Motor learning relies on integrated sensory inputs in ADHD, but over-selectively on proprioception in Autism spectrum conditions

Jun Izawa(1,2), Sarah E Pekny(1), Mollie K Marko(1), Courtney Haswell(1), Reza Shadmehr(1), and Stewart H Mostofsky(3,4).

(1) Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205
(2)ATR Computational Neuroscience Laboratories, Kyoto 619-0288, Japan
(3) Kennedy Krieger Institute, MD 21205
(4)Departments of Neurology and Psychiatry, Johns Hopkins University School of Medicine, MD 21205

To appear in: *Autism Research*

Correspondence to Jun Izawa, Email: jizawa@atr.jp Fax: +81 774 -95-1236

Running title: Distinct patterns of motor memory in Autism

Courtney Haswell's current address: Duke-UNC Brain Imaging and Analysis Center, Duke University, NC 27705

This research was supported by grants from the Autism Speaks Foundation and from NIH: R01 NS048527, MH078160, MH085328, NS37422, the Johns Hopkins University School of Medicine Institute for Clinical and Translational Research, an NIH/NCRR CTSA Program, UL1-RR025005, SRPBS(MEXT), and JSPS23700360.

Lay Abstract

Children with autism spectrum disorder (ASD) show deficits in development of motor skills, in addition to core deficits in social skill development. In a previous study (Haswell et al., 2009) we found that children with autism show a key difference in how they learn motor actions, with a bias for relying on joint position rather than visual feedback; further, this pattern of motor learning predicted impaired motor, imitation and social abilities. We were interested in finding out whether this altered motor learning pattern was specific to autism. To do so, we examined children with Attention Deficit Hyperactivity Disorder (ADHD), who also show deficits in motor control. Children learned a novel movement and we measured rates of motor learning, generalization patterns of motor learning, and variability of motor speed during learning. We found children with ASD show a slower rate of learning and, consistent with previous findings, an altered pattern of generalization that was predictive of impaired motor, imitation, and social impairment. In contrast, children with ADHD showed a normal rate of learning and a normal pattern of generalization; instead, they (and they alone), showed excessive variability in movement speed. The findings suggest that there is a specific pattern of altered motor learning associated with autism.

Scientific Abstract

The brain builds an association between action and sensory feedback to predict the sensory consequence of self-generated motor commands. This internal model of action is central to our ability to adapt movements, and may also play a role in our ability to learn from observing others. Recently we reported that the spatial generalization patterns that accompany adaptation of reaching movements were distinct in children with Autism Spectrum Disorder (ASD) as compared to typically developing (TD) children. To test whether the generalization patterns are specific to ASD, here we compared the patterns of adaptation to those in children with Attention Deficit Hyperactivity Disorder (ADHD). Consistent with our previous observations, we found that in ASD the motor memory showed greater than normal generalization in proprioceptive coordinates compared with both TD children and children with ADHD; children with ASD also showed slower rates of adaptation compared with both control groups. Children with ADHD did not show this excessive generalization to the proprioceptive target, but did show excessive variability in the speed of movements with an increase in the exponential distribution of responses (τ) as compared with both TD children and children with ASD. The results suggest that slower rate of adaptation and anomalous bias towards proprioceptive feedback during motor learning is characteristic of autism; whereas increased variability in execution is characteristic of ADHD.

Introduction

Formation of internal models of action is critical to development of social and communicative, as well as motor, behavior. When the brain learns to perform a movement, it builds an association between motor commands and sensory feedback so that it can predict the sensory consequences of self-generated action. Prediction of one's sensory consequence is necessary for choosing an optimal action plan to achieve the intention of the action (Izawa et al., 2008; Shadmehr and Krakauer, 2008); this process is thereby central to development of skilled movements involved in a wide range of human behavior. Furthermore, this linking of perception to action is not only critical to optimizing execution of skilled behavior; it may also contribute to the processes by which we learn to interpret the meaning of these actions when performed by others (Rizzolatti et al., 2001, 2002; Miall, 2003; Mattar and Gribble, 2005). Theoretical constructs, dating back to J. Piaget (1896-1980), have emphasized formation of action models as being critical to the development of perceptual models of the world around us, and recent theories of embodied cognition and enactive minds posit the importance of action model formation for development of theory of mind and related aspects of social cognition (Rizzolatti et al., 2002; Klin et al., 2003).

Autism is characterized by both an impaired ability to acquire social skills as well as to infer the meaning of others' behavior (Frith, 2001). In parallel, children with ASD show profound impairments in their ability to perform skilled motor gestures, characteristic of a "developmental dyspraxia" (Mostofsky et al., 2006; Dziuk et al., 2007; Dowell et al., 2009), as well as impaired ability to recognize these gestures in others (Dowell et al., 2009). Given the developmental nature of autism, it may be that abnormalities in the processes underlying the formation of internal models of action might help explain core deficits in skill development (social and communicative, as well as motor, skills) and associated impairments in their ability to infer others' actions. Recognizing this, we undertook a series of experiments designed to examine autism-associated differences in motor learning (Gidley Larson et al., 2008; Haswell et al., 2009), proposing this could advance understanding of the neural basis of autism and help guide therapeutic interventions targeted at improving social, communicative and motor skills.

In a series of studies (Gidley Larson et al., 2008; Haswell et al., 2009), we examined processes by which children with ASD form internal models of action, and attempted to see if these processes were fundamentally different from that in TD children. These studies led to a critical observation: when learning a novel action pattern children with ASD appear to excessively rely on proprioceptive feedback from their own internal joint space and tend to discount feedback from the extrinsic visual world around them (Haswell et al., 2009). When we examined generalization patterns, which are thought to allow one to infer the receptive fields involved in forming the internal action model (Shadmehr and Moussavi, 2000; Malfait et al., 2002; Donchin et al., 2003; Poggio and Bizzi, 2004; Malfait et al., 2005; Hwang et al., 2006; Krakauer et al., 2006; Darainy et al., 2009; Mattar and Ostry, 2010), we found that children with ASD showed excessive generalization in the intrinsic coordinate system as compared with the extrinsic coordinate system, suggesting that they

tend to build a much stronger than normal association between self-generated motor commands and proprioceptive feedback, but a weaker than expected association with visual feedback. Furthermore, we found that the bias towards generalization in the intrinsic coordinate system was a robust predictor of social, as well as motor, impairment in autism (Haswell et al., 2009).

A weakness of our prior work was that it only compared children with ASD to TD children. It remains unclear whether the anomalous pattern of motor learning is specific to autism. Addressing this, in the present paper, we examined patterns of generalization in an additional clinical group of children, those with attention deficit/hyperactivity disorder (ADHD), a developmental disorder which, like autism, has been found to be associated with impairments in motor execution and control (Mostofsky et al., 2003; Cole et al., 2008; Macneil et al., 2011).

