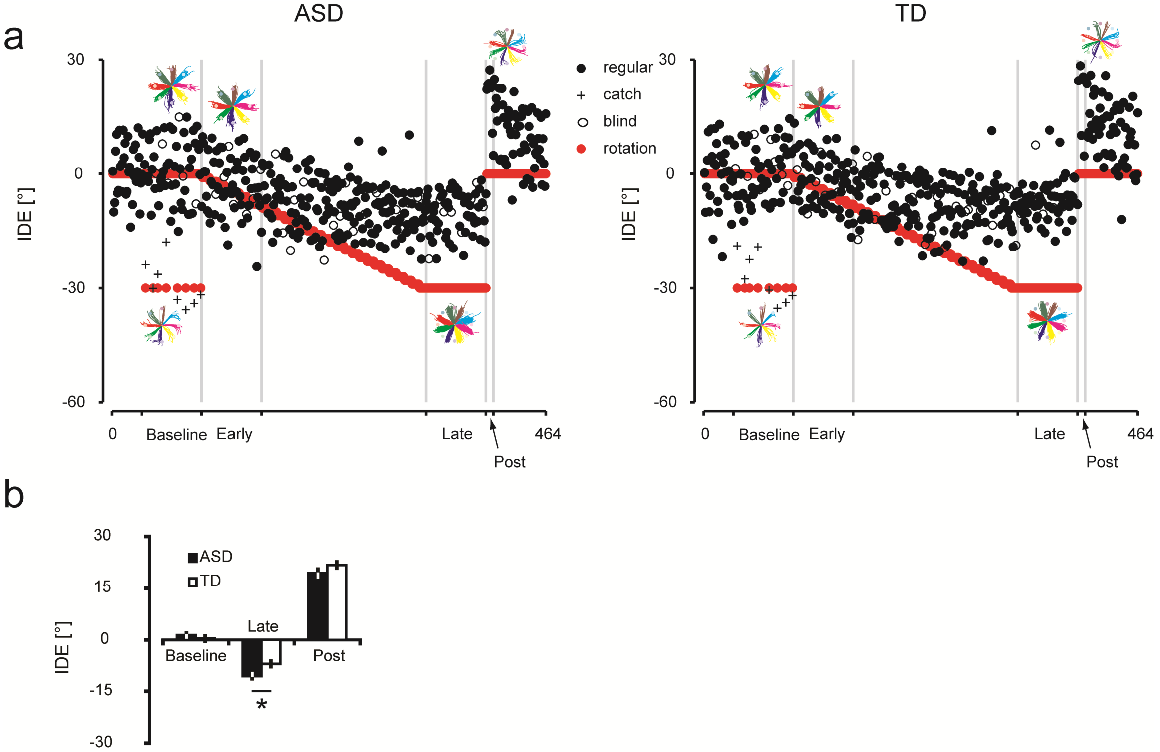

Figure 4-2: Reaching with incremental rotation. (a) Initial direction errors [IDE] averaged across children with ASD [left] and TD children [right] shown in black. Blind trials are represented by open circles and catch trials are represented by '+' symbols. Rotation applied to the cursor shown in the negative direction in red. Insets: all hand-paths color-coded by target during trials 33-96 [baseline and catch trials], 97-160 [early training], 337-400 [late training], and 401-408 [post exposure] (b) Bar plot of average IDE for the ASD group [filled] and the TD group [open] during baseline, late training, and post exposure. Error bars represent ± 1 SEM, here and elsewhere. * $p < 0.05$.

To investigate the integrity of automatic sensorimotor adaptation, we compared IDE values across participant groups within the baseline, late training, and post-exposure phases of the experiment (Figure 4-2b). Linear mixed model analysis found a main effect of experimental phase ($F_{2, 34} = 578.91$, $p < 0.001$) and an interaction between group and experimental phase ($F_{2, 34} = 3.72$, $p = 0.035$). Considering the main effect, we found that IDE was negligible during baseline practice (IDE = 0.90 ± 2.51°). IDE decreased somewhat in the counter-clockwise direction by the end of training (IDE = -8.86 ± 3.33°), which suggests incomplete compensation for the imposed rotation. IDE *increased* abruptly in the clockwise direction immediately (i.e. within the first cycle of trials) after the rotation was removed (IDE = 20.45 ± 3.80°), suggesting a strong aftereffect of exposure to the visuomotor rotation. Post-hoc analysis of the interaction between group and experimental phase revealed that IDE did not differ significantly across groups during baseline or post-exposure trials ($p \geq 0.097$ in each case); thus, both groups of participants demonstrated comparable ability to plan and execute the required reaching movements. By contrast, we observed a significant group difference during late training ($p = 0.013$). That is, the children with ASD exhibited less complete adaptation than did TD children during steady-state exposure to the visuomotor rotation.

Importantly, aftereffects of exposure to the rotation persisted in both groups for many trial cycles after the rotation was removed, rather than quickly returning to baseline levels. For each participant group, we performed a series of 1-tail t-tests comparing average IDE in each successive post-exposure trial cycle to the IDE observed during the last cycle of baseline training (excluding the catch trial and the trial immediately following it), to determine the first post-exposure trial cycle in which IDE was less than or equal to that of baseline. For both participant groups, we found that average IDE in all of the post-exposure cycles were greater than IDE in the last cycle of baseline training. Thus, participants never regained baseline performance during all 8 cycles of post-exposure. This observation strongly suggests that the adaptive behavior we observed in response to a slowly-accumulating visuomotor rotation was mediated predominantly via automatic sensorimotor adaptation rather than volitional strategic compensation (cf. Kagerer et al., 1997). Taken together, our results indicate that despite small differences in steady-state compensation at the end of training, children in both groups exhibited comparable abilities to engage mechanisms mediating automatic sensorimotor adaptation.

Volitional Strategic Compensation for Sudden Reflection

We sought to compare the way in which TD children and children with ASD use visual information of upcoming target motions to plan and execute strategic compensations for the sudden reflection of the visuo-proprioceptive reference frame.

Reaching

Participants were attentive to the reaching task, failing to move on less than 1% of all trials (average number of botched trials in the TD group: 1 ± 1 trial; ASD group: 3 ± 2 trials). Figure 4-3a plots the IDE magnitude as a function of trial, averaged across children with ASD (left) and TD children (right). As in the reaching task with incremental rotation, participants in both groups again made straight and accurate movements with low IDE values during baseline training when visual feedback was veridical (bottom inset to Figure 4-3a - Baseline). Hand paths curved slightly and they were not accurate on average when cursor coordinates were reflected about the participant's midline during baseline catch trials (top inset to Figure 4-3a - Baseline). We used a linear mixed model to compare IDE magnitude averaged across 'catch' trials between ASD and TD groups with target direction (horizontal, diagonal, vertical) as a repeated factor. We found a main effect of target direction ($F_{2, 36} = 2693.62$, $p < 0.001$) but no main effect of group and no interaction between group and target direction (both $p \geq 0.789$). Thus, imposed perturbations resulted in errors of similar magnitude during initial exposure in both groups of children. IDE values were large during early training (when visual feedback was persistently reflected about the midline; inset to Figure 4-3a - Early), decreased throughout the training period, and remained larger than those established during baseline practice during late training (inset to Figure 4-3a - Late). When reflection was suddenly removed (i.e. post-exposure), IDE values quickly returned to baseline levels, consistent with a volitional strategy to select a motor plan in response to veridical visual feedback (inset to Figure 4-3a - Post).

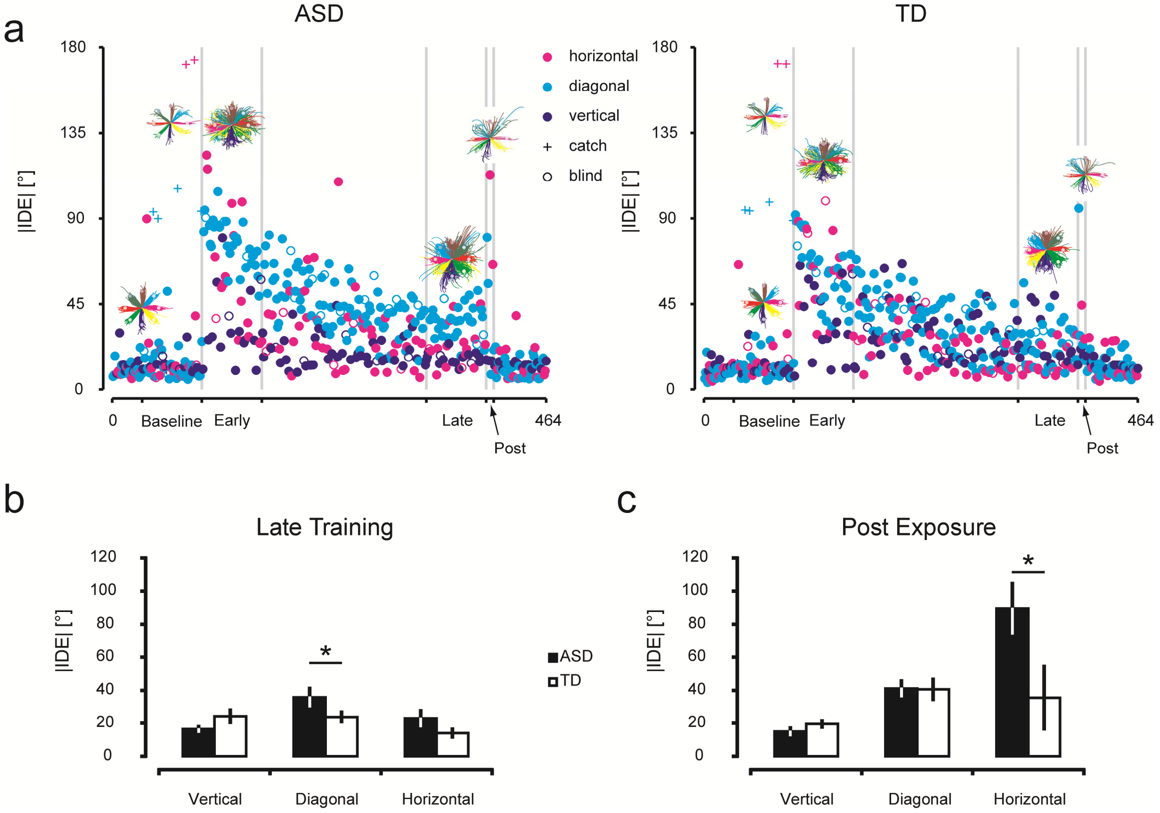

Figure 4-3: Reaching with sudden reflection. (a) Initial direction error [IDE] magnitudes over trials averaged across children with ASD [left] and TD children [right], color-coded by target direction: magenta – left/right, cyan – diagonal, blue – top/bottom targets. Blind trials are represented by open circles and catch trials are represented by '+' symbols. Insets: all hand-paths, color-coded by target, during trials 33-96 [baseline and catch trials], 97-160 [early training], 337-400 [late training], and 401-408 [post exposure] (b-c) Bar plot of average IDE magnitude for the ASD group [filled] and the TD group [open] for each of the three target direction types during late training (b) and post-exposure (c). * $p < 0.05$.

To investigate the accuracy of volitional compensation strategies, we compared IDE values across participant groups within the baseline, late-training, and post-exposure phases and within target directions (horizontal, diagonal, vertical) {Figure 4-3b}. Linear mixed model analysis found main effects of trial type ($F_{2, 144} = 30.97$, $p < 0.001$) and target direction ($F_{2, 144} = 8.91$, $p < 0.001$) and a three-way interaction between participant group, experimental phase, and target direction ($F_{4, 144} = 4.40$, $p = 0.002$). Considering the main effect of experimental phase, post hoc tests revealed that IDE magnitude was low during baseline ($|IDE| = 11.80 \pm 5.39°$). IDE magnitude increased during late training ($|IDE| = 23.13 \pm 14.16°$), suggesting that the volitional strategy was inadequate to compensate for the novel imposed perturbation. IDE increased abruptly during the first cycle of post-exposure ($|IDE| = 41.06 \pm 40.42°$). Considering the main effect of target direction, we found that IDE magnitudes of the vertical targets (|IDE| = 16.23 ± 8.21°) were lower than those of the diagonal targets (|IDE| = 27.42 ± 18.40°) and the horizontal targets (|IDE| = 32.33 ± 41.98°). Since the imposed reflection only perturbed cursor feedback in the x-direction, there was no need for participants to select a new strategy for the vertical targets which required motion in the y-direction. To investigate the three-way interaction between participant group, experimental phase, and target direction, we performed three post-hoc linear mixed model tests (one for each experimental phase) to compare IDE magnitudes across participant groups with target direction as a repeated factor. During baseline, we found no main effect of group and no interaction between group and target direction (both $p > 0.42$). However, we found an interaction between participant group and target direction during late training ($F_{2, 36} = 8.256$, $p = 0.001$) such that IDE magnitudes were greater in children with ASD compared to TD children for the diagonal targets ($p = 0.045$; Figure 4-3b). We also found an interaction between participant group and target direction during post-exposure ($F_{2, 36} = 5.695$, $p = 0.007$) such that IDE magnitudes were greater in children with ASD compared to TD children for the horizontal targets ($p = 0.001$; Figure 4-3c). Thus, we identified ASD-related deficits in the ability to select a compensation strategy for a known transformation between visual feedback and motor commands, even after many (~240) training trials.

Importantly, aftereffects of exposure to the visuospatial reflection diminished quickly in both groups after the reflection was removed. For each participant group, we performed a series of 1-tail t-tests comparing average IDE magnitude in each successive post-exposure trial cycle to the IDE magnitude observed during the last cycle of baseline (excluding the catch trial and the trial immediately following it). For both participant groups, post-exposure IDE values exceeded their baseline values for 1 trial cycle, indicating that aftereffects disappeared after approximately 8 trials. These observations strongly suggest that the behavior we observed in response to reflected visual coordinates was mediated predominantly via volitional strategic compensation rather than automatic sensorimotor adaptation (cf. Kagerer et al., 1997). Our results indicate that children with ASD exhibit deficits in the ability to select and execute motor plans in response to a sudden known transformation between visual feedback and motor commands.

<u>Pursuit Tracking</u>

We further characterized ASD-related deficits in strategic compensation for a sudden exposure to visuomotor reflection by controlling the amount and timing of visual information available for planning strategic compensations. Log likelihoods of LE and OE were used to plot 2-dimensional histograms of cursor position with respect to the target in the direction of the target's motion (Figure 4-4a).

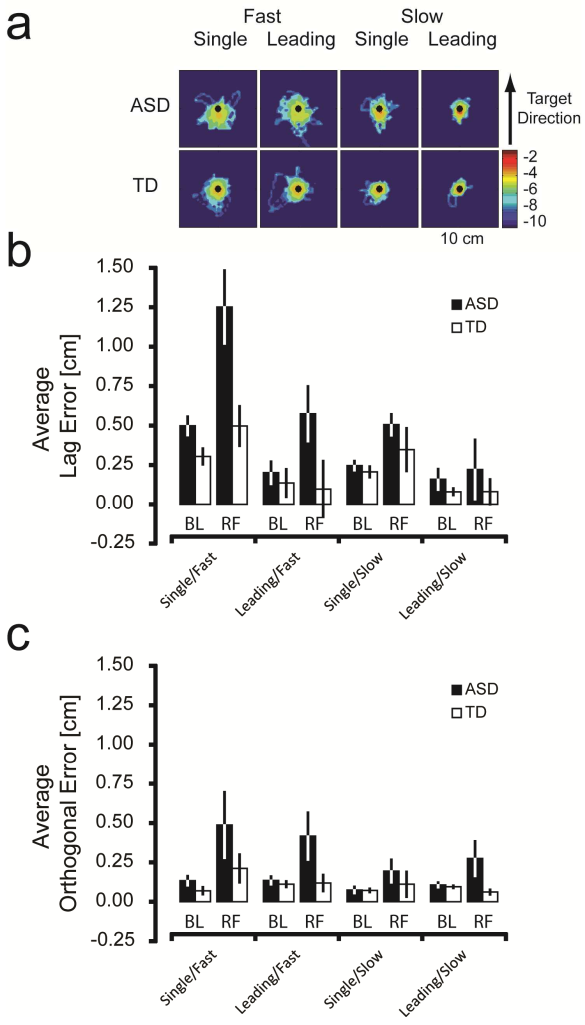

Figure 4-4: Movement error while tracking a moving target along a pseudo-random path. (a) 2-D color histograms of the log likelihood of cursor position with respect to the target (black circle) for a representative child with ASD [participant A4, top] and a TD child [participant T8, bottom] for four tracking conditions. (b) Average error in the direction opposite the target's motion (i.e. lag error) and (c) average error in the direction orthogonal to the target's motion during baseline [BL] and reflection [RF] for children with ASD [filled] and TD children [open].

The way in which LE scaled with conditions of temporal and spatial target information provided a measure of how well participants planned their movements. We compared LE across participant groups with experimental phase, target speed, and target length as repeated factors (Figure 4-4b). The linear mixed model found main effects of group ($F_{1,\ 18} = 5.40$, $p = 0.032$), target length ($F_{1,\ 126} = 28.82$, $p < 0.001$), experimental phase ($F_{1,\ 126} = 16.32$, $p < 0.001$), and target speed ($F_{1,\ 126} = 15.83$, $p < 0.001$) and interactions between participant group and experimental phase ($F_{1,\ 126} = 7.11$, $p = 0.009$), between participant group and target speed ($F_{1,\ 126} = 6.17$, $p = 0.014$), and between experimental phase and target length ($F_{1,\ 126} = 4.83$, $p = 0.030$). Considering the main effect of participant group, post-hoc tests revealed that LE was larger in children with ASD (LE = 0.46 ± 0.54 cm) compared to TD children (LE = 0.22 ± 0.33 cm). For the main effects of target length, experimental phase, and target speed, we found that LE was larger during the most difficult experimental conditions: single target cursor ($LE_{single} = 0.50 \pm 0.48$ cm, $LE_{leading} = 0.20 \pm 0.42$ cm), reflected visual feedback ($LE_{reflection} = 0.47 \pm 0.61$ cm, $LE_{baseline} = 0.23 \pm 0.22$ cm), and fast target speed ($LE_{fast} = 0.46 \pm 0.56$ cm, $LE_{slow} = 0.24 \pm 0.33$ cm) relative to the easier experimental conditions. For the interaction between participant group and experimental phase, post-hoc tests revealed that within the ASD group, LE was larger when the reflection was imposed compared to veridical cursor feedback ($p < 0.001$), and LE was larger in children with ASD compared to TD children when cursor feedback was reflected about the midline ($p = 0.003$) suggesting that children with ASD were impaired in their ability to compensate for the novel transformation between hand position and visual feedback. Considering the interaction between participant group and target speed, post-hoc tests revealed that within the ASD group, LE was larger during the fast target speed compared to the slow speed ($p < 0.001$) and LE was larger in children with ASD compared to TD children during the fast target speed ($p = 0.003$), suggesting that children with ASD were impaired in their ability to update motor commands when temporal goal information was reduced (i.e. during the fast target speed). For the interaction between experimental phase and target length, post-hoc tests found that LE was larger during reflection compared to baseline when the goal was represented by a single cursor ($p < 0.001$) and LE was larger for the single cursor target compared to the cursor with leading indicators during both baseline and reflection phases (both $p \leq 0.027$), suggesting that participants were successful in using the leading indicators to predict the target's motion.

Errors in the direction orthogonal to the target motion (OE) served as a control to measure movement error independent of target direction. We next compared OE across participant groups with experimental phase, target speed, and target length as repeated factors (Figure 4-4c). The linear mixed model found main effects of experimental phase ($F_{1,\,126} = 13.28$, $p < 0.001$) and target speed ($F_{1,\,126} = 5.40$, $p = 0.022$) and an interaction between participant group and experimental phase ($F_{1,\,126} = 6.47$, $p = 0.012$). Similar to the LE results, post-hoc tests of the main effects of experimental phase and target speed of OE revealed that OE was larger during the most difficult experimental conditions: reflected visual coordinates ($OE_{reflection} = 0.25 \pm 0.40$ cm, $OE_{baseline} = 0.10 \pm 0.07$ cm), and fast target speed ($OE_{fast} = 0.22 \pm 0.36$ cm, $OE_{slow} = 0.13 \pm 0.20$ cm) relative to the easier experimental conditions. For the interaction between participant group and experimental phase, post-hoc tests revealed that within the ASD group, OE was larger during reflected visual coordinates compared to veridical visual coordinates ($p < 0.001$) and OE was larger in the ASD group compared to the TD group when visual feedback was reflected ($p = 0.019$), suggesting that planning deficits related to visuospatial compensation identified in the LE analysis above could not be distinguished from movement problems in general. Taken together, the results identify deficits in the way children with ASD update motor commands when the target moved at the fast speed. However, both groups of children were successful in using advanced spatial goal information to predict target motion and movement problems could not be distinguished from planning deficits during compensation for a novel transformation between visual coordinates and motor plan updating.

Movement Execution

Reaching

We sought to identify whether movement execution is impaired in children with ASD by comparing performance measures across participant groups for each of the two reaching experiments. For the reaching task with incremental rotation, we sought to verify that the group difference in steady-state compensation did not simply reflect general differences in the amount of time spent planning and executing movement (i.e. RRT, RMT) or in movement kinematics (AR, SYM). We performed RM-MANOVA and post-hoc linear mixed model analyses to test the null hypothesis that performance variables (AR, SYM, RRT, RMT) were equivalent across participant groups and experimental phase (the repeated factor). RM-MANOVA identified a main effect of experimental phase ($F_{8, 10} = 5.38$, $p = 0.008$), but no effect of group ($p = 0.622$) and no group by phase interaction ($p = 0.984$). Post-hoc linear mixed model analysis of each variable also found no main effect of group or interaction between group and experimental phase (all $p \geq 0.104$). These results provide further evidence that the group difference in steady-state compensation we observed was not a result of group differences in the ability to prepare and execute straight and smooth goal-directed reaching movements. By contrast, we did find main effects of experimental phase for all four measures, suggesting that these measures were sensitive to learning-related changes in performance: AR ($AR_{baseline} = 0.062 \pm 0.021$, $AR_{late} = 0.062 \pm 0.015$, $AR_{post} = 0.100 \pm 0.035$; $F_{2, 34} = 23.12$, $p < 0.001$), SYM ($SYM_{baseline} = 0.049 \pm 0.048$, $SYM_{late} = 0.045 \pm 0.039$, $SYM_{post} = 0.022 \pm 0.044$; $F_{2, 34} = 3.43$, $p = 0.044$), RRT ($RRT_{baseline} = 320 \pm 35$ ms, $RRT_{late} = 335 \pm 38$ ms, $RRT_{post} = 337 \pm 40$ ms; $F_{2, 34} = 9.39$, $p = 0.001$), and RMT ($RMT_{baseline} = 417 \pm 100$ ms, $RMT_{late} = 425 \pm 103$ ms, $RMT_{post} = 466 \pm 122$ ms; $F_{2, 34} = 7.99$, $p = 0.001$).

