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Neural Correlates of Visuomotor Learning in Autism

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Abstract

Motor impairments are prevalent in children with autism spectrum disorder (ASD). The Serial Reaction Time Task (SRTT), a well-established visuomotor sequence learning probe, has produced inconsistent behavioral findings in ASD. Moreover, it remains unclear how neural processes underlying SRTT learning in autism compare to processes for TD children. Neural activity differences were assessed using fMRI during a visuomotor sequence learning task in children with and without autism. Though there was no group difference on SRTT performance, underlying patterns of neural activation significantly differed when comparing sequence (i.e. learning) to random (i.e. non-learning) blocks. Children with autism demonstrated decreased activity in brain regions implicated in visuomotor sequence learning: superior temporal sulcus, and posterior cingulate cortex. The findings implicate autism-associated differences in brain mechanisms necessary to initial sequence learning and may help to explain behavioral observations of autism-associated impairments in skill development (motor, social, communicative) reliant on visuomotor integration.

Keywords

Motor Learning; Procedural Learning; Autism

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Disclosure Sections

Declaration of Conflicting Interests. Elizabeth Sharer, Deana Crocetti, John Muschelli, Anita Barber, Mary Beth Nebel, Brian Caffo, Jim J. Pekar, and Stewart Mostofsky have no conflicts of interest.

Introduction

Autism Spectrum Disorder (ASD) is a pervasive diagnosis defined by impairments in social reciprocity and communication as well as the presence of restricted repetitive behaviors[1]. Growing evidence demonstrates atypical motor functioning and development is not only prevalent in ASD but may be one of the earliest detectable signs, well before sociocommunicative deficits. Motor function difficulties in ASD are evident in infancy[2], persist through childhood and into adulthood[3–5], and effectively distinguish children with high functioning autism from typically developing (TD) controls as well as children with other developmental disabilities[6–8]. Motor impairments can have a significant negative impact on classroom and workplace performance and the ability to have adaptive social engagement[9].

Overlapping mechanisms may contribute to impaired development of motor, social, and communicative skills in ASD. Procedural learning, the process of implicit skill development through repetitive exposure and experience, underlies social, communicative, and motor skill acquisition[10,11]. Consistent with this model, the severity of motor impairments have been found to correlate with communicative and social deficits in children with ASD[4,5,12]. Converging evidence implicates anomalous bias for proprioceptive input over visual input which may be due to aberrant visuomotor connections[13–17]. Procedural learning strategies may be more explicit in ASD populations[18]. Atypical procedural learning may put complex skills necessary for adaptive social-communicative behavior at a developmental disadvantage.

Using a modified version of Nissen and Bullemer's[19] serial reaction time task (SRTT), a classic probe of procedural learning, we sought to characterize potentially anomalous motor sequence learning in children with ASD. Previous SRTT studies demonstrate ASD participants have impaired implicit motor sequence learning[10,20], although findings are not consistent throughout the field[18,21]. Even when behavioral findings indicate equitable performance, the active neural structures engaged in the SRT task can differ between groups[18,22,23]. Discrepancies across studies may reflect differences in *how* ASD participants perform the task, such as differential recruitment of neural resources and compensatory strategies, rather than overall ability, for acquiring motor sequences. We hypothesized that, with a younger cohort, the ASD group would demonstrate both impaired sequence learning and abnormal activation patterns during SRTT visuomotor learning.

Methods

Participants

fMRI SRTT data were collected on 17 children with ASD (14 male; mean age 10.52 ± 1.36 years SD; 13 right-handed, 3 left-handed, 1 mixed-handed) and 36 TD children (28 male; 10.63 ± 1.31 years SD; 30 right-handed, 2 left-handed, 4 mixed-handed). Handedness was determined using the Edinburgh Handedness Inventory[24]. Intellectual ability was assessed using the Weschler Intelligence Scale for Children, fourth edition[25] (WISC-IV). All children had a Full Scale IQ (FSIQ) of 80 or greater. The Perceptual Reasoning Index (PRI), a measure of the nonverbal abilities and subscale of the FSIQ, was used as a measure of

cognitive abilities. This is in line with recommendations to individualize the measures best suited for the participants to get an accurate estimate of their cognitive abilities[26]. Groups were balanced for age, gender, handedness, SES, and PRI. Only subjects with behavioral accuracy rates of at least 80% for each run and less than 25% of the image volumes surpassing 3 degrees rotational motion and 3 mm translational motion were included in these analyses.

