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RESEARCH ARTICLE | *Control of Movement*

Cortical and subcortical alterations associated with precision visuomotor behavior in individuals with autism spectrum disorder

Kathryn E. Unruh,[1,2] Laura E. Martin,[3] Grant Magnon,[4] David E. Vaillancourt,[5] John A. Sweeney,[6] and Matthew W. Mosconi[1,2]

[1]*Schiefelbusch Institute for Life Span Studies and Clinical Child Psychology Program, University of Kansas, Lawrence, Kansas;* [2]*Kansas Center for Autism Research and Training, University of Kansas Medical School, Kansas City, Kansas;* [3]*Hoglund Brain Imaging Center and Department of Preventive Medicine and Public Health, University of Kansas Medical Center, Kansas City, Kansas;* [4]*University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania;* [5]*Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, Florida; and* [6]*Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio*

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Unruh KE, Martin LE, Magnon G, Vaillancourt DE, Sweeney JA, Mosconi MW. Cortical and subcortical alterations associated with precision visuomotor behavior in individuals with autism spectrum disorder. *J Neurophysiol* 122: 1330–1341, 2019. First published July 17, 2019; doi:10.1152/jn.00286.2019.—In addition to core deficits in social-communication abilities and repetitive behaviors and interests, many patients with autism spectrum disorder (ASD) experience developmental comorbidities, including sensorimotor issues. Sensorimotor issues are common in ASD and associated with more severe clinical symptoms. Importantly, sensorimotor behaviors are precisely quantifiable and highly translational, offering promising targets for neurophysiological studies of ASD. We used functional MRI to identify brain regions associated with sensorimotor behavior using a visually guided precision gripping task in individuals with ASD (n = 20) and age-, IQ-, and handedness-matched controls (n = 18). During visuomotor behavior, individuals with ASD showed greater force variability than controls. The blood oxygen level-dependent signal for multiple cortical and subcortical regions was associated with force variability, including motor and premotor cortex, posterior parietal cortex, extrastriate cortex, putamen, and cerebellum. Activation in the right premotor cortex scaled with sensorimotor variability in controls but not in ASD. Individuals with ASD showed greater activation than controls in left putamen and left cerebellar lobule VIIb, and activation in these regions was associated with more severe clinically rated symptoms of ASD. Together, these results suggest that greater sensorimotor variability in ASD is associated with altered cortical-striatal processes supporting action selection and cortical-cerebellar circuits involved in feedback-guided reactive adjustments of motor output. Our findings also indicate that atypical organization of visuomotor cortical circuits may result in heightened reliance on subcortical circuits typically dedicated to motor skill acquisition. Overall, these results provide new evidence that sensorimotor alterations in ASD involve aberrant cortical and subcortical organization that may contribute to key clinical issues in patients.

NEW & NOTEWORTHY This is the first known study to examine functional brain activation during precision visuomotor behavior in autism spectrum disorder (ASD). We replicate previous findings of elevated force variability in ASD and find these deficits are associated with atypical function of ventral premotor cortex, putamen, and posterolateral cerebellum, indicating cortical-striatal processes supporting action selection and cortical-cerebellar circuits involved in feedback-guided reactive adjustments of motor output may be key targets for understanding the neurobiology of ASD.

autism spectrum disorder; cerebellum; precision grip; putamen; sensorimotor

INTRODUCTION

Autism spectrum disorder (ASD) is defined by deficits in social communication and the presence of restricted and repetitive behaviors and interests (American Psychiatric Association 2013). The majority of individuals with ASD also experience one or more comorbid conditions, including neuropsychiatric, behavioral, medical, or cognitive issues (e.g., Veenstra-VanderWeele and Blakely 2012). Diversity across affected individuals in terms of both the constellation of symptoms that are present and their severity presents significant challenges for characterizing neurobiological processes associated with ASD and determining pathophysiological mechanisms.

Neuroimaging studies have successfully identified multiple anatomical and functional brain alterations associated with ASD (e.g., Schumann and Amaral 2006; Uddin et al. 2013), but many of these findings have been difficult to replicate or link to clinical outcomes. Several challenges limit progress. First, many recent functional (f)MRI studies in ASD have focused on resting state brain functions and connectivity (Hull et al. 2017; Uddin et al. 2017) that may not relate as directly to behavior as measures of brain function during behavior (Finn et al. 2015; Greene et al. 2018). Second, ASD features vary dimensionally throughout the population and overlap with distributions for healthy individuals and other developmental disabilities (Constantino and Todd 2005). These findings suggest that dimensional approaches that characterize linkages between brain and behavioral traits may offer important information in addition to traditional case-control approaches that

Address for reprint requests and other correspondence: M. W. Mosconi, Schiefelbusch Institute for Life Span Studies and Clinical Child Psychology Program, Univ. of Kansas, Lawrence, Kansas 66045 (e-mail: mosconi@ku.edu).

may not fully capture variation within the ASD population (Ameis 2017; Uddin et al. 2017). Such approaches also are consistent with the research domain criteria emphasized by National Institute of Mental Health and leveraging the continuous distributions of traits implicated in neuropsychiatric disorders including ASD. Third, task-based fMRI studies of discrete brain networks known to be associated with distinct behaviors in ASD are useful for limiting findings based on smaller signal-to-noise ratios that may not always be linked directly to underlying neurobiology (Finn et al. 2017).

Sensorimotor behaviors offer a promising target for studies aimed at characterizing neurobiological dimensions in ASD. Atypical sensorimotor behaviors are among the most common comorbid features in ASD (De Jong et al. 2011; Green et al. 2002), and they can be precisely quantified across a wide range of ages and ability levels. Sensorimotor issues also are related to social and cognitive deficits and predictive of worse functional outcomes in ASD (Bhat et al. 2012; Sutera et al. 2007; Travers et al. 2017). Furthermore, the neural networks that underlie sensorimotor behaviors have been well characterized in nonhuman primates and rodent models suggesting that they represent highly translational targets, and identification of spared and affected circuits in ASD may be interpreted in the context of detailed knowledge of functionally discrete circuits (Ferezou et al. 2007; Takagi et al. 2000; Vaillancourt et al. 2003).

Studies of sensorimotor behavior in ASD have repeatedly documented increased motor variability, including reaching movement accuracy (Glazebrook et al. 2009), eye movement accuracy (Johnson et al. 2013; Mosconi et al. 2013), and postural control (Fournier et al. 2010; Wang et al. 2016). Greater motor variability appears to be related to more severe social-communication abnormalities in ASD suggesting common mechanisms may underpin these separate clinical issues (Mosconi et al. 2015; Wang et al. 2015). Still, sensory and motor processes associated with increased sensorimotor variability are not yet well understood. Haswell et al. (2009) demonstrated both increased reliance on proprioceptive feedback and decreased integration of visual-spatial information in ASD during motor learning suggesting atypical sensory processes may contribute to greater motor variability in patients. We have demonstrated that individuals with ASD show increased force variability during visually guided precision gripping compared with controls and that the severity of this deficit varies as a function of both the level of force that is required as well as the quality of visual feedback (Mosconi et al. 2015; Wang et al. 2015). These findings suggest both motor control and sensory processing dysfunctions may contribute to elevated sensorimotor variability in ASD. Functional neuroimaging studies of discrete sensorimotor behaviors are needed to clarify mechanisms that contribute to increased sensorimotor variability in patients.