Methods

Subjects

Table 1. Characteristics of the children. PRI: perceptual reasoning index. PANESS: Revised Physical and Neurological Examination of Subtle Signs. SRS: Social Responsiveness Scale.

Approval was granted for this study from the Johns Hopkins Medicine Institution Review Board. After description of the study, parents of participants signed written consent, and participants provided written assent. All participants were right-handed with no history of neurologic illness, including epilepsy or traumatic brain injury. Children in all groups were recruited from advertisements posted in the local communities through local magazines, pediatricians' offices, outpatient clinics at the Kennedy Krieger Institute local schools, local chapters of national organizations (local Autism Society of America chapters and local Children and Adults with ADHD (CHADD) chapters) and through word of mouth. Study participants included 23 children (3 girls) with ASD (age 10.4±1.7), 17 children (3 girls) with ADHD (age 10.8±1.8) and 20 TD children (4 girls) (age 10.9±1.2) (Shown in Table 1). The data from 9 typically developing children and 14 children with ASD had been reported in a previously published paper (Haswell et al., 2009). Children with autism met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (AmericanPsychiatricAssociation, 1994). ASD diagnoses were established using the Autism Diagnostic Interview - Revised (ADI-R: (Lord et al., 1994)) , the Autism Diagnostic Observation Schedule - G, Module 3 (ADOS-G: (Lord et al., 2000)) , and the clinical judgment of the

Group	Sex	Age	PRI	Total PANESS Score	SRS Total T- Score
Control	M:16 F:4	10.9 +/- 1.2	108.5 +/- 11.7	24.4 +/-10.2	42.3 +/- 3.9
ASD	M:20 F:3	10.4 +/-1.7	105.2 +/-14.3	39.3 +/-12.7	77.0 +/-11.3
ADHD	M:14 F:3	10.8 +/-1.8	105.6 +/-13.7	34.0 +/-9.4	58.0 +/-9.9

examiners. Participants were required to meet criteria for ASD based on the clinical judgment of the examiner and either the ADOS-G, the ADI-R, or both. All participants met criteria for ASD based on the ADOS-G and clinical impression, with diagnosis confirmed by a child neurologist (S.H.M.). Nine children with ASD were being prescribed stimulants at the time of the study. One of the subjects prescribed stimulant medication was also prescribed a Selective Serotonin Reuptake Inhibitor (SSRI). An additional four subjects were being prescribed SSRIs, one of whom was also prescribed an atypical neuroleptic (risperidone). One additional subject was being prescribed atomoxetine. SSRIs, risperidone, and atomoxetine were not discontinued for this study. As with the ADHD subjects, the stimulant medications were discontinued the day prior to the study (providing at least a 36 hour washout period).

Children with ADHD met DSM-IV criteria, with diagnosis confirmed using a structured parent interview (Diagnostic Interview for Children and Adolescents, Fourth Edition; DICA-IV) (Reich, 2000) and ADHD-specific and broad behavior rating scales (Conners' Parent Rating Scale-Revised—CPRS) (Conners, 1997) and the ADHD Rating Scale-IV, home and school versions (DuPaul et al., 1998). Diagnosis was confirmed by a child neurologist (S.H.M.) prior to participation. Children meeting criteria for diagnosis of conduct, mood, generalized anxiety, separation anxiety, obsessive-compulsive disorders were excluded; they were also excluded if they had an immediate family member (sibling or parent) with autism or another pervasive developmental disorder. In addition, none of the children with ADHD had a history of speech/language disorder or a Reading Disability, and all had a basic reading standard score of 85 (16th percentile) or higher on the Word Reading subtest from the Wechsler Individual Achievement Test, Second Edition (WIAT–II). Children with ADHD taking psychotropic medications other than stimulant medication were excluded from participation and all children taking stimulant medication were asked to withhold medication on the day prior and day of testing.

Children were excluded from the control group if they had a history of a developmental disorder or a psychiatric disorder based on responses from a standardized parent interview, the DICA-IV (Reich et al., 1997). They were also excluded if they had an immediate family member (sibling or parent) with autism or another pervasive developmental disorder.

Procedures

Each participant was administered the Wechsler Intelligence Scale for Children - 4th Edition (WISC-IV; (Wechsler, 2003)) to assess intellectual functioning. Recent research supports the notion that using a task-specific measure of intelligence is a more appropriate assessment of intellectual functioning in children with ASD than a more general measure (Mottron, 2004). Therefore, the present study used the Perceptual Reasoning Index (PRI) from the WISC-IV as the primary measure of intellectual functioning, rather than the Full Scale IQ (FSIQ), taking into account that the three tasks performed by the participants were nonverbal, perceptually based motor tasks. All participants had a PRI greater than 80, except for one child with ADHD who had a significant (>15 point) discrepancy

between IQ factor scores with a PRI standard score of 79 and a Verbal Comprehension Index (VCI) standard score of 110.

Throughout each motor examination, verbal instructions were simple and standardized in order to minimize any confounding elements of language and comprehension. All participants appeared to understand the directions and any questions were answered before beginning the task.

Reach adaptation task

We adapted the paradigm from (Haswell et al., 2009). Subjects held the handle of the robotic arm that was covered by the horizontal screen. The screen prevented the subject's view of their hand and the robotic arm. Instead, an LED housed in the robotic handle provided a real-time visual feedback of the hand position. The starting position and the target position were provided by an overhead projector. The starting positions were determined for both the left and right workspaces by measuring the subject's upper and lower arm length, keeping their arm's posture on the horizontal plane so that it would position the arm at a shoulder angle of 90 degrees and elbow angle of 90 degrees for the left workspace, and shoulder angle of 45 degrees and elbow angle of 90 degrees for the right workspace. In the left workspace, there is one potential target position (Target 1), whereas in the right work space there are two potential targets (Target 2 or 3). We projected one of these three potential targets for each trial. We refer to Target 1 as the "learning target", Target 2 as the "visual target", and Target 3 as the "proprioceptive target".

The subjects completed three blocks of 54 trials for the familiarization of the task, reaching to all three targets randomly without force perturbations. In the last half of the third block, the baseline force produced by the subjects was measured by introducing error clamp trials where the robot enforces a straight line movement to the target by producing stiff walls that minimize the movement errors (Scheidt et al., 2000; Smith et al., 2006; Criscimagna-Hemminger and Shadmehr, 2008). The familiarization blocks were followed by two blocks (the 4th and 5th blocks) of adaptation trials. During the adaptation trials, the subjects repeatedly reached to the learning target (Target 1 in Fig. 1B) while a counter clockwise force field perturbation was applied, except every 15th trial when there was one error clamp trial to each of three target directions. The amplitude of the applied force was proportional to the hand velocity while its orientation was perpendicular to the movement direction: $F = B\dot{x}$, with $B = \begin{bmatrix} 0 & -13 \\ 13 & 0 \end{bmatrix}$, where F is the applied force and $\dot{x}$ is the hand velocity. In the 6th block, the subjects experienced error clamp trials to all three targets.

