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Simultaneous Robotic Manipulation and Functional Magnetic Resonance Imaging: Feasibility in Children with Autism Spectrum Disorders

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ABSTRACT

An unanswered question concerning the neural basis of autism spectrum disorders (ASD) is how sensorimotor deficits in individuals with ASD are related to abnormalities of brain function. We previously described a robotic joystick and video game system that allows us to record functional magnetic resonance images (fMRI) while adult humans make goal-directed wrist motions. We anticipated several challenges in extending this approach to studying goal-directed behaviors in children with ASD and in typically developing (TYP) children. In particular we were concerned that children with autism may express increased levels of anxiety as compared to typically developing children due to the loud sounds and small enclosed space of the MRI scanner. We also were concerned that both groups of children might become restless during testing, leading to an unacceptable amount of head movement. Here we performed a pilot study evaluating the extent to which autistic and typically developing children exhibit anxiety during our experimental protocol as well as their ability to comply with task instructions. Our experimental controls were successful in minimizing group differences in drop-out due to anxiety. Kinematic performance and head motion also were similar across groups. Both groups of children engaged cortical regions (frontal, parietal, temporal, occipital) while making goal-directed movements. In addition, the ASD group exhibited task-related correlations in subcortical regions (cerebellum, thalamus), whereas correlations in the TYP group did not reach statistical significance in subcortical regions. Four distinct regions in frontal cortex showed a significant group difference such that TYP children exhibited positive correlations between the hemodynamic response and movement, whereas children

with ASD exhibited negative correlations. These findings demonstrate feasibility of simultaneous application of robotic manipulation and functional imaging to study goal-directed motor behaviors in autistic and typically developing children. The findings also suggest the presence of marked changes in neural activation during a sensorimotor task requiring goal-directed movement.

Keywords: blood oxygen level-dependent signal, motor control, high-functioning autism

1. INTRODUCTION

Autism spectrum disorders are a group of developmental disorders characterized by stereotyped and repetitive behaviors as well as delays in communication and social interaction [1]. Motor impairment is often reported in autism [2-4], although severity of motor impairment varies widely across the spectrum of autism and it is not currently recognized among diagnostic criteria. Movement differences have been observed in autism as early as 4 to 6 months of age [5] and there is increasing interest in specific motor deficits among children and adults, including deficits related to planning [6-8], task sequencing [9] and postural control [10-11]. Moreover, movement abnormalities correlate with deficits of language development [12] and social interaction [13], which are defining features of autism.

While the etiologies of many characteristics of autism are unknown, neuroanatomical differences have been quantified by neuroimaging [14-15] of individuals with ASD. There appear to exist correlations between anatomical abnormalities and scores on standardized tests of motor performance [16-17]. For example, one study has measured functional magnetic

resonance imaging (fMRI) during self-paced or visually-triggered button-press tasks to compare functional brain activity between children with autism and typically developing children [18]. The visually-triggered task demanded more attention than the self-paced (motor) task. It was found that autistic individuals showed greater cerebellar motor activation and less cerebellar attention activation, suggesting that developmental cerebellar abnormality has differential functional implications for cognitive and motor systems.

However, no one has measured brain activity while children with autism perform goal-directed reaching movements, which require the execution of memory-dependent, feed-forward control actions [19]. We have developed a simple robotic tool and video game task that permit children with autism and typically developing controls to perform reaching tasks while functional magnetic resonance images are simultaneously recorded. As we recently showed in neurologically normal adult subjects, our approach permits visualization and quantification of the formation/recall of sensorimotor memories as well as integration of those memories for the predictive control of movement [20].