During the majority of sensorimotor behaviors, visual feedback information is processed in primary visual cortex and then relayed to inferior and superior parietal lobules in posterior parietal cortex (PPC; Fig. 1; Mishkin and Ungerleider 1982). Afferent inputs to primary (M1) and premotor cortex guide precision motor commands translated to the periphery (Stein and Glickstein 1992). Visual-spatial information from PPC and efference copies of frontally generated motor commands also are relayed via cortico-pontine projections to distinct lateral (Crus I-II), anterior (I-IV), and posterior (VIIb/VIII) lobules of the cerebellum (Buckner et al. 2011; Glickstein 2000; Stoodley and Schmahmann 2010). Within the cerebellar cortex, the differences between sensory feedback and predicted sensory consequences of actions are computed and used to dynamically adjust motor commands to refine ongoing behavior (Stein 1986; Vaillancourt et al. 2003). Basal ganglia nuclei, including

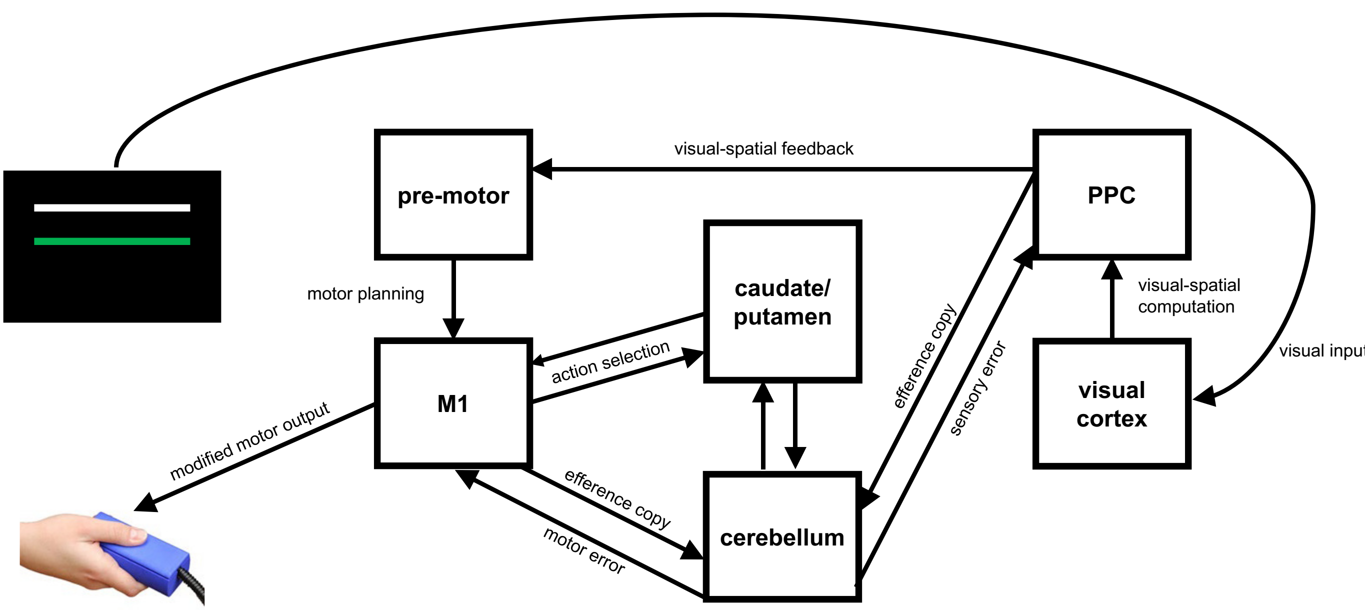

Fig. 1. Simplified schematic representation of the visuomotor system. Visual input is processed in the primary visual cortex and relayed to inferior and superior lobules of posterior parietal cortex (PPC). Visual-spatial information is sent via afferent inputs to premotor and primary motor cortex (M1) to guide precision motor commands translated to the periphery. Efference copies of frontally generated motor commands and visual-spatial information from PPC are relayed to cerebellum where differences between sensory feedback and predicted sensory consequences of actions are computed and used to dynamically adjust ongoing motor behavior. Reciprocal connections between basal ganglia nuclei, including caudate and putamen, and cerebellum and motor cortex are involved in initial stages of visuomotor behavior acquisition, particularly during action selection processes.

caudate and putamen, are involved in the initial stages of visuomotor learning and behavior, particularly during motor planning and action selection processes (Prodoehl et al. 2009; Wasson et al. 2010). These findings indicate that greater sensorimotor variability in ASD could reflect atypical processing of sensory feedback information in PPC, deficits in cerebellar circuits involved in translating sensory error information, failures of motor cortex during the modification of the central motor command, dysfunction of basal ganglia circuits for motor skill acquisition, or a combination of these processes.

fMRI studies of ASD have documented atypical regional and network level function associated with sensorimotor processes. During rest, altered interregional connectivity of sensorimotor networks in children and adults with ASD has been demonstrated (Khan et al. 2015; Mostofsky et al. 2009; Nebel et al. 2014). During internally generated gross motor behavior (e.g., finger-tapping), both hypo- and hyperactivation of sensorimotor cortex and cerebellum have been observed in ASD, and atypical recruitment of nonmotor brain networks has been reported (Mostofsky et al. 2009; Müller et al. 2003; Takarae et al. 2007). Similarly, anatomical MRI and histopathological studies have repeatedly implicated sensory and motor cortices as well as the cerebellum in ASD. For example, structural MRI studies have documented cortical thinning of superior and inferior parietal lobules and pre- and postcentral gyri in patients as well as enlargement of basal ganglia nuclei (Hadjikhani et al. 2006; Langen et al. 2007; Wallace et al. 2010). Post mortem histological studies have identified reduced Purkinje cell density within posterolateral lobules (Crus I and II) (Skefos et al. 2014) known to be involved in cognitive (Stoodley et al. 2012) and sensorimotor behaviors (Spraker et al. 2012; Vaillancourt et al. 2006). While these functional and anatomical studies provide strong evidence that cortical and subcortical circuits that support sensorimotor behavior in ASD are compromised, the functional properties of these circuits during precision behavior are not known.

The purpose of the current study was to characterize relationships between deficits in sensorimotor behavior and brain activation in ASD. During fMRI, participants completed a visually guided precision gripping test similar to that used in our previous laboratory studies of ASD (Mosconi et al. 2015; Neely et al. 2019; Wang et al. 2015). We identified regions of activation associated with task performance across the full sample of study participants, compared the strength of these associations across ASD and controls, and assessed differences between groups in brain activation within each of these regions of interest (ROIs). We predicted precision sensorimotor variability would be related to activation in PPC, primary and premotor cortices (Ehrsson et al. 2000), anterior nuclei of the basal ganglia (Prodoehl et al. 2009), and anterior cerebellar lobules I-IV and posterior lobules VIIb-VIII (Bostan et al. 2013) and that the strength of these relationships would differ in ASD relative to control participants.