Subjects were asked to keep the cursor inside the starting box until a 6-mm target box appeared 8cm away from the start position. As soon as they perceived the appearance of the target, they moved the handle to the target as quickly and accurately as possible. The start box appeared either in the left workspace or the right workspace. If the hand reached to the target in less than 500ms, the subjects scored 1 point.

Clinical measures of social, motor, and imitation function

Social impairment was assessed using the ADOS-G, a standardized interview/observational assessment battery that assesses social, communicative, and stereotyped behaviors diagnostic of autism (Lord et al., 1999). Module 3 is appropriate for children with fluent speech ages 4 years or older and was therefore used for the ASD participants in this study. Social impairment was also assessed using the Social Responsiveness Scale (SRS) (Constantino, 2005), a questionnaire that can be administered to a parent and/or teacher (only parent ratings were used in this study). It inquires about a child's ability to engage in emotionally appropriate reciprocal social interactions in naturalistic settings and includes items that ascertain social awareness, social information processing capacity for reciprocal social responses, social anxiety/avoidance, and characteristic autistic preoccupations/traits. The SRS generates a singular score (total t score) that can be used as a measure of severity of social impairment.

Imitation was assessed as a part of a praxis examination adapted from the Florida Apraxia Battery modified for children (Mostofsky et al., 2006), which also included sections assessing the ability to perform gestures to command (GTC) as well as gestures with actual tool use (GTU). During the gesture to imitation (GTI) section, the child was asked to watch the examiner perform an action and then immediately repeat it. For example, the examiner would perform a motion resembling twisting a cap with one hand while holding an imaginary bottle with the other hand (a meaningful action), or a motion consisting of a fist that opened and closed (a meaningless action). During the GTC section, children were asked to perform actions to verbal command (e.g., "Show me how you brush your teeth"). Finally, during the GTU section, participants were given actual objects and asked to demonstrate how they would use them (e.g., key, cup, hammer). The examination was videotaped and later scored independently by two raters. Each gesture was examined for the presence of errors according to criteria described in (Mostofsky et al., 2006). At least 80% concurrence between raters was achieved for each assessment to ensure reliability of scoring. Detailed descriptions of the praxis battery, scoring methodology, and reliability data are provided in (Mostofsky et al., 2006; Dziuk et al., 2007).

Basic motor control was assessed using the Revised Physical and Neurological Examination of Subtle Signs (PANESS) (Denckla, 1985) . The PANESS is a structured, norm-referenced motor examination with good test-retest reliability within an age range of 5 to 17 years. Tasks include untimed assessment of gaits and stations and timed assessment of rapid/sequential movements of the feet, hands, and tongue. These were used to generate a total PANESS score, with higher total PANESS scores indicative of poorer motor function. Studies of autism using the PANESS reveal that it offers a high level of discrimination in distinguishing children with ASD from TD children (Jansiewicz et al., 2006);. Furthermore, the PANESS has proven useful in analysis of brain-behavior correlations in autism, with increased primary white matter volume having been shown to be strongly predictive of higher PANESS scores (worse motor function) in children with ASD (Dziuk et al., 2007).

SRS data were available for 22 of 23 ASD children, 11 of 17 ADHD children and 17 of 20 TD children. PANESS was available for 22 of 23 ASD children, 16 of 17 ADHD children, and all 20 TD children. Praxis data were available for 22 of 23 ASD children 11 of 17 ADHD children, and all 20 TD children.

As would be expected, there were significant effects of the three children groups on SRS score ($F(2,50)=62.9$, $p<0.001$). In Bonferroni post hoc analysis, the SRS scores differed significantly between TD and ASD ($p<0.0001$), between TD and ADHD ($p<0.0001$) and between ASD and ADHD ($p<0.0001$). Also there were significant effects of three groups on basic motor skill (PANESS score) ($F(2,56)=9.81$, $p<0.001$). In Bonferroni post hoc analysis, the differences between TD and ASD ($p<0.001$) and between TD and ADHD ($p<0.01$) were significant. Furthermore, the effect of groups on praxis score was significant ($F(2,51)=4.37$, $p=0.018$). In Bonferroni post hoc analysis, only difference between TD and ASD was significant ($p<0.001$).

Ex-Gaussian analysis

Performance of children with ADHD often exhibits occasional movements that appear as 'outliers'. This results in a distribution that is not Gaussian, but has a longer than usual tail, called 'ex-Gaussian'. To quantify the characteristics of the distribution of movement parameters (such as peak velocity), we performed an ex-Gaussian analysis (Ratcliff, 1993; Leth-Steensen et al., 2000; Geurts et al., 2008; Vaurio et al., 2009). The ex-Gaussian distribution is generated by the convolution of a Gaussian and an exponential distribution. When we assume x represents the peak speed, the ex-Gaussian distribution is given by

$$f(x \mid \mu,\sigma,\tau) = \frac{1}{\tau\sqrt{2\pi}} \exp\left(\frac{\sigma^2}{2\tau^2} - \frac{x-\mu}{\tau}\right) \cdot \int_{-\infty}^{(x-\mu)/\sigma-\sigma/\tau} \exp(-\frac{y^2}{2})dy$$

The above expression contains three parameters: μ,σ, and τ. μ represents the mean of the Gaussian function and σ represents the SD of the Gaussian function. τ is the mean of the exponential component that reflects the tail of the distribution. The ex-Gaussian distribution has a long tail on the positive side, which has been used to model the distribution of reaction times (Ratcliff, 1993; Leth-Steensen et al., 2000; Geurts et al., 2008; Vaurio et al., 2009). We estimated the best fit parameters using a maximum likelihood method.

