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Impaired motor skills and atypical functional connectivity of the sensorimotor system in 40-65 year old adults with Autism Spectrum Disorders

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Abstract

Background: Impairments in fine and gross motor function, coordination, and balance early in development are common in autism spectrum disorders (ASDs). It is unclear whether these deficits persist into adulthood, and whether they may be exacerbated by additional motor problems that often emerge in typical aging.

Methods: We assessed motor skills and used resting state functional magnetic resonance imaging (fMRI) to study intrinsic functional connectivity of the sensorimotor network in 40–65 year-old adults with ASDs (n=17) and typically developing matched adults (n=19).

Results: Adults with ASDs scored significantly lower on assessments of motor skills compared to an age-matched group of typical control (TC) adults. Additionally, functional connectivity of the sensorimotor system was reduced, and the pattern of connectivity was more heterogeneous in adults with ASDs. A negative correlation between functional connectivity of the motor system and motor skills, however, was only found in the TC group

Conclusions: Findings suggest behavioral impairment and atypical brain organization of the motor system in middle-age adults with ASDs, accompanied by pronounced heterogeneity.

Keywords

autism; ASD; motor; MRI; connectivity; middle-age

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Disclosures

All authors have nothing to disclose.

1. Introduction

Autism Spectrum Disorders (ASDs) are a group of neurodevelopmental disorders featuring pervasive deficits in social communication along with restricted and repetitive behaviors and interests. Although ASDs emerge early in childhood, they usually persist throughout the lifespan (American Psychiatric Association, 2013). Neuroimaging studies have tried to unravel underlying neural mechanisms, but most have exclusively focused on childhood and adolescence with little information about how ASDs manifest in older adults.

Impairments in fine and gross motor function, coordination, and balance are common during early development in ASDs, persisting into adolescence (Freitag, 2007; Ghaziuddin and Butler, 1998; Green et al., 2002; Jansiewicz et al., 2006; McPhillips et al., 2014; Miyahara et al., 1997). Motor deficits have been shown to increase with age, as children with ASD fall further behind (Lloyd et al., 2013), and there is additional evidence of motor abnormalities in young adults with ASDs (Fukui et al., 2018; Glazebrook et al., 2006). While little is known about motor function in older adults with ASDs (Hallett et al., 1993; Happé and Charlton, 2012; Mukaetova-Ladinska et al., 2011; Piven et al., 2011), increased frequency of parkinsonism in adults with ASDs may indicate worsening motor abnormalities with age (Croen et al., 2015; Starkstein et al., 2015).

Along with impaired motor performance, altered functional connectivity of sensorimotor regions has been observed in children, adolescents, and young adults with ASDs. Findings include reduced interhemispheric connectivity of sensorimotor cortex in resting state fMRI (Anderson et al., 2011; Floris et al., 2016; Lee et al., 2016) and reduced functional connectivity within motor networks during finger tapping (Mostofsky et al., 2009). Reduced intrahemispheric connectivity has been reported for postcentral gyrus (Lee et al., 2016), whereas findings on precentral gyrus include overconnectivity among subregions (Nebel et al., 2014a; Nebel et al., 2014b) and reduced asymmetry of functional connectivity (Carper et al., 2015). Inconsistent hypo- and hyper-connectivity findings are common in the ASD literature, with recent suggestions of “idiosyncrasy” (increased interindividual variability (Hahamy et al., 2015)). Consistent with this conceptualization, a recent study in 6–64 year-olds with ASDs (n=422) utilizing data from the Autism Brain Imaging Data Exchange I & II (Di Martino et al., 2017; Di Martino et al., 2014), found idiosyncratic organization of the sensorimotor network (Nunes et al., 2018), with more variable functional connectivity of sensorimotor cortex shown across participants with ASDs than typically developing controls. Atypical motor-related activation with increased interindividual variability has been found in young adults with ASDs (Müller et al., 2001), while reduced motor connectivity (Mostofsky et al., 2009) and functional differentiation within motor cortex (Nebel et al., 2014b) has been reported in children and adolescents. More widespread activity during simple motor tasks has also been found in the cerebellum (Allen et al., 2004). Atypical cerebellar participation in motor functions in ASDs is further supported by findings of aberrant functional connectivity (Arnold Anteraper et al., 2018; Khan et al., 2015) and neuroanatomical differences (Fatemi et al., 2012; Rogers et al., 2013).