METHODS

Participants. Twenty participants with ASD (18 males and 2 females) and eighteen healthy controls (16 males and 2 females) matched on age (14–33 yr), IQ, handedness, and gender completed a task of visual feedback-guided precision gripping during fMRI (Table 1). Seventeen participants with ASD and 15 controls were included in final analyses; three participants with ASD and two control participants were excluded from final analyses due to excess motion (as defined in *Image preprocessing and analysis*). One control participant was excluded from analyses due to anatomical abnormalities and one was excluded from brain-behavior analyses due to hardware malfunction affecting sensorimotor data. ASD diagnoses were confirmed using the Autism Diagnostic Inventory-Revised (ADI-R; Lord et al. 1994), using Modules 3 (n = 13) or 4 (n = 7) of the Autism Diagnostic Observation Schedule–Second Edition (ADOS; Lord et al. 2000), and based on expert clinical opinion using DSM-V criteria. Participants with ASD were excluded for known genetic or metabolic disorders associated with ASD (e.g., fragile X syndrome, tuberous sclerosis). Control participants were assessed for ASD symptoms using the Social Communication Questionnaire (Rutter et al. 2003) and excluded if their total score was greater than 8. IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler 2011), and only participants with a Full-Scale score >70 were include in this study (Table 1). The Physical and Neurological Examination for Soft Signs (PANESS; Guy 1976) was administered to all participants to assess handedness. The handedness subscale requires participants to indicate the hand with which they perform 11 different daily living activities. Handedness was calculated as the proportion of items for which a participant indicated a right-hand preference. Higher values reflect greater right-hand preference. Handedness preference scores did not differ between groups (t = 1.28, P = 0.21).

Table 1. *Matched demographic characteristics of participants with ASD and healthy controls and autism severity scores*

	Group	
	Control (n = 18)	ASD (n = 20)
Age	22.62 ± 4.96	21.11 ± 6.80
%Male	89%	90%
Performance IQ	117.77 ± 11.04	110.59 ± 15.13
Verbal IQ	118.69 ± 12.47	110.76 ± 18.61
Laterality index*	0.93 ± 0.12	0.76 ± 0.37
MVC	55.95 ± 15.85	54.76 ± 16.86
ADOS Calibrated Severity Score	–	7.64 ± 1.86

Intelligence quotient (IQ) was measured using the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler 2011). ADOS, Autism Diagnostic Observation Scale; ASD, autism spectrum disorder; MVC, maximum voluntary contraction; PANESS, Physical and Neurological Examination for Soft Signs. *Laterality index = PANESS right hand total/(PANESS left hand total + PANESS right hand total).

General exclusion criteria included self or caregiver report of any history of substance dependence or abuse within the previous 6 mo, history of nonfebrile seizures or head trauma with loss of consciousness, or current medications known to interfere with test performance including stimulants, antipsychotics, anticonvulsants, or benzodiazepines (Reilly et al. 2008). Additionally, individuals with ASD were excluded if they or their caretakers reported difficulty during the pregnancy, labor, delivery, or immediate neonatal period. Healthy controls were excluded if they had a known lifetime history of psychiatric or relevant medical disorder, had a family history of a psychiatric disorder in their first-degree relatives, or had a history of ASD in first- or second-degree relatives. Participants refrained from caffeine, nicotine, and alcohol on the day of testing and over-the-counter drugs with sedating properties (e.g., drowsy cold medicine) within 12 h of testing. Written informed consent was obtained from all participants, with assent and parental consent obtained for minors. The study procedures were approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Grip force fMRI task. Each participant's maximum voluntary contraction (MVC) was measured before MRI scanning using a custom Bragg grating fiber optic force transducer (Neuroimaging Solutions, Gainesville, FL). The transducer was housed in a precision grip apparatus that was held between the right thumb and index finger in a modified precision grip (Fig. 2*A*; e.g., Burciu et al. 2017). The transducer and its housing were constructed from rigid, nonmetallic materials.

During the precision force task, participants were presented with a visual display containing two horizontal bars that were set against a black background: a white target bar and a red force bar that turned green to indicate the beginning of each trial (Fig. 2*B*). Stimuli were presented on a 290 × 212 mm EPSON PowerLite 7300 projector with a resolution of 1,024 × 768.

Participants completed one 4.5-min run of the precision grip force task using their right hand only (Fig. 2*B*). The force level was set at 20% of the participant's MVC. The run began with a 24-s rest block (no-force) in which participants passively viewed the two horizontal bars, followed by five 24-s force blocks alternating with 24-s no-force blocks. During force blocks, participants were instructed to *1*) press the transducer as quickly as possible with their right hand until the force bar reached the level of the target bar, and *2*) keep pressing so that the force bar stayed as steady as possible at the level of the target bar.

Force data acquisition and analysis. Participants produced force using a custom fiber-optic transducer with 0.025-N resolution (Neuroimaging Solutions). Force data were digitized at 125 Hz by an si425 Fiber Optic Interrogator (Micron Optics, Atlanta, GA), converted to Newtons (National Instruments, Austin, TX) and analyzed using custom software written in MATLAB. Time series data were digitally filtered using a fourth-order Butterworth filter with a 30 Hz low-pass cutoff.

Force data were analyzed with a custom algorithm and scoring program developed previously by our group using MATLAB (MathWorks; Wang et al. 2015). The first 2 s and the last 1 s of each force trace were excluded from analyses due to variability in the rate at which individuals reached the target force and terminated the trial (Robichaud et al. 2005). Trials for which participants produced <15 s of continuous force data were excluded from analyses. Trials also were excluded if the mean force exceeded twice the target force or was less than half of the target force. Force data were linearly detrended to account for systematic changes in the mean force over the duration of the trial. Force variability was defined as the standard deviation of this linearly detrended sustained force time series (SD). Mean force of the time series also was examined.

fMRI data acquisition and preprocessing. MRIs were collected using a 3.0T whole body scanner with a 32-channel head coil (Phillips Achieva). Participants lay supine in the scanner while performing the task. Scanner noise was attenuated using earplugs and noise-reducing headphones. Functional images were obtained using a T_2*-weighted single-shot, gradient-echo echo-planar pulse sequence [echo time (TE): 30 ms; time to repeat (TR): 2,000 ms; flip angle: 60°; field of view (FOV): 220 mm^2; imaging matrix: 64 × 64; 36 axial slices with 1-mm gap; and voxel size: 3 × 3 × 4 mm^3]. Anatomical images were coregistered to brain volumes obtained using a high-resolution T_1-weighted MPRAGE sequence (TE: 3.73 ms; TR: 8.1 ms; flip angle: 12°; FOV: 256 × 204 × 160 mm; imaging matrix: 256 × 204 × 160; 160 sagittal slices; voxel size: 1 mm^3; and 0-mm gap between slices).

