Cognitive and Brain Measures in Middle-Aged Autistic Spectrum Disorder Individuals: Where are the Differences?

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Abstract

Introduction: As the aging ASD cohort becomes larger, there continues to be a paucity of research to assess their needs. This study is the beginning of one of the first longitudinal cognitive and brain studies in aging ASD. We hypothesized that the older ASD group would show change in brain structure and function that will match lower performance on frontal lobe-dependent cognitive measures.

Methods: We examined 16 ASD and 17 age-matched typically developing individuals from ages 40 to 65. All subjects completed cognitive testing. Structural MRI scans, diffusion tensor images, and Functional MRI were obtained. Working memory, fluency, and visual search tasks were obtained.

Results: Group analyses showed that the ASD cohort had thinner cortex in the frontal lobe and smaller volumes of the hippocampi, cerebellum white matter, and corpus callosum. The ASD group had decreased white matter integrity throughout the hippocampus, corpus callosum, and cerebellum, as well as greater frontal and parietal lobe activation during EF tasks and reduced resting-state DMN connectivity.

Conclusion: Our results supported our hypothesis that differences in older adults with ASD as measured by white and gray matter volumes, structural and functional connectivity, and cognitive data often center on the frontal lobe.

Introduction

Autism spectrum disorder (ASD) is characterized by impairments in social communication as well as restricted, repetitive behaviors and/or interests [1]. The spectrum is extremely diverse among individuals, encompassing various developmental symptoms and neurological differences, which can plague independence and quality of life [2]. In the past 30 years, the cohort of older adults with ASD has grown substantially; however, there remains little research to assess their needs.

Knowledge Gap for Aging ASD

Individuals with ASD often experience compromised cognitive functioning. In particular, individuals with ASD often struggle with executive functioning (EF), which includes cognitive skills vital to living an independent and productive life, such as working memory, inhibition, and set shifting, and is largely supported by the frontal lobe (FL), the most anterior region of the brain [3]. Interestingly, EF deficits are also a hallmark of normal cognitive aging [4], which makes determining if aging ASD individuals incur reduced EF abilities beyond what has been observed in normal aging a very important question [5, 6]. To date, Geurts and Vissers (2012) is the only published study investigating cognitive functioning in an elderly ASD cohort. Compared to healthy typically developing (TD) individuals, the ASD group had reduced EF in domains of attention, working memory, and fluency. A gold standard instrument for detecting executive functioning deficits is the Wisconsin Card Sorting Task (WCST). The WCST requires intact EF abilities across three skills: working memory, response inhibition, and set shifting, making it one of the most robust instruments in detecting EF deficits in ASD and normal aging cohorts [8, 9]. However, because Geurts and Vissers (2012) used a modified version of the WCST that is less sensitive, a comprehensive understanding of EF deficits among aging ASD

individuals is still unknown [7]. Further, there are no publications to date which have evaluated cognition and related brain function and structure in older adults with ASD.

Background Research

A common neurobiological underpinning for EF deficits observed in both ASD and normal aging individuals is compromised FL function [3]. As a part of normal aging, the brain undergoes cortical thinning which follows an anterior-to-posterior gradient of severity, with the FL often being most affected [10]. Due to the anterior-to-posterior gradient of age-related brain changes, white matter integrity reductions are also preferentially found in the FL[11]. Additionally, the brain exhibits functional age-related changes such as hypoconnectivity – a decrease in correlated neural activity across brain regions [15]. Also following along an anterior-to-posterior gradient, age related hypoconnectivity is often found to be disconnected relationships between FL and posterior regions [15]. Additionally, decrements in connectivity have implications for impaired attention, memory, and EF [15]. But to date the impact of brain aging in ASD is still largely unknown.