In neurotypical aging, a decline in motor function beginning in the 6th decade is common (Leversen et al., 2012; Potvin et al., 1980), with deficits in fine motor skills (Contreras-Vidal

et al., 1998; Darling et al., 1989; Hoogendam et al., 2014; Smith et al., 1999), coordination (Seidler et al., 2002), and balance (Laughton et al., 2003; Woollacott and Tang, 1997). Importantly, these domains of motor decline resemble profiles of motor impairment in young people with ASDs (Ghaziuddin and Butler, 1998; Green et al., 2002; Jansiewicz et al., 2006).

Functional neuroimaging findings related to motor decline in typical aging have been mixed. Some studies have found decreased connectivity within sensorimotor networks (Hoffstaedter et al., 2015; Huang et al., 2015; Wu et al., 2007) and reduced interhemispheric connectivity of sensorimotor regions (Roski et al., 2013) with increasing age, while others have found increasing sensorimotor connectivity (He et al., 2017; Song, J. et al., 2014; Song, X. et al., 2014; Tomasi and Volkow, 2012). Furthermore, increased sensorimotor connectivity has been found to correlate with better motor performance in some studies (Langan et al., 2010; Seidler et al., 2015), but with worse motor performance in others (Fling and Seidler, 2012; Solesio-Jofre et al., 2014). Mixed findings likely result from methodological and cohort differences, with varying average ages. For example, some studies compared groups of younger and older adults (Bernard et al., 2013; Fling and Seidler, 2012; Langan et al., 2010), others performed correlational analyses cross-sectionally (Seidler et al., 2015; Solesio-Jofre et al., 2014). Additionally, different types of motor tasks were used to assess motor skills, e.g., visuomotor tasks requiring participants to move a joystick to a target (Langan et al., 2010), novel bimanual visuomotor tasks (Solesio-Jofre et al., 2014), or grip force and finger tapping (Seidler et al., 2015). In the context of persistent motor and coordination deficits known to be present even in very young children with ASD, the neurofunctional changes seen in these same domains during typical aging may put older individuals with ASD at increased risk (e.g. to new neurological diagnoses or challenges to daily living).

To begin to address the gap in knowledge regarding motor systems in older adults with ASD, the present study examined motor performance and functional connectivity of sensorimotor networks in mature adults with ASDs compared to age-matched typical controls (TC). Given previous findings of impaired performance on a range of motor tasks in children and adolescents with ASDs (Fournier et al., 2010; Leversen et al., 2012), we expected lower performance in older adults with ASD (compared to TC peers) on all measures of motor performance. Similarly, we expected to find altered functional connectivity within sensorimotor regions (Anderson et al., 2011; Lee et al., 2016; Nebel et al., 2014a). However, given mixed findings for age-related changes in functional connectivity and the relationship with motor performance in the typically aging population (Fling and Seidler, 2012; Langan et al., 2010; Seidler et al., 2015; Solesio-Jofre et al., 2014), we did not entertain directional hypotheses on the relationship between the functional connectivity of motor regions, age, and motor performance.

2. Methods and Materials

2.1 Cohort

We initially recruited 33 adults with ASD and 27 typical control (TC) participants aged 40 to 65 through community advertising as part of an ongoing longitudinal study. Individuals with comorbid ASD-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis,

epilepsy), or other neurological conditions (e.g., Tourette syndrome) were not eligible for participation. Exclusionary criteria for the TC group were: personal or family history (first degree relatives) of ASDs, neurological disorders, schizophrenia, bipolar disorder, severe major depressive disorder, obsessive-compulsive disorder, psychosis, or other developmental disorders. Additionally, 6 adults inquired about the study with suspected ASD, but did not meet criteria for ASD following the initial diagnostic assessment, and 3 TC participants who expressed interest in the study then declined to participate. All participants were safety-screened for MRI contraindications (e.g., claustrophobia, ferrous material in body). Informed consent was acquired from all participants or their conservators, and participants were compensated for their time. The study protocol was approved by the institutional review boards of the University of California San Diego and San Diego State University.