The purpose of this study was to evaluate whether or not our experimental approach might be feasible in cohorts of typically-developing and autistic children. We anticipated several challenges during our experiment. First, children with autism exhibit greater levels of anxiety as compared to typically developing children [21], which could lead to excessive drop-out rates in the autism group. Four adjustments were made to our published protocol to minimize participant anxiety: 1) children practiced the video game in two sessions prior to the final MRI session, 2) a parent was present during all three sessions, 3) children held a ‘comfort’ button that they were instructed to press if they felt discomfort, and 4) children were allowed to rest quietly in the scanner between scans. Another challenge was that the loud sounds and small enclosed space of the MRI scanner could cause greater sensory discomfort, especially in children with autism who exhibit sensory abnormalities [22-23]. In addition to the standard safety precautions (eg. required use of ear plugs), each child was required to participate in a mock scanner session which simulated the sounds and small space of the scanner prior to the real MRI session. Finally, we anticipated that it might be a challenge for child participants to remain still during the scanning session. To mitigate this possible confound, only high-functioning children were recruited into the study and we placed padding around the head so as to minimize head movements.

We used four performance criteria to assess feasibility of our approach. First, we quantified the extent to which children with and without autism spectrum disorders exhibit anxiety in the MRI environment. We then assessed ability to comply with task instructions by quantifying reaction time, movement time, and kinematic accuracy, (i.e. the magnitude of target capture errors and number of botched trials). For a basic assessment of the quality of fMRI data, we evaluated our ability to control head movement within the MR scanner in separate cohorts of typically developing children and children with autism as they perform a goal-directed reaching task. Finally, we identified preliminary group differences in brain activity related to the goal-directed movement task.

2. METHODS

Participants

Eleven children and their parents/guardians were recruited to participate in three experimental sessions that spanned three separate days. Five out of the six children with autism spectrum disorders (ASD) [1 female, aged 15.6 ± 2.1 years (mean \pm standard deviation, here and elsewhere)] and four out of five typically developing (TYP) children [4 male, aged 15.3 ± 1.5 years] were able to complete all experimental sessions including the final MRI session (Table 1). Autism diagnoses were confirmed with the Autism Diagnostic Observation Schedule [24] and typically developing children were screened using the Autism Spectrum Screening Questionnaire [25]. The Edinburgh Handedness Inventory confirmed that all children were right-handed or ambidexterous (laterality index > -40) [26]. The Kaufman Brief Intelligence Test, 2nd Edition confirmed that all children were high-functioning (verbal IQ > 70) [27]. All procedures were approved by the local ethics committee and complied with guidelines established by the Declaration of Helsinki.

Table 1: Research Participant Demographics

| Group | Child | Sex | Age | Hand | Verb IQ | Tot IQ | Med |
|-------|-------|-----|------|------|------------|-----------|-------------------|
| ASD | 1 | M | 17.4 | -18 | 116 | 110 | S |
| | 2 | M | 13.5 | 26 | 117 | 115 | AD |
| | 3 | F | 18 | 0 | 92 | 101 | BC, AP, AH, AD |
| | 4 | M | 13.7 | 53 | 107 | 117 | * |
| | 5 | M | 15.2 | 71 | 112 | 122 | S |
| TYP | 1 | M | 14.9 | 79 | 101 | 109 | * |
| | 2 | M | 13.4 | 80 | 124 | 125 | B |
| | 3 | M | 16.7 | 70 | 118 | 119 | * |
| | 4 | M | 16.1 | 58 | 122 | 116 | * |

Abbreviations: ASD autism spectrum disorder, TYP typically-developing, M male, F female, Hand handedness score, Verb verbal, Tot total, Med medication, S stimulant, AD anti-depressant, BC birth control, AP anti-psychotic, AH anti-hypertensive, B bronchodilator

Behavioral Task

Participants played a video game that required goal-directed wrist flexion/extension movements while fMRI data were simultaneously recorded. Prior to the scanning session, participants completed two practice sessions. The first was performed “at the lab bench” (i.e. in a seated upright posture) and was intended to familiarize participants with the movement task and visual feedback provided by the video game. The second session was performed in a mock scanner to acclimate participants with the small enclosed space and loud sounds of the MRI scanner. Children who successfully completed both practice sessions were invited to participate in the final MRI session.