Results

Figure 2A illustrates average trajectories when the subjects reached to Target 1 in the left work space. In the baseline period in which no perturbation was present, subjects in all three groups produced straight reaching movements (Fig. 2A Baseline). When the force field was present, the hand trajectories were perturbed and deviated from the straight line (Fig. 2A). Figure 2B illustrates the maximum lateral deviation over trials. Across the three groups, the deviation of the hand trajectory during force field trials declined with training ($F(89,5078)=15.86$, $p<0.001$). The patterns of decline of lateral deviation differed significantly for the three groups ($F(178, 5073)=1.25$, $p<0.05$). To better

understand the nature of this difference, we fit the performance of each subject to a double-exponential for each adaptation block:

$$(\text{Lateral Deviation}) = \beta_1 \exp(-\beta_2(\text{trial})) + \beta_3 \exp(-\beta_4(\text{trial}))$$

The first exponential function represents the faster decay of the lateral deviation and the second represents the slower decay (i.e., $\beta_2 \geq \beta_4$). The lines in Fig. 2B illustrate the best fit curves for the averaged lateral deviation over all subjects. Note that this double exponential function produces good fits (TD: $R^2 = 0.91$, ASD: $R^2 = 0.9$, ADHD: $R^2 = 0.73$). A blow-up of the first 20 trials is shown in Fig. 2C. This view of the data suggested that the ASD children exhibited a slightly slower rate of adaptation. To quantify this, we compared the distribution of each of the four parameters β_1, β_2, β_3, and β_4 across the three groups. We found a significant effect of group on β_2, the decay rate of the fast system ($F(2,59)=6.31$, $p<0.005$). post-hoc analysis revealed that β_2 of ASD was significantly smaller than that of TD ($p<0.001$) and that of ADHD ($p<0.013$), while these three groups were indistinguishable regarding the other parameters of the two adaptation blocks. These results suggest that the motor adaptation of ASD children showed a slightly slower learning rate than TD and ADHD.

A closer look at the lateral deviations in Fig. 2B suggests that there may have been greater trial-to-trial variability in the performance of the ADHD group than that of TD and ASD. Lateral deviations arise from a force field that pushes the hand to one side. The strength of this field is dependent on the velocity of the hand toward the target. Therefore, we looked whether the velocity of the hand along the direction of the target showed greater trial-to-trial variability in ADHD than other children. To perform this analysis, we binned movements in 15 trial segments and measured the variance of the peak velocity in the direction of the target for each child. The distribution of this variance is plotted in Fig. 2D. We found that in the adaptation sets there was a greater variability in the speed of movements in ADHD than the other groups (main effect of group, $F(2,342)=3.34$, $p<0.04$). In post hoc analysis, ADHD was significantly more variable than TD ($p<0.048$, Dunnet t-test), whereas ASD was indistinguishable from TD ($p=0.996$, Dunnet t-test). To examine this difference of the movement variability further among the three groups, we plotted the histogram of the peak speeds during the learning blocks (Fig. 3A), which shows the skewed distribution with the long tail on the higher speed in ADHD.

To quantify skewness of the distribution, we performed ex-Gaussian analysis, where it is assumed that the distribution of the trial-to-trial variation of the peak speed can be modeled by the combination of a normal and an exponential distribution. Fig. 3B shows the estimated parameters of

ex-Gaussian function. μ and σ correspond to the mean and the standard deviation of the Gaussian component. τ is the mean of the exponential component. In the analysis of μ, there was a significant main effect of group ($F(2, 114)=7.726$, $p<0.001$), but not of condition (Learning vs. Baseline, $F(1,114)=0.315$, $p=0.576$) or interaction of group and condition ($F(2, 114)=0.958$, $p=0.387$). Post-hoc analysis revealed that TD had significantly higher μ than ASD ($p<0.005$, Bonferroni corrected) and ADHD ($p<0.05$, Bonferroni corrected). These results suggest that TD has higher mean speed compared with both ASD and ADHD subjects. In the analysis of σ, there was no effect of group; however, the effect of adaptation approached significance ($F(1, 114)=3.612$, $p=0.06$), with increased σ in the learning condition as compared with the baseline. There was no significant group by condition interaction ($F(2,114)=0.685$, $p=0.51$) In the analysis of τ, there were significant main effects of the group ($F(2,114)=8.86$, $p<0.001$)) and condition ($F(1,114)=6.475$, $p<0.05$). Also, the interaction of these two factors was significant ($F(2, 114)=3.11$, $p<0.05$). Post-hoc analysis revealed that children with ADHD showed significantly increased τ as compared to both TD children ($p<0.001$, Bonferroni) and children with ASD ($p<0.05$, Bonferroni). The effect of condition for τ was significant for ADHD children ($p<0.001$, Bonferroni) with an increase in the learning condition as compared with baseline; there was no significant effect of condition on τ in the TD group ($p=0.917$, Bonferroni) or the ASD ($p=0.425$, Bonferroni) group. These results suggest that ADHD children had a significantly higher number of 'outliers' in their measures of peak speed, and that the probability of these outliers was increased during learning.

In order to make a straighter hand path to the target, the subjects should produce forces that compensate for the perturbation. We quantified the amount of adaptation/generalization via error-clamp trials in which we measured the force that subjects produced against channel walls that guided the hand to the target. These error clamp trials were presented in randomly selected trials during the learning period. For Target 1 (training target), six out of 96 trials were error clamp trials, whereas all trials were error clamp for the other targets. Therefore, for Targets 2 and 3, the subjects were never trained in a force field and never experienced error. This design allowed us to simultaneously assay learning and generalization.

Figure 4A illustrates the peak force that subjects produced on each error-clamp trial. There were no differences among the groups during the baseline or adaptation periods ($F(2,57)=0.84$, $p=0.44$). In the post-adaptation test period, all movements were in error-clamp trials, resulting in a gradual decay of the forces ($F(17,969)=3.64$, $p<0.001$). The decay was comparable for all groups ($F(34,969)=0.42$, $p=0.978$). We plotted the average of the first six test trials in Fig. 4B: for Target 1, the force was comparable for all groups ($F(2,57)=1.57$, $p=0.21$). This suggests that by the end of training toward Target 1, performance was indistinguishable between the groups. However, the generalization of this adaptation was different toward Target 3. To quantify the generalization patterns, we normalized the measured force of Target 2 and Target 3 with respect to force in Target 1. We found that all groups generalized to a greater extent to Target 3 than to Target 2 ($F(1,57)=81.29$, $p<0.0001$). Second, we found that the generalization patterns were markedly different across the three

groups ($F(2,57)=8.28$, $p<0.001$). Post hoc analysis revealed that children with ASD generalized to Target 3 to a greater amount than did the TD children (Sidak-corrected post hoc t-test, $p<0.001$), whereas the generalization to Target 3 was not distinguishable between TD and ADHD (Sidak-corrected post hoc t-test, $p=0.29$). The difference between ASD and ADHD was close to significant (Sidak-corrected post hoc t-test, $p=0.06$), with the ASD group showing greater generalization in Target 3 than the ADHD group.