For the reaching task with sudden reflection, we sought to verify that the group differences in steady-state compensation and post-exposure aftereffects did not reflect general movement execution deficits. We performed RM-MANOVA and post-hoc linear mixed model analyses to test the null hypothesis that performance variables (AR, SYM, RRT, and MRT) were equivalent across participant groups with repeated factors of experimental phase and target direction. RM-MANOVA identified main effects of experimental phase ($F_{8, 11} = 16.18$, $p < 0.001$) and target direction ($F_{8, 11} = 6.08$, $p = 0.004$) and an interaction between experimental phase and target direction ($F_{16, 3} = 21.56$, $p = 0.014$) but no effect of group ($p = 0.867$) and no interactions with group ($p \geq 0.240$). For RRT, the post-hoc linear mixed model revealed main effects of experimental phase ($RRT_{baseline} = 336 \pm 45$ ms, $RRT_{late} = 506 \pm 106$ ms, $RRT_{post} = 452 \pm 99$ ms; $F_{2, 144} = 133.46$, $p < 0.001$) and target direction ($RRT_{horizontal} = 423 \pm 105$ ms, $RRT_{diagonal} = 451 \pm 125$ ms, $RRT_{vertical} = 420 \pm 105$ ms; $F_{2, 144} = 5.15$, $p = 0.007$) and an interaction between participant group and experimental phase ($F_{2, 144} = 5.59$, $p = 0.005$). Considering the interaction between participant group and experimental phase, RRTs were significantly different across each experimental phase within the TD group (all $p < 0.001$), and RRTs during baseline were different than those of late training and post-exposure within the ASD group (both $p < 0.001$). However, post-hoc tests revealed no difference between groups within each experimental phase (all $p \geq 0.121$), suggesting that the group differences in steady-state compensation and post-exposure aftereffects were not related to ASD-related deficits in movement execution. None of the other performance measures revealed main effects of group or interactions between group and experimental phase and/or target direction (all $p > 0.161$). For AR, we found main effects of target direction ($AR_{horizontal} = 0.056 \pm 0.018$, $AR_{diagonal} = 0.093 \pm 0.050$, $AR_{vertical} = 0.087 \pm 0.053$; $F_{2, 144} = 16.89$, $p < 0.001$) and trial type ($AR_{baseline} = 0.063 \pm 0.026$, $AR_{late} = 0.088 \pm 0.044$, $AR_{post} = 0.085 \pm 0.059$; $F_{2, 144} = 8.77$, $p < 0.001$) and an interaction between target direction and trial type ($F_{4, 144} = 6.24$, $p < 0.001$). For SYM, we found a main effect of target direction ($SYM_{horizontal} = 0.114 \pm 0.104$, $SYM_{diagonal} = 0.059 \pm 0.052$, $SYM_{vertical} = 0.034 \pm 0.075$; $F_{2, 144} = 19.20$, $p < 0.001$) and an interaction between target direction and trial type ($F_{4, 144} = 2.54$, $p = 0.043$). For RMT, we found main effects of trial type ($RMT_{baseline} = 430 \pm 105$ ms, $RMT_{late} = 524 \pm 164$ ms, $RMT_{post} = 507 \pm 159$ ms; $F_{2, 144} = 24.94$, $p < 0.001$) and target direction ($RMT_{horizontal} = 458 \pm 132$ ms, $RMT_{diagonal} = 509 \pm 146$ ms, $RMT_{vertical} = 493 \pm 168$ ms; $F_{2, 144} = 6.70$, $p = 0.002$) and an interaction between trial type and target direction ($F_{4, 144} = 4.02$, $p = 0.004$).

We next sought to confirm that IDE was primarily sensitive to planning errors (and insensitive to visual feedback corrections) by comparing IDE between trials with visual feedback and ‘blind’ trials. We used a linear mixed model to compare IDE between participant groups with visual feedback condition (present or absent) and experimental phase (baseline, transformation) as repeated factors for both reaching experiments and target direction (vertical, horizontal, diagonal) as a repeated factor for the reaching experiment with sudden reflection. Importantly, we found no main effect of visual feedback condition and no interactions with visual feedback condition (all $p \geq 0.150$) for both reaching experiments. This test confirmed that IDE was a reasonable estimate of feedforward planning because hand position was not influenced by visual feedback early in the movement trajectory (i.e. within 80 ms).

Pursuit Tracking

We sought to identify whether ASD-related deficits during the tracking experiment were supported by movement execution deficits. We performed RM-MANOVA and post-hoc linear mixed models and t-tests to test the null hypothesis that performance variables (standard deviation of LE, standard deviation of OE, Submovement Count, and Submovement Regression Slope) were equivalent across participant groups with experimental phase, target speed, and target direction as repeated factors. RM-MANOVA found main effects of target speed ($F_{4, 15} = 30.80$, $p < 0.001$), experimental phase ($F_{4, 15} = 14.34$, $p < 0.001$), and target length ($F_{4, 15} = 9.12$, $p = 0.001$) and an interaction between target speed and experimental phase ($F_{4, 15} = 8.35$, $p = 0.001$), but no main effect of group ($p = 0.251$) and no interactions with group (all $p \geq 0.081$). We performed four post-hoc linear mixed models (one each for the standard deviation of LE, the standard deviation of OE, the Submovement Count, and the Submovement Regression Slope) to compare each performance variable across participant groups with experimental phase, target speed, and target length as repeated factors.

For the standard deviation of LE (Figure 4-5a), the linear mixed model found main effects of experimental phase ($\sigma_{\text{reflection}} = 1.25 \pm 0.74$ cm, $\sigma_{\text{baseline}} = 0.60 \pm 0.25$ cm; $F_{1, 126} = 102.58$, $p < 0.001$) and target speed ($\sigma_{\text{fast}} = 1.14 \pm 0.69$ cm, $\sigma_{\text{slow}} = 0.71 \pm 0.49$ cm; $F_{1, 126} = 46.67$, $p < 0.001$) and interactions between participant group and experimental phase ($F_{1, 126} = 5.02$, $p = 0.027$) and between experimental phase and target speed ($F_{1, 126} = 7.02$, $p = 0.009$). Considering the interaction between participant group and experimental phase, post-hoc tests found that both groups exhibited increased standard deviation of LE during the reflection phase compared to baseline (both $p < 0.001$), but there was no difference in standard deviation of LE between groups during baseline or reflection phases (both $p \geq 0.052$), suggesting that planning deficits in ASD were not related to deficits in movement variability in the direction of the target's motion. Considering the interaction between experimental phase and target speed, post-hoc tests found that the standard deviation of LE was greater during reflection compared to baseline for both target speeds (both $p < 0.001$) and the standard deviation of LE was larger during the fast target speed compared to the slow target speed during both phases (both $p \leq 0.004$).

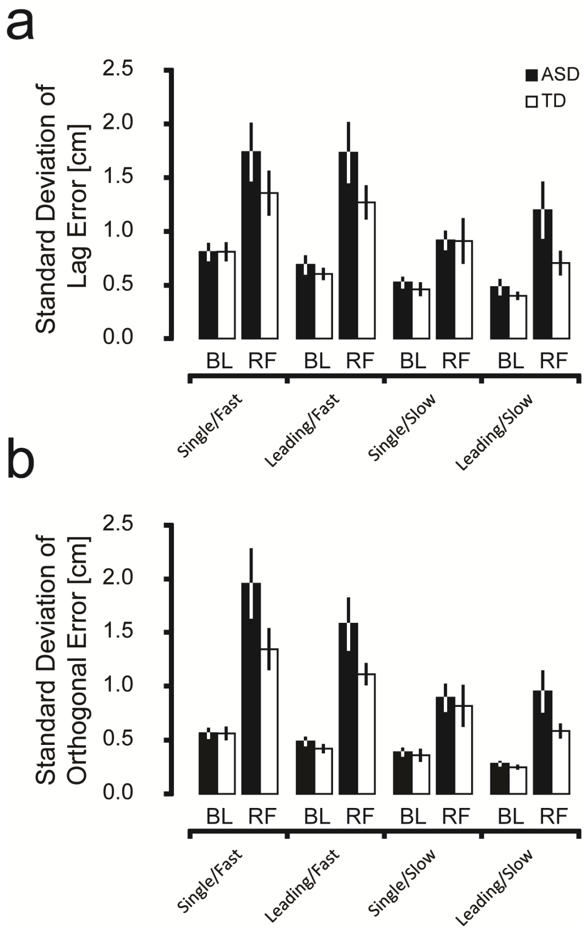

Figure 4-5: Standard deviation of movement error while tracking a moving target. (a) Standard deviation of error in the direction opposite the target's motion (i.e. lag error) and (b) standard deviation of error in the direction orthogonal to the target's motion during baseline [BL] and reflection [RF] for children with ASD [filled] and TD children [open].

For the standard deviation of OE (Figure 4-5b), the linear mixed model found main effects of experimental phase ($\sigma_{\text{reflection}}$ = 1.17 ± 0.75 cm, σ_{baseline} = 0.41 ± 0.16 cm; $F_{1,\ 126} = 143.01$, $p < 0.001$), target speed (σ_{fast} = 1.02 ± 0.77 cm, σ_{slow} = 0.57 ± 0.43 cm; $F_{1,\ 126} = 50.01$, $p < 0.001$), and target length (σ_{single} = 0.87 ± 0.72 cm, σ_{leading} = 0.72 ± 0.59 cm; $F_{1,\ 126} = 6.10$, $p = 0.015$) and interactions between participant group and experimental phase ($F_{1,\ 126} = 7.86$, $p = 0.006$) and between experimental phase and target speed ($F_{1,\ 126} = 15.99$, $p < 0.001$). Considering the interaction between group and experimental phase, post-hoc tests found that both groups had increased standard deviation of OE during reflection compared to baseline (both $p < 0.001$) and the standard deviation of OE was higher in children with ASD compared to TD children during reflection ($p = 0.011$), but not during baseline ($p = 0.816$), suggesting ASD-related deficits in movement variability during compensation for a novel visuospatial transformation. For the interaction between experimental phase and target speed, we found that the standard deviation of OE was greater during reflection compared to baseline during both fast and slow target speeds (both $p < 0.001$) and the standard deviation of OE was greater during the fast target speed compared to the slow target speed during both phases (both $p \leq 0.032$).

We next plotted the target path and overlapped the hand's position color-coded by movement speed (Figure 4-6a). From the figure, it is clear that participants made updates to the hand's position as seen by regions of high movement speed which were bounded by local minima in movement speed (i.e. submovements). We counted the total number of submovements (which is inversely related to movement smoothness, cf. Rohrer et al., 2002) across each experimental phase. For the Submovement Count (Figure 4-6b), the linear mixed model found main effects of target speed ($n_{fast} = 370 \pm 51$, $n_{slow} = 407 \pm 33$; $F_{1, 126} = 77.97$, $p < 0.001$), experimental phase ($n_{reflection} = 372 \pm 47$, $n_{baseline} = 406 \pm 40$; $F_{1, 126} = 70.31$, $p < 0.001$), and target length ($n_{single} = 383 \pm 45$, $n_{leading} = 394 \pm 47$; $F_{1, 126} = 7.07$, $p = 0.009$) and an interaction between target speed and experimental phase ($F_{1, 126} = 7.50$, $p = 0.007$). Considering the interaction between target speed and experimental phase, post-hoc t-tests found that the Submovement Count was greater for the slow target speed compared to the fast target speed during both experimental phases (both $p < 0.001$) and the Submovement Count was higher during baseline compared to reflection for both target speeds (both $p < 0.001$).

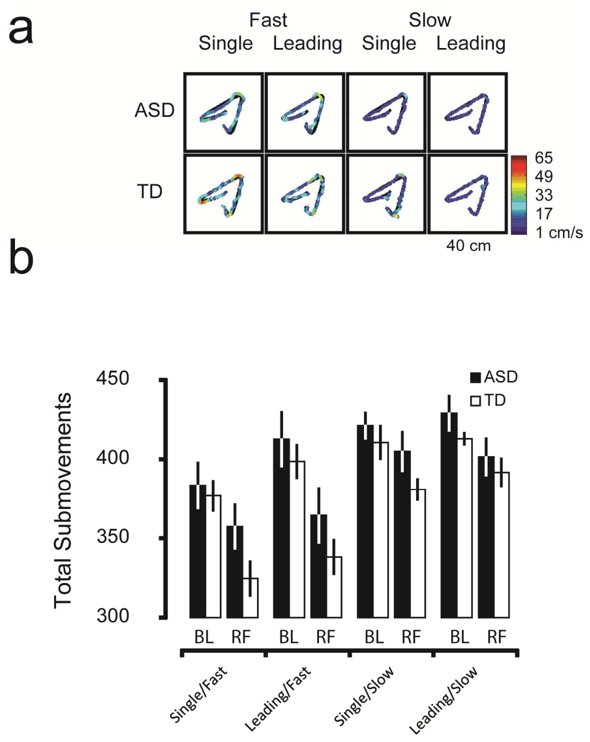

Figure 4-6: Submovements while tracking a moving target along a pseudo-random path. (a) Target paths [black] and hand paths color-coded by hand speed for a representative child with ASD [participant A2, top] and a TD child [participant T9, bottom] for four tracking conditions. (b) Submovement Count during baseline [BL] and reflection [RF] for children with ASD [filled] and TD children [open].

For each submovement (Figure 4-7a), we measured the speed amplitude and duration. We then plotted speed amplitude as a function of duration (Figure 4-7b) for each participant and each of the eight combinations of experimental phase, target speed, and target length. A line was fit to the amplitude vs. duration plots and the slope of the line (Submovement Regression Slope, Figure 4-7c) was used to characterize the stereotypy of corrective submovements (cf. Roitman et al., 2004; Pasalar et al., 2005). The linear mixed model found main effects of target speed ($m_{fast} = 10.41 \pm 3.11$ cm/s^2, $m_{slow} = 7.02 \pm 2.06$ cm/s^2; $F_{1, 126} = 140.28$, $p < 0.001$), experimental phase ($m_{baseline} = 7.93 \pm 2.32$ cm/s^2, $m_{reflection} = 9.50 \pm 3.62$ cm/s^2; $F_{1, 126} = 29.22$, $p < 0.001$), and target length ($m_{leading} = 8.16 \pm 2.71$ cm/s^2, $m_{single} = 9.27 \pm 3.43$ cm/s^2; $F_{1, 126} = 16.20$, $p < 0.001$) and an interaction between participant group and target length ($F_{1, 126} = 4.27$, $p = 0.041$). Considering the interaction between participant group and target length, post-hoc tests revealed that TD children had higher Submovement Regression Slopes during the condition in which the target was represented by a single cursor compared to the condition in which the target had leading indicators (p <

0.001), but there was no such trend in children with ASD ($p = 0.147$) and there was no difference in Submovement Regression Slopes between groups for either target length (both $p \geq 0.199$). Together, these findings suggest that the ASD-related deficits in compensation for novel visuospatial distortion were not supported by general movement execution deficits during both reaching and tracking tasks.

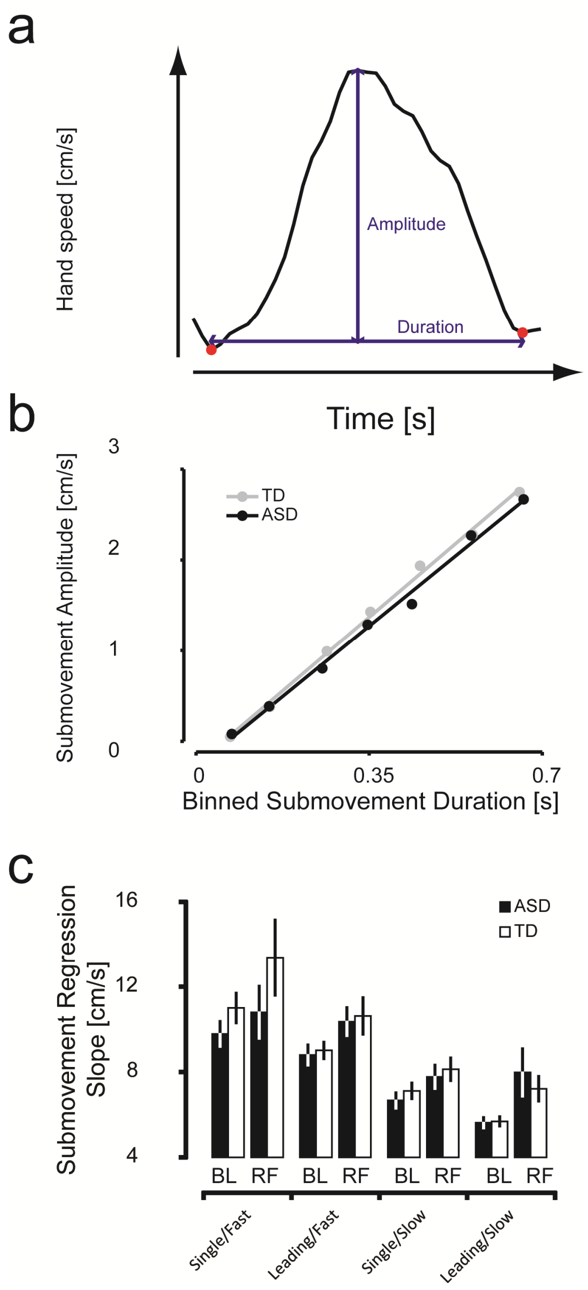

Figure 4-7: Kinematics of submovements while tracking a moving target. (a) Amplitude and duration of a single, representative submovement. Red circles identify the local minima bounding the submovement. Blue arrows identify the time period between bounding local minima (i.e. duration) and the difference in height magnitude between the peak speed and the average speed of the bounding local minima (i.e. amplitude). (b) Amplitudes and durations of submovements of a representative child with ASD [participant A4, black] and a TD child [participant T1, gray] were binned and plotted. A line was fit to the submovement amplitude as a function of duration to obtain the slope which characterized movement corrections. (c) Slopes of submovement amplitude as a function of duration measured during baseline [BL] and reflection [RF] for children with ASD [filled] and TD children [open].

Discussion

We assessed the abilities of children with ASD and TD children to make goal-directed reaching and tracking movements using automatic sensorimotor adaptation and volitional strategies to compensate for visuospatial distortion. While reaching with visuospatial rotations that were incrementally-imposed, children with ASD exhibited subtle deficits in reaching errors at the end of training compared to TD children. While reaching with visuospatial reflection that was suddenly-imposed, children with ASD made larger errors during late training and post-exposure compared to TD children. While tracking with suddenly-imposed visuospatial reflection, children with ASD lagged behind the target to a greater extent than TD children. Together, these findings suggest that children with ASD exhibit deficits in volitional strategic compensation, but only subtle differences in automatic sensorimotor adaptation. These findings were not supported by ASD-related deficits in movement execution because movement kinematics were not different between participant groups.

Subtle ASD-related Deficits in Automatic Sensorimotor Adaptation

Automatic sensorimotor adaptation was assessed in both groups of children during reaching with incrementally-imposed rotations of visual feedback. Children with ASD exhibited larger errors at the end of training, when the rotation reached its maximum of 30°. Others have used reaching experiments with incrementally-imposed rotation to characterize automatic sensorimotor adaptation in neurologically-intact adults (Kagerer et al., 1997; Klassen et al., 2005); however, ours is the first to characterize reaching performance against incrementally-imposed rotations in children with ASD. In a study by Gidley Larson and colleagues (2008), children with ASD and TD children moved a robotic handle to control a cursor on a video screen. Participants completed two versions of the task, which differed in the type of visuomotor distortion that was suddenly-imposed. During the force-field experiment, participants performed reaching movements against a clockwise curl field such that the magnitude of the force scaled with hand velocity. During the visual-rotation experiment, the cursor was rotated 19° in the clockwise direction with respect to the hand's actual position. Even though sensorimotor distortions were large and suddenly-imposed, automatic sensorimotor adaptation likely contributed to learning because when the distortions were suddenly removed, movement errors were large and persistent (Gidley Larson et al., 2008). Gidley Larson and colleagues (2008) found no group-wise difference in movement errors during their reaching task, which contradicts our finding of increased movement errors in the ASD group at the end of training. On average, children with ASD exhibited a slower rate of adaptation compared to TD children, but this finding was not confirmed with statistical hypothesis testing of individual participant data. However, in a following study, in which adaptation was modeled with a double-exponential to yield a fast and a slow time constant for each participant, Izawa and colleagues (2012) found that children with ASD exhibited a slower rate of adaptation for the fast time constant compared to TD children. Our experiment was fundamentally different from those of Gidley Larson et al. (2008) and Izawa et al. (2012) because we designed rotations to be small and imperceptible. Thus, ASD-related deficits in our study were the result of automatic sensorimotor adaptation to predictable sensorimotor distortions.

ASD-Related Deficits in Volitional Strategic Compensation

During the reaching task with sudden reflection, children in both groups produced large errors at the onset of reflected visual coordinates. Errors decreased somewhat after many training trials; however, participants were unsuccessful in selecting a compensation strategy to achieve errors within the level established by baseline practice. When the reflection was suddenly removed, errors quickly returned to baseline values, suggesting that volitional compensation rather than automatic sensorimotor adaptation were employed to compensate for the reflected visual coordinates. It was not surprising that initial direction errors remained high in both groups after many (~240) training trials with reflected visual feedback. Mazzoni and Krakauer (2006) measured reaching error in response to sensorimotor distortion. In their study, typical adults reached to targets while a 45° counterclockwise rotation was applied to cursor feedback. Half of the participants were told the exact nature of the distortion, when it occurred, and they were told to aim for the neighboring clockwise target to compensate for the rotation. The other half of participants received no such instruction or advanced knowledge of the rotation. Participants who were given a compensation strategy made increasingly larger errors whereas participants who were not told of the rotation made increasingly smaller errors. In our study, children were told that the visual coordinates would be reflected about the midline, but they were not told when it would occur or how to compensate for it. They were successful in reducing error across the transformation block, but error remained high at the end of training. Unlike the study by Mazzoni and Krakauer (2006), error was also high at the beginning of the transformation block when cursor feedback was suddenly reflected about the midline. This difference may be due to the explicit strategy given to the participants in the Mazzoni and Krakauer (2006) study, whereas the participants in our study were required to identify an appropriate strategy to compensate for the novel sensorimotor transformation.

During the tracking task, children with ASD lagged behind the target to a greater extent than TD children, especially when the target moved at the fast speed and when visual feedback was reflected about the midline. Grigorova and Bock (2006) recorded hand paths and eye positions while healthy adults tracked a moving target while visual feedback was reflected about the midline. In their study, one group of participants was instructed to look at the target, whereas another group of participants was instructed to look at the cursor. Interestingly, eye position recordings found that both groups of participants actually looked at the target. However, participants who were instructed to look at the cursor performed the task with less error than those who were instructed to look at the target. They concluded that the group which was instructed to look at the cursor distributed their spatial attention between the target and the cursor which improved their performance compared to those who only paid attention to the target. Eversheim and Bock (2001) characterized hand paths while participants tracked a moving target while visual feedback was reflected in the up-down direction (i.e. the “acquisition task”), and while they concurrently performed a button-press task in response to visual stimuli (i.e. the “loading task”). During the loading task, participants were to press one of four response buttons to correspond to a visual stimulus that appeared in one of four locations. Participants completed four versions of the loading task which differed in the cognitive load required: the *control* task was performed as described above, the *attention* task included a pre-cue to indicate the location of the next visual stimulus, the *tapping* task required a short-long-short sequence of button presses, and the *rotation* task required selecting responses that were rotated 90° from the visual stimulus. The pattern of errors measured from the acquisition task varied across the four loading tasks, suggesting that spatial attention was in high demand early in the learning sequence, while movement preparation was in high demand late in the learning sequence. Thus, the pattern of ASD-related errors in our reaching and tracking tasks with sudden reflection suggests that children with ASD exhibit deficits in movement preparation.

Intact Movement Execution in ASD

Our primary performance measures (IDE for the reaching tasks, and LE for the tracking task) were used to identify group-wise differences in compensation for visuospatial conflict. When sensorimotor distortion was applied to visual feedback, children with ASD made more errors than TD children; however, errors were indistinguishable between the groups during baseline conditions, suggesting that movement execution is intact in children with ASD. We further characterized movement execution by comparing movement curvature (AR), smoothness (SYM), and the time to prepare (RRT) and execute movements (RMT) across participant groups during the reaching tasks and by comparing the standard deviations of LE and OE, the Submovement Count, and the Submovement Regression Slope across participant groups during the tracking task. Each of these comparisons found no difference in performance variables across participant groups, confirming our conclusion that movement execution is intact in ASD.

These findings contradict those of Stoit and colleagues (2013). In their study, children with ASD and controls performed reach-to-grasp movements in which they grasped one of two objects, which were cued by object location or grip. The authors concluded that movement execution, but not planning, was impaired in ASD. However, their experiment was different from our experiments because they characterized planning based on reaction time and the number of errors the participant made in selecting and grasping the object, whereas we characterized movement planning with errors in the reaching and tracking trajectories. Stoit and colleagues (2013) defined movement execution deficits as delayed movement times in children with ASD compared to controls. Our experimental paradigm of the reaching task was designed to control for movement time because accurate movement speed was required to successfully obtain the targets, and we displayed a warning following reaching movements that were too slow. Our feasibility study (Salowitz et al., 2014) of goal-directed reaching has shown that children with

ASD are able to make fast movements if they receive training prior to kinematic testing and if they are provided knowledge of results of total movement time.

Limitations, Future Directions, and Conclusions

Our method of using consecutive local minima in speed to identify corrective submovements during the continuous tracking experiment has two potential sources of error. First, friction and/or inertia associated with the robot could lead to fewer local minima in the speed profile which would reduce the Submovement Count. However, we found that the Submovement Count and the Submovement Regression Slope both scaled with the amount of spatial information in the goal which could not possibly affect the friction or inertia of the robot because spatial goal information is a visual display which does not affect robot characteristics. Therefore, differences in the Submovement Count and Submovement Regression Slope must have been caused by the way in which participants used information from the leading indicators compared to the single cursor to minimize error in their movements. The second source of error in our method of detecting submovements is that identifying consecutive local minima in the speed profile assumes that submovements do not overlap (Pasalar et al., 2005). However, Pasalar and colleagues (2005) have demonstrated that Submovement Regression Slopes scale with task difficulty even when overlapping submovements are identified using a minimum jerk method. Therefore, it is unlikely that our method of identifying local minima in speed masked significant differences in the number and characteristics of submovements between participant groups, experimental phases, and/or temporal and spatial target information.