Children played the video game by making 50 wrist flexion/extension movements while holding the handle of a single degree-of-freedom pneumatic robot (Fig. 1a; for robot details see [28]), which applied a spring-like load against the hand (0.13 Nm°). Moving the robot’s handle controlled a red cursor on a video screen. Each trial began with a Go cue

consisting of a pair of black target rings displayed on the screen (“Go”; Fig. 1b). Participants were instructed to ‘move the handle over-and-back so as to capture the goal without pause’. The cursor disappeared at movement onset (hand speed > 5°/s), but after the hand returned to the start position, knowledge of results pertaining to movement extent at reversal and movement duration (“Feedback”; Fig. 1b) were displayed for 1.25 s. Children could earn 2 points on each trial for achieving desired extent ($\pm 1^\circ$ of goal) and an additional 2 points for completing the movement within the desired movement duration (700 - 900 ms). They lost 1 point if movement extent was outside the target bounds and/or an additional point if the movement was too fast or too slow. Subjects were instructed to “Relax” after completing each movement (Fig 1b). The time between Go cues varied randomly between 8 and 18 with a mean of 10 s such that the video game lasted ~8.5 min. Operation of the robot and post-processing of data were performed using MATLAB software (Natick, MA).

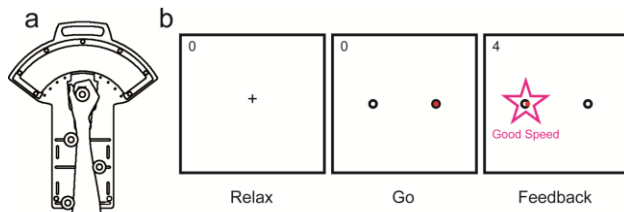


Figure 1 (a) Schematic representation of pneumatic manipulandum and (b) illustration of visual cues, summary feedback and task instructions.

During testing “on the bench” (session 1) children in both subject groups tended to make movements that were too slow to meet the requirements of the video game. We therefore required all children to complete > 30 training movements prior to the MRI session, wherein cursor feedback was visible for the entire movement. The first 15 of these training trials also included a ‘teacher’ represented by a blue cursor that moved with the desired movement duration and desired extent.

MR Imaging

During the final session, participants rested supine in a 3 T GE short-bore M750 scanner. Visual stimuli were projected onto a screen and viewed by prism glasses attached to a standard single-channel commercial head coil. The robotic device was attached to the participant’s hip using a custom-made support structure. Participants rested quietly in the scanner and watched a cartoon 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). We collected functional echo planar (EP) images while participants made goal-directed wrist flexion/extension movements as required by the video game. We used a single-shot, blipped, gradient EP pulse sequence (TE = 25 ms, TR = 2 s, FOV = 240 mm, 64 x 64 matrix) to collect 42 contiguous axial 3.7-mm-thick slices with a voxel size of 3.75 x 3.75 x 3.70 mm³. Functional MR data were collected continuously as subjects performed the 50 required movement trials.

Data Analysis

We used for our primary measure of anxiety the number of participants from each group who dropped from the study between the second (mock) and third (MRI) sessions due to the expression of feelings of anxiety or claustrophobia.

Position, velocity, and acceleration of hand movements were plotted and visually-inspected. Reaction time, RT, was the interval between Go cue presentation and movement onset as defined as the moment in time that wrist angle first exceeded 5°/s. Movement time, MT, was the interval between movement onset and movement reversal, defined as the moment in time when the wrist angle attained its peak flexion value. Movements were discarded (i.e. defined as “botched”): 1) if the peak flexion angle was less than half the desired extent, 2) if movement occurred in anticipation of the Go cue (RT < 100 ms), 3) if participants were inattentive (RT > 800 ms), 4) if outward movements were slow (MT > 800 ms) or 5) if return movements were slow (total duration > 1500 ms). We compared the ability of ASD and TYP participants to follow task instructions by comparing the total number of botched trials using a 2-sample t-test. We evaluated whether experimental controls encouraged desirable consistency of performance across groups by comparing the average RT, MT, extent, and magnitude of extent [i.e. the absolute value of the quantity (desired – actual extent)] using 2-sample t-tests. We tested the hypothesis that the ASD group exhibited increased variability across trials by comparing the standard deviations of target capture errors across subject groups using 2-sample t-tests. Statistical hypothesis testing was performed using Minitab software (State College, PA).