These results suggest that the children with ASD built a motor memory that more strongly relied on proprioceptive coordinates than did TD children (and, to some degree, than did ADHD children). In contrast, there was no apparent difference in the pattern of generalization between ADHD children and TD children.

To examine whether the autism-associated bias in the generalization patterns during motor adaptation could predict clinical impairment, we looked for correlations between how much subjects generalized to Target 3 and clinical measures of motor, imitation, and social impairment. We found that, for children with ASD, ADOS-G Module 3 Reciprocal Social Interaction score was significantly correlated with generalization to Target 3, such that the greater the generalization, the greater the impairment in social function (Fig. 5A, $R=0.49$, $p<0.02$). Furthermore, this correlation of social ability and reliance on proprioceptive coordinates was observed across all children, in each of three groups. To standardize the amount of generalization for each of the three groups, we used the normalized generalization index of the Target 3. Figure 5B shows the total T score from the SRS was significantly correlated with the normalized generalization index of the Target 3, such that the greater the impairment in social function across all children, the greater the reliance on the intrinsic coordinates ($R=0.4$, $p<0.01$). However, the correlation in the TD group alone was not significant ($R=-0.37$, $p=0.1$). When we removed TD children and analyzed the correlation in the ASD group, the strength of the correlation was similar to that of the TD group and it nearly reached significance ($R=-0.32$, $p=0.06$). Therefore, it appears that both groups are in fact, contributing to the correlations of SRS with generalization patterns.

We also found that the bias towards reliance on proprioceptive coordinates was correlated with measures of motor imitation and basic motor control. As shown in Figure 5C, there was a correlation between generalization to Target 3 and total PANESS score ($R=0.38$, $p<0.005$), suggesting that the proprioceptive bias predicted impairment in basic motor control. Finally, we noted that the greater the generalization in proprioceptive coordinates, the greater the impairment in the ability to imitate actions ($R=0.29$, $p<0.05$).

Discussion

In this study we confirmed our previous findings (Haswell et al., 2009) that during adaptation of reaching movements the acquired motor memory in ASD showed atypical generalization patterns: the ASD children generalized their learning in proprioceptive coordinates to a greater degree than did TD children, while generalization in visual coordinates remained indistinguishable. Furthermore, we

considered a new subject group of ADHD children and found evidence suggesting that the anomalous property of the motor memory was specific to ASD children. Our results showed that ADHD was indistinguishable from TD children in terms of generalization pattern, and there was a near significant trend for children with ASD showing greater generalization in proprioceptive coordinates than children with ADHD. Nine of the 23 subjects with ASC were prescribed stimulant medication at the time of the study, raising the possibility that some proportion of this cohort also met criteria for ADHD. While this might be expected to minimize differences between the ASC and ADHD groups, we nevertheless found clear distinction in the patterns of motor learning. Therefore, the findings provide initial support for the hypothesis that the anomalous pattern of motor learning, characterized by increased reliance on proprioceptive feedback relative to visual feedback, is specific to autism. Generalization patterns that accompany learning are thought to be a signature of the neural system that is engaged in representing the new information (Poggio and Bizzi, 2004; Shadmehr, 2004). For example, generalization pattern of the motor memory for the reach adaptation task is consistent with neural coding in the primary motor cortex (Thoroughman and Shadmehr, 2000; Hwang and Shadmehr, 2005). In contrast, generalization patterns in visuomotor rotations appear more consistent with an encoding similar to cells in the posterior parietal cortex (Tanaka et al., 2009). In this framework, the difference in the generalization patterns between ASD and TD may have its roots in the wiring of the brain of children with autism. We speculate that an altered pattern of neural connectivity present in autism (Belmonte et al., 2004; Herbert et al., 2004; Casanova et al., 2006) with an overgrowth of localized U-fiber connections between adjacent brain regions, including those in primary sensorimotor cortex, may contribute to an up-regulation of proprioceptive input; and that undergrowth of distant cortical and subcortical connectivity present in autism may result in a discounting of visual feedback in action model formation as this depends on distant parietal-premotor connections. Consistent with this, we found (Mostofsky et al., 2007) that increased volume of primary sensorimotor white matter was robustly predictive of motor impairment in autism. In contrast, for TD children and children with ADHD, the opposite pattern was observed – increased primary motor white matter volume correlated with better (rather than worse) motor skill performance (Mostofsky et al., 2007). The combined results from these prior studies and that of the present study (revealing excessive generalization to the proprioceptive target) suggest that autism-associated abnormalities in neural structure/connectivity in the primary motor cortex may produce anomalous generalization patterns characterized by a bias toward proprioception.

In addition to the distinct generalization patterns in ASD, we found that the rate of learning in ASD during the initial adaptation phase was significantly slower than TD and ADHD. In theory, the system for updating motor memory is composed of at least two interacting systems with distinct time scales (Smith et al., 2006; Kording et al., 2007). One system appears to learn strongly from error but has fast forgetting, while another system learns less from error but has strong retention. There is evidence that distinct neural structures support these two timescales (Keisler and Shadmehr, 2010). Non-invasive potentiation of the cerebellum appears to increase the initial rate of learning and

produce faster forgetting, suggesting that the cerebellum may have a particular role in the fast timescale of motor memory that is necessary for error-dependent learning (Galea et al., 2010). Consistent with these findings, individuals with cerebellar injury show slower rates of adaptation compared with healthy individuals (Lang and Bastian, 1999). Cerebellar pathology is one of the more consistent findings on post-mortem studies of autism (Bauman, 1991) and abnormalities of the cerebellar vermis have been reported in MRI studies (Courchesne et al., 1994; Kates et al., 1998). It is possible that the smaller than normal rate in the fast timescale of adaptation that we observed here in ASD is a reflection of a cerebellar anatomical deficit.

In contrast to children with ASD, those with ADHD showed normal rates of adaption and generalization pattern of motor memory, but a larger trial-to-trial variability throughout the adaptation period. These findings are consistent with those from studies of reaction time (RT) in individuals with ADHD. Findings from several studies reveal that children with ADHD show increased variability in RT, and that this increased variability is principally reflected by an increase in the exponential distribution of responses (τ). Given that the average of the peak speed in ADHD group was not increased during the learning blocks, it appears that the larger τ during the learning session might not have been due to signal dependent noise in the motor execution level (Harris and Wolpert, 1998). Rather, we speculate that this increased τ is due to an increase in "lapses of attention" (Vaurio et al., 2009), the cause of which might be excessive temporal discounting with a preference for impulsively directing attention to more immediately rewarding stimuli. We recently found that a lack of reward during reach adaptation session increased trial-to-trial reach variability (Izawa and Shadmehr, 2011). It follows that the increased τ in children with ADHD might be a consequence of excessive active search noise due to anomalous response to immediate vs. delayed reward (i.e., anomalous temporal discounting).