During the reaching task with gradual rotation of visual feedback, we found that children with ASD exhibited larger errors at the end of training compared to TD children. One possible explanation for increased IDEs in the ASD group compared to the TD group is that children with ASD may have delays in updating their motor plan. Since we found no group difference in IDE measured during initial exposure to the 30° rotation of visual feedback and we found no group difference in baseline performance with veridical feedback, it is unlikely that TD children had a pre-existing advantage of motor execution compared to children with ASD. Therefore, increased errors at the end of training in the ASD group compared to the TD group likely resulted from impairments in using the prior training trials with incrementally-imposed rotations to update their motor commands. The increment (1° per cycle) may have been too large for children with ASD to automatically update their motor commands at the level observed in the TD group. In fact, one participant in the ASD group reported that he perceived the applied rotations. A future study could be designed with smaller increments of 0.5° per cycle to determine the extent to which children with ASD are able to minimize movement errors in response to rotation when they have more training trials at smaller rotational increments, and when they are less likely to perceive the applied rotations.

The series of experiments presented in this study found that children with ASD exhibited subtle deficits in their ability to compensate for small differences between visual feedback and motor commands and they were impaired in their ability to compensate for large, noticeable differences between visual feedback and motor commands compared to TD children. The latter deficits were present during both discrete reaching and continuous tracking movements. These results were unrelated to motor execution because movement kinematics did not differ between groups. Thus, the results suggest that both automatic sensorimotor adaptation and volitional strategic compensation are impaired in children with ASD during goal-directed movements of the hand.

CHAPTER 5: INTEGRATION OF VISUAL AND PROPRIOCEPTIVE PERCEPTION OF MOVEMENT KINEMATICS IN CHILDREN WITH AND WITHOUT AUTISM SPECTRUM DISORDER

Children with autism spectrum disorder (ASD) often exhibit deficits in sensory information processing, yet the nature and consequence of these deficits is unclear. An important goal of sensory information processing is the integration of multiple modalities (e.g. visual and somatosensory information) for perception of body and limb movements in space. Here we test the hypothesis that children with ASD exhibit deficits in multimodal sensory integration for motion perception relative to typically developing (TD) children. Ten high-functioning children with ASD and ten TD children performed a two-interval, forced choice, hand path curvature discrimination task. We characterized the ability to discriminate between hand and/or visual cursor paths (both called endpoint paths) of differing curvature and to characterize relative importance of vision vs. proprioception in the perception of endpoint motion. Children performed the task under single-modality (visual or proprioceptive stimuli) or bimodal conditions (simultaneous visual and proprioceptive stimuli). We additionally investigated how uncertainty in the visual stimuli might influence perception by varying the width of the cursor's Gaussian spatial distribution on different trials. We estimated two psychometric variables from standard cumulative Gaussian functions fitted to the task response data: the standard deviation of the underlying psychometric models and the point of subjective equality (PSE). We used these variables to estimate the contributions of vision and proprioception to the perception of endpoint motion. Standard deviations (also called discrimination thresholds) of the psychometric models are inversely related to the precision in which participants could discriminate between curvatures. Children with ASD exhibited increased discrimination thresholds during the bimodal condition as compared to TD children, and as compared to discrimination thresholds estimated from the single-modality experiments. These findings support the hypothesis that the neural processes underlying multisensory integration are compromised in children with ASD. By contrast, both groups of children exhibited systematic re-distribution of sensory weights such that visual dominance over proprioception decreased as the amount of visual uncertainty increased. Contrary to our original hypothesis, we found no evidence for ASD-related deficits in the re-weighting of visual and proprioceptive information for perception of hand-path kinematics. Thus, ASD-related deficits in multimodal sensory integration do not appear to result from deficits in sensory re-weighting during perception of hand path kinematics.

Introduction

The ability to combine sensory information from vision and proprioception to perceive the position and motion of the body and limbs serves several critical functions, including the coordination of gross and fine movements (Ziviani et al., 1982), the perception and use of body language (de Gelder, 2006), and for developing an awareness of personal body space (Spence et al., 2000). Vision and proprioception provide complementary information related to limb position. As a result, people retain the ability to perceive limb state when one of these modalities becomes unreliable (due to aging, disease, or environmental effects) by increasing the contribution of the other intact modality.

For perceptual tasks, such as estimating the size of a hand-held object (Ernst and Banks, 2002), locating the position of the hand relative to the body (van Beers et al., 1999, 2002a) and assessing the geometry of hand path (Reuschel et al., 2010), multisensory cue integration is well characterized such that each sensory estimate $\hat{S}_i$ contributes to a unified, multisensory estimate of state $\hat{S}_{MS}$ in inverse proportion to the variance σ_i^2 inherent to the individual estimates

$$\hat{S}_{MS} = \sum_i \hat{w}_i \hat{S}_i \qquad [5\text{-}1]$$

with

$$\hat{w}_i = \frac{\sigma_i^{-2}}{\sum_j \sigma_j^{-2}} \qquad [5\text{-}2]$$

where *i* and *j* are indices over the set of sensory information channels. We can estimate the relative contribution of each sensory source to the multisensory state estimate based on the relative uncertainty within each of the unimodal signals (Ernst and Banks, 2002). If only vision and proprioception are used to estimate limb position, *Eq 5-1*and *Eq 5-2* reduce to

$$\hat{S}_{MS} = \hat{w}_v \hat{S}_v + \hat{w}_p \hat{S}_p \qquad [5\text{-}3]$$

where

$$\hat{w}_v = \frac{\sigma_p^2}{\sigma_v^2 + \sigma_p^2} \qquad [5\text{-}4a]$$

and

$$\hat{w}_p = 1 - \hat{w}_v \qquad [5\text{-}4b]$$

Here, subscripts *v* and *p* refer to vision and proprioception, respectively. If the uncertainty in the perception of one of these sensory modalities (e.g. vision) increases, then the contribution of the other sensory modality (e.g. proprioception) would increase. We assume that the noises in each sensory modality are independent. If noises in the individual sensory modalities covary, then sensory integration would not be optimal and the resulting bimodal estimate would have greater uncertainty than predicted.

The distribution of sensory weights for perception is well-characterized in healthy adults, who rely on visual information more than other sensory modalities, including haptics (Ernst and Banks, 2002; Helms Tillery et al., 1991; Battaglia et al., 2003), and healthy adults are able to redistribute sensory weights in response to variations in visual uncertainty (Ernst and Banks, 2002; Burns and Blohm, 2010). Sensory information processing is impaired in people with ASD who exhibit hyper- and hyposensitivity, temporary loss of sensation, the incorrect attribution of one sensory modality to another (i.e. synesthesia) and sensory-seeking behaviors (Lane et al., 2010; Ornitz, 1974, 1983; O’Neill and Jones, 1997; Wiggins et al., 2009; Gerrard and Rugg, 2009; Hermelin and O’Connor, 1970; for reviews see Ben-Sasson et al., 2009; Baranek, 2002; Dawson and Watling, 2000; Marco et al., 2011). Yet sensory integration and the distribution of sensory weights have not been characterized in children with ASD and it is unknown whether the ability to redistribute sensory weights in response to environmental uncertainty varies across the broad spectrum of autism.

Some have reported that during sensorimotor integration tasks, children with ASD as a group prefer haptic modalities over visual modalities to a greater extent than TD children who favor vision (Frith and Hermelin, 1969; Masterton and Biederman, 1983; Haswell et al., 2009). In a puzzle completion task, TD children produced increasingly more errors as visual cues decreased (kinesthetic cues increased) while children with ASD exhibited the opposite relation (Frith and Hermelin, 1969) suggesting that children with ASD assign greater importance to kinesthetic over visual stimuli to align puzzle pieces. Others have measured reaching movements during adaptations to prism displacement (Masterton and Biederman, 1983) and to a velocity-dependent force field (Haswell et al., 2009) and they found increased transfer of sensorimotor adaptation between left and right hands (Masterton and Biederman, 1983) and between regions of the workspace requiring identical joint motion (Haswell et al., 2009) in children with ASD compared to TD children. These authors (Masterton and Biederman, 1983; Haswell et al., 2009) concluded that children with ASD have a greater reliance on proprioception compared to controls. Within the ASD group studied by Haswell et al. (2009), those who showed the most reliance on proprioception also exhibited the greatest impairment in motor function, social interaction, and imitation, three main symptoms of the disorder that contribute to delayed development. In each of these studies (Frith and Hermelin, 1969; Masterton and Biederman, 1983; Haswell et al., 2009), sensory dominance was inferred from measures of motor performance such as the number of errors, transfer of sensorimotor adaptation between hands and between regions of the workspace, and the rate of adaptation.

In the current study, children performed a two-interval, forced choice task in which they attended to a series of two movements, which were presented visually (by watching a moving cursor on a video screen), or proprioceptively (by grasping a moving robot handle), or both (bimodal condition). Participants pressed a button to indicate which of the two movements was more curved. We used psychometric analysis to fit a cumulative Gaussian function to button press response data. The standard deviation of the Gaussian function (i.e. discrimination threshold) was inversely related to the precision of participant’s responses, and the mean of the Gaussian function from the bimodal condition was used to measure the relative influence of vision over proprioception for perception. We hypothesize that empirical multisensory discrimination thresholds can be predicted from single-modality measures in TD children, but are non-optimal in children with ASD and we hypothesize that children with ASD favor proprioception over vision to a greater extent than TD controls. The results of our study will determine the extent to which children with ASD integrate visual and proprioceptive information for the perception of hand path kinematics.

Methods

Ten children with ASD [aged 15.1 ± 2.0 years (mean ± standard deviation, here and elsewhere); three female] and ten TD children [aged 15.3 ± 1.9 years; three female] participated in this study. Testing was comprised of three experiments spanning two days spaced > 7 days apart. All study procedures were approved by the Marquette University Institutional Review Board, in compliance with the Declaration of Helsinki. All children gave informed assent after we obtained informed parental consent. Upon enrollment, parents were asked to complete the Child Behavior Checklist for ages 6-18 (CBCL; Achenbach and Rescorla, 2001) and a questionnaire to report their child's medication use. Prior diagnoses of ASD for children in the ASD group were confirmed using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1994): a total score > 7 confirmed presence of ASD. Parents of children who did not have a prior diagnosis of ASD completed the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers et al., 1999); children receiving a total score > 13 were excluded from the TD group because they exhibited behaviors characteristic of ASD.

We performed additional assessments to control potential confounds including intelligence, handedness and social status. All children were administered the Kaufman Brief Intelligence Test, second edition (KBIT2; Kaufman and Kaufman, 2004) to measure intelligence quotients (IQ). Only children with verbal IQ scores > 70 ("high-functioning" children) were included in the study. Each child's handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), which yielded a laterality index (LI) score to determine whether participants were predominately right-handed (LI > 40), left-handed (LI < -40) or ambidextrous (-40 ≤ LI ≤ 40). Parents of children in both groups completed the Barratt Simplified Measure of Social Status (Barratt, 2006). Vision was normal or corrected to normal in all participants except one (participant A3) who had a prosthetic left eye. Table 5-1 presents participant characteristics.

Table 5-1 Participant Characteristics

Group	Participant	Sex	Age	Laterality	SS	KBIT2	*ADOS / ASSQ	Medication
			(years)			T (V, N)	T (C, S) / T	
ASD	A1	F	18.7	0	45	101 (92, 109)	18 (6, 12)	BC, AH, AD, AP
	A2	M	14.6	26	31	115 (117, 108)	7 (2, 5)	AD
	A3	M	16.6	-100	59	104 (87, 119)	14 (5, 9)	AD, AP
	A4	F	14.6	60	53	110 (106, 111)	10 (3, 7)	ST, AD, AP, AH
	A5	M	16.6	100	53	114 (117, 106)	9 (3, 6)	-
	A6	F	11.2	70	48	122 (118, 119)	7 (3, 4)	ST
	A7	M	15.3	-40	43	74 (74, 81)	13 (5, 8)	ST, AH
	A8	M	13.7	90	53	116 (112, 114)	10 (3, 7)	ST, AD, AP
	A9	M	16.2	78	53	96 (100, 92)	7 (2, 5)	ST, AP, AH, AC
	A10	M	13.9	88	48	131 (135, 118)	10 (4, 6)	ST, AD
	M ± SD		**15.1 ± 2.0**	**37 ± 66**	**49 ± 8**	**108 ± 16**	**11 ± 4**	
TD	T1	M	16.4	58	66	116 (122, 105)	0	-
	T2	F	13.0	88	66	139 (130, 139)	0	-
	T3	F	13.9	88	37	78 (86, 72)	1	-
	T4	M	14.2	100	46	116 (105, 122)	1	-
	T5	M	16.7	100	42	104 (110, 96)	0	-
	T6	M	15.3	89	37	93 (91, 97)	1	-
	T7	M	12.2	68	60	129 (130, 121)	0	-
	T8	M	15.7	80	42	115 (114, 111)	0	-
	T9	M	17.8	100	61	82 (93, 76)	0	-
	T10	F	17.5	53	42	106 (108, 104)	0	-
	M ± SD		**15.3 ± 1.9**	**82 ± 17**	**50 ± 12**	**108 ± 19**	**0.3 ± 0.5**	

Abbreviations: ASD autism spectrum disorder, TD typically developing, SS social status, KBIT2 Kaufman Brief Intelligence Test, 2nd Edition, ADOS Autism Diagnostic Observation Schedule, ASSQ Autism Spectrum Screening Questionnaire, T total, V verbal, N nonverbal, C communication, S social, M male, F female, BC birth control, AH anti-hypertensive, AD anti-depressant, AP anti-psychotic, ST stimulant, AC anti-convulsant, **M** mean, **SD** standard deviation

* ADOS reported for ASD; ASSQ reported for TD

Apparatus

Participants sat in a darkened room and held the handle of a horizontal planar robotic manipulandum with their dominant hand (Figure 5-1a). They viewed computer-generated stimuli projected onto a screen placed 10 cm above the plane of hand motion. The dominant arm was supported against gravity using a custom-made sling. An opaque screen prevented direct view of the arm. Participants held a 2- button response box in the non-dominant hand. Two brushless DC servomotors (M-605-A Goldline; Kollmorgen, Radford, VA) drove the robot's handle through pre-defined paths while participants grasped the handle. Handle position relative to the robot's frame was measured to within 0.038 mm using optical encoders (A25SB17P180C06E1CN, Gurley Precision Instruments, Troy, NY) mounted onto the motor shafts. Robot kinematics and button box state were sampled at a rate of 1000 samples per second. Robotic control signals were also generated at 1000 samples per second. The visual display was updated at 40 frames per second. Robot control and post-processing of data were performed using MATLAB software (Natick, MA). Additional details of the robot design and control can be found in (Scheidt et al., 2010).

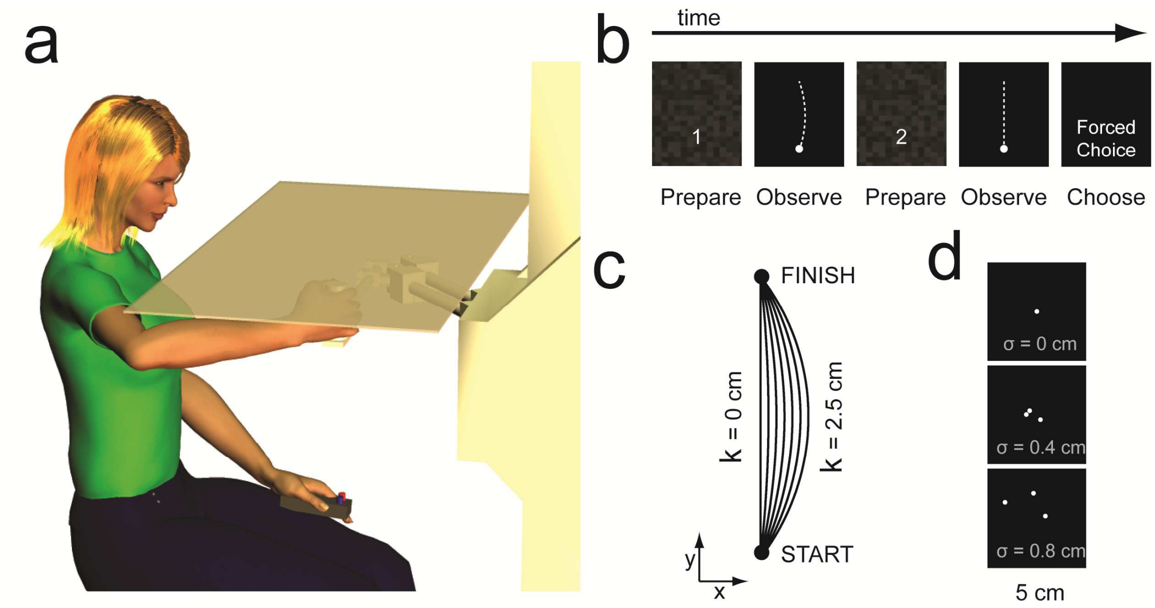

Figure 5-1: Experimental setup. (a) Seated participants grasped the handle of a horizontal planar robotic manipulandum with their dominant hand and held a button response box with their non-dominant hand while they viewed a screen. (b) Task instructions and visual feedback were projected onto the screen. Trials began with a large numeral “1” (Prepare), followed by the first movement. Similarly, the second movement was preceded by the numeral “2” (Prepare). Both movements (dashed lines) were presented with proprioceptive stimuli (the moving robot handle) or visual stimuli (the moving cursor) or both (Observe). Participants were to identify which of the two trajectories was more curved by pressing a button (Choose). (c) Movement trajectories of the visual and proprioceptive stimuli were selected from seven possible straight or curved movement paths with equally-spaced peak horizontal displacement, κ, between 0 and 2.5 cm. (d) Cursor feedback for the visual stimulus was shown by a single cursor (top) or three cursors randomly selected from a 2-dimensional Gaussian with standard deviation of 0.4 cm (middle) or 0.8 cm (bottom).

Task

Each child performed three, two-alternative forced choice, hand-path curvature discrimination experiments that were designed to compare how children with ASD and TD children integrate visual and proprioceptive information during point-to-point reaching movements of the hand. Each experiment consisted of a series of 84 to 756 trials wherein they attended to a series of two movements that were made one after the other (Figure 5-1b). They then pressed a button to indicate whether they perceived the first or second movement to be more curved. In two of the experiments, movement-related feedback was presented in just one sensory modality: ***proprioception only (PO)*** - participants grasped the robot handle while it moved in the absence of moving visual stimuli; ***vision only (VO)*** - participants watched a cursor (0.5-cmdia yellow circle) move on the display screen while the dominant hand rested in the lap. In the third experiment, ***bimodal (vision + proprioception, VP)*** feedback was provided - participants grasped the robot handle as it moved while simultaneously watching a visual cursor move on the screen. In this case, cursor motion started and ended immediately above the hand's actual location, but the cursor and hand could follow paths having different amounts of curvature. In all cases, movements were directed away from the body from a START target (located 25 cm from the sternum) to a FINISH target (located 15 cm beyond START in the sagittal and horizontal planes). Movements had bell-shaped velocity profiles in the y-direction (700 ms duration with 37.8 cm/s peak speed) whereas the x-position was constrained to the perimeter of a circle passing through the two targets (cf. Scheidt et al. 2010). Seven different paths were defined such that their peak horizontal displacements (i.e. maximum x-deviations) equally sampled the range 0 to 2.5 cm (Figure 5-1c). Movements always curved toward the participant's dominant side. After each movement in the PO and VP experiments, the handle returned to the START position via a smooth, straight path; participants were instructed to ignore the handle's return to START. The handle was constrained to the START target between movements.

To prompt participants to attend to the movements, a large numeral "1" was projected onto the screen for 700 ms preceding the first movement whereas a "2" was displayed preceding the second movement (Figure 5-1b). Movements began 500 ms after the numeral disappeared. After the second movement was presented, participants were instructed to "Press the LEFT button if movement 1 was more curved than movement 2; press the RIGHT button if movement 2 was more curved". Participants completed 5 practice trials prior to each experiment to familiarize themselves with the task requirements. Data from these practice trials were discarded. Several ~2 minute break periods were included in each experiment to allow participants to rest.

During preliminary testing, two of four pilot subjects reported using a strategy wherein they visually fixated at the location of the cursor's peak displacement in the first movement throughout the inter-observation interval. This strategy allowed participants to compare pairs of cursor movements without forming a memory of the initial movement. To discourage this "visual fixation" strategy, which could only be applied during VO and VP experiments, we applied a scintillating, low-contrast, random-dot, background in all experiments whenever prompting numerals were displayed on the screen. The scintillating background was formed by a grid of 1 cm x 1 cm dots having intensity values randomly sampled from a uniform distribution of luminance values (14.14 ± 0.06 cd/m^2 to 16.78 ± 0.18 cd/m^2). The random dot background was updated at the display rate of 40 frames per second.

Day 1: Single-Modality Experiments

On Day 1, each participant completed the PO and VO experiments in ~1 hr. These experiments were used to characterize sensory perception of vision and proprioception, independent of each other and to make a prediction of sensory perception when both modalities were combined in the bimodal experiment. In both PO and VO experiments each trial included a *standard* movement (1.25 cm peak displacement) which was compared to a *probe* movement for which peak displacement was pseudo-randomly selected from seven possible values: {0.00, 0.42, 0.83, 1.25, 1.67, 2.08, 2.50} cm. The order of movements (standard and probe) was randomized within trials.

In the PO experiment, participants completed 84 trials (12 trials for each of the seven probes) divided into four blocks of 21 trials each. The presentation order of probes was pseudo-randomized within each block but was the same for all participants.

During the VO experiment, we additionally investigated the extent to which uncertainty in the spatial location of the visual stimuli (Figure 5-1d) might influence perception of hand-path curvature. In one third of the trials, the visual stimulus was a single cursor with no experimentally-imposed uncertainty. For the remaining two thirds of the trials, the visual stimulus was a "twinkling" cluster of three cursor elements, randomly selected from a 2-dimensional Gaussian that had a standard deviation of either 0.4 cm or 0.8 cm. The cursor clusters were updated and displayed (40 times per second) centered on the desired path coordinates (Figure 5-1d). Both movements within each trial always had the same level of visual uncertainty. Participants completed 252 VO trials consisting of seven blocks of 36 trials each (12 trials for each of the three levels of visual uncertainty and seven probes). The order of imposed visual uncertainty values was pseudo-randomized across trials but the sequence was the same for all participants. The order of PO and VO experiments was counter-balanced across participants.

Day 2: Bimodal Experiment (assessing visuo-proprioceptive integration)

During the second experimental session (~2.0-hour), participants performed the version of the hand-path curvature discrimination task wherein visual and proprioceptive stimuli were simultaneously presented (VP). This experiment was used to characterize sensory perception when vision and proprioception were integrated. Here, the moving cursor might deviate from the hand's actual path by some predetermined amount. The two movements of each trial consisted of: a *standard*, in which the peak visual and proprioceptive path displacements differed by an amount Δ pseudo-randomly selected from the set {-0.83 cm, 0.00 cm, 0.83 cm} (the average path displacement was 1.25 cm in each case), and a *probe*, in which the visual and proprioceptive peak path displacements were equal to each other and pseudo-randomly selected from the seven possible peak displacements: {0.00, 0.42, 0.83, 1.25, 1.67, 2.08, 2.50} cm. By separating visual and proprioceptive path displacements in the standard movement by Δ, (designed to be imperceptible to participants), participants had to choose whether to rely on the visual stimulus, the proprioceptive stimulus, or more likely, a combination of both stimuli for perception. Thus, we were able to empirically determine the extent to which participants relied on one sensory modality compared to the other for perception of movement kinematics. The within-trial order of standard and probe was randomized. Participants completed 756 VP trials consisting of nine blocks of 84 trials each (12 trials for each combination of three Δ levels, three visual uncertainty levels, and seven probes). The order of trials was pseudo-randomized within blocks and was the same for all participants.

Data Analysis

Psychometric Function Estimation

The button response from each trial (i.e. each standard/probe pair) was used to determine – for each of the seven probe values – the percentage of trials in which participants perceived the probe to be more curved than the standard. We then fit (MATLAB function `fmincon`) cumulative Gaussian functions to the data obtained for the PO condition, for each level of visual uncertainty in the VO condition and for each of the nine combinations of Δ and visual uncertainty in the VP condition. Two psychometric measures were obtained from each fitted cumulative Gaussian: the point of subjective equality (PSE) and the standard deviation (σ). PSE is defined as the probe displacement for which the standard and probe could not be distinguished from each other (i.e. peak probe displacement for which the two possible responses were equally probable). The standard deviation is a measure of participants' ability to discriminate between curvatures and is the difference in displacement between the PSE and the probe displacement value that was perceived more curved than the standard value 84% of the time (see also Ernst and Banks, 2002). We furthermore constrained the Gaussian fit such that the standard deviation was always greater than some arbitrary small value ($\sigma \geq 0.002$). The purpose of this constraint was to handle possible situations wherein participants might respond with perfect accuracy at and above some value of probe displacement and at chance for all sample points below that value. In such cases, enforcing a minimum σ coerced the optimization to yield σ^2 values centered within the range bounded by the sample points spanning the transition.