Image preprocessing and analysis. Data processing and analysis were performed using custom shell scripts created in AFNI (Automated Functional Neuroimaging: https://afni.nimh.nih.gov/). The first five volumes of each functional run were discarded to allow for magnetization equilibration. The functional time series were corrected for slice-timing effects and head motion using standard AFNI procedures, by which spatial deviations between the reference and remaining functional images are estimated (3dVolReg). Volumes were discarded if motion in the *x*, *y*, or *z* planes exceeded 0.5 mm on consecutive volumes. On average 2.38% (SD = 4.83) of volumes per run were censored from control participant data and 3.52% (SD = 5.59) were censored from ASD participant data. Remaining volumes were registered to the first volume, aligned to skull-stripped anatomical data, and transformed to Montreal Neurological Institute space in

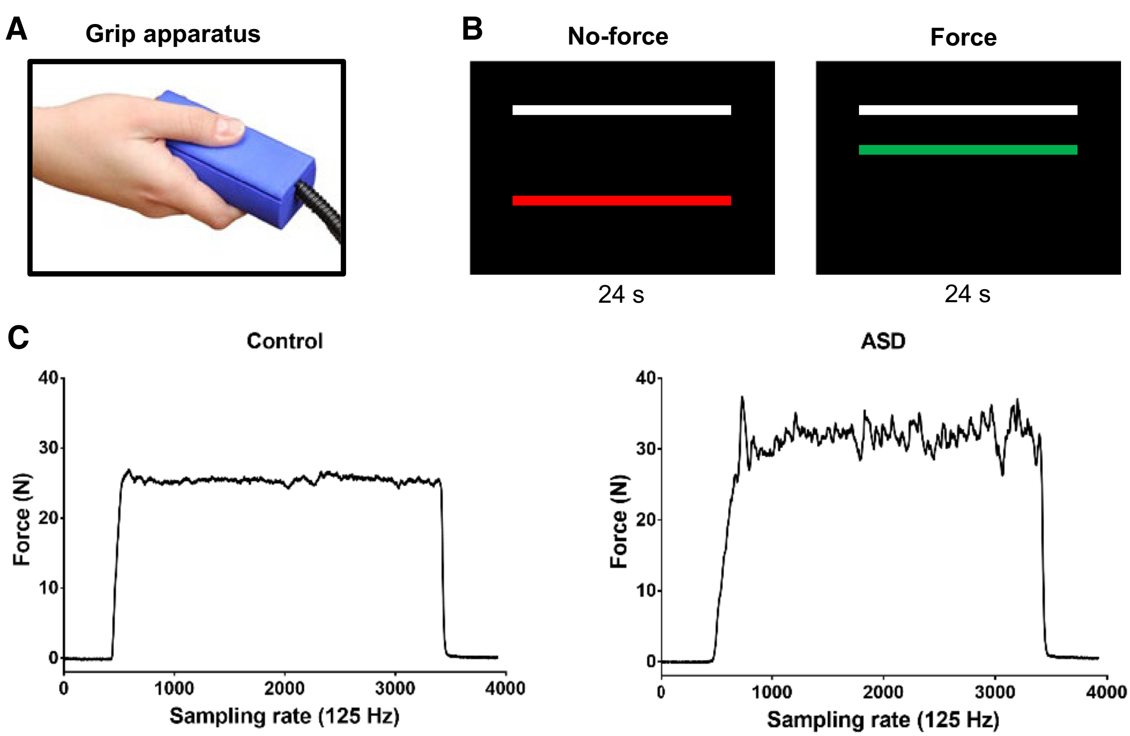

Fig. 2. Grip force functional MRI task and sample output. *A*: custom Bragg grating fiber optic force transducer (Neuroimaging Solutions) housed in precision grip apparatus and illustration of modified precision grip. *B*: task schematic corresponding to 24-s no-force (rest) and force blocks. Force blocks were initiated when the force bar turned from red to green. During force blocks, participants were instructed to press the transducer so that the force bar (green) reached the level of the target bar (white) and maintain this force for the duration of the trial. *C*: sample force output from a control (*left*) and autism spectrum disorder (ASD; *right*) participant.

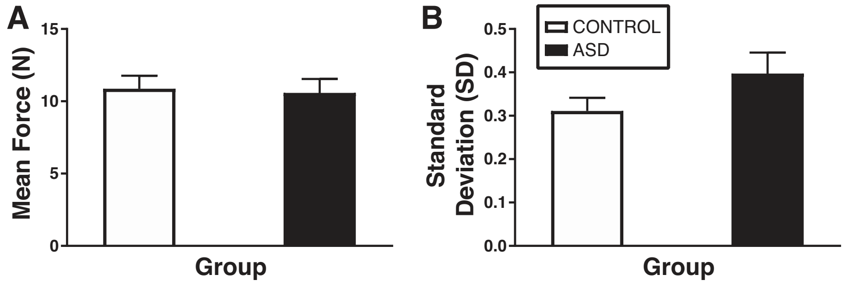

Fig. 3. Sustained force performance for participants with autism spectrum disorder (ASD) and healthy controls. *A*: groups did not differ on mean force output (20% of maximum voluntary contraction). *B*: groups did not differ on force variability (SD).

AFNI. Volume-registered data were spatially smoothed to a full-width half-maximum of 5 mm using a finite difference approximation (3dBlurtoFWHM). Each functional data set was regressed to a standard block function. The dependent variable for regression analyses was the estimated β-coefficient (scaled to percent signal change) and its associated t statistic.

A group statistics map was created by testing the mean of the input data set (force vs. no-force contrast) against zero using AFNI program 3dttest++. This analysis was corrected for multiple comparisons using methods recently outlined by Cox et al. (2017) to address concerns regarding inflated false-positive rates in fMRI research (Eklund et al. 2016). The newly implemented cluster simulation method within 3dttest++ simulates noise volumes by randomizing and permuting input data sets and is the current best recommended method for controlling false-positive rates in AFNI. Given that regions of interest for the visuomotor network include both very large (e.g., primary motor cortex) and relatively small (e.g., anterior cerebellar lobules) regions, we additionally utilized AFNI's equitable thresholding and clustering procedure (ETAC) to simulate spatially variable cluster-sized thresholds. With the use of these methods, a family-wise error rate of $\alpha < 0.01$ was maintained by including only clusters consisting of ≥23 contiguous voxels (voxel size = 2 × 2 × 2 mm) with a voxel-wise $P < 0.0015$.

Statistical analyses. Force data were analyzed using independent samples t tests to determine group differences for mean force and force SD. Effect sizes also were computed using Cohen's d formula [mean1 − mean2/mean(SD1, SD2)]. Imaging data were analyzed in two ways. First, visuomotor ROIs were identified by testing the mean of the force versus no-force contrast data set against zero using AFNI program 3dttest++ and extracting clusters meeting ETAC thresholds (see above). Second, we assessed the relationship between the maximum β-coefficient extracted from each ROI with force SD and mean force and examined whether the strengths of these relationships varied as a function of group membership (ASD vs control). Multiple linear regression analyses were conducted for each ROI using a model with group (ASD vs. control) and force performance (mean force or force SD) entered as predictors at the first step and their interaction term (group × force) entered at the second step. Separate regression models were tested for mean force and force SD.

The associations between clinical symptoms of ASD and both force behavior and blood oxygen level-dependent (BOLD) signal change in visuomotor ROIs were analyzed for ASD participants using Spearman correlations. ADOS calibrated severity scores (CSS) were used to measure overall ASD severity, including social-communicative abnormalities and restricted, repetitive behaviors. These scores are computed based on raw total percentiles that allow for comparisons of symptom severity across ADOS modules (Gotham et al. 2009). The Repetitive Behavior Scale-Revised (RBS-R; Lam and Aman 2007) was used to measure repetitive behavior severity, with higher scores indicating increased severity. Spearman correlations were computed using RBS-R subscales (stereotyped motor movements, self-injurious behavior, rituals, compulsions, insistence on sameness, and restricted interests) and total scores. To minimize the effects of multiple comparisons, conservative cutoffs were used and correlations were only considered significant if $P < 0.05$ and $r > 0.5$.