Autism is characterized by impaired development of social and communicative skills. Consistent with this, children with ASD also show profound impairments in their ability to perform skilled movements, including those involving imitation of gestures as well as performance of gestures to command and with actual tool use (Dowell et al., 2009). Interestingly, children with ADHD do not show similar impairment in performance of these skilled gestures (Dewey et al., 2007). Given the developmental context of autism, impaired development of skilled gestures necessary to motor, as well as social, function may be secondary to a fundamental problem with how those motor action plans are acquired. Our findings suggest that there is a difference in how children with ASD form internal models of action. When learning a novel movement pattern, children with ASD show an abnormal bias towards reliance on proprioceptive feedback from their own bodies, as opposed to visual feedback from the external world. This anomalous pattern of action model formation might not only contribute to impaired motor skill development in autism, with resulting development dyspraxia (Mostofsky et al., 2006; Dewey et al., 2007; Dziuk et al., 2007; Dowell et al., 2009), it may also contribute to core features of impaired social and communicative development that characterize autism.

In support of this interpretation, we found that the bias toward reliance on proprioceptive feedback was correlated with both impaired motor, as well as social function. The association of proprioceptive generalization with the core social features of autism was, in fact, seen both within children with ASD (as measured using the ADOS) and across the three groups of subjects (as measured using the SRS).

Many investigators have hypothesized that the internal models that are the basis of learning skilled movements are also the basis with which our brain understands the actions of others (Rizzolatti et al., 2002; Klin et al., 2003). Theory suggests that in learning to perform a movement, the brain builds an association between self generated motor commands and sensory feedback, forming an internal model that allows it to predict the sensory consequences of self-generated motor commands (Synofzik et al., 2008). While this ability is crucial for performing skillful movements, it may also play a fundamental role in the ability of our brain to imitate actions of others, and in doing so, develop an ability to infer the purpose and consequences of the actions that we see (Rizzolatti et al., 2001; Miall, 2003) often referred to as "theory of mind."

This association has long been recognized in models of praxis, where the ability to perform skilled gestures is related to the ability to correctly identify those gestures when performed by others (Ochipa et al., 1997). Recent studies of praxis in autism reveal that children with ASD are not only impaired in their ability to perform skilled gestures, but also in their ability to correctly identify these gestures when performed by others (Dowell et al., 2009). The findings from these studies of motor function in autism clearly parallel those of social function: children with autism are not only impaired in their ability to perform social skills, they are also impaired in their ability to correctly identify and interpret the meaning of others' social actions (Cattaneo et al., 2007).

From a developmental perspective, impaired action model formation may therefore contribute not only to impaired skill development in autism, it may also contribute to impaired social cognition. We found that the children with ASD place a greater than normal reliance on their own proprioception while they discount visual information. This is congruent with the fact that they are impaired in their ability to acquire models of action through visually-based imitation (Rogers et al., 1996). This impaired ability to learn internal models on the basis of visual coordinate might impaired understanding of social and communicative behavior of others. Put another way, the consequence of a weaker than normal association between motor commands and visual feedback, which is mediated by connections between posterior parietal and premotor cortices, is that children with ASD may develop a "dyspraxia" for social (as well as motor) skills. Impaired social skills and motor dyspraxia in the ASD brain may share a common neural pathogenesis.

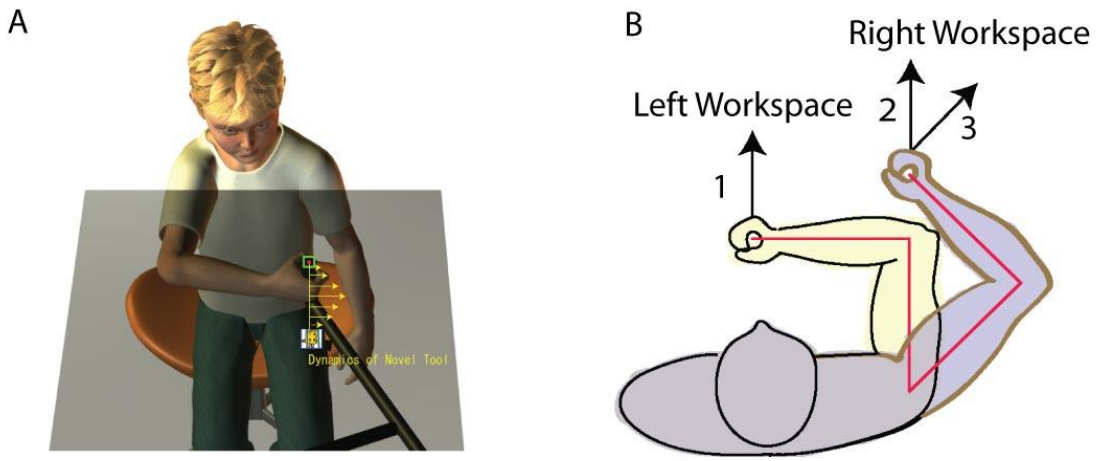

Figure 1 Task configuration (A) Children held the handle of a robotic arm and played a game in which the objective was to capture animals that had escaped from a zoo. At the start of the trial, the robot moved the child's arm to a starting posture. Next, an animal would appear at the target location (8cm). If the child could reach the target in time (0.5+/- 0.05s), the animal would be captured and the child was given points. The robot produced a velocity-dependent curl force field. (B) Learning took place in the left posture (1) and generalization was quantified in the right posture (2, identical hand motion as 1; 3, identical joint motion as 1). The target sequence was random.