All participants included in the ASD group met diagnosis for autism as determined by a clinician using DSM-IV[1]. In addition, diagnoses were confirmed using clinical insight and either Autism Diagnostic Observation Schedule – Generic[27] (ADOS-G) module 3 or Autism Diagnostic Interview – Revised[28] (ADI-R). 7 subjects completed the more recent Autism Diagnostic Observation Schedule – Second Edition[29] (ADOS-2) instead of the ADOS-G. To create comparable ADOS total scores, two additional categories from the ADOS-G were assessed on these 7 subjects and the amount of reciprocal social communication was not included in the calculation of the ADOS total score.

No participants in either group presented or had a history of intellectual disability, seizure or other neurological disorder, chronic medical disorders, genetic disorders, or psychotic disorders. Psychopathology was assessed using the Diagnostic Interview for Children and Adolescents-IV[30], parent version (DICA IV). TD children were additionally screened for speech and language disorder and a family history of first-degree relatives with autism spectrum disorder. ADHD diagnosis was based on DSM-IV criteria using the DICA-IV. Additional assessments for ADHD symptoms were administered including the Conner's Parent and Teacher Rating Scales – Revised[31], Long Version (CPRS-R and CTRS-R) and the ADHD rating scale – IV[32], home and school versions (ADHD-RS). Participants must have all three to meet criteria for comorbid ADHD: 1). an ADHD diagnosis from the DICA, 2). a T-score of 60 or higher on inattentive scale (L) and/or hyperactive-impulsive scale (M) from either CPRS-R or CTRS-R, and 3). an endorsement of 2 or 3 on 6 out of 9 inattentive and/or hyperactive-impulsive symptoms from the ADHD-RS. Final confirmation was based on clinical judgment of the investigators. In the ASD cohort, 8 met criteria for combined type ADHD and 4 met criteria for inattentive type ADHD. 2 children with ASD met OCD diagnosis and 3 children with ASD met ODD diagnosis based on DSM-IV criteria using the DICA-IV.

No TD participants were on prescribed psychotropic medications. 8 of the 17 children in the ASD cohort were on psychotropic medication. To avoid effects on cognitive and behavioral measures, stimulant medications were discontinued the day prior to and day of testing. Participants were allowed to continue treatment with other psychotropic medications that would normally require a longer washout period, for both ethical and practical reasons. Table 1 contains demographic information for diagnostic groups.

Participants were recruited using advertisements posted in local pediatricians' and psychologists' offices, local schools, social service organizations, chapters of the Autism Society of America, the Interactive Autism Network database, outpatient clinics at Kennedy Krieger Institute, and word of mouth. This study was approved by the Johns Hopkins

Medical Institutional Review Board. Written consent was obtained from a parent or legal guardian and verbal assent was obtained from the participating child.

The Serial Reaction Time Task

A modified SRTT was performed by all participants during fMRI data acquisition. Tasks were introduced to participants as reaction time tests. Visual cues appeared at one of four horizontally arranged positions during each individual trial (Figure 1). Subjects were instructed to press the corresponding response button as quickly as possible using a separate finger, both left and right index and middle fingers, for each key. Stimuli were presented for 75 milliseconds followed by a 75 millisecond intersimulus interval. Participants performed three runs of the SRTT task. Before and after each run participants attended a cross-hair fixation and ceased responding for 5 seconds of rest. Each run contained 5 task blocks separated by a 25 second rest block. Within a task block, cues were presented in either a pseudorandom sequence or a patterned sequence. The sequence was not explicitly told to the participant. Blocks 1 and 5 had 24 pseudorandom trials. Blocks 2–4 used an 8-trial sequence pattern (1-3-4-2-3-2-1-4, where 1 is the furthest left position) repeated 5 times for a total of 40 trials (Figure 2). Reaction time and response accuracy were recorded.

A projector was used to rear-project stimuli onto a translucent plastic screen behind the participant while in the scanner. The participant was able to see the screen using a mirror attached to the head coil. Participants made their responses on a fiber optic button response system that had four buttons for the left-hand and right-hand middle and index fingers. Participants pressed the left middle finger for the stimuli appearing in position 1, left index finger for stimuli appearing in position 2, right index finger for stimuli appearing in position 3, and right middle finger for stimuli appearing in position 4. The task was coded, performed and recorded using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

fMRI acquisition and processing

Images were acquired at Kennedy Krieger Institute's Kirby Research Center for Functional Brain Imaging on a Philips 3T scanner using an 8-channel head coil. A highresolution anatomical scan (MPRAGE, TR=7.99 ms, TE=3.76 ms, FA=8°) was acquired for image co-registration, segmentation and normalization processing steps. Three functional scans were acquired in each participant for 6 minutes and 6 seconds (2D-SENSE EPI, TR=2500 ms, TE=30 ms, FA=70°). Preprocessing of functional images was performed using Statistical Parametric Mapping Software (SPM8) and Matlab including ascending slice time correction, motion correction, co-registration, segmentation, and normalization.