RESULTS

Sensorimotor behavior in ASD versus controls. Groups did not differ on mean force (Fig. 3*A*; $t = 0.22$, $P = 0.83$, $d = 0.09$). Individuals with ASD showed greater force SD compared with controls ($d = 0.59$), although this difference was not significant (Fig. 3*B*; $t = -1.51$, $P = 0.14$).

Brain activation during visuomotor behavior. Fourteen ROIs showed greater activation during force compared with no-force (Table 2), including contralateral primary motor cortex (M1), ipsilateral ventral premotor cortex (PMv), bilateral extrastriate cortex (V3), bilateral middle temporal visual area (V5/MT), ipsilateral precuneus, right posterior parietal cortex including both superior and inferior parietal lobules (SPL/IPL), right primary somatosensory cortex (S1), supplementary motor area (SMA), contralateral putamen, ipsilateral anterior cerebellar lobules I-V, and bilateral cerebellar lobule VIIb. All ROIs are illustrated in Fig. 4. Regions that showed greater activation

Table 2. *Peak activation coordinates for each region that showed greater activation during visuomotor behavior compared with rest*

Region	k Voxels	MNI Coordinates x	y	z	Maximum z Statistic
R inferior occipital cortex (V3)	203	27	99	−12	5.29
R superior parietal lobule (SPL)	203	45	−45	66	2.08
R middle occipital cortex (V5/MT)	176	45	−66	0	5.61
L precentral gyrus (M1)	164	−45	−15	63	5.29
R inferior frontal gyrus (PMv)	110	60	9	45	5.15
L middle occipital cortex (V5/MT)	107	−48	−78	−6	5.53
L inferior occipital cortex (V3)	82	−30	−96	−12	5.44
R postcentral gyrus (S1)	71	66	−15	42	5.57
R cerebellar lobule VIIb	32	3	−78	−36	4.26
R cerebellar lobules I-IV	32	15	−54	−15	5.89
R precuneus	32	27	−69	42	5.42
L putamen	30	−27	0	3	4.92
Medial frontal gyrus (SMA)	27	0	−3	60	4.24
L cerebellar lobule VIIb	23	−21	−72	−48	4.2

Comparisons are at a voxel-wise $P < 0.0015$, $k \geq 20$. L, left; M1, primary motor area; MNI, Montreal Neurological Institute; PMv, ventral premotor area; R, right; S1, primary somatosensory area; SMA, supplementary motor area; SPL, superior parietal lobule; V3, extrastriate cortex; V5/MT, middle temporal visual area.

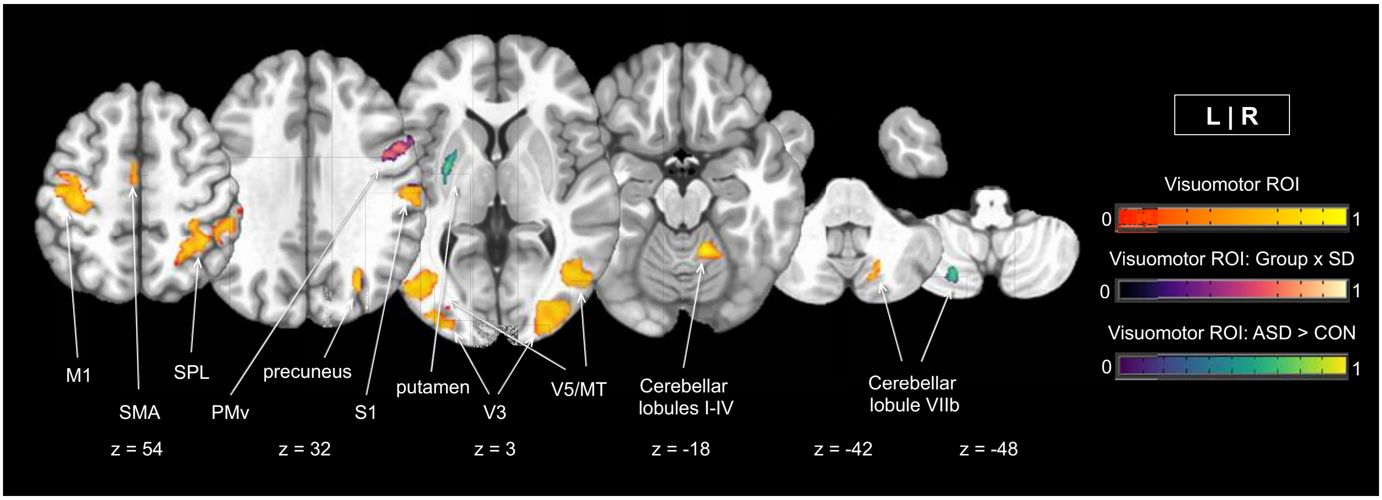

Fig. 4. Brain network activity during visually guided precision force. Full sample analyses revealed significant clusters of activation in contralateral primary motor area (M1), bilateral extrastriate cortex (V3), bilateral middle temporal visual area (V5/MT), right posterior parietal cortex extending into superior parietal lobule (SPL) and inferior parietal lobule (IPL) and primary somatosensory area (S1), ipsilateral ventral premotor area (PMv), contralateral putamen, and bilateral cerebellar lobule VIIb. Scaled gradients indicate standardized β-weights. Red-yellow regions indicate visuomotor regions of interest (ROIs) that showed greater activation during force compared with no-force, purple-peach regions indicate ROIs that showed group × force interactions, and indigo-green regions indicate ROIs that showed group effects. SMA, supplementary motor area; L, left; R, right. Cluster threshold: $\alpha < 0.01$, $P < 0.0015$, $k \geq 23$.

during force compared with no-force but did not show significant group associations are highlighted in red-yellow, regions showing significant group × behavior interactions are highlighted in purple-peach, and regions showing significant group differences are highlighted in indigo-green. Supplementary figures illustrating the relationships between brain activation and task performance for each group can be accessed at https://doi.org/10.6084/m9.figshare.8083037.

BOLD activation differences in ASD versus controls. The overall model for BOLD activation in right PMv, including group, force SD, and the group × force SD interaction term as predictors, was significant [Fig. 5; $F_{(1,26)} = 7.04$, $P = 0.01$, adjusted $R^2 = 0.18$]. The interaction of group × force SD was significant (standardized $\beta = 1.37$, $t = 2.64$, $P = 0.01$), indicating that greater BOLD activation in PMv was associated with greater force SD in healthy controls, while this relationship was not present for individuals with ASD.

The overall model for BOLD activation in left putamen, including group and mean force as predictors, was significant [Fig. 6*A*; $F_{(2,27)} = 3.54$, $P = 0.04$, adjusted $R^2 = 0.15$]. Group was the only significant predictor (standardized $\beta = -0.37$, $t = -2.10$, $P = 0.04$), indicating that individuals with ASD showed greater activation in left putamen than controls.