Structural and functional images were analyzed using the Analysis of Functional NeuroImages (AFNI) software package [29]. For functional data, slice values were time shifted to the midpoint of the corresponding volume using Fourier interpolation (*3dTshift*) and the first four volumes were removed to account for start-up transients. Subject-specific structural and functional images were cubically interpolated to 1 mm³ voxels, co-registered and converted to stereotaxic coordinate space following the method of Talairach and Tournoux [30]. 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 (rotations about the inferior/superior, right/left, and anterior-posterior axes as well as translations along each of those axes) were identified (*3dvolreg*). For each of the six head motion parameters, we compared the mean absolute magnitude (referenced to the first volume) and the mean relative displacement magnitude (i.e. the difference between the current and previously acquired volumes) across subject groups using 2-sample t-tests. In addition, we followed the method of Van Dijk and colleagues [31] (cf. [32]) to compute: 1) a three-dimensional (3-D) measure of mean displacement using root-mean-square of the three relative translations and 2) a 3-D measure of rotation using the Euler angle of the three relative rotations. 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.

Finally, we sought to identify task-related changes in blood oxygen level-dependent (BOLD) data. We therefore 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. This time series was then convolved with a gamma variate function resembling the canonical hemodynamic response [33]. 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 subject, we identified correlations between BOLD activity and the task-specific time series (i.e. Go-related activity) using program *3dDeconvolve* to calculate the regression coefficient. For each subject group, we used program *3dttest* to identify regions of the brain in which the regression coefficient was significantly different from 0.0. Then, we compared regression coefficients across groups using a 2-sample t-test. Cluster size and individual voxel p-value thresholds were estimated by performing 10,000 Monte Carlo simulations using *3dClustSim*. We used a minimum cluster size of 1145 μl and an individual voxel probability of $t_{\text{ASD}} = 3.496$ and $t_{\text{TYP}} = 4.176$ for the 1-sample t-tests and $t = 2.842$ for the 2-sample t-test ($p = 0.025$) to yield a whole brain family-wise error threshold of $\alpha = 0.001$.

3. RESULTS

Although our sample size was rather small, we observed no marked difference in the level of anxiety expressed by our two groups of children. Of the children who participated in the mock scanning session, only 1 child with ASD and 1 TYP child dropped out of the study due to anxiety. Table 1 presents demographic characteristics for the 9 child participants who completed the study.

Children with ASD and TYP children were equally capable to understand and follow task instructions. The number of botched trials did not differ across subject groups (ASD: 5 ± 2 trials, TYP: 3 ± 2 trials; $t_{(7)} = 1.6$, $p = 0.15$). Kinematic performance measures did not differ between the groups and thus children with ASD performed the goal-directed reaches in a manner indistinguishable from TYP children. Planned two-sided t-tests found that the average RT (ASD: 459 ± 53 ms, TYP: 481 ± 45 ms), MT (ASD: 459 ± 53 ms, TYP: 481 ± 45 ms), extent (ASD: $-2.27 \pm 2.35^\circ$, TYP: $-0.41 \pm 1.46^\circ$), magnitude of extent (ASD: $2.91 \pm 1.80^\circ$, TYP: $1.70 \pm 0.31^\circ$), standard deviation of extent (ASD: $2.05 \pm 0.46^\circ$, TYP: $1.85 \pm 0.39^\circ$), and standard deviation of error magnitude (ASD: $1.64 \pm 0.47^\circ$, TYP: $1.48 \pm 0.42^\circ$) did not differ between groups ($t_{(7)} \leq 1.6$, $p \geq 0.1$ in each case). Because our experimental controls (task instructions, summary feedback, etc.) were effective in minimizing differences in performance across the two subject populations, differences in functional neural activity across the groups cannot be due to systematic differences in movement kinematics.