Data Analysis

Behavioral Analyses—Reaction time was recorded for each trial of the experiment using E-Prime 2.0 Software (Psychology Software Tools, Pittsburgh, PA). Trials that fell below 200 milliseconds (0.014% of trials) were removed to eliminate anticipatory errors. Every subject's median reaction time was used to summarize performance in the each random and sequence block while being resistant to outlier reaction times due to attention lapses. A group average for the median correct reaction time characterized each block.

Learning occurs when reaction time decreases in sequenced trials across time and increases, or rebounds, upon the reintroduction of random trials. Rebound disambiguates sequence specific learning from general task adaptation. Learning was initially assessed two ways. Mixed factor repeated measures ANOVAs were used to examine if the two groups differed in their reaction time changes during sequence blocks across runs. Paired t-tests were used to assess rebounds in reaction time between the last sequence block and the last random block within each run. Visual inspection revealed a potential confound introduced by the study design. Immediately following a rest block the reaction times decreased significantly. This calls into question the sensitivity of the rebound metric for learning within this paradigm. Each sequence block was trimmed to be an identical length as the random blocks. An additional mixed factor repeated measure ANOVA was performed to assess how the effect of run on performance during random blocks and sequence blocks differed.

Imaging Analyses—The brain activation data were analyzed using SPM8. First-level general linear models were generated for every subject and included a regressor for each sequence and random block. Each of these regressors was convolved with the canonical hemodynamic response function. Second-level, one-sample t-tests were performed across participants to produce group-level activation maps for each sequence and random block. Statistical maps were superimposed on normalized T1-weighed images. Visuomotor learning was examined using a block design contrast between the sequenced and random blocks. These analyses identified voxels that were significantly more active with the presence of an implicit sequence movement pattern as opposed to random movements. Analyses were conducted both across runs and within each run. Between-group contrasts (ASD vs. TD) were modeled using t-test comparisons. The statistical significance of voxel-wise activation was determined at an uncorrected height threshold ($p<0.001$) with an extent threshold of 30 voxels. Both within- and between-group contrast clusters were selected at a . 05 p-value (FWE-corrected).

Results

Groups were balanced for age ($t(51)=-0.299$, $p=.766$, $d=-0.084$), gender ($X^2(1)=0.825$, $p=0.306$, $\phi=0.113$), handedness ($t(51)=-0.823$, $p=.414$, $d=-0.231$), SES ($t(50)=-0.675$, $p=.503$, $d=-0.191$) and PRI ($t(51)=-1.922$, $p=0.060$, $d=-0.538$). Average reaction time across the entire task did not differ between groups ($t(20.566)=-0.952$, $p=.352$, $d=-0.420$) nor did the first random block prior to sequenced motor pattern introduction ($t(21.091)=-0.708$, $p=.487$, $d=0.308$). Accuracy rates did not significantly differ between groups. Because subjects had high levels of accuracy to begin with further analysis examining improvement of accuracy rates was not performed.

Behavioral analysis across diagnostic groups revealed a significant effect of run on sequence block reaction time ($F(2,102)=20.848$, $p<.001$, $d=1.377$). Post-hoc analysis revealed a significant effect of block within the first run alone (Run 1: $F(2,102)=3.248$, $p=.043$, $d=0.543$; Run 2: $F(2,102)=2.219$, $p=1.114$, $d=.447$; Run 3: $F(2,102)=.570$, $p=.568$, $d=.226$). There was no significant effect of diagnosis on reaction time either across runs ($F(1,51)=1.204$, $p=.278$, $d=0.331$) or across blocks within runs (Run 1: $F(1,51)=0.874$, $p=.354$, $d=0.282$; Run2: $F(1,51)=1.512$, $p=.224$, $d=0.371$; Run 3: $F(1,51)=1.073$, $p=.305$,

d=0.312) on sequence block performance. There was no interaction of diagnosis and run (F(2,102)=0.153, p=.858, d=0.118) or block (Run 1: F(2,102)=0.436, p=.648, d=0.199; Run2: F(2,102)=1.285, p=.281, d=0.342; Run 3: F(2,102)=0.147, p=.863, d=0.116) on performance. Separate analyses for each diagnostic group revealed a significant effect of run within both the ASD group (F(2,102)=7.994, p=.002) and the TD group (F(2,102)=16.732, p<.001).