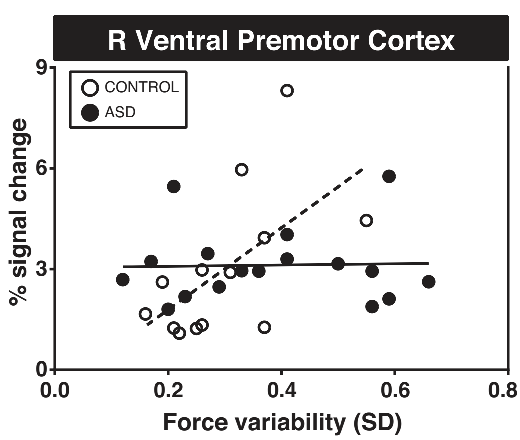

Fig. 5. Blood oxygen level-dependent signal change in cortex is predicted by force variability in controls but not in autism spectrum disorder (ASD). Activation of right ventral premotor area scales with increased force variability in controls but not in ASD. ASD: $n = 17$; control: $n = 15$.

Similarly, BOLD activation in left cerebellar VIIb was predicted by a model containing group and mean force [Fig. 6*B*; $F_{(2,27)} = 3.41$, $P = 0.04$, adjusted $R^2 = 0.14$] and indicated that individuals with ASD showed greater activation in left lobule VIIb than controls (standardized $\beta = -0.43$, $t = -2.38$, $P = 0.02$).

BOLD activation associated with visuomotor behavior. BOLD activation in right V3 was predicted by a model containing group and mean force [$F_{(2,27)} = 3.27$, $P = 0.05$, adjusted $R^2 = 0.14$]. Force was the only significant predictor (standardized $\beta = 0.44$, $t = 2.56$, $P = 0.02$), indicating that BOLD activation in right V3 increased with greater levels of mean force.

Similarly, BOLD activation in right S1 was predicted by a model containing group and mean force [$F_{(2,27)} = 4.79$, $P = 0.02$, adjusted $R^2 = 0.21$]. Force was the only significant predictor (force: standardized $\beta = 0.40$, $t = 2.41$, $P = 0.02$), indicating that BOLD activation in right S1 increased with greater levels of force.

Clinical associations with visuomotor behavior and brain activation in ASD. Higher clinical ratings of ASD severity (ADOS CSS) were associated with greater activation in right precuneus (Fig. 7*A*; $r = 0.60$, $P = 0.02$) for individuals with ASD. Higher RBS-R ratings of repetitive behavior also were associated with increased task-related activation in left cerebellar lobule VIIb (Fig. 7*B*; $r = 0.64$, $P = 0.02$). Analyses of RBS-R subscales indicated that more severe compulsive, ritualistic, and sameness ratings were correlated with increased activation in left cerebellar lobule VIIb (compulsive: $r = 0.61$, $P = 0.03$; ritualistic: $r = 0.61$, $P = 0.04$; sameness: $r = 0.70$, $P = 0.01$). More severe restricted interests were related to increased activation in right cerebellar lobules I-IV ($r = 0.59$, $P = 0.04$), while more severe stereotyped behaviors were related to decreased activation in left putamen ($r = -0.60$,

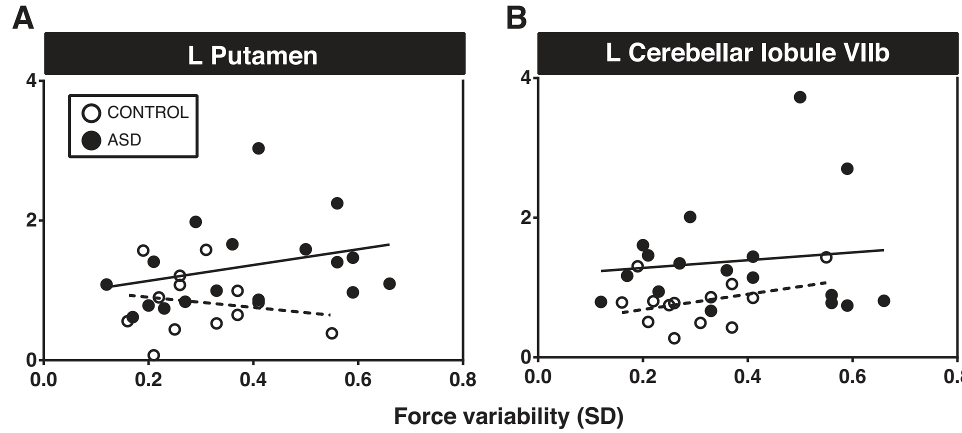

Fig. 6. Blood oxygen level-dependent signal change in subcortical regions is greater in autism spectrum disorder (ASD) than controls. *A*: activation in left putamen is increased in ASD relative to controls. *B*: activation in left cerebellar lobule VIIb is increased in ASD relative to controls. ASD: $n = 17$; control: $n = 15$.

$P = 0.04$). No visuomotor behavioral measures were associated with ratings of ASD severity.

DISCUSSION

In the present study, we examine the linkage between visuomotor behavior and brain function in ASD using both traditional case-control comparisons as well as a dimensional approach that allowed us to determine the relationship between task-dependent changes in brain function and precision motor control. Behavioral results replicate multiple studies from our group and others documenting increased sensorimotor output variability in ASD (Glazebrook et al. 2009; Mosconi et al. 2015; Wang et al. 2015). Our fMRI results identified 14 ROIs involved in visuomotor behavior; these regions were consistent with prior studies that have established a discrete network of cortical and subcortical circuits involved in basic sensorimotor processes (Vaillancourt et al. 2003). One of these ROIs showed strong associations with force variability in our study that varied in ASD relative to controls. Specifically, activation of ipsilateral PMv was related to precision motor variability in healthy controls but not in participants with ASD suggesting atypical organization of cortical sensorimotor processing in patients. Additionally, both left putamen and left cerebellar lobule VIIb showed greater activation in ASD compared with controls, implicating network reorganization that may selectively emphasize subcortical processes during sensorimotor behavior. We also found that BOLD activations of right V3 and right S1 scaled with mean force production similarly in individuals with ASD and controls suggesting basic visual and somatosensory processing during sensorimotor behavior is intact in patients. Lastly, we observed associations between activation in right precuneus, left cerebellar lobule VIIb, and left putamen with clinically rated ASD symptoms suggesting that alterations of sensorimotor brain networks are associated with a broad range of developmental disruptions in patients.

Increased motor variability in ASD. Despite finding no significant differences in force variability between individuals with ASD and controls in the present study, we document a medium effect size ($d = 0.52$) that is similar to that reported in our previous studies of relatively low force levels (5–25% MVC) at identical visual angles (Mosconi et al. 2015; Wang et al. 2015). These prior studies also demonstrate that the magnitude of force SD differences between individuals with ASD and controls increases at higher force levels and at either smaller or larger visual angles. Overall, greater sensorimotor variability in ASD has been demonstrated repeatedly across multiple behaviors and task conditions (Mosconi et al. 2015; Schmitt et al. 2014) and suggests that patients' ability to rapidly integrate multisensory information to reactively and precisely adjust motor output is compromised. Reduced ability to maintain steady-state levels of sensorimotor output may contribute to multiple developmental issues affecting social-communication abilities and cognitive processing. This hypothesis is consistent with prior findings indicating that elevations in sensorimotor variability are associated with more severe symptoms of ASD (Mosconi et al. 2015; Wang et al. 2015). While we did not see significant associations between force SD and ASD symptoms in the present study, it is possible that the restricted range of symptom severity for our sample limited these analyses. Furthermore, more dimensional mea-