Both subject groups exhibited minimal head motion while generating goal-directed reaching movements. Mean absolute and relative head motion for the six parameters were not different between ASD and TYP groups ($p \geq 0.3$ in each case). Furthermore, we found no group difference in mean 3-D relative displacement (ASD: 0.188 ± 0.027 mm, TYP: 0.171 ± 0.188 mm; $t_{(7)} = 0.98$, $p = 0.36$) and mean 3-D relative rotation (ASD: $0.101 \pm 0.027^\circ$, TYP: $0.157 \pm 0.131^\circ$; $t_{(7)} = 0.95$, $p = 0.37$). The magnitude of absolute head motion in these children was less than or equal to the amount of motion we previously observed in neurotypical adults performing a similar task in the MR scanner [20]. The magnitude of relative head motion we observed here in children was greater than that previously observed using a similar experimental approach in adults (the adults averaged 0.05 ± 0.02 mm mean 3-D relative displacement and $0.04 \pm 0.02^\circ$ mean 3-D relative rotation).

We identified regions of the brain in which the Go cue regression coefficient was significantly different from 0.0 separately for each subject group. Cortical regions were more widespread in the TYP group compared to the ASD group (Fig 2). Both groups engaged frontal, parietal, temporal, and occipital cortices. Only the ASD group engaged the angular gyrus and superior frontal gyrus, whereas only the TYP group engaged the cingulate cortex, medial frontal gyrus, inferior frontal gyrus, superior temporal gyrus, cuneus and lingual gyrus. Interestingly, the ASD group exhibited negative correlations between the Go cue regressor and BOLD signal in superior and middle frontal gyri, as well as angular gyrus, middle temporal gyrus and inferior parietal lobule (Fig 2, blue). The TYP group did not exhibit negative correlations between the Go cue regressor and BOLD signal. Subcortical regions (thalamus, cerebellum lobules III - VI) were identified in the ASD group but did not reach statistical significance in the TYP group.

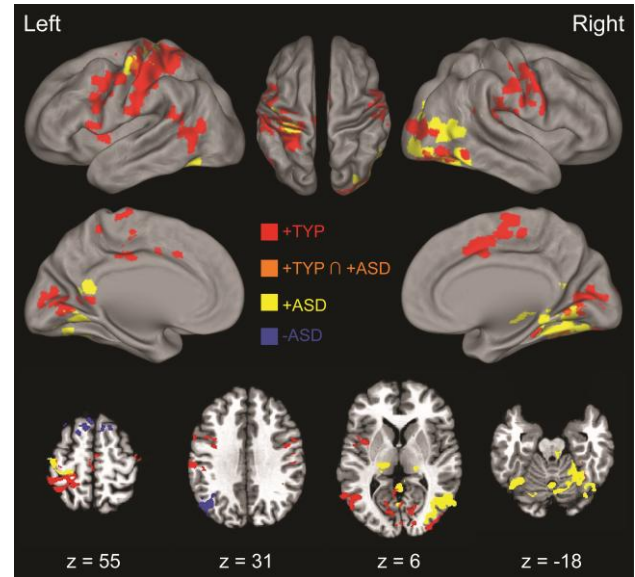


Figure 2: Voxel-wise t-tests compared fit coefficient values versus 0, identifying regions that showed a statistically significant positive correlation between the hemodynamic response and the Go cue regressor for children with ASD (yellow), TYP children (red) or both (orange) as well as regions in which the correlation coefficient was negative for the ASD group (blue) overlaid on a standard anatomical reference

A 2-sample t-test compared the magnitude of the Go cue regression coefficient between ASD and TYP groups. We found a group difference in Go cue regression coefficient in the superior middle frontal gyrus (BA Brodmann Area 6, 8), including pre-supplementary motor area (pre-SMA), left middle frontal gyrus (BA 6, 9), and left inferior frontal gyrus (BA 46) at the threshold levels described above. Specifically, regression coefficients were positive in the TYP group and negative in the ASD group in these regions (Fig 3).