Model of Multisensory Integration for Perception

We sought to characterize the ability of children with ASD and TD children to discriminate movement curvatures using visual and/or proprioceptive perception. The discrimination threshold, σ, was determined for the PO condition, for each level of visual uncertainty in the VO condition, and for the nine combinations of Δ and visual uncertainty in the VP condition. Discrimination thresholds of the PO and VO experiments were used to form a prediction of the multisensory discrimination threshold in the bimodal condition. An increase in multisensory discrimination threshold, σ_{vp}, corresponded to an increase in variability in the participant's responses. The predicted multisensory discrimination threshold, $\hat{\sigma}_{vp}$, was determined by scaling the visual and proprioceptive variances determined from the PO and VO experiments by the relative sensory weights (*Eq 5-3,5- 4a, 5-4b*; see also Ernst and Banks, 2002)

$$\hat{\sigma}_{vp} = \sqrt{\frac{\sigma_v^2 \sigma_p^2}{\sigma_v^2 + \sigma_p^2}} \qquad [5\text{-}5]$$

The multisensory discrimination threshold was predicted from the PO experiment and each level of uncertainty in the visual stimulus in the VO experiment. Assuming that noises in the different sensory channels are independent and Gaussian-distributed, the multisensory estimate is optimal in that it has lower multisensory variance σ_{vp}^2 than either of the individual sensory estimates, σ_v^2 and σ_p^2 (Ghahramani et al., 1997) and therefore, the estimate also has lower multisensory discrimination threshold (*Eq 5-5*) than either of the individual sensory estimates. In this way, the neural mechanisms that integrate sensory information for perception appear to use knowledge of the statistical properties of the individual sensory cues to optimize the overall state estimate.

The multisensory discrimination threshold was determined empirically from the VP experiment by averaging the standard deviations of the cumulative Gaussian fits across the differences, Δ, between visual and proprioceptive path displacements in the standard stimulus

$$\sigma_{vp} = \frac{1}{3}\sum_{\Delta}\sigma_{\Delta} \qquad [5\text{-}6]$$

The multisensory discrimination threshold was determined empirically from the VP experiment for each level of uncertainty in the visual stimulus. If participants integrate vision and proprioception in a statistically optimal way, then the empirical multisensory discrimination threshold (*Eq 5-6*) should equal the predicted estimate of multisensory discrimination threshold (*Eq 5-5*).

Relative Sensory Dominance in the VP Testing Condition

The relative influence of vision compared to proprioception was empirically measured during curvature perception in the bimodal experiment when both modalities were simultaneously presented in each trial. Under the assumption that the estimators are on average unbiased (i.e. the estimates $\hat{S}_v$ and $\hat{S}_p$ from *Eq 5-1* and *Eq 5-3* can be replaced by the actual cursor and robot path displacements S_v and S_p, respectively), it is possible to compute the relative visual weight during the VP condition from *Eq 5-3* by making the additional assumption that the multisensory estimate, S_{MS}, is equal to the point of subjective equality, PSE, when both vision and proprioception are given. Recalling *Eq 5-4b* and defining Δ as $S_v - S_p$ we obtain:

$$PSE = w_v \Delta + S_p \qquad [5\text{-}7]$$

We used PSE to obtain the relative weights for each level of visual uncertainty in the VP experiments. More specifically, we plotted PSE as a function of Δ for each level of visual uncertainty. We used linear least squares regression to fit a line (constrained to pass through the proprioceptive displacement $S_p = 1.25$ cm when $\Delta = 0$) to each of the plots. The slope of the resulting line (i.e. the relationship between PSE and Δ) is a measure of the relative visual and proprioceptive weights such that when vision dominates ($w_v = 1$) the slope is 0.5 and when proprioception dominates ($w_v = 0$) the slope is -0.5 (cf. Helbig and Ernst, 2008).

Validation of Experimental Methods

Since we measured the ability of participants to discriminate between very small (0.42 cm) displacements in robot path curvature in the PO and VP experiments, we verified whether the robot accurately produced the desired peak horizontal displacement. For each participant, we determined the maximum horizontal displacement for each of the two movements in every trial of the PO and VP experiments. We then plotted the actual peak horizontal displacement as a function of the desired displacement and fit a line to the data. If the measured data were accurate on average, we would expect the slope to be very close to 1 and if the data were well characterized by the regression line, we would expect the coefficient of determination, R^2, to be close to 1.

Since we quantified sensory perception and integration using two measures (discrimination thresholds, relative sensory weights) derived from fitted models, we wished to evaluate the quality of the cumulative Gaussian model fitted to observed proportion data and the quality of the linear regression of PSE as a function of Δ. The quality of the psychometric model fits were evaluated by computing the correlation, R, between the observed proportion of trials in which participants indicated the probe more curved than the standard and the fitted proportion averaged across models for each participant. If R equals

1, the observed proportions were perfectly described by the fitted model, but if R equals 0, there is no agreement between observed proportions and the model or there is no variation in the data. The linear fits of PSE as functions of Δ were also evaluated by computing R which is appropriate for the linear models of PSE as a function of Δ as well as the nonlinear cumulative Gaussian models of the observed proportion data. However, if participants were just as likely to rely on vision as proprioception during the bimodal experiment, their plot of PSE as a function of Δ would have a slope of 0, and therefore the correlation coefficient, R, would also equal 0. Thus we did not impose a constraint on R for the plots of PSE as a function of Δ because we did not want to exclude participants who were just as likely to rely on vision as proprioception for perception (i.e. $w_v = 0.5$).

Statistical Hypothesis Testing

We sought to compare the way in which children with ASD and TD children integrate visual and proprioceptive information for the perception of hand path kinematics. First, we tested the hypothesis that the discrimination threshold of the PO experiment, σ_p, was the same as the discrimination threshold of the VO experiment, σ_v, when there was no uncertainty in the visual stimulus. To test this hypothesis, we used a linear mixed model with compound symmetry covariance matrix to compare discrimination thresholds across participant groups (ASD, TD) with modality type (proprioception, vision) as a repeated factor. We anticipated that uncertainty in button press responses during the PO experiment, σ_p, would be smaller than the uncertainty in responses during the VO experiment with no imposed uncertainty, σ_v. Therefore, we sought to determine the amount of uncertainty in the visual stimulus which would lead to a discrimination threshold of the VO experiment equivalent to that of the PO experiment with no imposed uncertainty in the stimulus. We plotted the uncertainty in the visual stimulus as a function of the discrimination threshold of the VO experiment averaged across participants in each group. We then fit a line to each plot and used interpolation to report the average amount of uncertainty in the visual stimulus in which the discrimination threshold of vision was equivalent to the discrimination threshold of proprioception for each group.

Next, we used a linear mixed model to test the hypothesis that multisensory discrimination thresholds in the single-modality experiment ($\hat{\sigma}_{vp}$, *Eq 5-5*) could predict empirical multisensory discrimination thresholds measured from the bimodal experiment (σ_{vp} , *Eq 5-6*) repeated within participants, across the ASD and TD groups with the amount of uncertainty in the visual stimulus (0.0, 0.4, 0.8 cm) as a within-subject repeated factor. It is possible that empirical discrimination thresholds were influenced by the differences in displacement, Δ, between the visual stimulus and the proprioceptive stimulus in the standard movement which would lead to a difference between the predicted discrimination threshold and the empirical threshold. Where we found a difference between the predicted threshold and the empirical threshold, we planned a post-hoc linear mixed model test (within group) to test the hypothesis that empirical discrimination thresholds differed with the displacement, Δ, with the amount of uncertainty in the visual stimulus as a repeated factor.

Finally, we used a linear mixed model to test the null hypothesis that the relative influence of vision over proprioception during sensory integration (w_v, *Eq 5-7*) were the same across participant groups with the amount of uncertainty in the visual stimulus as a within-subject repeated factor. We performed post-hoc t-tests with Bonferroni correction to examine significant main effects and interactions. Statistical tests were performed using the SPSS 21 (IBM, Armonk, NY) software package. Effects were considered statistically significant at the $\alpha = 0.05$ threshold.

Results

One child with ASD was unable to follow task instructions and was therefore dropped from the study. All other children (Table 5-1) successfully completed the first day of testing (VO and PO experiments). Three children were unable to complete the second day of testing (VP experiment) and their data from the VP experiment was excluded: one child with ASD (A06) complained of “boredom” and did not wish to complete the task, one TD child (T06) could not be contacted to return for the second experimental session; another TD child (T07) randomly guessed which button to press. All other children were attentive to the task on both days of testing.

Group statistics for age, social status, IQ, handedness, ADOS and ASSQ scores are presented in Table 5-1. Participant groups were well matched for age ($t_{18} = -0.15$, $p = 0.89$), social status ($t_{18} = -0.27$, $p = 0.79$), and total IQ ($t_{18} = 0.06$, $p = 0.95$). None of the children in the TD group were identified as having behaviors characteristic of an ASD as measured by the ASSQ and none of the children in the TD group attained scores within the clinical range of the CBCL. As determined by the ADOS, all children in the ASD group met criteria for ASD. All children in the TD group were right-handed, whereas in the ASD group, six children were right-handed, two children were left-handed and two children were ambidextrous.

We next determined whether the robot was able to accurately produce the peak horizontal displacements in the PO and VP experiments. The robot performed well such that the peak horizontal displacements generated by the robot accurately matched the desired displacements (slope of 1.02) and peak horizontal displacements were consistent across movements (R^2 realized displacement vs. desired displacement = 0.99).

Button-press data from the single-sensory-modality experiments of Day 1 were well fit by cumulative Gaussian functions as determined by the correlation coefficients between observed proportions and model fits ($R_{ASD} = 0.93 \pm 0.05$, $R_{TD} = 0.95 \pm 0.04$) and as shown for the selected individuals from the two participant groups (Figure 5-2a). All children had correlation coefficients greater than 0.80. On average across participants, the PSE fell within 0.09 cm of the standard displacement (PSE = 1.34 ± 0.09 cm vs. κ = 1.25 cm, Figure 5-2a, bottom), indicating that when the probe displacement was equal to the standard, participants selected between the two response options with bias that was four times smaller than the minimum difference between peak curvature displacements ($\Delta\kappa$ = 0.42 cm). Bar plots show the standard deviations of the cumulative Gaussian functions for the PO condition, and for each level of uncertainty in the VO condition (Figure 5-2b). Within the VO experiment, the standard deviations of the cumulative Gaussian functions increased as visual uncertainty increased. Moreover, across the two experiments, the average σ_v when the visual stimulus had no imposed uncertainty was smaller than σ_p. This finding was confirmed with a linear mixed model which rejected the hypothesis that the discrimination threshold of the PO condition was equal to that of the VO condition when there was no imposed uncertainty ($F_{1, 18.0} = 15.47$, p = 0.001). However, there was no main effect of participant group and no modality x group interaction indicating that uncertainty in button-press responses did not differ between children with ASD and TD children during the single-modality experiments. Linear regression analysis of the relationship between the amount of uncertainty in the visual stimulus and the average discrimination thresholds in the VO experiment found that the discrimination threshold in the PO experiment would be equivalent to the discrimination threshold in the VO condition were the visual stimulus to have a standard deviation of 0.78 cm (ASD) or a standard deviation of 0.75 cm (TD).

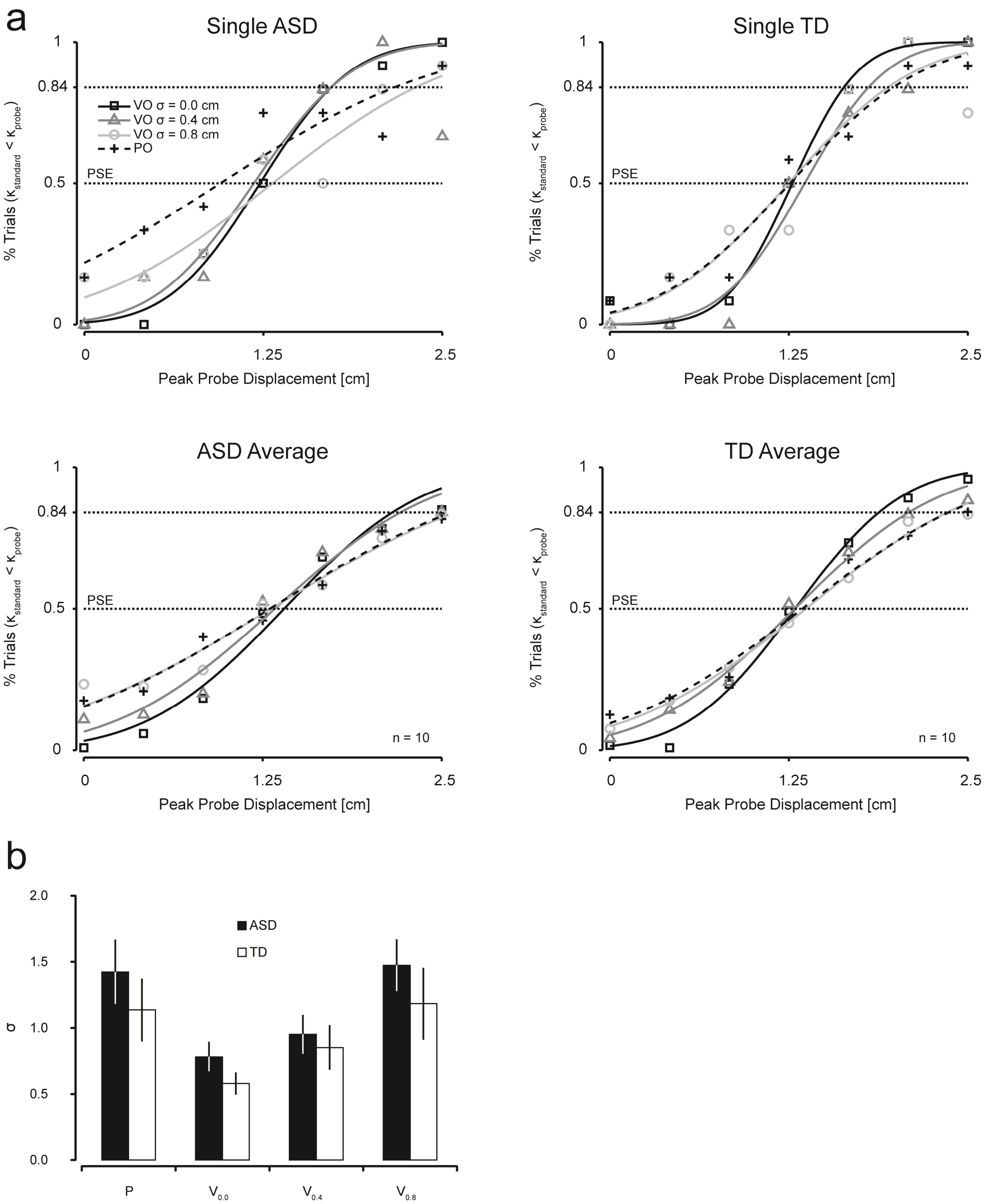

Figure 5-2: Psychometric function estimation of single-modality experiments. (a) Cumulative Gaussian functions were fit to the proportion of trials in which the probe was perceived more curved than the standard as a function of peak probe displacement during the PO (dashed) and VO (solid) testing conditions with no uncertainty (black) and with visual uncertainty σ = 0.4 – 0.8 cm (gray). Results are shown for a single participant (top) and group averages (bottom) of children with ASD (left) and TD children (right). Dotted horizontal lines represent the PSE (50%) and standard deviation (84% - PSE) of the cumulative Gaussian functions. (b) Group averages of discrimination thresholds for children with ASD (filled) and TD children (open). Vertical error bars: ± 1 SEM.

We then fit cumulative Gaussian functions to the three levels of visual uncertainty and the three levels of Δ in the VP experiment of Day 2 (Figure 5-3a). As in the unimodal experiments, the bimodal Day 2 data were well fit by cumulative Gaussian functions ($R_{ASD} = 0.88 \pm 0.12$, $R_{TD} = 0.97 \pm 0.03$). For each cumulative Gaussian function we obtained the standard deviation and the PSE. We plotted PSE as a function of Δ for each level of uncertainty in the visual stimulus and fit a line to the data ($R_{ASD} = 0.77 \pm 0.22$, $R_{TD} = 0.88 \pm 0.13$). The slope of PSE as a function of Δ was used to compute the relative visual weight (*Eq 5-7*).

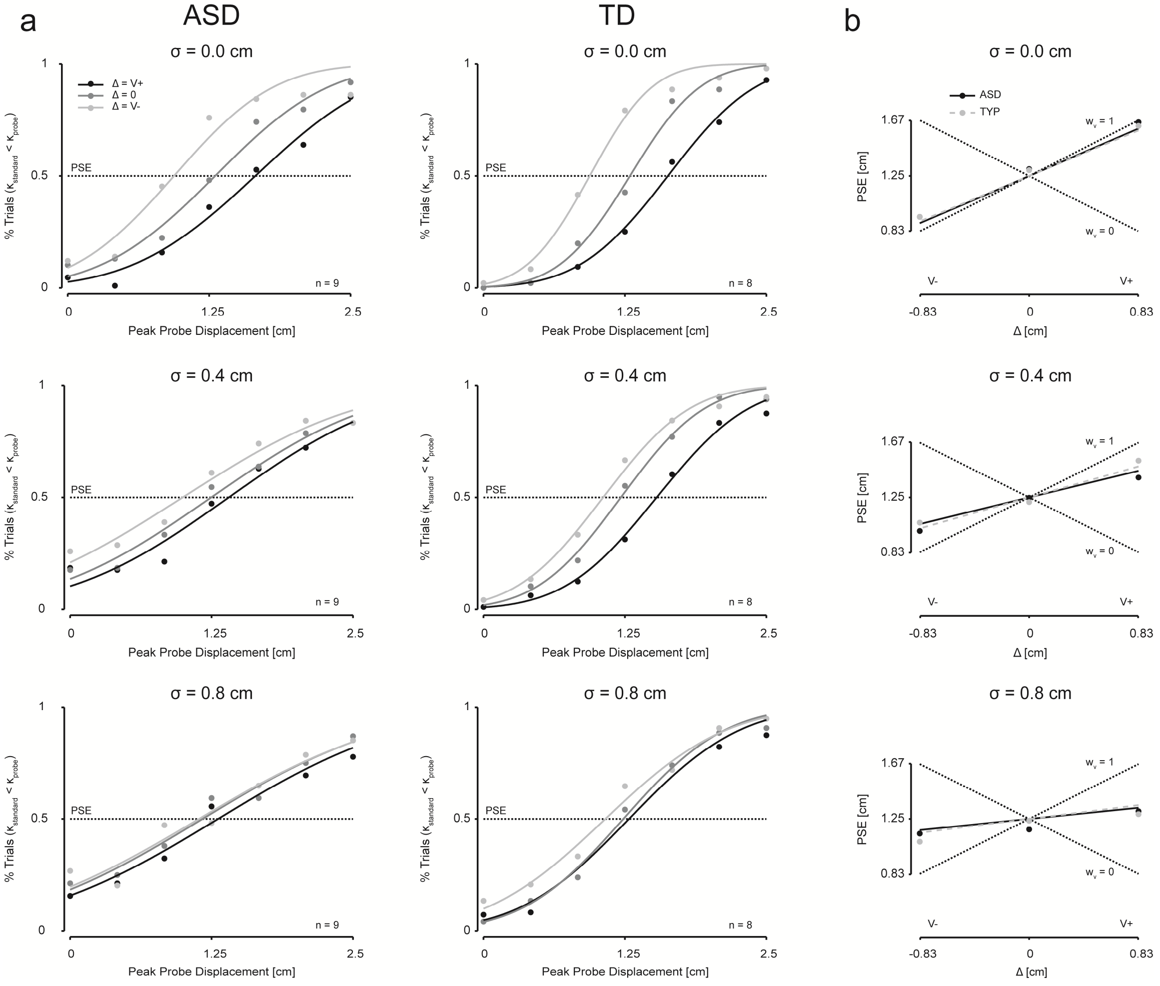

Figure 5-3: Multisensory integration in the VP experiment. (a) Psychometric function estimation of the VP experiment. Cumulative Gaussian functions were fit to the proportion of trials in which the probe was perceived more curved than the standard as a function of peak probe displacement during the VP testing condition with no uncertainty (top) and with visual uncertainty σ = 0.4 cm (middle) and σ = 0.8 cm (bottom). During the standard movement, the cursor and robot differed by an amount Δ in which the cursor was more curved than the robot (V+, black) the robot was more curved than the cursor (V-, light gray) or the two paths were the same (0; medium gray). Results are averaged for the ASD (left) and the TD (right) groups. Dotted lines represent the PSE used to determine the measured visual weights in (b) PSE as a function of Δ. The slope of the fitted line is used to compute the measured visual weight during the VP experiment for the ASD group (black, solid) and the TD group (gray, dashed). Dotted lines represent the conditions in which vision is exclusively used ($w_v = 1$; slope = 0.5) or proprioception is exclusively used ($w_v = 0$; slope = -0.5).

We next sought to identify whether multisensory discrimination thresholds obtained from the VO and PO experiments could predict empirical multisensory discrimination thresholds in the VP task in children with ASD and TD children (Figure 5-4a). A linear mixed model found a main effect of condition (predicted vs. empirical: $F_{1,\,83.5} = 19.41$, $p < 0.001$) and an interaction between participant group and condition ($F_{1, 83.5} = 10.09$, $p = 0.002$). We investigated the interaction between participant group and condition by performing four post-hoc tests with Bonferroni correction to compare predicted and empirical discrimination thresholds across the participant groups. We found that empirical discrimination thresholds measured during the bimodal experiments differed between the ASD and TD groups ($p = 0.01$). Empirical discrimination thresholds in the ASD group differed from those predicted from data collected during the single-modality experiments ($p < 0.001$). However, post-hoc testing did not reject the hypothesis that empirical thresholds in the TD group were predicted by the single-modality experiments ($p = 0.40$) nor did it reject the hypothesis that predicted thresholds were the same in the two groups ($p = 0.57$). The finding that empirical discrimination thresholds were much higher in the ASD group compared to the empirical TD thresholds and the predictions (from unimodal threshold measures) indicates the presence of an ASD-related deficit in multimodal sensory processing for the perception of movement kinematics. The same linear mixed model test also found a simple main effect of visual uncertainty ($F_{2, 81.2} = 11.31$, $p < 0.001$). Post-hoc tests found that discrimination thresholds of the single cursor stimulus differed from those measured when the visual stimuli had uncertainty with standard deviations of 0.4 and 0.8 cm (both $p < 0.03$), which did not differ significantly from each other ($p = 0.12$). As seen in Figure 5-2, the discrimination threshold in the VO conditions increases as uncertainty in the visual stimulus increases for both groups.

We next sought to determine whether increased bimodal discrimination thresholds in children with ASD might result from the presence of conflict between visual and proprioceptive feedback in the standard movement (i.e. in trials with non-zero values of Δ in the standard stimulus). We therefore performed a post-hoc linear mixed model test within the ASD group to determine whether thresholds differed by the hand/cursor displacement Δ {-0.83 cm, 0.00 cm, +0.83 cm}, with level of visual uncertainty as a repeated factor. Although we found a main effect of visual uncertainty ($F_{2, 64} = 8.08$, $p = 0.001$), we observed no main effect of Δ and no interaction between visual uncertainty and Δ (both $p > 0.75$). Thus, increased empirical discrimination thresholds in the ASD group did not depend on the presence or absence of sensory discord in the standard movement.

Finally, we sought to determine whether empirical visual weights measured from the VP experiment (*Eq 5-7*) varied across imposed visual uncertainty levels and/or across participant groups

(Figure 5-4b). Variations across imposed uncertainty levels would be expected if the neural mechanisms mediating sensory integration for perception combine the different sensory information sources in a way that minimizes uncertainty in the overall, multimodal estimate. Our final, planned linear mixed model test found a main effect of visual uncertainty level ($F_{2,\,30.0} = 17.40$, $p < 0.001$), but no main effect of participant group and no uncertainty x group interaction. A post-hoc test was performed (with Bonferroni correction) for each pair of visual uncertainty levels. All post-hoc tests rejected the hypothesis that relative visual weights were the same across visual uncertainty levels (all $p < 0.02$). These results are supported by the psychometric plots of Figure 5-3a, which show that the PSE for each Δ moved closer to the proprioceptive standard S_p as uncertainty in the visual stimulus increased. They are also supported by the plots of PSE as a function of Δ (Figure 5-3b), which show that the slopes (equivalent to the relative visual weight, w_v) decreased as uncertainty in the visual stimulus increased. Thus, ASD-related deficits in multimodal sensory processing (demonstrated through analysis of bimodal discrimination thresholds) do not appear to result from deficits in sensory re-weighting (as revealed by analysis in the relative contributions of visual and proprioceptive sensation, which were similar across participant groups but varied as uncertainty in the visual feedback was experimentally increased).