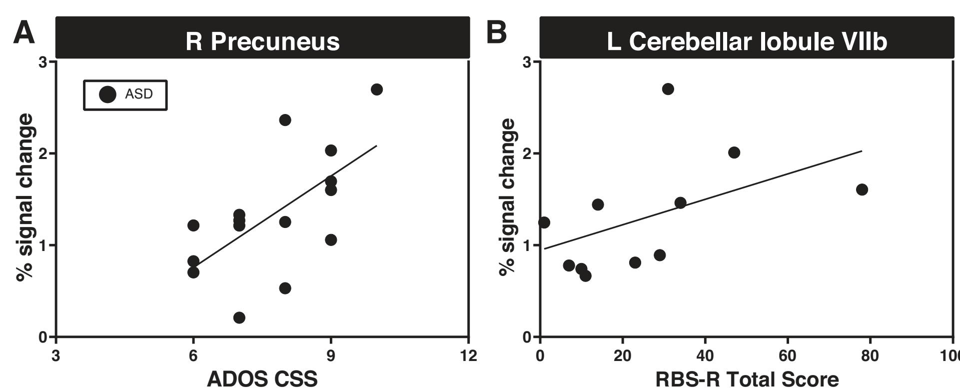

Fig. 7. Blood oxygen level-dependent (BOLD) signal change is associated with severity of clinically rated symptoms of autism spectrum disorder (ASD). *A*: overall autism severity [Autism Diagnostic Observation Scale Calibrated Severity Score (ADOS CSS)] is positively associated with BOLD activation in right precuneus. *B*: severity of restricted, repetitive behaviors [Repetitive Behavior Scale-Revised (RBS-R) Total Score] is positively associated with BOLD activation in left cerebellar lobule VIIb.

sures of ASD symptoms are needed to clarify the relationships between sensorimotor variability and core social-communication and repetitive behavior issues.

Despite consistent findings of elevated sensorimotor variability in ASD, we saw significant overlap between individuals with ASD and controls in terms of force SD. Such overlap also is seen in ASD studies of social behavior, communication ability, and cognitive processes (Chiang et al. 2008; Jones and Klin 2013; Lombardo et al. 2007), indicating that ASD traits are continuously distributed in the population, and that precise, dimensional measures of developmental skills are critical for understanding phenotypic variation and determining underlying biological processes. We leveraged the quantitative nature of our sensorimotor measures to help clarify neurophysiological processes associated with both sensorimotor and core symptoms in patients.

Neural processes associated with visuomotor variability. The discrete networks associated with visuomotor behavior have repeatedly highlighted circuits in premotor and motor cortex, PPC, basal ganglia, and cerebellum (Glickstein 2000; Johnson et al. 1996; Mushiake and Strick 1995). Our analysis of ROIs that showed greater activation during precision gripping identified a network of cortical and subcortical circuits that was highly similar to previously defined visuomotor networks (Vaillancourt et al. 2003, 2006). Specifically, we established associations between sensorimotor behavior and fourteen ROIs including contralateral M1, ipsilateral PMv, bilateral V5/MT, ipsilateral precuneus, right posterior parietal cortex, bilateral V3, SMA, contralateral putamen, ipsilateral cerebellar lobules I-IV, and bilateral cerebellar lobule VIIb. These ROIs comprise a cortical-subcortical network that supports the processing of visual motion in V3 and V5; integration of visual, proprioceptive, and haptic feedback in PPC; and translation of sensory feedback into a modified motor plan in premotor cortex and then M1 (Glickstein 2000). Additionally, striatal input supports the control of M1 output, while cerebellar processes serve to continuously modify error feedback information relayed from PPC via pontine nuclei (Stein and Glickstein 1992). Therefore, our brain-behavior approach identifies a visuomotor network that is highly consistent with previous human and nonhuman primate studies of visuomotor processing.

Our finding that activation in right PMv scaled with force SD in healthy controls but not individuals with ASD suggests that individuals with ASD fail to modulate premotor cortical circuits according to sensory feedback error information. Right PMv interacts with right SPL to generate modified motor plans in response to sensory feedback (Desmurget et al. 1999; Sakata et al. 1997). Our analysis of healthy controls shows greater PMv activation related to increased force SD suggesting amplification of motor planning processes as error increases. In contrast, individuals with ASD do not appear to modulate cortical planning circuits in relation to error feedback, which may result in a reduced ability to precisely and dynamically adjust motor output. Consistent with this interpretation, previous studies have demonstrated that during motor learning, individuals with ASD show reduced reliance on external sensory cues, which are thought to be represented within premotor-parietal cortical networks (Haswell et al. 2009; Izawa et al. 2012). Findings of disrupted functional connectivity of visual and motor systems in ASD (Nebel et al. 2016) suggest that the integrity of visual sensory feedback may be compromised during visually guided motor behavior. Our finding implicating premotor cortical circuits also is consistent with recent studies demonstrating atypical connectivity within sensorimotor and visual networks in young children with ASD (Chen et al. 2018) and suggests premotor cortical circuit dysfunction may represent a key neurodevelopmental mechanism in ASD.

Subcortical activity during visuomotor behavior. We found that both left putamen and left cerebellar lobule VIIb showed elevated activation during visuomotor behavior in ASD relative to controls. Combined with our cortical findings, these results suggest atypical organization of brain networks involved in visuomotor control in ASD and implicate a heightened reliance on subcortical circuit processes.

Externally guided motor behaviors, such as those directed by visual sensory cues, are supported by distinct neural networks from those guided by internally generated cues. Nuclei of the basal ganglia, including the putamen, show greater activation during internally generated motor movements (Mushiake and Strick 1995). The putamen is involved in the selection and acquisition of specific motor skills, showing increased activation during periods of motor planning (Elsinger et al. 2006) and a reduction in activation once a motor behavior has become automatized (Poldrack et al. 2005). Our findings of increased putamen activation in individuals with ASD may indicate a deficit in the transition that occurs during entrainment from basal ganglia circuits for action selection toward cortical control of motor processes. Atypical organization of motor processes previously has been reported during tasks of internally guided motor behavior (e.g., finger-tapping) in which individuals with ASD failed to show expected shifts from effortful cortical control of motor behavior toward habitual execution (Mostofsky et al. 2009). Previous findings of reduced connectivity within sensorimotor circuits (Mostofsky et al. 2009; Turner et al. 2006) and recruitment of nonmotor circuits during simple motor tasks (Müller et al. 2003) along with increased connectivity between primary sensory cortexes and basal ganglia in ASD (Cerliani et al. 2015) also suggest disorganization of sensorimotor systems that may be reflected in increased utilization of subcortical motor networks.

The cerebellum comprises multiple microcomplexes that form cortico-cerebellar networks involved in refining ongoing behavior and updating internal action representations based on feedback information relayed via olivary climbing fibers and mossy fiber inputs (Eccles et al. 1967; Ramnani 2006; Vogel et al. 1996). These refinements allow for greater accuracy of subsequent output. Although the cellular structure of these microcomplexes is relatively invariant (Ito 2008), there exists a functional topography across cerebellar lobules that is defined by distinct inputs from neocortex (Buckner et al. 2011; Stoodley and Schmahmann 2010). Our finding of increased sensorimotor-related activation of cerebellum in ASD is consistent with previous reports of greater and more diffuse activation of cerebellum during simple motor tasks (Allen and Courchesne 2003; Allen et al. 2004). However, studies also have documented reductions in cerebellar activation compared with healthy controls during motor behavior (Mostofsky et al. 2009; Takarae et al. 2007). Unlike previous studies of manual motor behavior that used finger tapping tasks known to be supported by internally generated motor circuits, the current task examined precision motor control guided by external sensory cues that required integration of visual-spatial feedback. Lobule VIIb has been implicated in visual-spatial integration and shows functional connectivity with prefrontal and parietal cortex (Krienen and Buckner 2009). Specifically, left lobule VIIb is involved in reciprocal inhibition of right PPC (Stoodley et al. 2012) suggesting that heightened cerebellar activation may reflect defects in parietal-cerebellar circuits involved in processing visual-spatial error feedback during behavior.