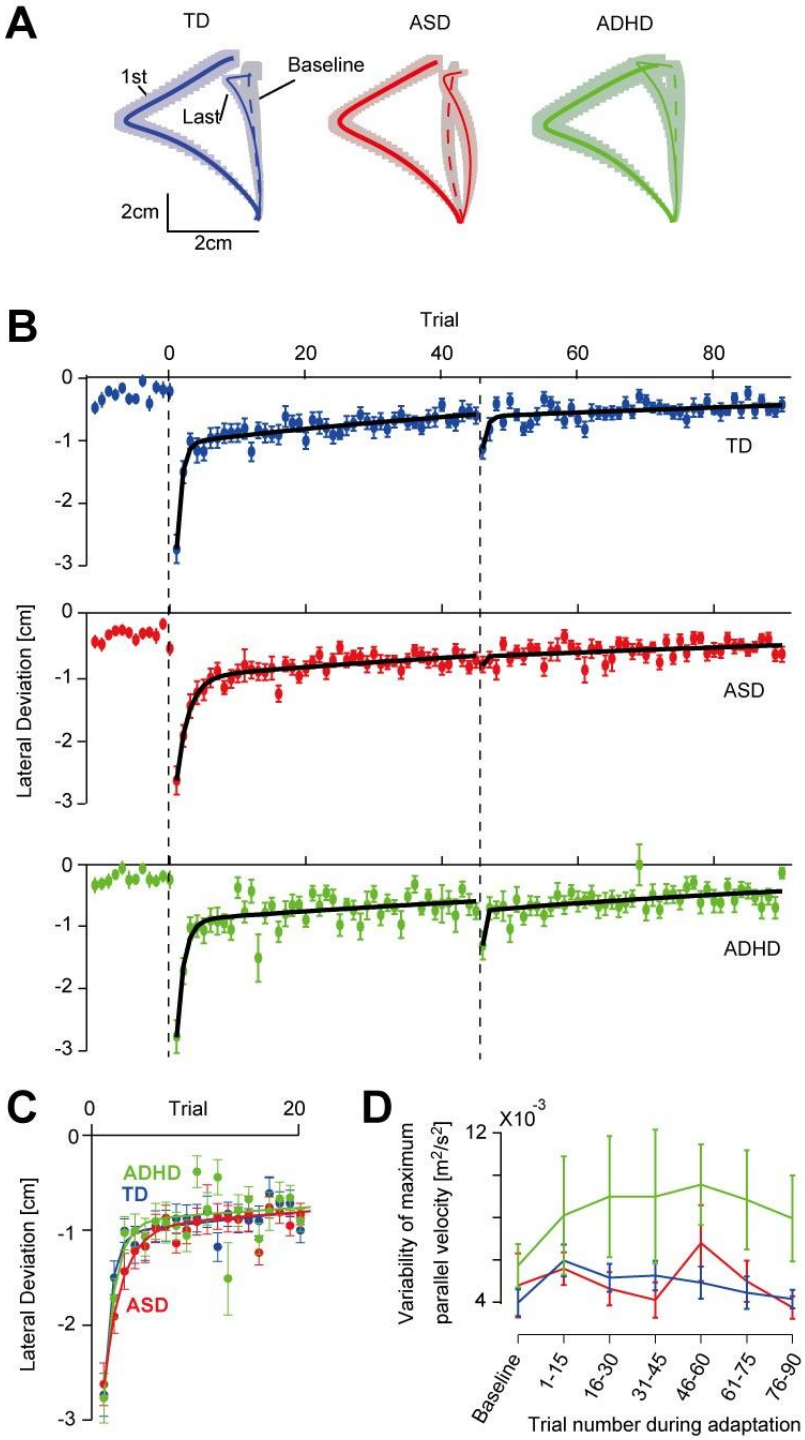

Figure 2 Adaptation profiles. (A) Across subject mean +/- s.e.m. hand path during the last trial of the baseline block and the first and last trials of the learning block. The blue line represents children with TD, the red line represents children with ASD, and green line represents children with ADHD. (B) The best fit learning curvatures superimposed on the profiles of lateral deviation over the trials excluded the channel trials for TD, ASD and ADHD groups respectively form the top row. The filled circles indicate the movement error mean +/- s.e.m. for Target 1; negative values indicate hand deviations to the left. The data of channel trials were excluded from this plot. The first 12 data points (between -12th and 0th trial) during the 3rd block were with no perturbation force. During the 4th block

(between 1st trial and 45th trial), the robot perturbed the subject's hand to the left. After the short break (between 45th trial and 46th trial), the subject experienced the perturbation force during the 5th block (46th trial and 90th trial). For the estimated learning curvature, we assumed the double exponential function: $(\text{Lateral Deviation}) = -\beta_1 \exp(-\beta_2 \text{trial}) - \beta_3 \exp(-\beta_4 \text{trial})$, where β_* are the free parameters. (C) Comparison of the learning curvatures at the initial stage of the adaptation among TD, ASD, and ADHD. The data and the fitted curvatures are identical to Fig.2B. (D) The variability of the peak parallel velocity over trial bins. The data points indicate across subject mean +/- s.e.m.

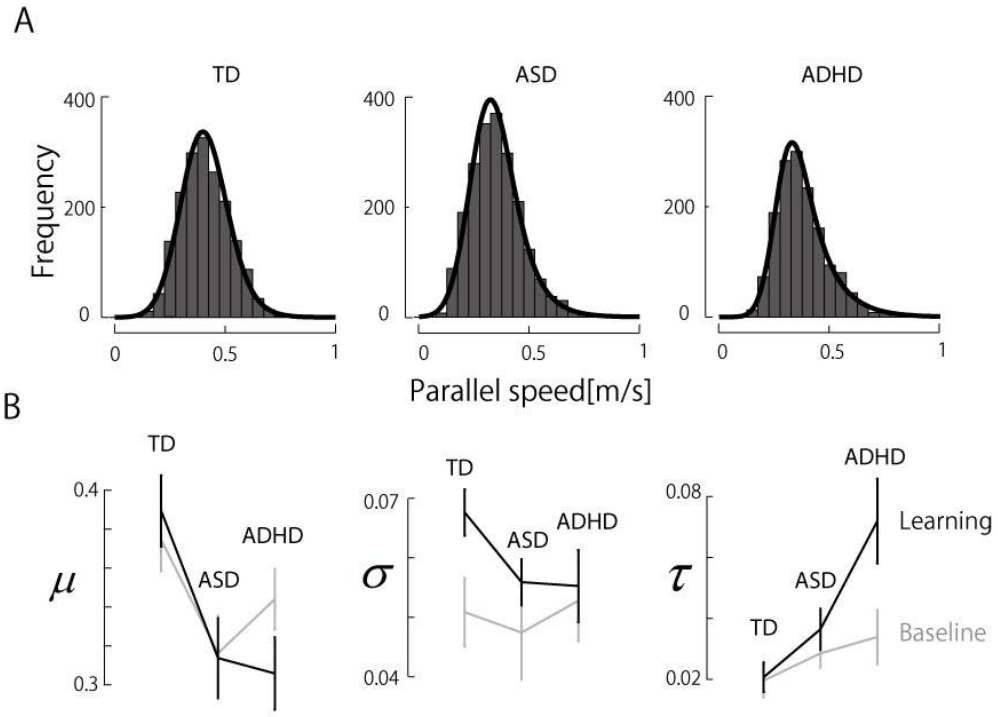

Figure 3 Variability in the peak speeds. (A)Histogram of the peak speed for TD, ASD, and ADHD. The thick lines are the best fit curvature of the ex-Gaussian function. (B) Each component of the ex-Gaussian distribution. μ and σ are the mean and the standard deviation of the Gaussian component. τ is the mean of the exponential component.