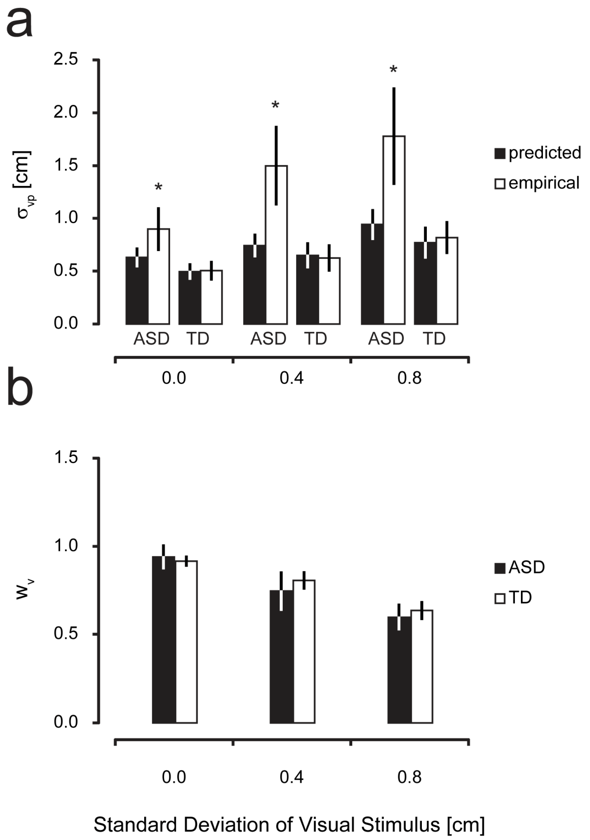

Figure 5-4: Statistical group averages. (a) Relative visual weights for children with ASD (filled) and TD children (open) and (b) predicted multisensory discrimination thresholds from the VO and PO experiments (filled) and empirical multisensory discrimination thresholds measured from the VP experiment (open). Vertical error bars: ± 1 SEM. * $p \leq 0.01$.

Discussion

Children with ASD and TD children performed a two-interval forced choice curvature discrimination task with three different levels of imposed visual uncertainty. In both groups, bimodal discrimination thresholds increased as uncertainty in the visual stimulus increased. However, bimodal empirical discrimination thresholds were significantly higher in children with ASD compared with empirical discrimination thresholds of TD children and compared with predicted discrimination thresholds in the ASD group. Visual weights were greatest and favored vision during the baseline condition with no uncertainty in the visual stimulus. As stimulus uncertainty increased, we found that visual weights decreased (and proprioceptive weights increased) in both groups of children with no measured difference between groups. Taken together, these findings suggest that the relative influence of vision over proprioception is intact in ASD, but the precision (i.e. inverse discrimination threshold) with which children with ASD integrate vision and proprioception to discriminate between hand and cursor curvatures is non-optimal.

Multisensory Integration is Non-Optimal in ASD

Discrimination thresholds are inversely related to the precision with which participants discriminate between movement curvatures. As discrimination thresholds increase, precision in their button-responses decrease. The discrimination thresholds of the PO and VO experiments were used to predict the empirical threshold when vision and proprioception were simultaneously presented. Our findings show that TD children combine vision and proprioception in a way that is predicted by the single-modality experiments, but children with ASD fail to combine vision and proprioception in an optimal way. A possible reason for increased empirical discrimination thresholds in children with ASD compared to TD children is that the assumption of independent noises for each sensory modality was violated in this population. If noise in the visual estimate varies with noise in the proprioceptive estimate in ASD, then we would expect to see increased empirical discrimination thresholds in this population.

Discrimination thresholds were measured from psychometric curves fit to button-press response data. The ability to press a button in response to serially-presented sensory stimuli requires cognitive processes to remember the stimuli, select which button to press, plan the motor commands to press the button and execute those commands. These cognitive processes were required for both the single-modality (PO and VO) experiments and the bimodal (VP) experiment; therefore, it is unlikely that empirical discrimination thresholds differed from predicted discrimination thresholds due to deficits in the ability to remember and recall sensory stimuli and/or to select and execute motor commands in children with ASD.

There is increasing interest in characterizing visual and proprioceptive precision in individuals with ASD. Fuentes and colleagues (2011) measured proprioceptive precision in an elbow angle matching task. Their study consisted of an active task in which participants moved their forearm so as to align it with a line depicted on a computer screen above the plane of motion and a passive task in which participants used a joystick to move the line on the computer screen to align with their forearm. Proprioceptive precision was measured as the standard deviation of the angular error between the computer-generated line and the actual forearm position measured across trials. Fuentes and colleagues (2011) found no difference in proprioceptive precision between adolescents with ASD and TD adolescents. Even though proprioception and vision were simultaneously available during their elbow angle matching task, it was fundamentally different from our bimodal task because they measured precision related to the proprioceptive modality alone, whereas we measured the discriminability integrated across both vision and proprioception. Furthermore, participants in the study by Fuentes and colleagues were aware of deviations between vision and proprioception, whereas deviations during our bimodal task (i.e. Δ) were small and designed to be imperceptible. It is unlikely that findings of increased discrimination thresholds in ASD in the current study were attributed to uncertainty caused by the discord, Δ, between the visual stimulus and the proprioceptive stimulus in the standard movement because post-hoc tests revealed that discrimination thresholds did not differ with Δ.

Characterizing visual ability is much more complex than characterizing proprioception. Measures of visual acuity (Ashwin et al., 2009), saccadic eye movements and smooth pursuit (for a review, see Brenner et al. 2007) can be used to describe visuomotor performance. On average, visual acuity is much better in adults with ASD (20:7) compared with controls (20:13) such that acuity in ASD is “so superior that it lies in the region reported for birds of prey” (Ashwin et al., 2009). Studies of whether saccadic eye movements are abnormal in ASD yield conflicting results (Brenner et al., 2007), although memory-guided saccade tasks in particular yield longer latencies and increased response suppression errors in adolescents with ASD compared to TD adolescents (Goldberg et al., 2002; cf Brenner et al., 2007). Closed-loop smooth pursuit gain is reduced in ASD compared to TD, although this finding is likely caused by deficits in prediction rather than deficits in processing sensory information (Takarae et al, 2004; cf. Brenner et al. 2007). One possible confound of our study is that the visual stimulus in our study (a cursor) did not look like a hand and the hand does not move in the VO experiment. Thus it was obvious to participants that the cursor was not a veridical representation of the hand. However, we see the same increase in discrimination thresholds in the VP experiment as uncertainty in the visual stimulus increased as in the VO experiment, suggesting therefore that differences between empirical and predicted discrimination thresholds were not due to participants' inability to reconcile the cursor with the hand.

Relative Influence of Vision over Proprioception is Intact in ASD during Perception

In both groups, the relative influence of vision over proprioception was greater than 0.5 when there was no uncertainty in the visual stimulus, indicating that vision was dominant during baseline conditions. This finding is consistent with that of Gori and colleagues (2008) who measured the relative influence of vision over haptics and reported stronger reliance on visual information compared to haptics in a two-interval forced-choice size discrimination task among children 8 to 10 years old. Here, we show that children with and without ASD – like adults (Ernst and Banks, 2002) - are able to re-distribute sensory weights in favor of proprioception as visual uncertainty increases. In very young children the ability to integrate multimodal sensory information is not developed. Gori and colleagues (2008) found that "prior to 8 years of age integration of visual and haptic spatial information is far from optimal, with either vision or touch dominating totally, even in conditions in which the dominant sense is far less precise than the other". All of our participants were 11 years or older and on average both groups relied on vision more than proprioception, although vision was not exclusively dominant because average visual weights were less than 1.0, suggesting that proprioception also influenced curvature perception.

Whereas sensory information processing deficits such as hyper- and hyposensitivity are commonly reported in ASD in firsthand accounts (O'Neill and Jones, 1997), caregiver questionnaires (Wiggins et al., 2009; Lane et al., 2010; Tomchek and Dunn, 2007; Watson et al., 2011) and observation (Watson et al., 2011), they are less often characterized using quantitative measures (Iarocci and McDonald, 2006; for an exception, see Fuentes et al., 2011). The prevalence of reports of hyper- and hyposensitivity in ASD led us to hypothesize that the relative influence of vision over proprioception during integration of the two sensory modalities might be increased in children with ASD compared to TD children (if vision is hypersensitive and/or proprioception is hyposensitive) or decreased (if vision is hyposensitive and/or proprioception is hypersensitive) during curvature discrimination. However, we did not find differences in sensory weights between our participant groups. Lack of group difference in sensory weights could be explained if both visual and proprioceptive sensitivities were greater than normal (hypersensitive) or both were lower than normal (hyposensitive) by similar amounts within each participant with ASD. In that case, sensory weights (which are ***relative*** measures of sensory dominance between vision and proprioception) would not differ across groups. We also considered that group differences in relative visual weights would not occur if some children with ASD had extremely large w_v and other children with ASD had very low w_v compared to TD children, causing a bimodal distribution in the ASD group centered about the mean visual weight in the TD group. This was not the case in our study. Both groups exhibited sensory weights that were normally distributed with equal variance across ASD and TD groups.

Prior studies have inferred that proprioception is dominant in ASD from motor tasks (Frith and Hermelin, 1969; Masterton and Biederman, 1983; Haswell et al., 2009; Izawa et al., 2012). A fundamental difference between these studies and the current study is that the current study measures sensory integration for a perceptual task, whereas others (Frith and Hermelin, 1969; Masterton and Biederman, 1983; Haswell et al., 2009; Izawa et al., 2012) and our pilot study (Salowitz et al., 2013) measured motor ability requiring active muscle force. Such measures conflate perception of limb states relative to some desired goal state with the ability to properly form and execute motor plans. The current study found that vision is dominant under baseline (no uncertainty) conditions during a purely perceptual task in children with ASD and TD children. The difference between proprioceptive dominance in the prior studies and visual dominance in the current study may be attributed to the type of task employed. Whereas prior studies used motor tasks requiring action, the current study involved a purely perceptual task in which only passive movements of the arm were employed (i.e. the task did not require muscle force production). Computation of sensory expectation depends on whether action or perception is involved (Brayanov and Smith, 2010). Sensory estimation for motor action follows Bayes’ law in which prior expectations contribute to sensory weights. In contrast, sensory estimation for perception defies Bayes’ law such that sensory weights are biased away from prior expectations (Brayanov and Smith, 2010). Furthermore, perception requires hundreds to thousands of trials to adapt sensory expectation (Flanagan et al. 2008; cf. Brayanov and Smith, 2010) whereas the motor system adapts sensory expectation in 3-5 trials (Flanagan and Beltzner, 2000; Grandy and Westwood, 2006; cf. Brayanov and Smith, 2010).

Deficits of sensorimotor memories might explain why proprioceptive dominance is observed in ASD during motor tasks, but not during the perceptual task described here. Spatial working memory is impaired in individuals with ASD (Steele et al., 2007) but it is unknown whether sensorimotor memories used to update motor commands are also impaired in this population. Sensorimotor memories can be used to predict future motor outcomes (Scheidt et al., 2001, 2012) and it has been suggested that children with ASD exhibit impairments of prediction and planning during motor learning (von Hofsten and Rosander, 2012; Schmitz et al., 2003; Glazebrook et al., 2006; Mari et al., 2003; Fabbri-Destro et al., 2009; Hughes, 1996; Forti et al., 2011), although some have reported that motor execution but not planning is impaired in ASD (Stoit et al., 2013). We are currently using a robotic task to identify sensorimotor memories involved in planning movements of the wrist and we are using magnetic resonance imaging to identify regions of the brain important for memory and prediction in children with ASD (Salowitz et al., 2014).

Limitations, Future Directions, and Conclusions

We used discrimination thresholds from the unimodal experiments to estimate the discrimination thresholds of the bimodal condition. However, simultaneous presentation of visual and proprioceptive stimuli (which occurred in the bimodal experiment) lead to higher visual and proprioceptive discrimination thresholds compared to those predicted by the unimodal experiments in children with ASD, who are known to have deficits in sensory integration. Thus, unimodal estimates of visual and proprioceptive discrimination thresholds might not be representative of those that occurred during the VP experiment. Therefore, a limitation of the current study is that we could not obtain the unimodal visual and proprioceptive discrimination thresholds during the bimodal condition. We propose a future study to measure visual and proprioceptive thresholds by replicating the VP experiment described above with two additions: [1] a visual channel would be applied in half of the trials such that the cursor would be constrained to pass through the standard path and [2] a proprioceptive channel would be applied to the other half of trials such that the robot handle would be constrained to pass through the same standard path. If we found that visual and proprioceptive discrimination thresholds measured during bimodal conditions were higher in children with ASD compared to TD children, then, it would explain the findings of the current study including increased bimodal discrimination thresholds, but no difference in the relative contributions of vision and proprioception in children with ASD compared to controls.

Sensory integration therapy is used to treat children with ASD. However, the efficacy of such therapies is rarely reported (Case-Smith and Bryan, 1999; Dawson and Watling, 2000). The exact treatments used in sensory integration therapy are rarely defined and are often individualized for each participant (Pfeiffer et al., 2011). Therefore, it is difficult to evaluate specific treatments of sensory integration therapy, and the mechanisms of such treatments in ASD are largely unknown. Our findings of non-optimal integration of vision and proprioception for perception in ASD suggest that sensory integration therapies should seek to train children with ASD to improve their ability to discriminate movements when more than one sensory modality is present. For example, our two-interval forced-choice curvature discrimination task with visuo-proprioceptive stimuli could be played as a video game in which participants receive points for correctly discriminating movement curvatures. Such a game would encourage participants to attend to very small differences in peak displacement between subsequent movement presentations and could possibly train them to enhance discrimination ability during integration of visual and proprioceptive perception.

In summary, we found support for the hypothesis that discrimination thresholds are non-optimal in children with ASD during multisensory integration, but we did not find support for the hypothesis that children with ASD favor proprioception over vision to a greater extent than TD children. Future studies should evaluate sensory integration therapies in the context of visuo-proprioceptive integration and should evaluate the extent to which proprioceptive preference might occur in ASD during active movement.

CHAPTER 6: NEURAL CORRELATES OF GOAL-DIRECTED REACHING MOVEMENTS IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND TYPICALLY DEVELOPING CHILDREN

The ability to predict the consequences of one's movements based on prior experience is important for maintaining accuracy in the presence of environmental uncertainty. Children with autism spectrum disorder (ASD) are known to have deficits in memory and planning. However, the extent to which children with ASD integrate memories of prior sensorimotor outcomes to form a motor plan and the underlying neural circuits which support memory-guided prediction in this population remain unclear. Nine children with ASD and 11 typically developing (TD) children performed a goal-directed wrist flexion/extension task against an applied load while magnetic resonance imaging data were simultaneously collected. The load remained constant (predictable) within an initial block of trials and then varied randomly within four additional blocks. Children with ASD produced movements that were more variable compared to those of TD children. We identified neural correlates of the goal-directed wrist flexion/extension task separately within each group. We observed marked differences in the extent and intensity of the neural activities supporting goal-directed reaching in children with ASD compared to TD children in both environmental conditions. The findings presented here provide preliminary evidence that TD children and children with ASD differ in the way they integrate sensorimotor memories to update motor commands. This work expands upon a feasibility study (Salowitz et al., 2014) presented at the World Multiconference on Systemics, Cybernetics, and Informatics which was awarded "Best Paper in its Section".

Introduction

Motor abilities are known to be impaired in ASD (Weimer et al., 2001; Minshew et al., 1997; Ming et al., 2007, for a review see Gowen and Hamilton, 2013) and movement disorders can be the earliest expressed features of ASD. ASD-related motor deficits are often observed in infancy (Teitelbaum et al., 1998), long before the expression of language and social deficits (cf. American Psychiatric Association, 2013; for reviews, see Gerlai and Gerlai, 2003; Rapin, 1997). However, the factors that contribute to motor control deficits in the autistic brain remain elusive. One reason for this may be because neuromotor control is intimately coupled with sensation (i.e. “you can only control what you sense”; Prochazka, 1996). Because sensory information processing can itself be impaired in ASD (American Psychiatric Association, 2013; Lane et al., 2010; Ornitz, 1974, 1983; O’Neill and Jones, 1997; Wiggins et al., 2009; Gerrard and Rugg, 2009; Hermelin and O’Connor, 1970; Kern et al., 2007; for reviews see Ben-Sasson et al., 2009; Baranek, 2002; Dawson and Watling, 2000), sensorimotor control deficits in ASD can be due to deficits of motor production, deficits of sensory information processing, or both.

One important goal of sensorimotor control is to maintain motor performance despite persistent environmental disturbance or perturbation. The process by which this happens is known as motor adaptation (Shadmehr and Mussa-Ivaldi, 1994; Thoroughman and Shadmehr, 2000; Scheidt et al., 2001). Motor adaptation is commonly studied using simple goal-directed reaching movements performed with the whole arm (Scheidt et al., 2001), the elbow (Scheidt et al., 2011) or the wrist (Scheidt et al., 2012). In the normal adult brain, the ability to adapt goal-directed wrist movements to changing environmental loads requires an intact ability to sense features of the environment that may degrade performance of the desired action, an ability to sense how the body responds to those “perturbations”, and an ability to use such information to predict and compensate for future changes in the environment (Scheidt et al., 2012). Memories of prior sensorimotor experience play a crucial role in the brain’s ability to predict future environmental perturbations and to minimize their impact by appropriate updating of motor commands (Judkins and Scheidt, 2014). Sensorimotor prediction is typically supported by a distributed network of cortical and subcortical brain regions; sensorimotor memories from prior movements are represented within frontal and temporal cortical regions known to support working memory whereas brain activities in multiple distinct brain regions (hippocampus, cerebellum and basal ganglia) are integrative in that they correlate with the one particular combination of memories that comprises a viable prediction of upcoming environmental perturbation (Scheidt et al., 2012). The finding of neural correlates of memory-based prediction within multiple brain structures suggests that prediction of environmental change is an important function of the human brain, one that can be performed using each of the brain structures most commonly associated with learning. Importantly, the literature describes structural and functional abnormalities in each of these brain regions in ASD, including frontal, parietal and temporal cortices, the hippocampus, the basal ganglia and the cerebellum (Courchesne and Pierce, 2005a, b; Carson et al., 2014; Müller et al., 1998; Casanova et al., 2002, 2006; Buxhoeveden et al., 2006; Zilbovicius et al., 2000; Gendry Meresse et al., 2005; Dager et al., 2007; Allen and Courchesne, 2003; Bauman and Kemper, 2005; Sears et al., 1999; Hollander et al., 2005; Qiu et al., 2010; Verhoeven et al., 2010; Brambilla et al., 2003; Cody et al., 2002).

Despite strong evidence for ASD-related structural and functional abnormalities in the brain, behavioral evidence for ASD-related deficits of predictive sensorimotor control has been equivocal. In a study by Schmitz et al. (2003), a load was placed on a platform which was affixed to the left forearms of children with and without ASD. Children were asked to remove the load with their right hand while elbow angle, force, and electrical activity of *B. brachii* were measured with a potentiometer, strain gauge, and electromyography (EMG), respectively. There was no difference between groups in the maximum elbow angle during the unloading reflex; however, children with ASD exhibited longer duration of unloading force. Furthermore, the latency of the unloading reflex was much longer in children with ASD such that EMG recordings revealed that TD children reduced muscle activity 15 ms *prior* to the onset of unloading, whereas children with ASD reduced muscle activity 51 ms *after* the onset of unloading. Thus, children with ASD in the Schmitz et al. (2003) study had a deficit of anticipatory postural adjustments which led them to depend primarily on feedback modes of control to stabilize forearm position. Salowitz and colleagues have also observed subtle deficits in the adaptive performance of a point-to-point reaching task (Salowitz et al., in preparation). In that study, TD children and children with ASD performed goal-directed arm movements within a simple virtual reality environment that altered visual feedback of hand motions by rotating visual feedback of task performance. Whereas children with ASD did exhibit some ability to adapt their movements to the altered feedback condition, they were less able to reduce target capture errors after extended practice than TD children. By contrast, studies of ball catching (Mostofsky et al., 2004), ball throwing (Gidley Larson et al., 2008), and reaching (Gidley Larson et al., 2008) have reported that children with ASD are able to adapt to suddenly-imposed and persistent environmental disturbance at rates comparable to those of TD children. During those studies, the experimenters induced sensorimotor adaptations by varying the weight of the ball (Mostofsky et al., 2004), rotating visual feedback of task performance (Gidley Larson et al., 2008), or by applying a force field (Gidley Larson et al., 2008). We speculate that diversity of reported findings is due to the multiplicity of predictive mechanisms in the brain;

for example, deficits of prediction in one adaptive mechanism (e.g. the cerebellum) might be mitigated, in part, by predictive control in another (e.g. the basal ganglia). But because the input and output pathways of the basal ganglia, cerebellum and hippocampus are distinct, redistributing the responsibility for predictive control amongst adaptive neural systems within the autistic brain may result in subtle performance deficits that may in fact differ from child-to-child, depending on his/her particular deficits of sensorimotor learning.

In the current study, children with ASD and TD children reclined in a magnetic resonance (MR) scanner and made goal-directed wrist flexion/extension movements against a spring-like load that was constant during some trials and then varied unpredictably from one trial to the next in the remaining trials. We recorded blood-oxygen-level-dependent (BOLD) signal as they performed the task to obtain functional MR images related to memory-based sensorimotor prediction. We analyzed kinematic performance measures to test the hypothesis that the two groups of children differed in the way they use memories of prior performances to update movements from one trial to the next. We analyzed the functional neuroimages using multilinear regression to test the hypothesis that relative to TD children, children with ASD recruit a different subset of adaptive neural systems to adjust their movements in response to changing environmental demands. We discuss our findings to advance understanding of sensorimotor learning deficits in children diagnosed with ASD.

Methods

Participants

Nine children with ASD [aged 15.8 ± 1.8 years (mean ± standard deviation, here and elsewhere); one female] and 11 TD children [aged 16.7 ± 1.7 years; three female] completed this study. All study procedures received institutional approval from Marquette University and the Medical College of Wisconsin in compliance with the Declaration of Helsinki. All children participated after giving informed assent and after obtaining informed parental consent. Potential participants were excluded from the study if they had ferrous objects within the body or a history of claustrophobia. Upon enrollment, parents were asked to complete the Child Behavior Checklist for ages 6-18 (CBCL; Achenbach and Rescorla, 2001).

Parents were also asked to complete a questionnaire to report their child's medication use and to report parents' or caregivers' occupations and highest educational degrees. Occupation and education data were used to determine social status with the Barratt Simplified Measure of Social Status (Barratt, 2006). Parents of children who did not have a prior diagnosis of ASD were asked to complete the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers et al., 1999); children receiving a total score > 13 exhibited behaviors characteristic of ASD and they were dropped from the study. Prior diagnoses of children in the ASD group were confirmed using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1994): a total score ≥ 7 confirmed presence of an ASD. Children in both groups were administered the Kaufman Brief Intelligence Test, second edition (KBIT2; Kaufman and Kaufman, 2004) to measure intelligence quotients (IQ). Only high-functioning children (verbal IQ > 70) were included in the study. Each child's handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). All children used their right-hand to complete the task and only children who were predominately right-handed (LI > 40), or ambidextrous (-40 ≤ LI ≤ 40) were included in the study. Participant characteristics are shown in Table 6-1.