Only right-handed participants were included for the analyses presented here given the focus on the motor system (4 left handers excluded). ASD and TC groups were matched on age, total brain volume (TBV) and in-scanner head-motion. In-scanner head-motion was calculated from the six rigid-body realignment parameters (see 2.4) as the root-mean-square-difference (RMSD; Power et al. 2014). An additional 4 participants were excluded from analyses due to excessive motion of average RMSD > 0.2mm across the two runs (3) or incidental findings of brain abnormalities (1). Demographics for all participants included in the analyses are summarized in Table 1.

2.2 Diagnostic, Neuropsychological and Motor Assessments

ASD diagnoses were confirmed based on Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria, (American Psychiatric Association, 2013) supported by clinical interviews and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2). (Lord, 2012) IQ was assessed using the Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II) (Wechsler, 2011). Motor skills and balance were assessed with the short form version of the Bruininks Motor Abilities Test (BMAT; (Bruininks and Bruininks, 2005). The BMAT assesses 5 subcategories of motor behavior: fine motor (e.g., drawing a line through a curved path), manual dexterity (e.g., stringing small wooden blocks), coordination (e.g., catching a ball with one hand), balance (e.g., standing on one leg), and strength and flexibility (e.g., wall pushups). The BMAT provides a standard score derived from the total number of points earned across all five subscales relative to a normative sample of similar-aged peers of the same sex. Differences in motor skills (BMAT standard and subscale scores) between the ASD and TC groups were tested using independent samples t-tests.

2.3 Magnetic Resonance Imaging Data Acquisition

MRI data were collected at the University of California San Diego Center for Functional MRI on a GE 3T Discovery MR750 scanner using a Nova Medical 32-channel head coil. A fast 3D spoiled gradient recalled (FSPGR) T1-weighted sequence was used to acquire high-resolution structural images (0.8 mm isotropic voxel size, NEX=1, TE/TI=min full/1060ms, flip angle 8°, FOV=25.6cm, matrix=320×320, receiver bandwidth 31.25hz). Motion during structural acquisitions was corrected in real-time using three navigator scans (PROMO, real-time prospective motion correction; (White et al., 2010)), and images were bias corrected

using the GE PURE option. A multiband EPI sequence which allows simultaneous acquisition of multiple slices was used to acquire two fMRI runs (6 minute duration each) with high spatial and temporal resolution (TR=800ms, TE=35ms, flip angle 52°, 72 slices, multiband acceleration factor 8, 2 mm isotropic voxel size, 104×104 matrix size, FOV 20.8cm, 400 volumes per run). Two separate 20s spin-echo EPI sequences with opposing phase encoding directions were also acquired using the same matrix size, FOV and prescription to correct for susceptibility-induced distortions. During the functional scans, participants were instructed to “Keep your eyes on the cross. Let your mind wander, relax, but please stay as still as you can. Try not to fall asleep.” Participants’ adherence to the instructions to remain awake, with eyes open, was monitored with an MR-compatible video camera. Heart rate and respiration during the functional scans were recorded continuously using a Biopac pulse oximeter and respiratory belt.

2.4 Imaging data preprocessing and denoising

MRI data were preprocessed, denoised and analyzed in FSL (v5.0.10), FreeSurfer (v 5.3.0) and Matlab 2015b (Mathworks Inc., Natick, MA, USA) using SPM12 (Wellcome Trust Centre for Neuroimaging, University College London, UK), the CONN toolbox v17f, and custom Matlab code available upon request.

The structural image was converted from dicom to nifti format and was coregistered to the mean functional image, segmented and normalized to MNI space using non-linear registration and the default tissue probability maps included with SPM12. The white matter (WM) probability maps obtained from segmentation of the structural image for each individual subject were thresholded at 0.95 and eroded by 1 voxel. Due to high variability in ventricle size across participants, the template CSF map was used to extract CSF time courses for all participants (thresholded at 0.5 and eroded by 1 voxel). There was no overlap with gray matter voxels for the eroded WM and CSF masks for any participant. WM and CSF time courses were extracted from the thresholded and eroded masks using aCompCor (Behzadi et al., 2007) for subsequent nuisance regression (see below). In order to obtain measures of total brain volume (TBV) for each participant, structural images were also processed using FreeSurfer version 5.3.0. Following semi-automated cortical reconstruction in FreeSurfer, TBV was calculated as the sum of supratentorial and cerebellar volume.