However the second metric of learning, the rebound effect, observed in the ASD group (Rebound 1: t(16)=0.992, p=.336, d=0.496; Rebound 2: t(16)=0.688, p=.501, d=0.344; Rebound 3: (t(16)=−1.141, p=.271, d=0.5705), it was also not replicated in the TD group (Rebound 1: t(35)=0.890, p=.380, d=0.301; Rebound 2: t(35)=−0.733, p=.468, d=−0.248; Rebound 3: (t(35)=1.059, p=.297, d=0.358). Visual inspection of reaction time changes across the task revealed that performance during the first 16 trials immediately following each rest block was notably faster than the remaining trials. There was a strong rest effect as demonstrated by the significant main effect of early versus late trial location across blocks on performance (F(1,51)=55.232, p<.001, d=2.241). With different proportions of random and sequence trials sped up by the rest we trimmed the sequence blocks to have proportional rest effect on the trials. Using these measures to summarize performance, there remained an effect of run on sequence performance (F(1.603,102)=16.783, p<.001, d=1.235). Furthermore there was a significant interaction of run on the two different conditions effectively differentiating general task learning from visuomotor pattern learning (F(2,102)=3.322, p=.040, d=0.549). Sequence reaction time reduced significantly from run 2 to run 3. Random reaction time reduced significantly early on in the task, from run 1 to run 2.

Within group imaging analysis demonstrated regions previously related to visual and motor integration were elicited in the sequence-random contrast. Clusters that were significantly more active during the sequence block compared to the random block include left fusiform gyrus (p=<.001, cluster size (k)=2409 voxels), left and right superior temporal sulcus (STS) (L: p<.001, k=538; R: p<.001, cluster size (k)=1574 voxels), left supramarginal gyrus (p<.001, cluster size (k)=249 voxels), left cerebellar tonsil (p=.002, cluster size (k)=109 voxels), right inferior occipital gyrus (p<.001, cluster size (k)=2345 voxels), right precuneus (p<.001, cluster size (k)=606 voxels), right middle frontal gyrus (p<.001, cluster size(k)=473 voxels), right uvula (p=.001, cluster size(k)=115 voxels), right inferior frontal gyrus (IFG) (p=.011, cluster size(k)=79 voxels), right and left culmen (p=.014, cluster size(k)=75 voxels), and right putamen (p=.018, cluster size (k)=72 voxels), in the TD cohort and the left inferior occipital gyrus (p<.001, cluster size(k)=290 voxels), anterior cingulate cortex (p=.027, cluster size(k)=66 voxels), and right middle occipital (p=.003, cluster size(k)=99 voxels) in the ASD cohort.

The imaging analysis revealed a significant effect of diagnosis on the sequence-random contrast. Peak activation MNI coordinates are reported in Table 2. Children with ASD showed less activation in the STS (p=.001, cluster size(k)=112 voxels) and right posterior cingulate cortex (PCC) (p=.013, cluster size(k)=77 voxels) compared to TD peers across all runs (Figure 3). Within run 1 the right STS (p<.001, cluster size(k)=265 voxels), right inferior parietal lobule (IPL) (p<.001, cluster size(k)=160 voxels), right IFG (p=.003, cluster

size(k)=101 voxels; p=.005, cluster size (k)=92 voxels), and right superior frontal gyrus (SFG) (p=.012, cluster size(k)=78 voxels) were recruited to a significantly lesser degree in children with ASD than those who were typically developing (Figure 4). No group differences were found in later runs and there was no neural activation greater in the ASD children compared to TD peers in the sequence v. random contrast.

Discussion

Consistent with findings from a number of prior neuroimaging studies using the SRTT, children with and without ASD both recruited a network of regions associated with visuomotor sequence learning, including clusters spanning the STS, MTG, and STG, as well as the occipital cortex[18,33]. Learning was observed in both groups at the behavioral level; however, significant group differences were present in the underlying patterns of neural activation when comparing sequence (i.e, learning) to random (i.e, non-learning) blocks. Children with ASD demonstrated reduced activity, as compared to TD peers, in the STS and PCC, regions known to be important in visuomotor control and sequence learning[34], and which have been found to be show atypical function in ASD.