4. DISCUSSION

The primary goal of our study was to assess the feasibility of using a robotically-enhanced functional imaging paradigm to evaluate neural control of movement in typically-developing children and children with ASD. Whereas the approach was previously developed to examine how the adult brain uses kinematic performance errors to shape subsequent actions [20],

nine out of eleven children performed the required target capture task within the MR scanner without expression of anxiety or claustrophobia. We conclude therefore that the approach appears to be a reasonable avenue of future investigation.

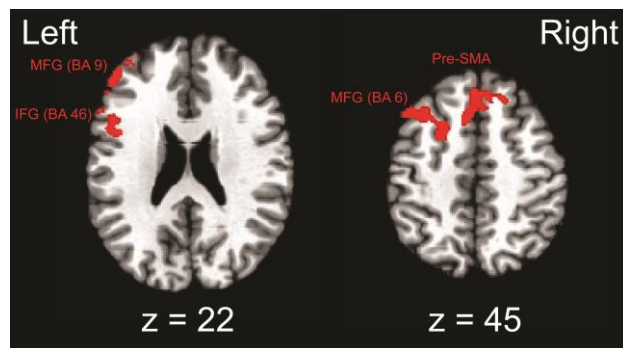


Figure 3: Voxel-wise t-tests compared fit coefficient values between the TYP and ASD groups overlaid on a standard anatomical reference. Although not shown, fit coefficients values were positive in the TYP group and negative in the ASD group.

It is known that anxiety is increased in high-functioning children with ASD compared to TYP children. However, most anxiety in participants with ASD is attributed to their insistence on consistency in stimuli [21]. We therefore designed the experiment to introduce new procedures to the participants gradually. The same research team member (NS) was present during all three sessions to reduce social anxiety among children with ASD. The mock session in particular was nearly identical to the real MRI session in all respects: Subjects rested in the mock scanner with the head in a mock coil, wore ear plugs and heard scanner sounds while playing the entire video game. They also practiced holding a comfort button during the mock session. These procedures were successful in reducing anxiety among participants as indicated by a high level of participant willingness to return for the final scanning session.

Typically developing children and children with autism were able to make quick and accurate movements while playing the target capture game. We found no difference in kinematic performance variables across the two subject groups. This was important because differences in kinematic performance of a task can confound the interpretation of group-wise differences in functional neural activity. Others have reported tendencies for increased movement duration in ASD [34-35] or no difference in movement duration in ASD [36] compared to TYP children. Rinehart and colleagues [7] report that movement duration is not different between ASD and TYP groups under normal conditions, but when target goal information is provided, TYP children utilize the information to reduce their movement duration while children with ASD were unaffected by goal information. Such findings suggest increased movement duration in ASD might be due to planning deficits. In our pilot study, we found that self-paced out-and-back target capture movements were longer than the desired 700-900 ms in both groups, but especially so in ASD. Therefore, we provided additional training using continuous online visual feedback of hand position to learn the task. Once learned, children continued making fast movements even when online visual feedback was unavailable. Moreover, we found that our experimental controls

sufficed to minimize group differences in kinematic performance on the day of the MRI scan. Three factors likely contributed to this outcome: the task was simple, children practiced the task extensively on two separate days prior to MR scanning, and all children were high functioning.

Although our sample size was rather small, separate t-tests of Go cue regression coefficients vs. 0 found hemodynamic activity to correlate with movement onset in both groups in brain regions known to contribute to the planning and execution of visually-directed movements. These included regions associated with generation of large muscle forces: pre- and post-central gyri [20, 37]. We also identified regions associated with visual perception necessary to process task instructions and visual target capture errors: middle occipital gyrus, middle temporal gyrus, and fusiform gyrus [20]. Finally, we identified regions associated with motor response selection, including inferior parietal lobule and prefrontal cortex [20].