Functional images were corrected for susceptibility-induced distortions using the two spin-echo EPI acquisitions with opposite phase encoding directions and FSL’s TOPUP tools (Smith et al., 2004). Subsequently, functional images were motion-corrected using rigid-body realignment as implemented in SPM12. The Artifact Detection Toolbox (ART, as installed with conn v17f) was used to identify outliers in the functional image time series from the resulting 6 motion parameters (3 translational and 3 rotational) that had frame-wise displacement (FD) >0.9mm and/or changes in signal intensity that were greater than five standard deviations. As oscillations due to respiration are prominent in motion parameters derived from multiband EPI realignment (Fair et al., 2018) and would result in unnecessary censoring of large chunks of data in some participants, the thresholds to detect outliers were more lenient than those used for standard resting state fMRI acquisitions with slower TRs (but see Supplementary Methods and Figure S3 for supplementary analyses with stricter

censoring thresholds). In order to ensure that none of our findings were due to differences in apparent motion between groups, participants were matched on RMSD calculated from rigid-body realignment of the raw data prior to TOPUP correction (Table 1). ASD and TC group did not differ in the number of time points detected as outliers (run1: $t(34)=-.085$, $p=.93$; run2: $t(34)=-1.04$, $p=.31$) and none of the results from the functional connectivity analyses were correlated with RMSD (see Supplementary Table S1 for further detail).

Functional images were directly normalized to MNI space with the same non-linear registration as used for the structural images. Since all analyses were run on averaged voxel time series within pre-defined ROIs, no prior smoothing was applied to the data. Band-pass filtering using a temporal filter of 0.008 to 0.08 Hz was carried out as part of the nuisance regression (“simult” option in the conn toolbox) which also included scrubbing of the motion outliers detected by the ART toolbox, and regression of the 6 motion parameters and their derivatives, as well as the first five PCA component time series derived from the CSF and white matter masks. The residuals of the nuisance regression were then used for all subsequent functional connectivity analyses.

Since inclusion of different noise regressors can substantially alter Pearson correlations between regions, we repeated nuisance regression including a) RETROICOR (Glover et al., 2000) physio regressors derived with the PhysIO toolbox (Kasper et al., 2017) from the pulse and respiratory recordings during the functional scans, and b) global signal regression (using the average timeseries of all voxels in the brain). Results from these additional analyses are presented in the Supplementary Material.

2.5 Functional Connectivity Analysis

2.5.1 Regions of interest—For the functional connectivity analyses 4 cortical regions of interest (ROIs) covering premotor area (PMA), as well as primary motor (M1), and primary and secondary somatosensory (S1 and S2) cortices were created from the Harvard-Oxford and Jülich Histological atlases provided by the FSL toolbox. Fslmaths was used to segregate the Jülich Histological atlas into separate regions for the left and right hemisphere. The probability maps from the Jülich Histological atlas were then thresholded by overlaying with corresponding motor ROIs from the Harvard-Oxford atlas in a winner-take-all analysis, and all ROIs were grey-matter masked. ROIs are shown in Figure S1. Two cerebellar ROIs (left and right cerebellar hemispheres) were also included.

2.5.2 Functional connectivity analysis—BOLD time series were averaged across all voxels within each ROI. Functional connectivity between all ROI pairs was then estimated using bivariate Pearson correlation standardized with a Fisher z-transform. A second-level general linear model tested for differences in correlation magnitude between pairs of ROIs in the ASD compared to the TC group. Significant differences are reported at a threshold of $p < .05$, False Discovery Rate (FDR) corrected for multiple comparisons. Functional connectivity (Fisher z) was Pearson correlated with age, separately in each group, to test for any age-related changes in sensorimotor connectivity.