Table 6-1 Participant Characteristics

Group	Participant	Sex	Age (years)	Laterality	SS	KBIT2 T (V, N)	*ADOS/ASSQ T (C, S) / T	Medication
ASD	A1	F	18.0	0	45	101 (92, 109)	18 (6, 12)	BC, AP, AH, AD
	A2	M	17.4	-18	51	110 (116, 100)	10 (3, 7)	ST
	A3	M	13.5	26	31	115 (117, 108)	7 (2, 5)	AD
	A4	M	13.8	53	47	117 (107, 122)	7 (3, 4)	-
	A5	M	15.2	71	47	122 (112, 125)	13 (3, 10)	ST
	A6	M	16.7	90	50	71 (77, 72)	17 (7, 10)	ST, AD, AD
	A7	M	16.9	44	45	107 (100, 112)	7 (3, 4)	ST
	A8	M	13.8	88	48	131 (135, 118)	10 (4, 6)	ST, AD
	A9	M	17.1	100	55	103 (96, 108)	9 (4, 5)	ST
	M ± SD		**15.8 ± 1.8**	**51 ± 41**	**46 ± 6**	**109 ± 17**	**11 ± 4**	
TD	T1	F	13.1	88	66	139 (130, 139)	0	-
	T2	M	16.1	58	66	116 (122, 105)	0	-
	T3	M	14.9	79	39	109 (101, 117)	0	-
	T4	M	17.0	100	53	104 (101, 105)	0	-
	T5	M	16.7	70	43	119 (118, 114)	0	-
	T6	M	17.3	100	42	104 (110, 96)	0	-
	T7	M	18.6	100	55	117 (118, 111)	0	-
	T8	M	16.0	80	42	115 (114, 111)	0	-
	T9	F	17.4	100	65	113 (110, 111)	0	-
	T10	M	18.9	100	65	101 (102, 99)	0	-
	T11	F	17.8	53	42	106 (108, 104)	0	-
	M ± SD		**16.7 ± 1.7**	**84 ± 18**	**52 ± 11**	**113 ± 11**	**0 ± 0**	

Abbreviations: ASD autism spectrum disorder, TD typically developing, SS social status, KBIT2 Kaufman Brief Intelligence Test, 2nd Edition, ADOS Autism Diagnostic Observation Schedule, ASSQ Autism Spectrum Screening Questionnaire, T total, V verbal, N nonverbal, C communication, S social, M male, F female, BC birth control, AP anti-psychotic, AH anti-hypertensive, AD anti-depressant, ST stimulant, **M** mean, **SD** standard deviation

* ADOS reported for ASD; ASSQ reported for TD

General Procedures

Each child participated in three experimental sessions, which were conducted on separate days and lasted between one and two hours each (Figure 6-1a). We performed clinical assessments at the beginning of the first session to determine whether children were eligible to participate in the second and third sessions. Motor control testing in the first session (bench testing) was performed with the participant grasping the handle of an air-powered plastic robot (Figure 6-1b) while seated at a desk in a research lab. The purpose of this testing session was to train participants on the spatial accuracy and timing requirements of the sensorimotor task to be performed in subsequent sessions. This first session also allowed us to determine whether the child was able to follow the necessary task instructions. The second session was performed as the child rested supine while grasping the robotic handle within a mock magnetic resonance

(MR) scanner at the Medical College of Wisconsin. This session was designed to acclimate participants to the close confines and loud acoustic scanning noises to be experienced during actual scanning. This second session also provided additional practice on-task. Children who successfully completed both the bench and mock scanning sessions were invited to participate in a final, actual, functional magnetic resonance imaging (FMRI) scanning session at the Medical College of Wisconsin.

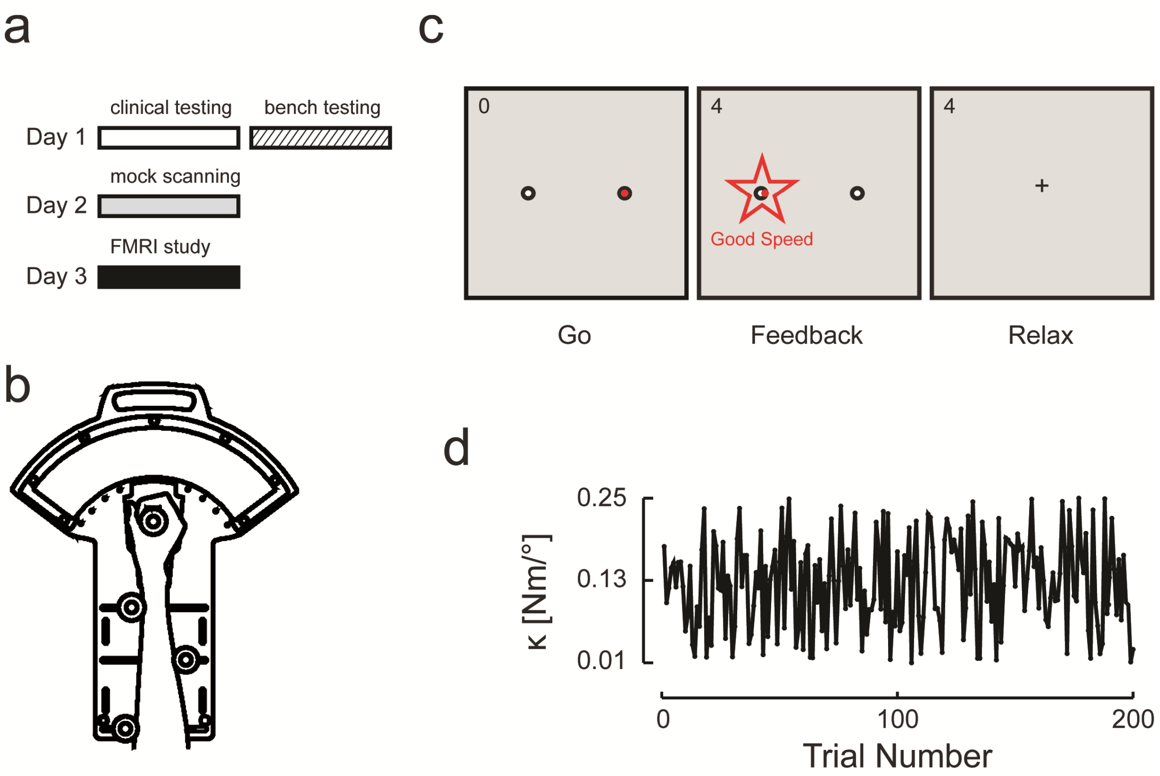

Figure 6-1: Experimental apparatus and procedure. (a) Structure of experimental sessions across the three days of testing (b) Schematic representation of a single degree-of-freedom MR-compatible pneumatic manipulandum. (c) Illustration of the visual cues, summary feedback and instructions provided to participants. Trials began with a "Go" cue wherein a pair of black circles appeared representing the home (right) and goal (left). There was a one-to-one correspondence between the subject's wrist angle and the location of a red cursor on the screen. No visual feedback was provided during the movement. Instead, "Feedback" of peak wrist angle and total movement time was presented after movement completion. Participants relaxed and visually fixated between trials ("Relax"). (d) The load applied to the hand varied from trial-to-trial during the last four blocks.

Behavioral Task

The experimental task was the same in each of the three sessions: participants performed 250 target capture movements, one movement per trial. The task required the children to perform fast, goal-directed, wrist flexion/extension movements while grasping the handle of the MR-safe robotic device (Figure 6-1b). Wrist position was recorded at a rate of 1000 samples per second. Participants made flexion/extension movements using the right hand, with the base of the robotic device rigidly attached to the forearm. For Day 1 testing, the base of the device was also fixed to a table top. For the sessions performed within the mock and real scanners, the base of the device was fixed to the hip and oriented such that the target-capture task could be performed comfortably. Participants watched a visual display screen (Figure 6-1c) placed in the line of sight. The visual display was updated at a rate of 60 frames per second. For details of the robotic device and its control, see Suminski et al. (2007b).

Participants were instructed to “move the robot handle ‘over-and-back,’ without pause, to capture the target”, which was displayed on the video screen. Because the purpose of this study was to examine the neural underpinnings of memory-based sensorimotor adaptation in children with and without ASD, we designed the flexion/extension task to minimize contribution of moment-by-moment feedback control mechanisms in determining performance accuracy, which instead required trial-by-trial updating of feedforward movement control (cf. Judkins and Scheidt, 2014). Thus we did not provide ongoing visual feedback of cursor motion during wrist movements, but instead provided summary feedback of task performance as described below. Children who initially were unable to make fast reaches without pausing at the target were allowed additional practice sessions until proficiency was achieved.

Trials began with the appearance of a “GO” cue (Figure 6-1c “Go”) -i.e., the appearance of a pair of 7-mm-dia black circles spaced 9 cm apart. The right circle represented the hand’s starting or “home” position (10° wrist extension) and the left circle represented the target or “goal” location (10° flexion), in which participants were to reverse their movement without pause. Direct view of the hand was precluded at all times, either by an opaque shield placed immediately above the hand (during lab sessions) or by the scanner bore (in the simulated and real scanning sessions). Feedback of task performance was provided by a cursor (5-mm-dia red circle) that mapped joint angular rotation onto cursor displacements along the horizontal axis. The cursor appeared with the GO cue and disappeared at movement onset (defined below).

Knowledge of results (KR) feedback was displayed after the hand returned within 3° of home (Figure 6-1c, “Feedback”). KR consisted of the cursor’s location at the moment the wrist reversed direction and a categorical indication of movement time (defined as the time between movement onset and the moment the wrist returned within 3° of home)[2]. A reinforcement signal (a large star concentric with the target) appeared if maximum extent was within ± 1° of the target. Participants earned two points if

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[2] Pilot testing found that KR using this definition of movement time encouraged fast out-and-back movements without pause in the neighborhood of the target.

maximum extent was within the desired range but they lost a point if maximum extent was outside the desired bounds. Total movement time was indicated by a textual cue: “Too Fast”, “Too Slow” or “Good Speed”. Participants earned an additional two points if total movement time was within the desired range (700 ms - 900 ms), but they lost a point if speed was outside the desired bounds. A total movement time within the desired range yielded flexion movement times equaling ~400 ms.

Participants rested quietly and fixated on a visual stimulus crosshair for a variable period of time between trials (Figure 6-1c, “Relax”). The time between GO cues varied randomly between 8 and 18 seconds with a mean of 10 seconds. This variable inter-trial-interval was designed to maximize the ability of FMRI deconvolution analysis (described below) to extract hemodynamic response functions (see Toni et al., 1999; Scheidt et al., 2012).

The 250 trials comprising each session were grouped into 5 blocks of 50 trials each. Participants were allowed to rest between blocks. In the first block of trials, the robot opposed wrist flexion with a spring-like load having a constant, predictable, stiffness of 0.13 Nm/°. This block allowed participants to practice performing the goal-directed wrist flexion/extension target capture movement with maximum likelihood of success. In the remaining four blocks, the robot applied a spring-like load K_i, which remained constant within any given trial, but which varied pseudo-randomly from one trial to the next. In these blocks, the load was randomly selected from a uniform distribution (ranging from 0.01 to 0.25 Nm/°) such that again, the average load across trials was 0.13 Nm/° (Figure 6-1d). This variable load was designed to challenge the ability of each child to move in the presence of considerable environmental uncertainty. The load sequence and the sequence of inter-trial-intervals were the same for all participants.

In the first experimental session, children additionally completed an initial training block of 30-45 trials in which they were provided with continuous visual feedback of hand position to better encourage the performance of fast flexion/extension movements without pause at the point of reversal. A ‘teacher’ (5-mm-dia blue circle) was displayed above the visual feedback cursor in the first 15 trials to model the desired kinematics. Children were encouraged to match their cursor with the teacher as they learned to capture the target quickly, accurately, and transiently (without pausing at the target). After 15 trials with the ‘teacher’ present, children completed a minimum of 15 trials without the teacher. Children then moved on to the behavioral task described above (i.e. with only KR performance feedback). Data from these training trials were not analyzed. Control of the pneumatic robot and post-processing of data were performed using MATLAB software (The Mathworks, Natick, MA).

MR Imaging

During the final session, children rested supine in a GE 3T short bore M750 scanner equipped with a standard, single-channel, commercial head coil. Visual stimuli were projected onto a screen that participants viewed using a mirror attached to the head coil. The robotic device was positioned comfortably over the participant's hip using a rigid support structure. Participants rested quietly in the scanner and watched a video while we acquired 180 high-resolution spoiled GRASS (gradient-recalled at steady-state) axial anatomic images (TE = 3.2 ms, TR = 8.2 ms, flip angle = 12°, NEX = 1, slice thickness = 1.0 mm, FOV = 240 mm, 256 x 280 matrix). These images allowed localization of functional activity and spatial co-registration between participants. Functional echo planar (EP) images were then collected while participants performed the target capture task. We used a single-shot, blipped, gradient EP pulse sequence (TE = 25 ms, TR = 2 s, FOV = 240 mm, 64 x 64 matrix). Forty-two contiguous axial 3.7-mm-thick slices were selected to provide coverage of the entire brain (3.75 x 3.75 x 3.70 mm voxel size). As in the first two experimental sessions, participants performed 5 blocks of 50 target-capture trials. Here, each block comprised an imaging run ~ 8.5 minutes in duration. An additional 4 volumes were collected at the beginning of each run to allow the FMRI signal to equilibrate and 7 more were added to the end of each run to accommodate the rise and fall of the hemodynamic response.

Data Analysis

Behavioral Data Analysis

Hand paths were low-pass filtered with a 2nd order, 10 Hz Butterworth filter prior to computing hand velocities. We computed three kinematic measures of task performance from the flexion phase of each movement. *Movement onset* occurred when wrist flexion velocity first exceeded 5°/s. *Movement reversal* occurred at peak movement extent (i.e. the joint angle of the first zero-crossing in wrist flexion velocity following its initial peak). *Movement error,* ε_i, was defined as the wrist's angular deviation from the target at movement reversal. We computed two measures to summarize kinematic performance across trials: average movement error, $\bar{\varepsilon}$, and standard deviation of movement error, σ. For the reaching task with constant load, these measures were computed across the last 40 trials (i.e. when steady state performance was achieved) and for the reaching task with randomly-varying load, these measures were computed across all 200 trials. For the reaching task with randomly-varying load, we removed the influence of the applied load by subtracting the linear fit of movement error as a function of load before computing the standard deviation of movement errors. This allowed us to characterize variability in performance errors that were due to the movements and not due to the random sequence of loads. We next computed secondary performance measures including *reaction time* (RT: the time interval between GO cue presentation and movement onset), and *flexion movement time* (MT: the interval between movement onset and movement reversal). Movements were considered unsuccessful if movement extent was less than 5°, if movement occurred in anticipation of the GO cue (RT < 100 ms), if participants were inattentive (RT > 800 ms), if flexion movements were slow (MT > 800 ms) or if the hand paused during the return home (total movement time > 1500 ms). Unsuccessful movements were excluded from further analysis.

Statistical Analysis of Behavioral Data

We sought to identify whether children with ASD were impaired in their ability to compensate for environmental uncertainty. Therefore, we compared movement kinematics across groups to characterize performance against a constant spring-like load and against a randomly-varying (i.e. unpredictable) sequence of loads. For each reaching task, we performed a 2-sample t-test to compare the standard deviation of movement error across groups and we performed a second 2-sample t-test to compare average movement error across groups. Our secondary analysis sought to identify whether children with ASD exhibited deficits in the time to prepare and execute movements. For each reaching task we performed a 2-sample t-test to compare RT across groups and we performed a second 2-sample t-test to compare MT across groups. Statistical analysis was performed with the SPSS 21 software package (Armonk, NY). Effects were considered statistically significant at the $\alpha = 0.05$ threshold.

Imaging Data Analysis

Structural and functional images were analyzed using the Analysis of Functional NeuroImages (AFNI) software package (Cox and Hyde, 1997). For functional data, voxel time series were shifted using Fourier interpolation (`3dTshift`) so that individual slices aligned with a temporal origin and the first four volumes were removed to account for start-up transients. For the first block of trials in which the robot applied a constant spring-like load, only the last 40 trials were analyzed when steady state performance was achieved. For the remaining four blocks of trials in which the robot applied a randomly-varying load, we concatenated the imaging data from these blocks (`3dTcat`). Subject-specific structural and functional images were cubically interpolated to 1 mm^3 voxels, co-registered and converted to stereotaxic coordinate space following the method of Talairach and Tournoux (1988). Functional images were blurred with a 4-mm full-width half-maximum Gaussian filter to compensate for subject-to-subject anatomical variations.

Six head motion parameters [translations in the inferior/superior (dS), right/left (dL), and anterior/posterior (dP) directions as well as rotations about each of these axes] were identified (`3dvolreg`) and referenced to the first volume. We used the method of Van Dijk and colleagues (2012, cf. Satterthwaite et al., 2012) to compute a three-dimensional (3-D) measure of displacement for each repetition time (TR) using the root-mean-square of the three relative displacements. Participants who exhibited relative 3-D displacement greater than 0.1 mm (cf. Van Dijk et al., 2012) during more than 70% of imaging volumes were dropped from the study. We used AFNI program `3dDeconvolve` to remove baseline drift (modeled as the linearly-weighted set of orthogonal Legendre polynomials inclusive to order 4) as well as the six head motion parameters from all images.

Statistical Analysis of Imaging Data

We sought to test the hypothesis that neural responses to environmental uncertainty in autistic brains differ from those in TD brains. We created a trial onset time reference function using a comb function (a series of 1’s and 0’s) with 1’s assigned to TR times of trial onset (the Go cue) and 0’s assigned to the remaining imaging intervals for each load sequence. These time series were then convolved with a gamma variate function resembling the canonical hemodynamic response (Cohen, 1997). Note that the Legendre polynomial modeling baseline drift (i.e. Legendre polynomial order 0) was fit only to functional data from TRs wherein the estimated hemodynamic response to the Go reference function fell below 1% of its maximum value, thereby removing the approximate mean of the raw BOLD signal while preserving those signal components having potential correlation with trial-by-trial fluctuations. For each participant, we identified correlations between BOLD activity and the task-specific time series (i.e. Go-related activity) using AFNI program `3dDeconvolve` to calculate the regression coefficient for each load sequence.

First, we identified brain regions in which the BOLD signal correlated with task onset during the reaching task with constant spring-like load. For each group, we performed a 1-sample t-test to compare regression coefficients to 0.0 using program `3dttest++`. For each statistical test in the imaging analysis, we estimated the minimum cluster size by performing 10,000 Monte Carlo simulations (`3dClustSim`) to yield a whole brain family-wise error threshold of $\alpha = 0.05$; the t-threshold was determined from the degrees-of-freedom (which differed across groups) and a desired significance level of $p = 0.001$. For the 1-sample t-test comparing regression coefficients within the ASD group to 0.0, we used a minimum cluster size of 110 μl and an individual voxel probability of $t = 5.925$. For the 1-sample t-test comparing regression coefficients within the TD group to 0.0, we used a minimum cluster size of 110 μl and an individual voxel probability of $t = 5.020$. This pair of 1-sample t-tests allowed us to identify brain regions that are important for reaching within each participant group. We next sought to determine whether the magnitude of regression coefficients differed between groups in the regions identified by these 1-sample t-tests. Therefore, we created a mask of the regions identified in the ASD group or the TD group (i.e. an OR-mask). Then, we used a 2-sample t-test to compare correlation coefficients between ASD and TD groups within the mask. Since the volume within the OR-mask was much smaller than the total brain volume used in the 1-sample tests, we were able to use a minimum cluster size of 30 μl with an individual voxel probability of $t = 4.126$ to maintain the family-wise error threshold during the 2-sample t-test.

We next identified brain regions in which the BOLD signal correlated with task onset during the reaching task with randomly-varying loads. For each group, we performed a 1-sample t-test to compare regression coefficients to 0.0. For the 1-sample t-test comparing regression coefficients within the ASD group to 0.0, we used a minimum cluster size of 110 μl and an individual voxel probability of $t = 5.925$. For the 1-sample t-test comparing regression coefficients within the TD group to 0.0, we used a minimum cluster size of 110 μl and an individual voxel probability of t = 5.020. We next sought to determine whether the regression coefficients differed between the constant load sequence and the randomly-varying load sequence for each group. For each group, we created an OR-mask of the regions identified by the 1-sample t-test of the constant load sequence and the 1-sample t-test of the randomly-varying load sequence. Within each participant group, we performed a paired 2-sample t-test to compare regression coefficients within the OR-mask between the constant load sequence and the randomly-varying load sequence conditions. For the ASD group, we used a minimum cluster size of 20 μl and an individual voxel probability of t = 5.925. For the TD group, we used a minimum cluster size of 37 μl and an individual voxel probability of t = 5.020. We next sought to determine whether the magnitude of regression coefficients during the randomly-varying load differed between participant groups. We created a mask of the regions identified in the ASD group or the TD group during the randomly-varying load sequence. Then, we used a 2-sample t-test to compare correlation coefficients between ASD and TD groups within the OR-mask. We used a minimum cluster size of 33 μl with an individual voxel probability of t = 4.126 for the 2-sample t-test comparing regression coefficients between groups during the randomly-varying load. Each of the imaging tests described above was performed with two cofactors: average movement error and standard deviation of movement error. These cofactors were used to account for potential differences in BOLD signal that were influenced by ASD-related deficits in kinematic performance.

Results

Of the participants who successfully completed the mock scan, three children with ASD were dropped from the study because one did not show up for his scheduled MRI and two others exhibited excessive head motion during the MRI scan. Two TD children were also dropped from the study due to excessive head motion. The remaining 20 participants were attentive to the task and successfully completed the MRI session.

Participant groups were well matched for age ($t_{18} = 1.16$, $p = 0.26$), social status ($t_{18} = 1.40$, $p = 0.18$), and total IQ ($t_{18} = 0.72$, $p = 0.48$). All children in the TD group (n = 11) were right-handed, whereas in the ASD group (n = 9), six children were right-handed, and three were ambidextrous. All children in the ASD group met criteria for ASD measured by the ADOS. No children in the TD group had behaviors characteristic of ASD as measured by the ASSQ and none of these children attained scores within the clinical range of the CBCL. Group statistics for age, social status, IQ, handedness, ADOS and ASSQ scores are presented (Table 6-1).

Behavioral Results

Constant Load Sequence

Both groups of children made quick over-and-back movements toward the target when moving against the constant spring-like load of 0.13 Nm/° (Figure 6-2a). Few reach trials were unsuccessful (unsuccessful trials in the TD group: 3 ± 2%; ASD group: 7 ± 5%). We fit a falling exponential to the movement error time series (Figure 6-2b). On average, both participant groups exhibited slight overshoot during initial task exposure. Movement extent decreased rapidly in both groups (a time constant of one trial for the ASD group and a time constant of three trials for the TD group). Since we were interested in characterizing performance after initial learning had subsided, we computed performance variables (standard deviation of movement error, average movement error, RT, and MT) during the last 40 trials when steady state performance was achieved.

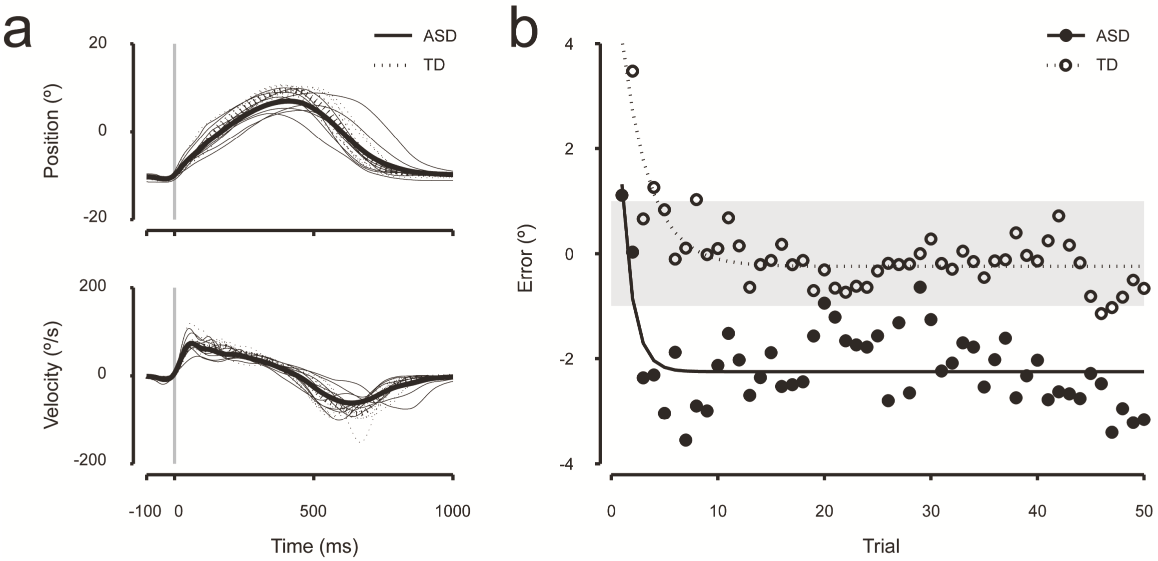

Figure 6-2: Kinematic behavioral results of constant load sequence. (a) Average time profiles of wrist displacements (top) and velocities (bottom) for children with ASD (solid) and TD children (dotted), aligned by movement onset (vertical gray line). Thick lines represent group averages. (b) Performance error as a function of trial averaged across ASD (filled) and TD (open) groups. Gray band indicates target tolerance.