We also saw differential patterns of BOLD signal activity across the two groups, with the TYP group exhibiting a more widespread activation of prefrontal and parietal cortices than the ASD group. By contrast, the ASD group exhibited widespread cerebellar activation as well as thalamic activation whereas correlations in the cerebellum and thalamus did not reach statistical significance among the TYP children. The cerebellum is particularly important for feedback stabilization of the wrist as previously shown in healthy adults [38]. In addition, Seidler and colleagues [39] have shown in healthy adults that cerebellar and thalamic activities increase whereas prefrontal activities decrease as the mode of control shifts along a continuum from feedforward to feedback control.

Others have examined neural correlates of cerebellar activity in individuals with autism during finger-tapping. As discussed in the INTRODUCTION, Allen and Courchesne [18] found greater cerebellar activity related to self-paced thumb tapping in autism compared to typically developing individuals, even though cerebellar structures were smaller in autism. Müller and colleagues [40] also found greater cerebellar activity in ASD compared to typically developing individuals during cued single-digit button pressing. In contrast, Mostofsky and colleagues [41] and Müller and colleagues [42] found increased cerebellar activity in typically developing children compared to children with autism during sequential finger-tapping tasks. The discrepancy might be attributable to differences between experimental paradigms. Sequential finger tapping experiments [41-42] most likely impose greater computational demands due to the selection, planning and coordination of movements across body segments whereas single-digit [18, 40] and single-segment tasks (eg. the current study) require production of a single, stereotyped movement. Elevated cerebellar involvement in stereotyped motor tasks ([18, 40] and this study) and reduced cerebellar engagement in ASD relative to TD children in a motor task that should have preferentially required feedforward motor planning [41-42] suggests a possible deficit in the coordination of feedforward and feedback actions during sensorimotor control tasks in ASD. The cerebellar and thalamic activities in our study suggest that during target capture movements, children with ASD may have preferentially invoked feedback control actions to a greater extent than did the TYP group. In contrast, the TYP children may have relied more heavily on feedforward control than did the children with ASD, as suggested by widespread prefrontal activity among the TYP (but not ASD) children. Additional research is needed to

determine the factors contributing to the different patterns in functional activity discussed above within the context of feedforward and feedback control actions. In particular, it would be interesting to compare cerebellar activity across single- and multi-segment tasks in groups of children with and without ASD, using a task similar to that employed by Seidler and colleagues [39]. By using the force produced by a single finger or multiple fingers to manipulate a cursor between targets of different sizes, such a study may disambiguate how cerebellar activity is modulated in both groups of children by task complexity (eg. tasks that require multiple segments vs. a single segment) along the continuum of feedforward- and feedback control actions (i.e. as a function of target size).

A planned contrast between the two subject groups found that TYP children exhibited positive correlations between the GO cue regressor and the hemodynamic response bilaterally in frontal lobe regions whereas children with ASD exhibited negative correlations. Frontal lobe regions such as pre-SMA are involved in discrete corrective movements of the wrist in response to persistent performance errors that are not resolved via moment-by-moment feedback control actions [38]. It is unclear whether negative BOLD responses such as those found in the ASD group are due to reduced neuronal activity in regions involved with the feedforward planning of movements, reduced hemodynamic changes such as 'vascular steal' in which a reduction of cerebral blood flow is used to support neighboring regions with increased flow, or both [43]. More research is needed to determine whether such negative BOLD responses are consistent across the spectrum of autism and how such differences might affect the neural networks that support goal-directed reaching movements.

Autism is a complex disorder and it is likely that abnormal function of many regions of the brain contribute to the motor and behavioral abnormalities observed in this population. Our study has shown that it is feasible to compare neural correlates of goal-directed movements between children with ASD and TYP children. Future studies should build on this work by combining functional imaging with specific motor tasks to explore the neural correlates of motor impairment in a larger sample of children with autism. In particular, additional data will need to be collected to confirm or reject the preliminary imaging results we have presented in this pilot study.

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