2.5.3 Pattern similarity analysis—The pattern of connectivity across all ROI pairs was compared between participants. Each 10 ROI x 10 ROI functional connectivity matrix

was triangulated and for each participant the connectivity pattern was compared with that of every other participant, using Pearson correlation. Correlations were Fisher z-transformed and the average similarity of an ASD participant to all other (n-1) ASD participants and to all TC participants was then calculated, and significant differences assessed using permutation testing (carried out in MATLAB, 1000 permutations with group labels randomly shuffled). We hypothesized that connectivity patterns would be more similar within group (ASD compared to other ASD participants) than across group (ASD compared to TC participants) – reflective of a different functional organization of the motor network in ASD and TC groups – and that similarity of connectivity patterns would be lower within the ASD than the TC group, reflecting a higher degree of idiosyncrasy within the ASD group. A flowchart illustrating the pattern similarity analysis in greater detail is provided in Supplementary Figure S2).

2.5.4 Relationship between functional connectivity of the sensorimotor system and motor skills—For ROI pairs with significant differences between the ASD and TC group (after FDR correction), partial correlations controlling for age were conducted for ROI-ROI connectivity z-scores with BMAT standard and subscale scores.

3. Results

3.1 Motor skills in adults with and without ASDs

The ASD group showed significantly impaired motor function, compared to the TC group, on the BMAT standard score and BMAT subscales for manual dexterity, coordination, and strength and flexibility (see Table 2). There were no differences between groups for the BMAT fine motor or balance and mobility subscales (see Table 2).

3.2 Functional connectivity of the sensorimotor system

Mostly strong synchronization of BOLD time courses, especially between homologous sensorimotor ROIs, was detected for both the ASD and TC groups (Figure 1A). However, functional connectivity was significantly weaker ($p < .05$, FDR corrected) in the ASD group compared to TC for right M1 with left M1, right and left S1, and right and left PMA, and for left M1 with left S1 (Figure 1A–B). No differences in cerebro-cerebellar functional connectivity were found. None of the functional connectivities correlated significantly with age (all $p > .1$). Importantly, functional connectivity was also not correlated with head motion (RMSD or % volumes censored, see Table S1) during the two fMRI scans for any ROI pair (all $p > .2$), and the pattern of results did not change when including RETROICOR physiological regressors (calculated using the PhysIO toolbox) from the pulse and respiratory recordings during the fMRI scans, or when including the global signal in the nuisance regression (see Supplementary Figure S4).

The similarity analysis revealed that adults with ASDs showed a more heterogeneous pattern of connectivity between sensorimotor ROIs compared to TCs. (Cohen's $d = -1.34$, $p < .001$): On average an adult with ASD was less similar in connectivity pattern to other adults with ASD (mean $z = .63$, $SD = .141$, range: .37–.83) than TC adults were to each other (mean $z = .83$, $SD = .158$, range: .55–1.01). Additionally, adults with ASDs were less similar in their

connectivity patterns to TC adults (mean $z=.69$, $SD=.212$, range: $.36-.99$) than TC adults were to each other (Cohen's $d = -.74$, $p < .05$, see Figure 2). Which ROI pairs showed the most variable functional connectivity (standard deviation of Fisher z -transformed Pearson correlations) in the ASD compared to the TC group is illustrated in Figure S5.

3.3 Relationship between motor skills and functional connectivity of the sensorimotor system

We next assessed whether sensorimotor connectivity was associated with motor skills for ROI pairs that showed significant differences between the ASD and TC groups. In the TC group, higher performance on the BMAT (standard score) was associated with lower functional connectivity of right M1 with right PMA, right S1, and left S1, and of left M1 with left S1 (see Table 3 and scatterplots in Figure 3). Also in the TC group, fine motor scores were inversely correlated with connectivity of right M1 with left M1 and right S1. Finally, higher performance on strength and flexibility was associated with lower connectivity of right M1 with right PMA and right S1. In the ASD group, no correlations between BMAT scores and connectivity measures, including functional connectivity similarity (see Table S3), were found.