After further breaking the task into three sections, group differences were found to be specific to the first run. Children with ASD demonstrated decreased activity across a wider network that again included STS and IPL, and also included IFG and SFG. This comparative reduced activity in children with ASD suggests that these children do not engage in the initial sequence learning in the same manner as TD children and may help to explain behavioral observations of autism-associated impairments in visuomotor learning

The STS, broadly, is a higher association area where sensory information converges[35–39] and form and motion integrate[36,40]. Though engaged during action observation, it is a higher-order perceptual region, and is not involved in action execution beyond the initial observational “pictorial” description of the motion[41]. The STS has been proposed to parse sequences of inputs in both language and social domains, with the strongest activation occurring for meaningful representations[42]. Our findings, which reflect a more active STS during visuomotor sequence learning block compared to the random sequence block, would fall in line with the proposed underlying STS function. The STS has been implicated as aberrant in individuals with ASD[43]. Studies of biological motion[44,45], meaningful speech[46,47], and mentalizing[48–51] demonstrate individuals with ASD have both reduced STS activity and worse task performance. The underutilitzation of this cortical region in children with ASD could reflect an atypical strategy to learn visuomotor sequences, which could have a strong impact on development of skills important to socialization and communication.

The PCC is involved in a number of cognitive functions relevant to visuomotor learning, including spatial memory[52], visuospatial characteristics of objects[53,54], and successful memory retrieval[55]. This region is heavily interconnected and is involved with the default mode network[56], dorsal attention network[57], and the frontoparietal control network[58]. Increased PCC activity has been associated with memory retrieval and planning[59,60] and may be involved in attending to changes in internal and external environments and in

facilitating novel behavior in response to those changes[61,62]. Individuals with ASD show abnormal functional PCC response[63] and demonstrate reductions in functional PCC connectivity[64]. Abnormalities in posterior cingulate responses during interpersonal interaction correlate with the severity of autistic symptoms[65,66]. Furthermore ASD is associated with structural and metabolic abnormalities of the PCC[67,68]. Thus the atypical functional response during initial SRTT learning could indicate atypical monitoring of environmental changes to inform behavioral choices that would easily impact the quality of procedural learning and thus motor, social, and communicative skills.

The IPL and IFG are highly integrated nodes necessary to forming and maintaining linked perception-action representations of skilled behavior. As relevant to praxis, this network has long been recognized as being crucial to the formation and production of gestures, including those involved in socialization and communication[69,70]. More recently, the IPL and IFG have been highlighted as being core to the mirror neuron system (MNS) coordinating imitation[71,72]. This network has thus been implication in action knowledge, motor planning, visual-motor learning, sensorimotor integration during movement control, and the imitation and spontaneous production of gestures[69,70,73–76]. Notably individuals with ASD have cortical thinning of the IPL and IFG[77]. Given the robust evidence for autism-associated impairments in praxis and motor imitation[5,12,78,79], it has been proposed that deficiencies in IPL-IFG under-connectivity in individuals with ASD may contribute to impaired formation of internal action models necessary to development of a range of skilled behaviors, including those necessary to motor, social, communicative functions[80].

Contrary to our hypothesis and previous findings in a population of ASD children[10,20], but in line with past adult ASD SRTT literature[18,22,23], both groups performed equitably on the SRTT. Visuomotor learning was demonstrated through a reduction in reaction time across the sequence patterned blocks and differentiated from general task adaptation through a different rate of reaction time reduction. Behavioral analyses revealed no effect of diagnosis on SRTT performance and thus groups had similar visuomotor learning.

The effect of rest confounded a large proportion of trials. Rebound effect, the gold standard of SRTT visuomotor learning, was not a sufficiently sensitive learning metric given the context of the data. Nevertheless there was an interaction of condition type and run on performance indicating that despite the rest effect we could demonstrate task adaptation was occurring in parallel with visuomotor pattern learning and the rate of gains differed therefore visuomotor sequence learning could be differentiated from general task adaptation. It would be advisable in the future to take the effect of rest into account when modifying the SRTT into an fMRI block design. Longer random blocks to offset those effected by rest and comparable to sequence blocks would be advised.

Procedural learning occurs outside conscious awareness. The SRTT can be performed with an explicitly defined sequence the participant is aware of or an implicitly defined sequence the participant is not aware of. Explicit learning and implicit learning occurs at different rates and though, there is great overlap, there are some structural differences in neural recruitment during task. The results may indicate the TD cohort leverages certain areas to a greater degree during sequence blocks. However data about explicit recall after the MRI

SRTT was never recorded. Therefore, we do not know how aware of the sequenced patterns the children were or if there was a group difference.