Gray matter, white matter, and functional connectivity abnormalities within the FL have been observed in infant to young adults with ASD [11, 16]. Several studies have found early brain overgrowth in ASD, often showing gray and white matter volume in the FL to be larger in ASD than TD children [11, 17]. Functionally, young adults with ASD show differences in brain activity when performing EF tasks. Functional magnetic resonance imaging (fMRI) provides a non-invasive means of measuring brain activity through the hemodynamic response of blood as it flows to neuronally "activated" regions of the brain. In recent years, fMRI has rapidly become the popular instrument for ASD studies [23]. Through various tasks, fMRI provides an understanding of the correlation between behaviors and neural activity of ASD individuals [24]. In an analysis of neural correlates and brain activation, Schmitz et al. (2006) found that adult ASD

individuals experienced greater activation of the frontal and parietal lobes during EF tasks [25]. Through several neuroimaging modalities, there appears to be an anterior to posterior gradient of brain abnormalities in ASD as well and this may explain why the pattern of difficulties in young adult individuals with ASD mirror those observed in late mid-aged TD [19]. Interestingly, cognitive functions subserved by posterior regions, such as semantic memory, remain intact in high-functioning ASD [11]. In fact, some functions of the most posterior region, such as local search within the visual cortex, are actually enhanced [20, 21, 22]. Taken together, an important question which remains to be answered is whether the ASD brain, which mirrors many brain changes associated with normal aging, is more vulnerable to the aging process.

Significance

There is 1) a dearth of knowledge concerning the effects of cognitive and brain aging for individuals with ASD, and 2) concerning parallels of cognitive and brain function between normal aging individuals and young adults with ASD that make the need to study this aging population imperative. For example, the Autism Brain Imaging Data Exchange contains only 16 ASD and 15 TD participants over the age of 39, totaling only 2.8% of the entire repository [29]. This study hopes to contribute more data to the ABIDE repository to advance future aging ASD research and be the first to follow older adults longitudinally, evaluating cognition and brain structure and function. Neuroimaging and behavioral data collectively are vital in the understanding of age-related changes in localized areas of the brain, as well as the consequences of regional brain dysfunction in ASD individuals. In addition, this study aims to make innovative advancements for the care of older adults with ASD. As the ASD population continues to grow, there is a need to progress treatment plans in order to maximize the quality of life.

Hypothesis

The main goal of this study is to determine whether older adults with ASD exhibit reduced cognitive functioning and increased brain degeneration, as compared to age-matched TD. It was hypothesized that the ASD individuals would demonstrate reduced EF but intact cognitive abilities such as semantic memory and visual search. Regarding brain integrity and function, we hypothesized that the ASD individuals would exhibit FL differences as measured by greater cortical thinning, reduced white matter integrity, hypoconnectivity, and overactivation during EF tasks.

Methods

Demographics

A total of 16 high-functioning ASD and 17 TD participants who were right-handed and between the ages of 40 and 65 years old were recruited from a local autism center for this study. All ASD subjects were diagnosed using gold-standard diagnostic assessment (Autism Diagnostic Observation Schedule [30]). Brief intellectual assessments (Kaufman Brief Intelligence Test 2nd edition [35]) were given in order to IQ match the ASD and TD subjects.

Cognitive Tasks

In addition to analysis of biological neural correlates, all of the participants completed neurocognitive testing. The WCST provided a primary measure of interest and was evaluated in both TD and ASD participants to detect EF deficits. Further analyses of EF and other cognitive abilities were evaluated using exploratory tests (Tower of London [36], Trails A and B [37], Controlled Oral Word Association Task [COWAT] [38], Categorical Fluency [39], Visual Reproduction subtest of the Wechsler Memory Scale-III [WMS Figure][54].Other tests given as "control tasks", which have not been previously shown to be impacted by ASD, were the Rey Auditory Verbal Learning Test [40], Embedded Figure Test [41], and Wechsler Adult Intelligence Scale-III [WAIS-III] Vocabulary [42]. A subset of participants (n=15) also performed a finger

oscillation test[53]. Scores were imported into Statview (Cary, NC, SAS Inc.), and groups were compared via t-test. Significance was set at $p \leq 0.05$ and effects of $p < 0.10$ were interpreted as trends for all t-tests.