4. Discussion

Motor deficits are common in children and adolescents with ASDs; however, much less is known about the motor system later in life. As hypothesized, we found that manual dexterity, coordination, strength, and flexibility were impaired in adults with ASDs past the fourth decade of life, in comparison with matched TC adults. Unexpectedly, we did not detect deficits in fine motor skills or balance and mobility. Impairments affecting most motor subdomains were accompanied by atypical functional connectivity between sensorimotor regions. Specifically, inter- and intra-hemispheric functional connectivity of the sensorimotor network was reduced, and the pattern of connectivity was distinct and more variable among adults with ASDs when compared to their matched controls.

Similar to our findings in older adults, reduced sensorimotor connectivity has also been found in children and young adults with ASDs (Anderson et al., 2011). Additionally, increased lateralization of the motor network — which might reflect reduced interhemispheric connectivity — has been observed in two independent studies assessing intrinsic functional connectivity of sensorimotor regions in ASDs (Floris et al. (2016): ages 8–12 years; Carper et al. (2015): ages 7–18 years). Using a large sample from ABIDE, another study found a mixture of over- and underconnectivity between regions of the precentral gyrus across a large age range from 6 to 40 years (Nebel et al., 2014a). Motor network underconnectivity in their study was associated with less severe social deficits, which the authors suggested to be driven by older individuals with ASDs, potentially reflecting compensatory mechanisms. Functional connectivity of the motor network has also been found to decrease with healthy aging (Roski et al., 2013; Wu et al., 2007). Interestingly, in our sample, functional connectivity was most variable between the PMA and primary motor and somatosensory regions in the ASD group, but between the cerebellum and primary motor and somatosensory regions in the TC group (see Figure S5). This may imply

greater divergence in the cortico-cortical motor network in ASD, but of cortico-cerebellar motor circuits in neurotypical adults. Our findings of atypical sensorimotor functional connectivity in 40–65 year old adults with ASDs might reflect compensatory mechanisms, possibly going back to adolescence or early adulthood. However, no conclusive interpretation is possible in the absence of longitudinal data, since no correlations between functional connectivity and age were observed in the current study in either the ASD or TC group and findings on healthy aging described above have not always been consistent (He et al., 2017; Song, J. et al., 2014).

4.1 Atypical functional connectivity and increased variability of motor networks in ASD

Sensorimotor network connectivity patterns were less similar across ASD than across TC participants, suggesting more variable functional organization of sensorimotor regions in ASDs. “Idiosyncratic” organization of the sensorimotor network was also observed in a recent study drawing upon fMRI data from the Autism Brain Imaging Data Exchange I & II (422 6–64 year-olds with ASDs (Nunes et al., 2018)). In addition to the increased heterogeneity within the ASD group, similarity between ASD and TC adults was lower than between individual TC adults, reflecting atypicality of connectivity patterns. As can be seen in Figure 2 (purple graph), connectivity patterns of some adults in the ASD group were highly dissimilar from those found in the TC group, while they were similar for others. This heterogeneity may reflect different variants of ASDs or different compensatory mechanisms that may have arisen intrinsically or in response to interventions and therapies received. For example, prescription medication usage in ASDs is more common than in healthy controls of the same age (Buck et al., 2014; Esbensen et al., 2009) and can influence resting state functional connectivity (Linke et al., 2017). In our cohort of adults with ASDs, information on current medication usage was available for 10, of whom 6 reported taking medications while only 1 of the 15 TC participants for whom this information was available did (see Table S2). The lack of detailed information on medication usage and treatment received is a limitation of the current study, but it is likely that differences in medication usage contribute to the heterogeneity in functional connectivity observed.

The cerebellum has been implicated in ASDs (Crippa et al., 2016; Stoodley et al., 2017) as well as in healthy aging (Boisgontier, 2015; Sjöbeck et al., 1999). Structural abnormalities of the cerebellum in ASDs are frequently observed (Fatemi et al., 2012; Rogers et al., 2013), accompanied by aberrant cerebro-cerebellar functional connectivity (Arnold Anteraper et al., 2018; Khan et al., 2015). We found no significant group differences in cortico-cerebellar connectivity nor correlations with age in the current study. However, we exclusively focused on connectivity within the sensorimotor system, and any potentially atypical cerebro-cerebellar connectivity outside motor circuits in older adults with ASDs was beyond the scope of the current study.