In summary, we found that while TD children and children with ASD demonstrated similar SRTT learning at the behavioral level, there were significant differences in neural recruitment during visuomotor learning, particularly within the initial stages of this learning process. Measures of task based connectivity could further elucidate visuomotor recruitment. Future study would benefit from methods to better isolate whether implicit and explicit learning strategies were being utilized in which groups. Isolating the kind of feedback received, either visual-based or motor-based, could also help to better inform whether attentional biases during the visuomotor learning, as indicated in certain paradigms, could explain the differential neural recruitment during the task. Disclosure Sections

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Figure 1.
Stimuli Presentation. Visual cues appear and the subject presses the corresponding response button.

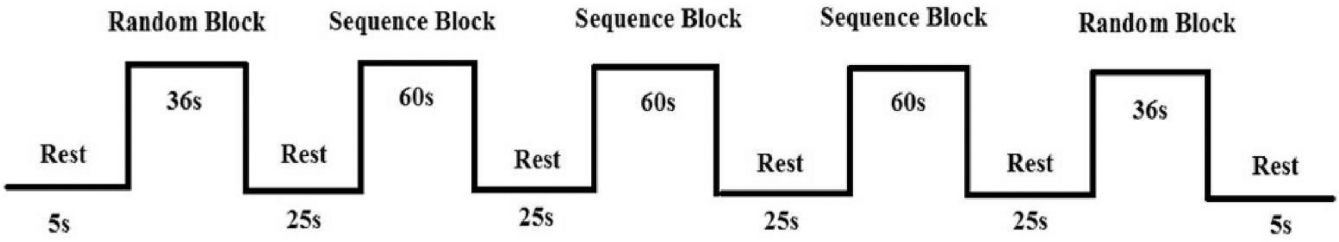

Figure 2.

Experimental design for the SRTT. Each run of the SRTT has 5 task blocks: 3 sequence blocks and 2 random blocks. Rests are interspersed between each task block and after each run.