Magnetic Resonance Imaging Parameters and Preprocessing

A 3-Tesla Philips Ingenia magnetic resonance imaging (MRI) scanner with maximum gradient strength of 45 mT/m was used to capture MRI data. We collected a high-resolution, T1-weighted anatomical scan (3D magnetization prepared rapid acquisition gradient echo [MPRAGE] 256×256 in-plane resolution, 240 mm FOV; 170 sagittal slices 1.2 mm) for gray matter thickness and volumetric analyses. Diffusion tensor images (DTI) were obtained for evaluation of white matter tract integrity; diffusion weighting was obtained along 32 directions using a b-value of 2500 s-mm^2 (48, 2-mm thick axial slices). Gradient-echo echo-planar images were collected to map brain activation by the blood-oxygen-level dependent (BOLD) response for resting state and task-based fMRI with TE (echo time) = 25 ms, TR (repetition time) = 3000 ms, flip angle=80°, 24 mm FOV, 64×64 in-plane resolution, with 3-mm-thick slices covering the entire brain. Following the completion of the fMRI scans, images were realigned, normalized, smoothed, and groups were compared, using statistical parametric mapping (SPM; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) in Matlab. For all imaging analyses, significance was set at a peak voxel threshold of $p < 0.001$ and an extent threshold of 30 voxels.

Task-Based fMRI

Participants performed three fMRI tasks -- the N-back, Fluency, and Embedded Figures Tasks. Participants performed each task twice (Runs A and B) in counterbalanced order.

The N-back task evaluated working memory, and has been used in young adult ASD and TD-aging studies [43]. This study used the 0-Back, 1-Back, and 2-Back conditions. In 0-Back,

participants responded by a button press when the letter on the screen matched a pre-specified letter. In 1-Back and 2-Back conditions, participants were required to press a button corresponding to the same letter seen "N" passes ago. Working memory load comparisons were made by the 2 vs. 0 and 1 vs. 0 contrasts. Reaction time and accuracy were recorded.

The Fluency task has also been used in young adult ASD and TD-aging studies [44]. This task required participants to generate words starting with a letter on the screen and then indicating the word generation with a button press. Comparisons were made by the word generation vs. resting contrast.

The embedded figures task (EFT) is a visual search task. This study used an EFT task conducted in a previous young adult ASD study [22]. EFT required participants to decide whether a target figure is embedded in a more complex figure placed next to it. Reaction time and accuracy were recorded. Comparisons were made between the visual search vs. resting contrast.

Resting State Functional Connectivity

While in the scanner, participants were asked to close their eyes and clear their minds for six minutes. Through a whole-brain voxel-wise approach, group independent component analysis (ICA) for fMRI Toolbox (GIFT; http://icatb.sourceforge.net) was used to decompose data into components. Components were then spatially sorted using a default mode network (DMN) template [45]. The DMN was chosen to assess the hypothesis of anterior-to-posterior hypoconnectivity in the ASD group because it contains relevant nodes involving long-range connections, including to/from the FL.

White Matter Analysis

The measure of interest from DTI was fractional anisotropy (FA). All FA scans were preprocessed, normalized, smoothed, and masked with each individual's white matter as measured by Voxel-Based Morphometry (VBM8) in MATLAB.

Cortical Thickness and Regional Volumes

Cortical thickness and regional brain volumes were measured via Free-Surfer automated parcellation (surfer.nmr.mgh.harvard.edu/). Values were then imported into Statview and groups were compared via t-test.

Results

Demographics and Cognitive Results

The participants were well matched according to age [$t(31)=0.02$; $p=0.98$] with no differences in education [$t(30)=1.06$; $p=0.29$] and IQ [$t(31)=1.37$; $p=0.178$] . For the cognitive tests, the ASD participants made more errors on the WCST [$t(31)=2.09$; $p<0.05$]. In addition, the ASD cohort showed slower performance on Trails A [$t(31)=0.02$; $p=0.05$], and named fewer colors during Stroop 1[$t(31)=2.41$; $p<0.05$]. ASD participants also showed a trend for slower finger tapping [$t(13)=1.84$; $p=0.089$] (Table 1).

fMRI Task Behavior

Two ASD participants were unable to be scanned and thus were not included in any neuroimaging analyses. For the Fluency task, ASD individuals showed a trend towards generating fewer words [$t(29)=1.74$; $p=0.09$]. TD participants were slightly more accurate during the N-back tasks, although both groups averaged over 90% accuracy [$t(29)=2.15$; $p=0.04$] (Table 1).

fMRI Task BOLD Results

Due to slightly different performance on the N-back and Fluency tasks, covariates of accuracy and words generated were added to the analysis. For the N-back task, the ASD group showed greater activation than the TD group of the left FL and bilateral parietal lobe when performing the working memory-taxing “2-Back” condition, as compared to the “0-Back” condition (Figure 1A / Table 2). There were no areas of greater activation in the TD group. For

the Fluency task, the ASD group showed greater activation than the TD group in the left frontal and parietal lobes while generated words, as compared to rest (Figure 1B / Table 2). There were no areas of greater activation in the TD group. The EFT showed no significant group differences between ASD and TD.