4.2 Brain-behavior links

High levels of fine motor skills (as measured by the BMAT) were associated with relatively lower connectivity between primary motor and somatosensory areas in the TC group, whereas this link was absent in the ASD group. The inverse relationship in the TC group (high performance with low connectivity), though seemingly counterintuitive, is consistent

with findings in healthy older adults. Fling and Seidler, 2012 reported a negative correlation between structural and functional connectivity of primary motor cortices in 65–76 year-old adults (n=15), and those with reduced functional connectivity were found to have better motor performance. In a study of 128 adults aged 18–80 years (mean 45.76 years), Solesio-Jofre et al. (2014) similarly found that decreasing interhemispheric functional connectivity of dorsal and ventral premotor areas with age was associated with better performance on a visuomotor task. The same research group subsequently trained a group of older (>60 years) and younger adults (<27 years) on a difficult bimodal tracking task (Solesio-Jofre et al., 2018). They observed that in the older adults training led to decreases in inter- and intrahemispheric resting state motor network connectivity, and that this reduction in connectivity was associated with improvements on the motor task. Conversely, in the younger group, improved task performance after motor training was related to *increased* functional connectivity.

Our findings in the TC group showing lower motor functional connectivity to be associated with better motor skills are consistent with these previous reports. However, no clear link between motor deficits and functional connectivity could be found in the ASD group. The absence of clear brain-behavior links suggests that underlying mechanisms might differ across ASD participants and, specifically, that the link found in TC adults (of lower sensorimotor connectivity being associated with better motor performance) did not apply to many adults with ASDs. Given the small sample size of our ASD cohort and a high degree of heterogeneity, however, the absence of associations between motor skills and functional connectivity of the motor system might also be explained by insufficient statistical power. Future studies with larger sample sizes are needed to determine those links.

4.3 Conclusions

Our findings in mid-age adults with ASDs show impairment across multiple motor subdomains and reduced functional connectivity within motor systems. This is potentially indicative of risk for accelerated decline within the motor system in ASD, or may be the direct outcome of early developmental deficits and concomitant or subsequent compensatory processes. These findings, in conjunction with increased heterogeneity of motor system connectivity in ASDs, and previous reports of elevated rates of parkinsonism (Croen et al., 2015; Starkstein et al., 2015), emphasize the importance of longitudinal monitoring of research participants (and clinical patients) and increasing sample size to determine if subgroups may be present that are at elevated risk of functional declines that could negatively impact quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Adults with Autism Spectrum Disorder show poorer motor function than typical adults
- Sensorimotor cortex functional connectivity is reduced in Autism Spectrum Disorder
- Sensorimotor cortex connectivity is more variable in Autism Spectrum Disorder
- No relationship between functional connectivity and motor skills

Figure 1.

A) BOLD time series correlations (Fisher z-transformed) between 10 ROIs of the sensorimotor system in TC adults (left) and in adults with ASDs (right). Warmer colors correspond to stronger positive correlations. Significantly reduced functional connectivity in the ASD compared to the TC group was observed between multiple ROI pairs, all involving primary motor cortex (* highlights significantly lower correlations in the ASD group, FDR-corrected for multiple comparisons). B) Diagrammatic brain rendering of ROIs and connections with significantly reduced functional connectivity.

Figure 2. Pattern similarity analysis. Similarity (average Fisher z-transformed correlation) of sensorimotor connectivity patterns within the TC group (blue, left), within the ASD group (red, middle) and when comparing each adult with ASD to the TC group (purple, right). Each dot shows the result for one participant, i.e. how similar connectivity patterns for this participant were (on average) to those of all other participants within their respective group (blue, red), or how similar an ASD participant's connectivity pattern was (on average) to those of all TC participants (purple).

Figure 3.
Correlations between motor skills (BMAT standard score) and sensorimotor (primary motor and primary somatosensory) intrinsic functional connectivity.

Table 1.