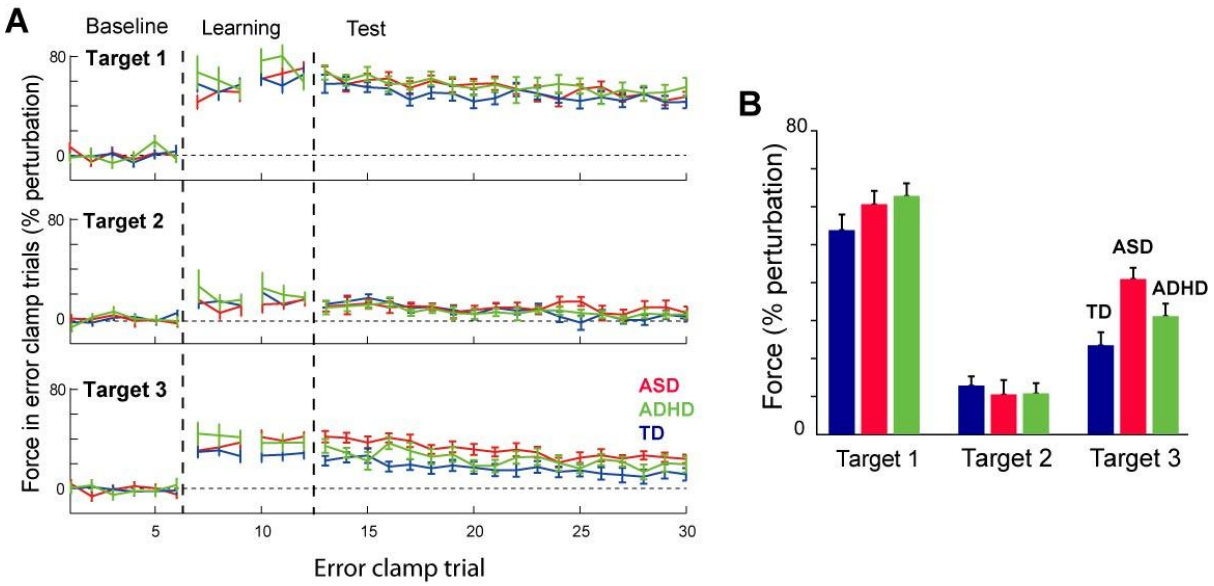

Figure 4 Force in error clamp trials. (A) In error clamp trials, the robot produced a channel from the start position to the target, essentially eliminating movement errors. We measured the force that the child produced against the channel walls. (B) The average of force in the first five error-clamp trials in the test block.

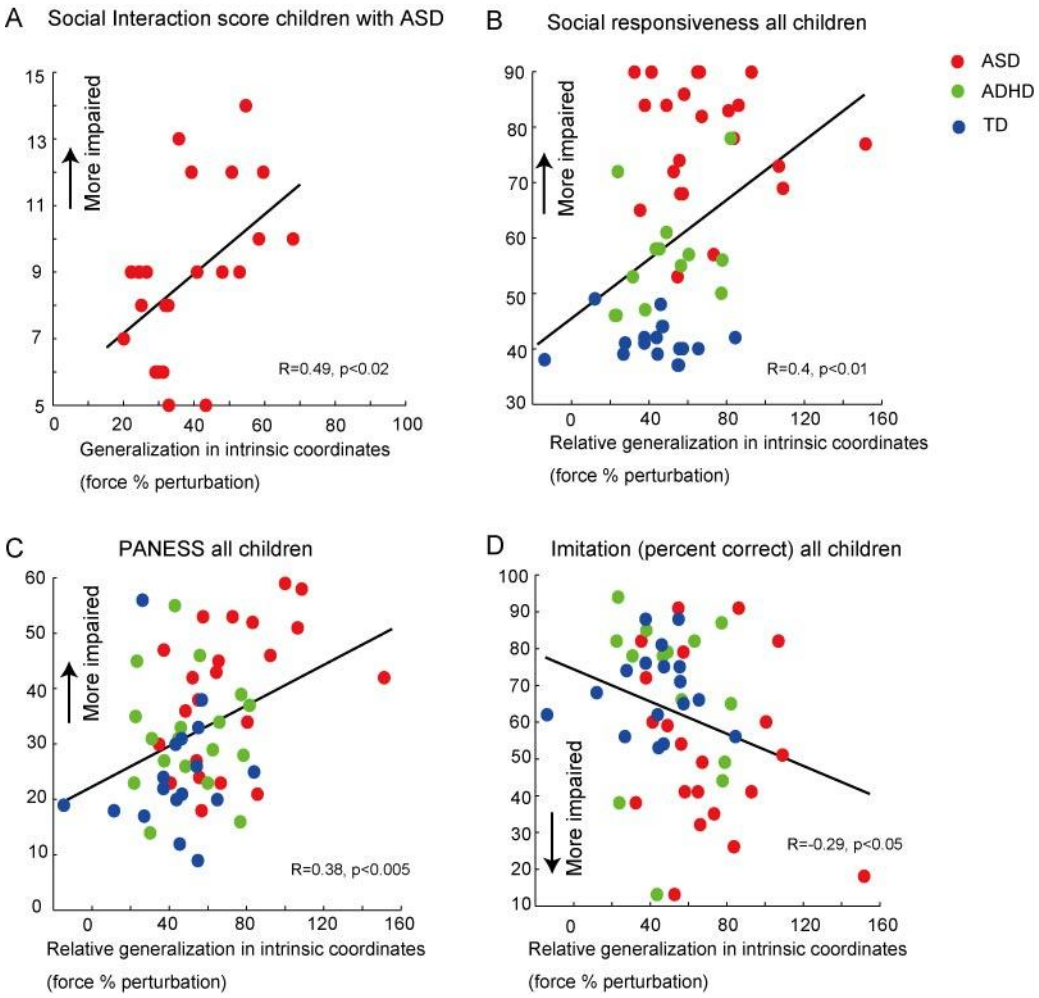

Figure 5 Motor generalization patterns as a predictor of social, motor, and imitation abilities. (A) The ADOS-G is the standardized interview and observational assessment of social, communicative and stereotyped behaviors used for diagnosis of autism. The x axis represents the force produced for the Target 3. (B) The Social Responsiveness Scale, a measure of social anxiety/avoidance in naturalistic settings. (C) Physical and Neurologic Examination of Subtle Signs (PANESS), with higher scores indicating poorer performance. (D) Imitation was measured by asking the child to reproduce a sequence of 36 actions (performed one at a time), some of which were meaningful and others of which were meaningless. The x axis presents the force produced during the test of generalization (T3/T1).

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