Our finding of cerebellar dysfunction in ASD also is consistent with prior anatomical studies. Histopathological studies in ASD frequently have documented reduced size and density of Purkinje output cells (Bauman and Kemper, 1985; Fatemi et al. 2002; Whitney et al. 2008). Voxel-based morphometry studies also have reported decreases in cerebellar gray matter that are associated with the severity of clinically rated social and repetitive motor symptoms and appear to be specific to ASD relative to other neurodevelopmental disorders (D'Mello and Stoodley 2015; Rojas et al. 2006). Although anatomical abnormalities specific to lobule VIIb have yet to be reported in the literature, the highly invariant structure of the cerebellum suggests that aberrant cellular and anatomical development of the cerebellum may impact multiple functional microcomplexes in ASD.

Associations between brain function and ASD symptoms. We report several associations between atypical brain function and clinically rated ASD symptoms. Higher ADOS severity scores were associated with increased activation in right precuneus, which together with premotor and parietal cortexes is involved in visual-spatial transformations during visually guided movements (Cavanna and Trimble 2006; Ferraina et al. 1997). Precuneus previously has been implicated in relation to ASD severity during tasks of motor learning (Travers et al. 2015) and sustained attention (Christakou et al. 2013) suggesting that deficits in spatial attention may be related to the severity of core ASD issues. We also report an association between increased severity of repetitive behavior and task-related activation in left cerebellar lobule VIIb. The cerebellum supports distinct sensorimotor and nonmotor processes, including language, affective, and executive abilities (Habas et al. 2009; Krienen and Buckner 2009) and therefore defects in this region may have widespread effects on cognitive development. This finding adds to several existing studies implicating the cerebellum in relation to repetitive behaviors (D'Mello et al. 2015; Rojas et al. 2006; Tsai et al. 2012), including a longitudinal study by Wolff et al. (2017) that demonstrated an association between white matter integrity of the cerebellum early in life and later RRB severity. In addition to its connectivity with neocortex, the cerebellum also is densely interconnected with basal ganglia, through which it is thought to influence both motor and nonmotor behaviors (Bostan and Strick 2018). In this way, cerebellar defects may have downstream effects on striatal regions associated with repetitive behaviors (Estes et al. 2011; Qiu et al. 2010). Consistent with this hypothesis, we find an association between increased activation in left putamen and severity of stereotyped behavior. This finding adds to existing literature implicating the striatum in the pathophysiology of RRBs (Langen et al. 2014; Lewis and Kim 2009). More specifically, structural alterations in the putamen have been associated with more severe stereotyped behaviors and deficits in motor control in ASD (Estes et al. 2011; Qiu et al. 2010). Together, these findings provide evidence to implicate aberrant function of cortical and subcortical structures important for sensorimotor behavior the pathophysiology of ASD.

Limitations and implications for future research. A primary limitation of this fMRI study is the relatively small sample size. While our behavioral and imaging results each are consistent with prior ASD studies of sensorimotor behavior and imaging studies of visuomotor network function (Vaillancourt et al. 2003, 2006), larger sample task-based fMRI studies of precision sensorimotor behavior are needed to characterize brain-behavior associations across a broader range of ability level in ASD. Second, although the visuomotor ROIs identified in the current study are consistent with those previously determined to underlie precision motor control, not all of these regions were associated with our measures of task performance. Force variability was chosen as the primary outcome in this study based on multiple previous studies that have documented increased motor variability in ASD. However, precision motor control reflects multiple distinct sensorimotor processes that arise from many interacting neurophysiological processes. For example, contralateral M1 activation has been linked to increases in force amplitude (Cramer et al. 2002), while specific regions of the cerebellum and basal ganglia scale with the rate and duration of initial force output (Prodoehl et al. 2009; Spraker et al. 2012). Studies are needed to further parse distinct sensorimotor processes and discrete circuits of the visuomotor network in ASD so that neurophysiological mechanisms of separate sensorimotor issues in ASD can be defined. Third, the current sample did not allow for comparison of potential sex differences (Supekar and Menon 2015) or variations in sensorimotor behavior and brain function across early periods of childhood development when sensorimotor processes may develop rapidly. Future studies will benefit from efforts to assess female participants with ASD and incorporation of cross-sectional or longitudinal designs to assess age-related changes in developmental processes that underlie precision motor behavior. In line with studies showing that sensorimotor skills support cognitive and socio-communicative abilities (e.g., Libertus and Needham 2011), this research may be particularly informative in addressing how alterations in the development of sensorimotor brain networks contribute to nonmotor clinical deficits. Fourth, studying precision visuomotor behavior across both hands may be informative for understanding motor cortical lateralization in ASD in the context of prior studies showing atypical lateralization of motor and brain functions in patients (Floris et al. 2016). Although handedness did not differ between groups in the current sample, previous reports of increased mixed handedness in ASD (Escalante-Mead et al. 2003) indicate that future studies may benefit from testing performance of both dominant and nondominant hands. Finally, our analyses of relationships between sensorimotor behavior and ASD symptoms rely on qualitative ratings of behavior, and more quantitative measures of core social-communication and repetitive behaviors are needed to better understand linkages with sensorimotor behavior and brain function.

Conclusions. The present study is one of the first fMRI studies of precision sensorimotor behavior in ASD. Despite studies consistently showing greater motor variability in ASD across different behaviors, sensorimotor issues remain an understudied aspect of ASD, and brain mechanisms remain unclear. Our findings that both cortical and subcortical circuit dysfunctions are associated with precision sensorimotor issues and core symptoms of ASD indicate that systematically assessing sensorimotor brain networks during behavior may provide new insights into neurodevelopmental processes core to the disorder. In the context of prior findings of altered corticocerebellar pathways in young children with ASD (Wolff et al. 2017) and studies demonstrating relationships between sensorimotor behaviors and functional outcomes in patients (Bhat et al. 2012; Travers et al. 2013), our results provide important new information on key neurodevelopmental processes underlying ASD.

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DISCLOSURES

D. E. Vaillancourt is the cofounder and manager of Neuroimaging Solutions, LLC. None of the other authors have any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

D.E.V., J.A.S., and M.W.M. conceived and designed research; M.W.M. performed experiments; K.E.U., L.E.M., and G.M. analyzed data; K.E.U., L.E.M., D.E.V., J.A.S., and M.W.M. interpreted results of experiments; K.E.U. prepared figures; K.E.U. drafted manuscript; K.E.U., L.E.M., G.M., D.E.V., J.A.S., and M.W.M. edited and revised manuscript; K.E.U., L.E.M., G.M., D.E.V., J.A.S., and M.W.M. approved final version of manuscript.

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