Participant demographics and group matching

	ASD (n=17)		TC (n=19)		t-value (p-value)
	mean (SD)	range	mean (SD)	range	
Age (years)	49.7 (6.6)	40.4–60.6	50.4 (6.3)	40.6–60.9	0.35 (.73)
TBV (cm ³)	1125 (93)	1070–1321	1162 (65)	876–1235	1.27 (.22)
RMSD	0.11 (0.05)	.04–.22	0.09 (0.05)	.05–.19	–1.14 (.26)
Volumes Censored (%)	0.69 (1.04)	0–3.88	0.38 (0.97)	0–4.13	–0.91 (0.37)
Years of Education	14 (2)	12 – 18	16 (2)	12 – 18	2.6 (0.02)
WASI-II					
Verbal	101 (29)	45–160	116 (16)	85–144	1.91 (.07)
Non Verbal	104 (24)	63–138	113 (11)	93–131	1.59 (.13)
Full Scale	102 (24)	57–147	120 (11)	102–139	2.74 (.01)
ADOS-2					
SA	10.6 (3.8)	(6–19)	--	--	--
RRB	3.5 (2.0)	(1–8)	--	--	--
Total	14.2 (4.2)	(8–23)	--	--	--
Female	n = 3		n = 1		1.29 (0.33) *

* Fisher's Exact Test

Table 2.

Group differences on the Bruininks Motor Ability Test (BMAT): ASD v. Control

Group	N	Standard Score **	Fine Motor	Manual Dexterity *	Coordination **	Balance & Mobility	Strength & Flexibility **
		<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>
ASD	17	441 (52)	6.5 (0.7)	6.0 (1.5)	4.1 (0.8)	4.3 (0.4)	6.5 (1.9)
TD	19	488 (20)	6.9 (0.3)	7.1 (0.6)	4.9 (0.3)	4.4 (0.4)	8.4 (1.0)

**
p<0.01*
p<0.05

Table 3.
Correlations Between Functional Connectivity and BMAT Scores (partial, controlling for age)

	Standard Score (p-value)	Fine Motor (p-value)	Manual Dexterity (p-value)	Coordination (p-value)	Balance (p-value)	Strength and Flexibility (p-value)
MIR-MIL	-0.18 (0.49)	-0.51* (0.03)	-0.16 (0.53)	0.04 (0.87)	0.06 (0.81)	-0.09 (0.71)
MIR-SIR	-0.58* (0.01)	-0.40 (0.10)	0.18 (0.48)	-0.23 (0.37)	0.36 (0.14)	-0.69* (0.00)
MIR-SIL	-0.48* (0.04)	-0.57* (0.01)	-0.04 (0.89)	-0.22 (0.39)	0.16 (0.52)	-0.45 (0.06)
MIR-PMAR	-0.57* (0.01)	-0.37 (0.14)	-0.18 (0.49)	-0.42 (0.09)	-0.23 (0.36)	-0.52* (0.03)
MIR-PMAL	-0.11 (0.66)	-0.10 (0.70)	0.06 (0.80)	-0.21 (0.41)	-0.20 (0.43)	-0.07 (0.79)
MIL-SIL	-0.48* (0.05)	-0.43 (0.08)	-0.14 (0.59)	-0.26 (0.29)	0.11 (0.68)	-0.45 (0.06)
MIR-MIL	0.17 (0.54)	-0.21 (0.43)	0.03 (0.90)	-0.17 (0.53)	-0.13 (0.64)	0.31 (0.24)
MIR-SIR	0.04 (0.89)	-0.20 (0.45)	-0.09 (0.73)	-0.33 (0.21)	-0.11 (0.69)	0.21 (0.43)
MIR-SIL	0.30 (0.27)	-0.07 (0.78)	0.06 (0.82)	-0.05 (0.87)	-0.01 (0.98)	0.40 (0.13)
MIR-PMAR	-0.17 (0.52)	-0.33 (0.22)	-0.29 (0.27)	0.03 (0.93)	-0.14 (0.60)	-0.16 (0.56)
MIR-PMAL	0.04 (0.87)	-0.26 (0.32)	-0.10 (0.70)	-0.09 (0.73)	-0.19 (0.47)	0.15 (0.58)
MIL-SIL	0.08 (0.76)	-0.10 (0.70)	-0.22 (0.40)	-0.10 (0.70)	-0.22 (0.42)	0.26 (0.34)

* p 0.05, uncorrected