Both groups undershot the target during steady-state exposure to the constant load sequence such that on average the TD group remained within the goal region of the target whereas the ASD group undershot the target by about 2° and performance errors were more variable in the ASD group relative to the TD group. A 2-sample t-test found a difference in standard deviation of movement error across groups (σ_{ASD} = 1.77 ± 0.39°; σ_{TD} = 1.25 ± 0.21°; t_{18} = 3.76, p = 0.001), suggesting that children with ASD produced movements that were more variable than those of TD children. A separate 2-sample t-test found a difference in average movement error across groups ($\bar{\varepsilon}_{ASD}$ = -2.18 ± 2.26°; $\bar{\varepsilon}_{TD}$ = -0.24 ± 0.83°; t_{18} = 2.65, p = 0.016), suggesting that children with ASD undershot the target to a greater extent than TD children. Since group differences in movement extent could potentially influence neuroimaging results, we included both the standard deviation of movement error and average movement error as co-factors in the imaging analyses.

ASD-related deficits in movement kinematics were unrelated to deficits in movement timing because the time to prepare and execute movements did not differ between groups. Two additional 2-sample t-tests revealed no group-wise difference in RT (p = 0.287) or MT (p = 0.237). Thus our findings of increased movement variability and decreased movement extent in ASD were unrelated to movement timing.

Random Load Sequence

During the random load sequence, participants made quick movements to the target (Figure 6-3a). Few reach trials were unsuccessful (unsuccessful trials in the TD group: 4 ± 4%; ASD group: 11 ± 8%). Movement errors varied proportionally with load stiffness (Figure 6-3b). When the load was weak, TD children tended to overshoot the target whereas children with ASD acquired the target on average. When the load was strong, TD children undershot the target, whereas children with ASD undershot the target to an even greater extent compared to the weak load stiffness. For each participant, we fit a line to movement error as a function of load. The relationship between movement error and load stiffness was approximately linear in both groups ($r^2_{ASD} = 0.71$, $r^2_{TD} = 0.77$). The slope of the line did not differ across participant groups ($p = 0.29$) suggesting that the perturbation magnitude influenced movement extent similarly across both groups of children.

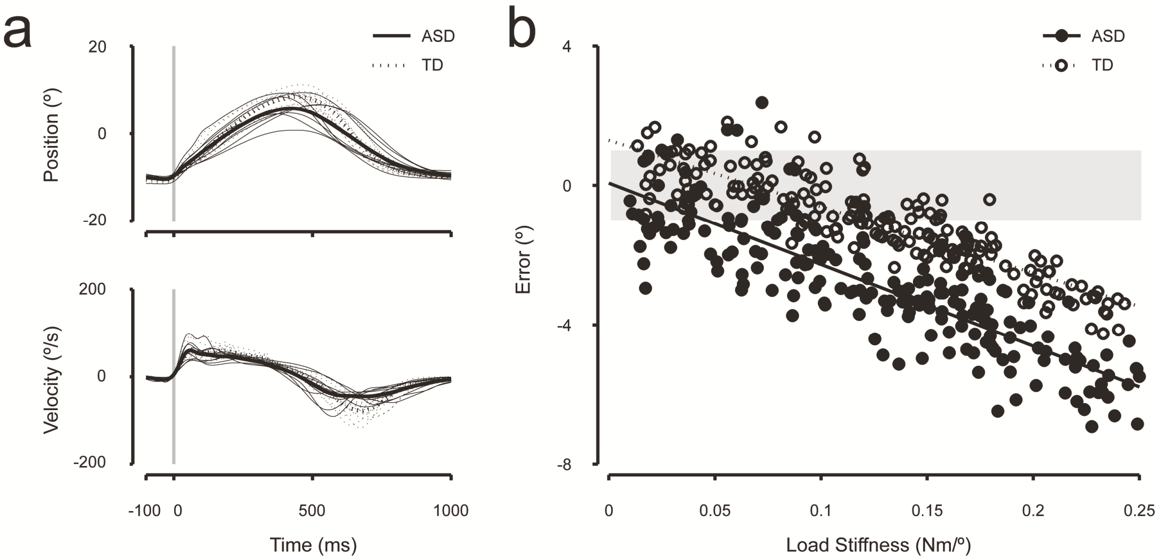

Figure 6-3: Kinematic behavioral results of random load sequence. (a) Average time profiles of wrist displacements (top) and velocities (bottom) for children with ASD (solid) and TD children (dotted) aligned by movement onset (vertical gray line). Thick lines represent group averages. (b) Performance error as a function of applied load averaged across ASD (filled) and TD (open) groups with fitted linear trend lines. Gray band indicates target tolerance.

Movement errors were more variable in the ASD group compared to the TD group. We removed the influence of load stiffness from movement error and computed the standard deviation of these movement error residuals. A 2-sample t-test found a significant group difference in the standard deviation of movement error ($\sigma_{ASD} = 2.20 \pm 0.30°$; $\sigma_{TD} = 1.59 \pm 0.24°$; $t_{18} = 5.03$, $p < 0.001$), suggesting that children with ASD produced more variable movements even after the influence of the randomly-varying perturbation sequence was removed. A separate 2-sample t-test found no difference in average movement error across groups ($p = 0.078$). Since group differences in movement extent could potentially influence neuroimaging results, we included both the standard deviation of movement error and average movement error as co-factors in the imaging analyses.

ASD-related deficits in movement variability were unrelated to deficits in movement timing because the time to prepare and execute movements did not differ between groups. Two additional 2-sample t-tests revealed no group-wise difference in RT ($p = 0.070$) or MT ($p = 0.743$). Thus our finding of increased movement variability in ASD was unrelated to movement timing.

Functional Imaging Results

Constant Load Sequence

We identified brain regions in which the BOLD signal correlated with task onset during reaching with a constant spring-like load. A 1-sample t-test found that regions of activation were widespread in the TD group, whereas a separate 1-sample t-test found that regions of activation were smaller in the ASD group. Total activation volume was more than six times greater in the TD group relative to the ASD group. Many of the regions identified in the current study overlapped with those of our adult study (Scheidt et al., 2012) of goal-directed wrist movements. We identified regions supporting right-handed reaching movements (Kawashima et al., 1995; Toni et al,. 1999; Dai et al., 2001): left central sulcus including primary sensory (S1) and primary motor (M1) areas, supplementary motor area (SMA), and dorsal premotor (PMd) area in both groups of children whereas only children with ASD exhibited activation within the posterior parietal cortices. We found regions supporting visual perception, the processing of visual cues and encoding of visual targets relative to hand position (Hadjikhani and Roland, 1998; Grieve et al., 2000): middle occipital gyrus, middle temporal gyrus, and fusiform gyrus in both groups of children, whereas only TD children exhibited activation within primary visual cortex (V1), lingual gyrus and superior colliculus and only the ASD group exhibited activation within the superior occipital gyrus and pulvinar nucleus of the thalamus. We identified regions which support motor response selection in the presence of uncertainty and movement errors (Grinband et al., 2006, Kayser et al., 2010; Paus, 2001): cingulate cortex in both groups of children, whereas only the TD group exhibited activation within the insular cortex, inferior parietal cortex, and medial dorsal (MD) nucleus of the thalamus. Within the TD group, we found regions supporting closed-loop feedback compensation for positional limb errors and postural stabilization and movement (Suminski et al., 2007a) including cerebellar lobules V – IX. Regions in which BOLD signal correlated with task onset are shown in Tables 6-2 and 6-3 as well as Figure 6-4.

Table 6-2 Location (center of mass) and volume of cortical activations related to Go cue during constant load sequence

		TD vs 0						ASD vs 0						ASD vs TD				
Anatomy Label	H	Vol	Coordinates			T	H	Vol	Coordinates			T	H	Vol	Coordinates			T
		µl	x	y	z			µl	x	y	z			µl	x	y	z	
PreCG (BA 4) {M1}, PoCG (BA 3) {S1}	L	10079	-35	-33	55	17.3	L	665	-29	-31	64	14.9						
PreCG (BA 6)	L	171	-35	-9	56	7.7												
	L	112	-59	3	38	7.3												
MFG (BA 6) {PMd}	L	see 171 µl above					R	309	40	-10	46	11.7	R	205	41	-10	46	7.4
PoCG (BA 2)	L	448	-57	-20	28	11.3												
IPL (BA 40)	L	see 448 µl above																
	L	see 10079 µl above																
	R	227	32	-48	50	8.4												
MeFG (BA 6) {SMA}	L/R	699	-2	-16	67	11.7	L	487	-5	-20	51	10.4						
	R/L	537	4	-2	51	9.3	L/R	226	1	7	45	11.1						
	L	351	-4	-18	49	11.2												
aCgC (BA32, 24)	L	see 351 µl above																
pCgC (BA 26)							R/L	162	3	-42	3	10.5						
SPL (BA 7)							L	120	-26	-63	51	11.7						
SOG (BA 19)							R	133	26	-69	36	9.7						
INS	L	155	-30	16	15	8.8												
	R	246	34	16	9	8.0												
MTG (BA 37)	R	129	53	-55	19	-7.9	R	123	42	-57	6	8.7						
MOG (BA 18, 19)	R	177	36	-83	10	14.9	R	220	43	-72	9	11.4						
							L	204	-34	-80	6	13.0						
FG (BA 37)	R	185	37	-52	-19	8.6	R	159	21	-53	-13	8.8						
							R	141	36	-71	-20	10.4						
FG (BA 37), MOG (BA 19)	R	1357	45	-66	-9	9.4												
	L	719	-47	-66	2	12.6												
	L	694	-30	-72	-13	14.1												
Cu (BA 17) {V1}, LG (BA 18)	R/L	1286	10	-64	2	8.9												

Abbreviations: TD typically developing, ASD autism spectrum disorder, H hemisphere, L left, R right, Vol volume, T peak T, BA Brodmann’s area, a anterior, p posterior, CgC cingulate cortex, Cu cuneus, FG fusiform gyrus, INS insula, IPL inferior parietal lobule, LG lingual gyrus, M1 primary motor cortex, MeFG medial frontal gyrus, MFG middle frontal gyrus, MOG middle occipital gyrus, MTG middle temporal gyrus, PMd dorsal premotor cortex, PoCG post-central gyrus, PreCG pre-central gyrus, S1 primary sensory cortex, SMA supplementary motor area, SOG superior occipital gyrus, SPL superior parietal lobule, V1 primary visual cortex

Table 6-3 Location (center of mass) and volume of subcortical activations related to Go cue during constant load sequence

		TD vs 0					ASD vs 0						ASD vs TD					
Anatomy Label	H	Vol	Coordinates			T	H	Vol	Coordinates			T	H	Vol	Coordinates			T
		µl	x	y	z			µl	x	y	z			µl	x	y	z	
TH (MD)	L	208	-11	-19	9	6.8												
TH (P)							L	144	-17	-24	9	7.6	L	107	-17	-24	8	6.3
SC	L/R	212	0	-30	0	10.4												
CER (lob V)	R/L	151	2	-59	-15	7.2												
	R	135	19	-45	-21	6.2												
CER (lob VI)	R/L	see 151 µl above																
CER (lob VII, VIII)	R	459	29	-52	-46	7.5												
	R	487	13	-62	-42	9.6												
CER (lob IX)	R/L	297	6	-40	-38	14.7												

Abbreviations: TD typically developing, ASD autism spectrum disorder, H hemisphere, L left, R right, Vol volume, T peak T, CER cerebellum, lob lobule, MD medial dorsal nucleus, P pulvinar nucleus, SC superior colliculus, TH thalamus

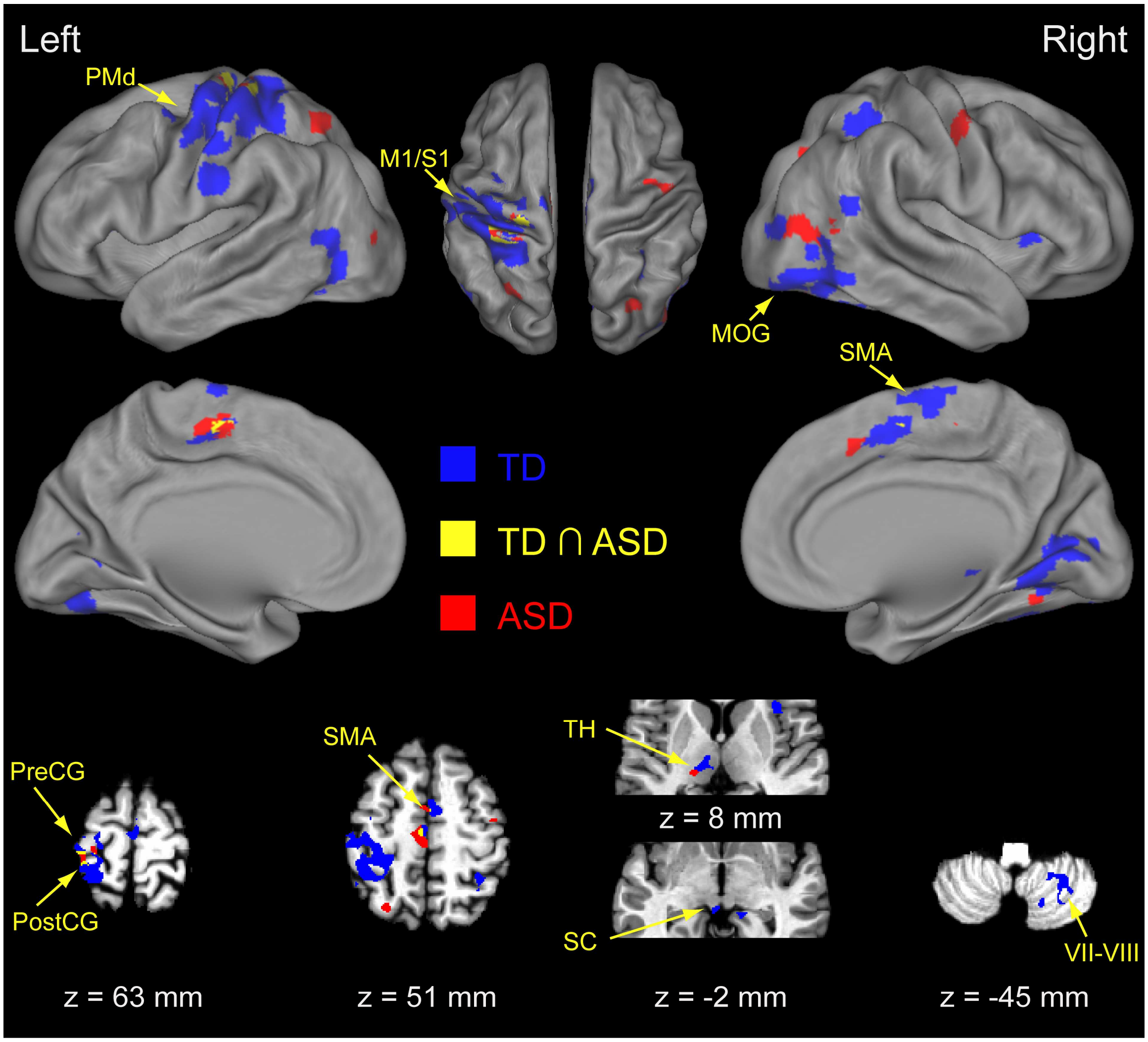

Figure 6-4: A pair of voxel-wise 1-sample t-tests compared fit coefficients versus 0.0 in children with ASD and TD children. Regions of activation are shown for the ASD group (red) and for the TD group (blue). Few regions overlapped between the two groups (yellow). Lateral, medial, and dorsal surface plots (top) and axial views (bottom) indicate regions in which BOLD signal correlated with task onset (i.e. Go cue) overlaid on a standard anatomical reference. Here and elsewhere, left hemispheric activities are shown to the left of each panel. Abbreviations: M1 primary motor cortex, MOG middle occipital gyrus, PMd dorsal premotor cortex, PostCG post-central gyrus, PreCG pre-central gyrus, S1 primary sensory cortex, SC superior colliculus, SMA supplementary motor area, TH thalamus, VII cerebellar lobule VII, VIII cerebellar lobule VIII.

We next compared the magnitude of regression coefficients across participant groups within the regions established by the pair of 1-sample t-tests (cf. Tables 6-2 and 6-3). The 2-sample t-test found that regression coefficients within dorsal premotor cortex (PMd) and the pulvinar nucleus of the thalamus were significantly different between groups (Tables 6-2 and 6-3; Figure 6-5a). Impulse response functions averaged across participants were greater in the ASD group relative to the TD group (Figure 6-5b) suggesting that BOLD signal increased during task onset to a greater extent in children with ASD compared to TD children in PMd and the pulvinar nucleus of the thalamus.

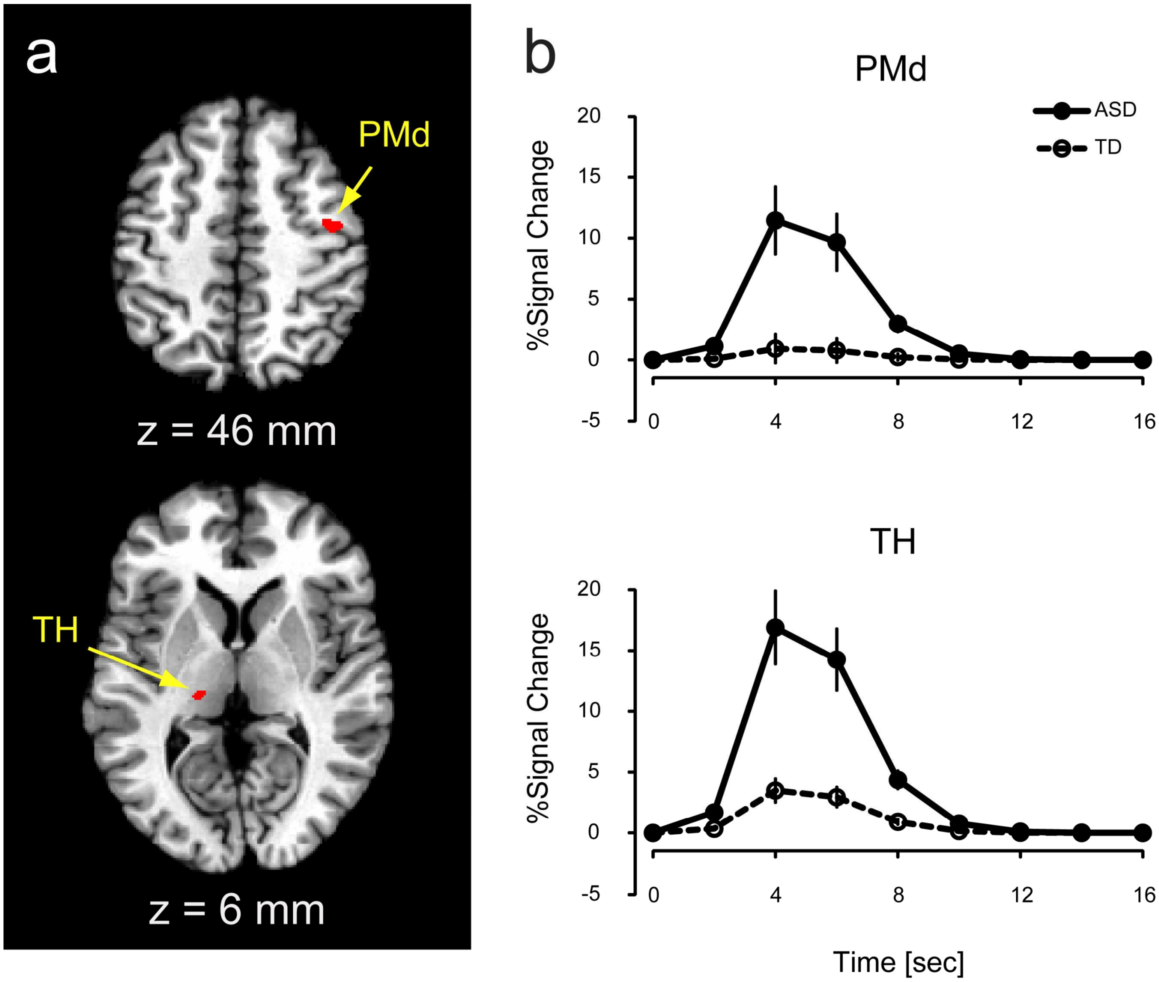

Figure 6-5: The voxel-wise 2-sample t-test compared fit coefficients between children with ASD and TD children during the constant load sequence. (a) Regression coefficients differed between groups in the dorsal premotor cortex (PMd, top) and the pulvinar nucleus of the thalamus (TH, bottom). (b) Impulse response functions averaged across participants were greater in the ASD group (filled, solid) compared to the TD group (open, dashed). Abbreviations: PMd dorsal premotor cortex, TH thalamus.

Random Load Sequence

We sought to determine whether neural correlates identified during goal-directed reaching against an unpredictable sequence of loads differed from the neural correlates identified during reaching against a constant sequence of loads. Within each participant group, 1-sample t-tests identified activation regions that were similar to those identified during the constant load sequence (cf. Tables 6-2 and 6-3, Figure 6-4). For each participant group, paired 2-sample t-tests found no difference between regression coefficients obtained during the constant load sequence compared to those obtained during the randomly-varying load sequence. Thus, each group of participants engaged similar neural networks for movements that were made against a constant load sequence compared to movements that were made against a randomly-varying load sequence.

We then performed a 2-sample t-test to compare regression coefficients across participant groups during the randomly-varying load sequence. The 2-sample t-test found that regression coefficients within the post-central gyrus, supplementary motor area (SMA) and middle temporal gyrus were significantly different between groups (Table 6-4; Figure 6-6a). Impulse response functions averaged across participants were greater in the ASD group relative to the TD group (Figure 6-6b) suggesting that BOLD signal increased during task onset to a greater extent in children with ASD compared to TD children within these three regions.

Table 6-4 Center of mass and volume of activations related to Go cue during random load sequence

		ASD vs TD				
Anatomy Label	H	Vol	Coordinates			T
		μl	x	y	z	
PostCG (BA 3)	L	51	-17	-36	68	5.7
MeFG (BA 6) {SMA}	R	154	5	-25	57	7.0
MTG (BA 37)	R	45	52	-62	3	6.0

Abbreviations: TD typically developing, ASD autism spectrum disorder, H hemisphere, L left, R right, Vol volume, T peak T, BA Brodmann’s area, MeFG medial frontal gyrus , MTG middle temporal gyrus, Post CG post-central gyrus, SMA supplementary motor area

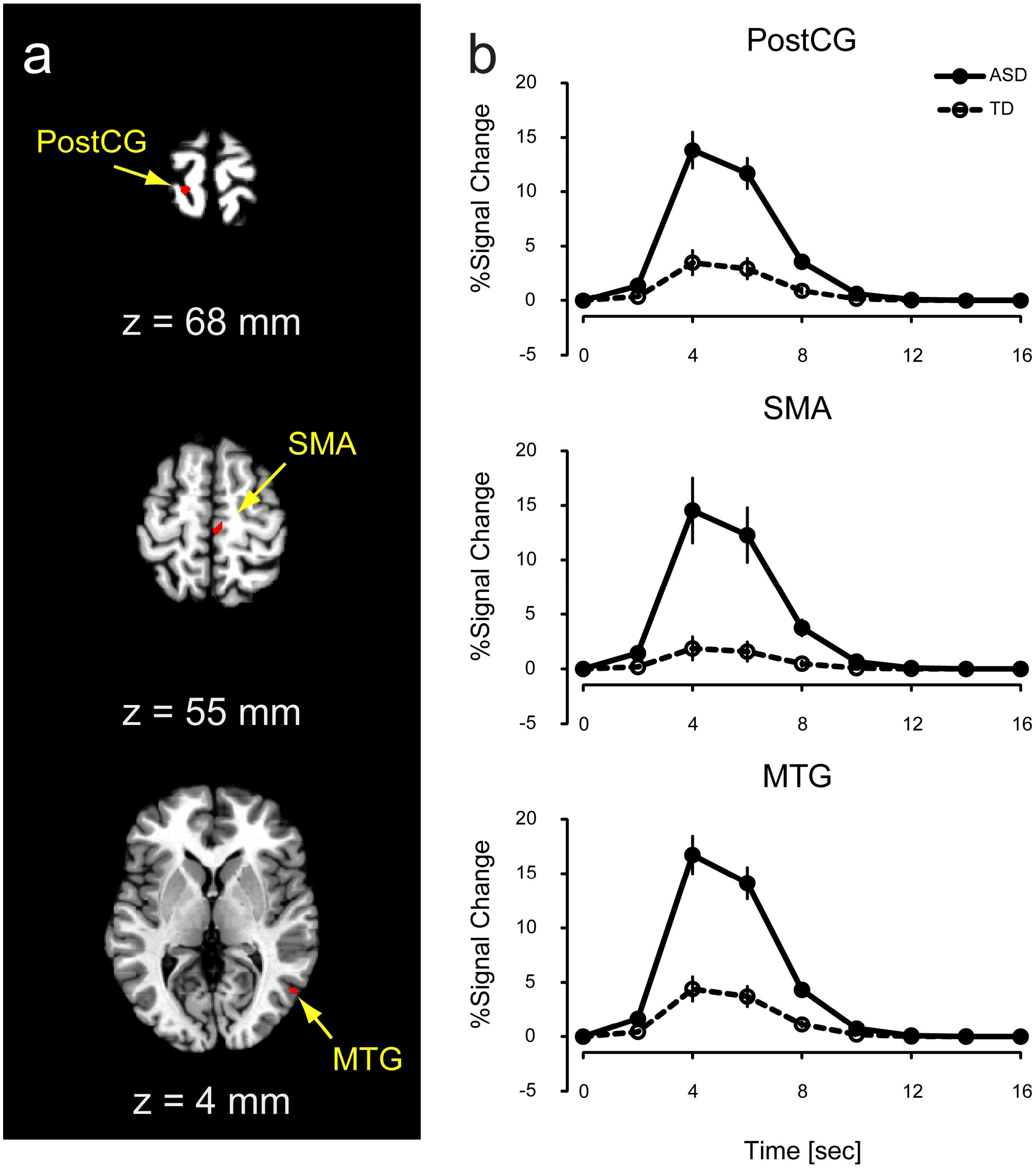

Figure 6-6: The voxel-wise 2-sample t-test compared fit coefficients between children with ASD and TD children during the random load sequence. (a) Regression coefficients differed between groups in the post-central gyrus (PostCG, top), the supplementary motor area (SMA, middle) and the middle temporal gyrus (MTG, bottom). (b) Impulse response functions averaged across participants were greater in the ASD group (filled, solid) compared to the TD group (open, dashed). Abbreviations: MTG middle temporal gyrus, PostCG post-central gyrus, SMA supplementary motor area.