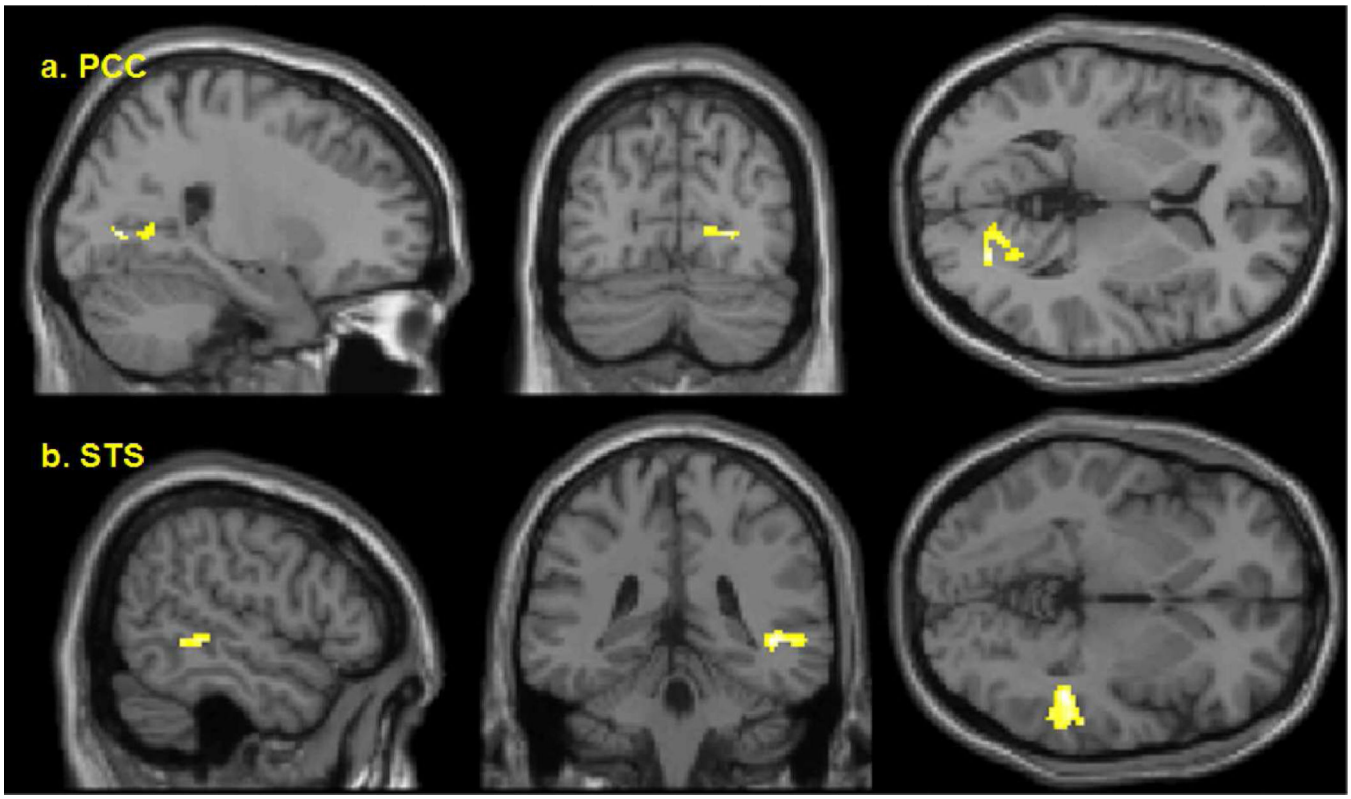

Figure 3.
Between group comparisons of sequence – random contrast across runs.

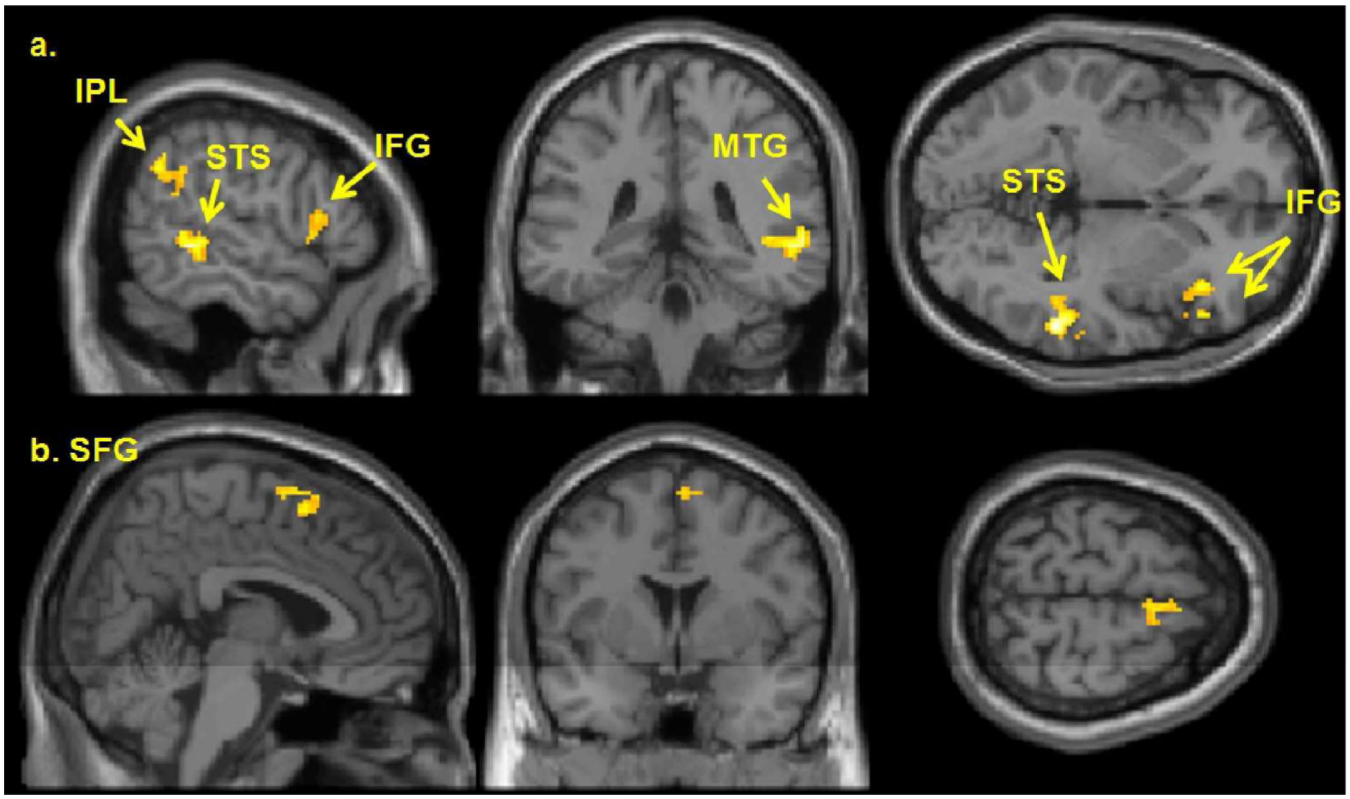

Figure 4.
Between group comparisons of sequence – random contrast within run 1.

Table 1

Participant Characteristics. The high functioning autism spectrum disorder (ASD) group and the typically developing group (TD) group were matched on gender, age, social economic standing (SES), and the Weschler Intelligence Scale for Children, Fourth Edition, Perceptual Reasoning Index (WISC-IV PRI).

Participant Characteristics					
	ASD (N = 17)		**TD (N = 36)**		**p**
Gender (M/F)	**15**	**2**	**28**	**8**	**0.825**
	Mean	**SD**	**Mean**	**SD**	**p**
Age	10.52	1.362	10.64	1.31	0.776
Handedness Integer	0.5353	0.61826	0.6708	0.53085	0.414
SES	52.71	7.981	54.33	8.197	0.503
FSIQ	103.5882	12.1761	116.8056	12.1557	0.001
PRI	107.5294	15.21971	115.2778	12.9498	0.06
VCI	107.5882	13.2432	119.4167	13.94351	0.005
WMI	100.7647	14.83884	112.527	14.83719	0.01
ADOS Total	14.6471	3.56968	-	-	-
Communication Subscale	3.7059	0.68599	-	-	-
Social Interaction Subscale	8.0588	2.22122	-	-	-
Conner's					
Inattentive Symptoms	72.2353	11.73419	44.8056	4.9154	<.001
Hyperactive/Impulsive Symptoms	66.7647	12.37704	46.6111	5.19493	<.001
ADHDRS					
Innattentive TScore	6.8235	2.00734	0.1111	0.39841	<.001
Hyperactive/Impulsive TScore	3.7059	2.66375	0.0833	0.3 6839	<.001
ADHD subtype					
Combined	8		-		-
Hyperactive/Impulsive	0		-		-
Inattentive	4		-		-

FSIQ – Full Scale IQ. VCI – Verbal Communication Index. WMI – Working memory index. ADOS – Autism Diagnostic Observation Schedule. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). The Weschler Intelligence Scale for Children, Fourth Edition (Weschler, 2003) was used to determine FSIQ, VCI, WMI, and PRI. Conner's Parent and Teacher Rating Scales – Revised, Long Version (CPRS-R and CTRS-R) (Conners, Sitarenios, Parker, & Epstein, 1998) and the ADHD rating scale – IV, home and school versions (ADHD-RS) (DuPaul, Power, Anastopoulos, & Reid, 1998) were used to characterize inattentive and hyperactive/impulsive symptoms.

Table 2

Between group comparisons of sequence – random contrast across runs and within run 1.

Peak Activation MNI Coordinates					
Region	**X**	**Y**	**Z**	**p-value**	**cluster size (k)**
ASD Sequence - Random	Thresholds: Voxel p > 0.001; Cluster p_{fwe} > 0.05				
Left Inferior Occipital Gyrus	−42	−82	−6	<0.001	290
Right Middle Occipital Gyrus	28	−90	−4	0.003	99
Left Anterior Cingulate	−16	44	−2	0.027	66
TD Sequence - Random					
Left Fusiform Gyrus	−38	−68	−12	<0.001	2409
Right Inferior Occipital Gyrus	36	−80	−12	<0.001	2345
Right Superior Temporal Sulcus	48	−36	−2	<0.001	1574
Right Cerebellum - Precuneus	2	−54	36	<0.001	606
Left Superior Temporal Sulcus	−46	−30	−8	<0.001	538
Right Middle Frontal Gyrus	46	16	30	<0.001	473
Left Supramarginal Gyrus	−54	−58	26	<0.001	249
Right Cerebellum - Uvula	26	−80	−36	0.001	115
Left Cerebellum - Cerebellar Tonsil	−10	−52	−42	0.002	109
Right Inferior Frontal Gyrus	16	16	8	0.011	79
Right/Left Cerebellum - Culmen	4	−36	−26	0.014	75
Right Putamen	34	20	−16	0.018	72
ASD < TD Sequence - Random					
Right Superior Temporal Sulcus	46	−38	−2	0.001	112
Right Posterior Cingulate Cortex	24	−72	4	0.013	77
ASD < TD Sequence - Random Run 1					
Right Superior Temporal Sulcus	49	−38	−2	<0.001	265
Right Inferior Parietal Lobule	56	−54	34	<0.001	160
Right Inferior Frontal Gyrus	38	26	−4	0.003	101

Region	Peak Activation MNI Coordinates			p-value	cluster size (k)
	X	Y	Z		
Right Inferior Frontal Gyrus	52	28	−2	0.005	92
Right Superior Frontal Gyrus	6	4	66	0.012	78