Discussion

Children with ASD and TD children performed a goal-directed wrist flexion/extension task by moving a robotic joystick against a constant, predictable load and by moving against a random sequence of loads. MRI data was simultaneously collected. Relative to TD children, children with ASD produced movements that were more variable during both load sequences and they undershot the target to a greater extent when the load was constant across trials.

Linear regression and statistical hypothesis testing identified regions of the brain in which the BOLD signal was modulated by task onset. Both groups of children engaged the primary sensorimotor cortices, dorsal premotor cortex (PMd), supplementary motor area (SMA), middle temporal gyrus, middle occipital gyrus, and fusiform gyrus. Activity was particularly widespread in TD children, whereas the magnitudes of regression coefficients were greater in children with ASD relative to TD children in PMd and pulvinar nucleus of the thalamus during the constant load sequence and in post-central gyrus, middle temporal gyrus, and SMA during the randomly-varying load sequence.

Movement Kinematics and Timing

Endpoint movements were more variable in children with ASD compared to TD children when the load was constant across trials. Movements were also more variable in the ASD group compared to the TD group during the randomly-varying load even when the influence of the load was removed. Together these findings suggest that increased endpoint variability in ASD relative to controls was related to deficits in movement performance and not due to deficits in adaptation. These results are consistent with those of Papadopoulos and colleagues (2012) who found increased endpoint variability in children with ASD compared to TD children during repetitive reaching (i.e. a Fitts' task). One explanation for increased endpoint movement variability in ASD is that these children might have deficits in feedforward control (Papadopoulos et al., 2012; Mostofsky et al., 2009; David et al., 2012; Schmitz et al., 2003; Bastian, 2006). In our study, children were encouraged to make fast over-and-back movements so that they would rely on feedforward control to update their internal model of the environment rather than rely on feedback control which is slow due to delays in processing sensory information (Seidler et al., 2004). Furthermore, since the visual display appeared above the head, but the hand was positioned above the hip, a visuo-motor transformation was required to align visual and proprioceptive coordinates. Another explanation for increased endpoint variability in ASD is that these children might exhibit deficits in shifting from an effortful mode of control during the beginning of the motor task to an automatic mode of control during steady state performance (Mostofsky et al., 2009; cf. Papadopoulos et al., 2012). Habitual execution is supported by the cerebellum (Mostofsky et al., 2009) which was not identified during goal-directed reaching movements in the ASD group of the current study.

Both groups of children undershot the target on average. TD children reversed wrist position within the boundary of the target such that they acquired the target on average, whereas children with ASD reversed wrist position below the target range such that they failed to acquire the target on average. Hardan and colleagues (2003) report overall weakness in individuals with ASD compared to controls during a task measuring grip strength. Although we did not measure wrist flexion strength in our study population, undershooting the target could have been due to weakness in our cohort of children with ASD. Children with ASD have performed reaching movements in a velocity-dependent force field in only a few studies (Gidley Larson et al., 2008; Haswell et al., 2009) which do not report endpoint error so it is unknown if undershooting occurred in response to external forces in those experiments. Others have found no difference in movement error between children with ASD and TD children during reaching when there is no external force applied to the hand (Rinehart et al., 2006; Glazebrook et al., 2006; Forti et al., 2011). Increased movement errors in the ASD group could also be explained by systematic aiming errors or a lack of motivation to perform the task. We could distinguish deficits due to weakness from those due to aiming errors or motivation using a modified version of the task in which there are no externally-applied loads. If the ASD-related deficits in movement extent were due to weakness, then we anticipate that children with ASD could produce accurate movements when there are no applied loads. However, if ASD-related deficits were due to aiming errors or motivational deficits, then we would expect to see the same pattern of errors in movement extent as in the current study.

We found no difference between groups in the time to prepare and execute reaching movements. During pilot testing, 8 children with ASD and 10 TD children made wrist flexion movements with no penalty for slow movement time and no training with continuous visual feedback. Although movement times and reaction times were comparable to those in the current study, children in both groups (but especially those with ASD) tended to pause at the target before reversing direction (unpublished data). In the current study, we added specific experimental controls (initial training trails with continuous visual feedback of wrist position as well as a movement time penalty/reward structure that was present throughout the entire testing session) to encourage participants to quickly reverse direction when attempting to capture the goal target (cf. Figures 6-2a and 6-3a). Our intent was to minimize kinematic differences between children with ASD and TD children and we were generally successful, with the exception of differences in movement extent and variability across participant groups. When experimental controls are not used, children with ASD have slower reaction times and movement times compared to TD children (Glazebrook et al., 2006, 2008, and 2009; for an exception see Papadopoulos et al., 2012).

Neural Correlates of Goal-Directed Reaching

We measured the extent to which BOLD signal correlated with task onset separately in both groups of participants while they made goal-directed movements against constant and random load sequences. For both load sequences, we found that significant correlations were more widespread in TD children compared to those with ASD (see also Müller et al., 2001). We found no difference in regions identified during the constant load sequence compared to the random load sequence within each group. Recall that the average applied load during the random load sequence was identical to the load used during the constant sequence. We then compared regression coefficients between ASD and TD groups and found that during both load sequences, the ASD group had larger correlation coefficients than the TD group in a few distinct regions of the brain. During the constant load sequence, we found significant group differences in BOLD signal correlations in the PMd, and the pulvinar nucleus of the thalamus. During the random load sequence, we found significant group differences in post-central gyrus, SMA, and middle temporal gyrus. The group-wise differences in activation regions across the two environmental loading conditions might be due to compensation for unpredictable motor outcomes that occurred during the randomly-varying load sequence.

To accurately perform the reaching task, participants were required to use memories of motor outcomes to update their motor plan on subsequent reach attempts. Therefore, we anticipated that regions of the brain involved in memory storage and retrieval would be strongly correlated with task onset. The ability to coordinate retrieval of stored memories is supported by a network which includes the superior colliculus, the medial dorsal nucleus of the thalamus and pre-motor cortex (Van Der Werf et al., 2003; Sommer, 2003). All three of these regions were identified in the TD group who exhibited less movement execution variability compared to the ASD group, suggesting that TD children used sensorimotor memories to form load predictions. In contrast, children with ASD were impaired in their ability to acquire the target on average, and they did not exhibit activation within the superior colliculus or the medial dorsal nucleus of the thalamus. Children with ASD are known to have deficits in memory (Steele et al., 2007; Minshew et al., 1997) and the neural network supporting memory-based prediction which was identified in the TD group was absent in the ASD group.

Children with ASD exhibit superior performance on visual search tasks compared to TD children (Plaisted et al., 2000) and they may have used a strategy involving visuospatial attention (rather than memory-based prediction) in the current study. Visuospatial attention is supported by the pulvinar nucleus of the thalamus (Karnath et al., 2002), and the middle occipital gyrus (Martinez et al., 1999). Both the pulvinar nucleus of the thalamus and the middle occipital gyrus were activated in children with ASD, but not in TD children. Importantly, the 2-sample t-tests confirmed that the correlation coefficients between BOLD signal and task onset were significantly different between ASD and TD groups in the pulvinar nucleus of the thalamus. Unlike the TD children who engaged neural networks supporting the retrieval of sensorimotor memories, children with ASD might have engaged neural networks supporting visuospatial attention.

Our goal-directed over-and-back reaching task was specifically designed to minimize the influence of feedback control by encouraging fast movements. We found increased endpoint variability in children with ASD compared to TD children suggesting that children with ASD were impaired in their ability to use feedforward control. Seidler and colleagues (2004) have shown that motor performance is influenced by a continuum of feedforward and feedback modes of control. In their study, participants made reaching movements to targets of varying diameter. As target size increased, participants were more likely to make ballistic movements using feedforward control. As target size decreased, participants made slower movements using feedback control. BOLD signal changes were correlated with increasing and decreasing target sizes to identify regions of the brain important for feedforward and feedback control, respectively. Seidler and colleagues (2004) found that left primary motor cortex, left dorsal premotor cortex, and insular cortex were important for feedforward modes of control. These same regions were identified in the TD group in our study, but only the left primary motor cortex was identified in the ASD group. By contrast, Seidler and colleagues (2004) identified regions supporting feedback modes of control; these included left cingulate motor cortex, bilateral cerebellum, and right insula. Both the ASD and TD groups in our study had significant task-correlated BOLD signal activities in the cingulate cortex and the TD group additionally exhibited significant activities in the cerebellum and right insula. Moreover, both groups in the current study exhibited correlations between BOLD signal and task onset during the constant load sequence within the SMA which is important for postural stabilization (Suminski et al., 2007a). Task-related BOLD signal changes in the SMA were much higher in the ASD group compared to the TD group during the random load sequence suggesting that the ASD group relied more on a feedback control strategy to perform the goal-directed reaching task, especially when the applied load was unpredictable. Comparisons between the current study and those of Seidler et al. (2004) and Suminski et al. (2007a) suggest that children with ASD relative to TD children invoke a different set of neural pathways to solve the task.

Courchesne and Pierce (2005a) reviewed several studies of brain growth in ASD and they have found that infants with ASD exhibit a period of abnormally accelerated brain growth by 6 to 14 months of age and the frontal lobes in particular exhibit the greatest growth compared to other brain regions. They also found that local circuitry is overdeveloped and disorganized within the frontal lobe and long-distance connections with other brain regions are underdeveloped (2005b) although there is some disagreement in the literature (Sundaram et al., 2008). If local circuitry is overdeveloped in ASD, then we might expect the percent signal change of the BOLD signal to be higher in children with ASD relative to TD children due to the increased metabolic load. This interpretation is supported by Figures 6-5b and 6-6b, which compare impulse response functions across study groups, indicating that the percent signal change of the BOLD signal was higher in children with ASD compared to TD children.

Conclusion and Future Direction

Our findings suggest that TD children used a memory-based prediction strategy to update motor commands. TD children had less movement variability compared to children with ASD, and they engaged regions of the brain such as superior colliculus, medial dorsal nucleus of the thalamus, and pre-motor cortex which are important for memory retrieval. In contrast, children with ASD engaged regions of the brain such as pulvinar nucleus of the thalamus and middle occipital gyrus which are important for visuospatial attention suggesting that children with ASD used the spatial position of the hand to update motor commands. This strategy was not as successful as the strategy employed by TD children because children with ASD produced movements with greater variability compared to TD children. Taken together, the preliminary findings presented here support the idea that the motor performance deficits are not caused by dysfunction in a single brain region, but likely result from functional abnormalities in several brain regions and the interactions between them.

The sample size of the current study is low and therefore, the results should be interpreted with caution. We are currently enrolling additional participants to increase the sample size. In the future, we will identify neural correlates related to learning signals obtained from performance variables such as reinforcement learning, supervised, and unsupervised learning in these two populations (cf. Scheidt et al., 2012). However, additional participants are necessary to provide adequate statistical power for these analyses.

CHAPTER 7: CONCLUSIONS, LIMITATION, AND FUTURE DIRECTIONS

Conclusions

We used robotic assessments of sensorimotor function and functional neuroimaging techniques to identify ASD-related deficits in the adaptive and strategic compensation for sensorimotor discord (Aim 1), in the integration of visual and proprioceptive information for perception of movement kinematics (Aim 2), and in the neural correlates of memory-guided prediction (Aim 3). In chapter 3, we found that children with ASD were impaired in their ability to imitate gestures of the hand and arm and these deficits were correlated with performance errors while tracing a shape with reflected visual coordinates. These findings suggest that visuospatial information processing deficits contribute importantly to functional motor coordination abnormalities in ASD. In chapter 4, we found that children with ASD exhibited large movement errors in response to large, known transformations of visual feedback and motor command updating; however, they exhibited subtle deficits in the steady-state response to incrementally-imposed rotations. These findings were unrelated to a general motor execution deficit because movement errors were similar across groups when there was no imposed perturbation of visual feedback and because performance variables did not differ across groups. In chapter 5, we found that children with ASD were impaired in their ability to discriminate movement kinematics when visual and proprioceptive information were integrated. However, children with ASD exhibited proficiency in their ability to update the relative contributions of vision and proprioception for perception of movement kinematics in response to controlled levels of visual uncertainty. Finally, in chapter 6, we characterized neural correlates of goal-directed reaching during adaptation to an unpredictable sequence of perturbations. Whereas TD children exhibited widespread neural activity related to the target capture task, children with ASD exhibited activities that were more narrowly-focused in a small number of focal regions that exhibited larger-than-normal correlations between the BOLD signal and task onset. Taken together, the results from these three studies support the hypotheses that children with ASD exhibit abnormalities in their ability to use sensory information to guide limb movements and that ASD-related abnormalities in sensorimotor information processing give rise to deficits in compensation for unpredictable environmental change during goal-directed movement.

Across the four studies, we found evidence of sensorimotor information processing abnormalities in ASD. During the mirror-drawing task (chapter 3) we found that some children with ASD made errors that were smaller than typical whereas other children with ASD made errors that were much larger than those of TD children, such that performance errors were characterized by a bimodal distribution in the ASD group. We hypothesized that large and small movement errors during mirror-drawing in the ASD group were caused by reactions to proprioceptive stimuli that were hyper- and hypo-sensitive, respectively. However, when we characterized multisensory integration (chapter 5), we found that the ASD group was impaired in their ability to discriminate movement kinematics, but sensory re-weighting was intact in this group. Furthermore, we found that discrimination thresholds and relative sensory weights were normally distributed with equal variance across groups (chapter 5), unlike the bimodal distribution of mirror-drawing errors (chapter 3). An alternative explanation for abnormal movement errors during mirror-drawing was that children with ASD were impaired in their ability to compensate for visuo-motor discord. This explanation was supported by the finding of increased initial movement errors during strategic compensation for reflected coordinates during reaching and tracking in ASD (chapter 4). Movement errors were compared across groups to characterize motor execution (chapter 4), spatial calibration (chapter 4) and sensorimotor adaptation (chapters 4 and 6). When visual feedback corresponded directly to hand position (chapter 4), we found no group-wise difference in movement error, suggesting that motor execution was intact in ASD. However, when visual feedback was perturbed from the hand’s actual position [by reflecting or rotating the cursor’s position from the hand’s position (chapter 4) or by mapping a curved movement to a linear trajectory (chapter 6)], we found ASD-related deficits in initial movement direction (chapter 4), movement extent (chapter 6) and endpoint variability (chapter 6), suggesting that children with ASD were impaired in their ability to compensate for sensorimotor discord. During reaching movements made with incrementally-imposed rotations of visual feedback (chapter 4) or randomly-varying loads (chapter 6), we found subtle ASD-related deficits in movement accuracy, suggesting that sensorimotor adaptation was impaired in this group. During reaching and tracking movements with suddenly-imposed reflection of visual feedback (chapter 4), we found large ASD-related errors, suggesting that strategic compensation was also impaired in this group. The findings across the four studies supported the hypotheses that multisensory integration, automatic adaptive compensation and volitional strategic compensation were impaired in ASD, but motor execution was intact.

The findings from these four studies have broad scientific and clinical impact. In the past, ASD was defined primarily by social and language deficits with little emphasis on sensorimotor information processing deficits (American Psychiatric Association, 1994). However, the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) indicates that sensorimotor information processing deficits are an integral part of ASD. The results of the studies presented in this Dissertation provide additional support for these recent updates to the diagnostic criteria of ASD. Sensory integration therapy is currently used to treat children with ASD. However, the efficacy of such therapies is rarely reported (Case-Smith and Bryan, 1999; Dawson and Watling, 2000). The results of the current studies may lead to improved treatment for sensorimotor information processing deficits in ASD. For example, each of the tasks in the experiments of chapters 4 through 6 could be modified by adding additional reward/penalty criteria so as to train individuals to improve sensorimotor information processing. Finally, by characterizing differences in neural activity in children with ASD, we can improve our understanding of the brain and identify alternate neural networks supporting goal-directed movements.

Limited Generalizability of Findings Across the Broad Spectrum of Autism

The broad spectrum of autism includes high-functioning individuals who exhibit average or above average intelligence as well as low-functioning individuals, who exhibit cognitive deficits. The children who participated in the current studies were all high-functioning (defined as having a verbal IQ > 70). Therefore, we have not tested whether the specific sensorimotor deficits observed in these high-functioning children with ASD would generalize to the entire population of children with ASD.

There are three methods commonly used to account for variability in cognitive deficits across the spectrum of autism. One option is to constrain the participant groups such that only high-functioning individuals with ASD and TD controls are included and to assume that the results of high-functioning individuals generalize across the entire spectrum of autism. This method was employed in the studies presented here as well as recent studies of ASD (Salowitz et al., 2013; Abu-Dahab et al., 2013; Kourkoulou et al., 2013; Fuentes et al., 2011; Forti et al., 2011; Fabbri-Destro et al., 2009; D'Cruz et al., 2009; Gidley Larson et al., 2008; Rinehart et al., 2006, 2001; Mostofsky et al., 2004; Müller et al., 2003, 2001; Minshew et al., 2004). Another option is to include individuals with low-functioning ASD but to also include a control group with cognitive deficits (MacDonald et al., 2013; Watson et al., 2011; Wiggins et al., 2009; Miyahara et al., 1997). However, there are two problems with this method: the control group with cognitive deficits is not representative of the TD population (Müller et al., 2003) and cognitive deficits are an integral part of ASD and they should not be factored out (Müller et al., 2001). Perhaps the best option is to include representative participants from the entire autism spectrum as well as two separate control groups, one with cognitive deficits and one with average or above average intelligence (Hughes, 1996; Masterton and Biederman, 1983; Frith and Hermelin, 1969). Then results from the ASD group could be compared separately with those of the two control groups to distinguish deficits that are related to cognitive delays from those that are attributable to ASD. However, inclusion of low-functioning individuals was not appropriate for the current studies because the experiments required the cognitive ability to understand and follow multi-step task instructions. The ability to understand task procedures was especially important for the experiment of Aim 3 in which children participated in a MRI scan. Children with ASD exhibit greater anxiety compared to TD children (Kim et al., 2000) and we were concerned that if the children were unable to understand the instructions and description of the MRI procedure (as might occur in low-functioning children), it might have led to increased anxiety related to the experimental procedures. Therefore, we constrained all three studies to only include high-functioning individuals who were able to understand and comply with task instructions.

Future Directions

Correlation Analysis of Clinical Assessments and Sensorimotor Performance Measures

Each of the experimental protocols was custom-designed to answer specific research questions about sensorimotor control in children with ASD. However, the techniques used to characterize sensorimotor performance (i.e. robotic manipulation, MRI scan) are not practical for use in the clinical or therapeutic setting because they are time-consuming and require specialized equipment. Therefore, our results would have more clinical utility if we were to find significant correlations between sensorimotor performance measures (from the experiments above) and scores from standard clinical tests. Such clinical tests must be easy to implement and score such as administering questionnaires and performing face-to-face assessments.

We are currently collecting clinical test scores from the participants who completed the experiments described above. Clinical tests include the Test of Pragmatic Language (TOPL; Phelps-Terasaki and Phelps-Gunn, 1992), Social Communication Questionnaire (SCQ; Rutter et al., 2003), Social Responsiveness Scale (SRS; Constantino and Gruber, 2002), Family Assessment Device (FAD; Epstein et al., 1983), Adult/Adolescent Sensory Profile (AASP; Brown and Dunn, 2002), and the 12-item version of the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007). The TOPL, SCQ, and SRS will be administered to both groups to characterize language and social deficits in ASD which are important symptoms of the disorder (American Psychiatric Association, 2013) as well as to verify that the control group was free of such impairments. The FAD will be used to assess family functioning in both groups and has six categories to assess problem solving, communication, roles, affective responsiveness, affective involvement, and behavior control. The AASP will characterize sensory processing in six categories (taste/smell processing, movement processing, visual processing, touch processing, activity level, and auditory processing). We anticipate that the AASP scores will correlate with the ability to discriminate hand path curvatures using visuo-proprioceptive integration (Aim 2). The IUS-12 will characterize the participants' ability to deal with environmental uncertainty. We anticipate that the IUS-12 score will correlate with the regression coefficient from the prediction model of chapter 6 in which participants adapted reaching movements in response to a random sequence of loads.

Correlation Analysis of Sensorimotor Performance Measures Between Experiments

We identified ASD-related deficits within three model components of limb position control (Figure 2-1) including: adaptive and strategic compensation for sensorimotor discord (Aim 1), integration of visual and proprioceptive information for perception of movement kinematics (Aim 2), and memory-guided prediction (Aim 3). The model predicts that each of these three model components is adaptable such that changes within one model component will likely influence the other model components. Thus, to maintain accurate performance in the presence of deficits in any one of these three model components of limb position control, one would need to exhibit superior behavioral performance in the other components to maintain accurate task performance. The three experiments presented above have identified ASD-related deficits in each of these model components of goal-directed reaching. However, it is unknown if children with ASD are able to update specific components of the model of limb position to compensate for deficits in other aspects of the model. Unfortunately, only 6 participants (3 participants with ASD and 3 TD participants) completed all three studies (chapters 4 through 6), thus we do not have enough data to determine if behavioral performance measures correlated across studies. However, a future study could be designed such that every participant completes each of the studies so that a correlation analysis can be performed to compare behavioral performance measures across studies.

Others have found a relationship between compensation for sensorimotor discord and sensory re-weighting (Burns and Blohm, 2010) and between adaptive learning and sensory re-weighting (Wei and Körding, 2010). Burns and Blohm (2010) measured visual and proprioceptive weighting while participants made goal-directed reaching movements. Participants performed the reaching task with three different head roll positions (-30°, 0°, 30°) so as to introduce sensorimotor discord between the visual stimulus and proprioceptive information. When participants rolled their heads by -30° or 30°, the relative contribution of vision decreased compared to the condition in which the head was not rolled (0°). The authors concluded that the brain used reliability of the sensorimotor reference to update the relative contributions of visual and proprioceptive information. In another study by Wei and Körding (2010), participants grasped a robotic device and made goal-directed reaching movements. Visual feedback was randomly perturbed across trials and the visual stimulus was represented by a single cursor (no visual uncertainty) or a cluster of cursors randomly selected from a Gaussian distribution with small or large standard deviation (small or large uncertainty in the visual stimulus). The authors found that the rate in which participants adapted to perturbations of visual feedback differed across the three levels of visual uncertainty. Results from our multisensory integration experiment suggest that sensory re-weighting occurred in response to uncertainty in the visual stimulus. Thus, adaptive learning in the study by Wei and Körding (2010) was likely influenced by sensory re-weighting. These relationships between components of limb position control provide motivation for a future study to compare kinematic performance measures across the three studies presented in this Dissertation.

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