Resting-State Functional Connectivity

The ASD group showed greater connectivity of the left parietal lobe, occipital lobe, and the cerebellum to the DNM; whereas the TD group showed greater connectivity in the right FL, parietal, and temporal lobes to the DMN (Figure 1C / Table 2).

White Matter Integrity

The ASD group showed reduced FA bilaterally in the cingulum white matter tracts, which provide connections to the hippocampi. There were no areas of greater FA in the ASD group. Since no significant group differences were observed within the frontal lobe, as hypothesized, we reduced the significance level to $p<0.005$ and conducted an exploratory analysis. At this threshold, the ASD group indeed showed reduced FA throughout the genu of the corpus callosum. In addition, reduced FA in the ASD group was observed bilaterally in the cortico-ponto-cerebellar tracts within the cerebellum (Figure 2 / Table 3).

Cortical Thickness and Regional Volumes

An area within the left caudal middle frontal cortex was significantly thinner in the ASD group [$t(29)=2.03$; $p=0.05$]. Further, the ASD group had a significantly smaller right hippocampus [$t(29)=2.4$; $p<0.05$] and showed a trend for a smaller left hippocampus [$t(29)=1.81$; $p=0.07$]. The mid-posterior region of the corpus callosum was also significantly smaller in the ASD participants [$t(29)=2.33$; $p<0.05$]. Finally, the cerebellum white matter showed trends of volume bilaterally in the ASD group in both the left [$t(29)=1.79$ $p=0.08$] and right [$t(29)=1.78$; $p=0.08$] (Table 4).

Discussion

The present study is among the first to evaluate the cognitive and neural differences between older adults with ASD and their age-matched TD peers. Perhaps the most striking finding is that across several cognitive and brain modalities, there were consistent brain regions that appear to function differently and/or show reduced structural integrity in older individuals with ASD as compared to age-matched TD. These regions were the FL, hippocampus, and cerebellum, and these findings converge with cognitive performance.

Frontal lobe

Our neuroimaging findings revealed both structural and functional brain differences within the frontal lobe between ASD and TD participants. We observed an area of thinner cortex within the frontal lobe in the ASD group and at a reduced significant threshold; we also observed areas of reduced white matter integrity within the genu of the corpus callosum fiber tracts that support the FL. These results are similar to findings of other studies with younger ASD participants [47, 48]. From the task-based fMRI results, the ASD group showed greater activation in the left FL, as well as the left and right parietal lobe for both the N-back and Fluency tasks. One way to interpret this finding is as the frontal lobe "working harder" in the ASD individuals than the TD to complete the EF tasks. Additionally, the ASD group recruited another brain region, the bilateral parietal lobe, to a greater degree than the TD group. This finding is in accordance with previous studies, which found that young adults with ASD had a compromised FL but no underconnectivity of the posterior lobe of the brain [56]. Lastly, when at rest, the TD group showed greater connectivity of the frontal lobe to the DMN than the ASD group. A similar study on children, adolescents, and young adults with ASD found that the children and adolescent cohorts experienced decreased "between-network connectivity" compared to TD. However, the young adult cohort (>18) had no significant differences in connectivity as compared to TD [49]. These

results suggest that connectivity differences in ASD may not be uniform over the life span. Our findings are in accordance with this theory and suggest that ASD individuals may experience exacerbated decreases in brain connectivity with age.

Differences within the frontal lobe converge with reduced performance on EF tasks, as the FL is vital for intact EF abilities [3]. ASD participants made more errors on the WCST, as hypothesized. In addition to the WCST, the Trails, Stroop, and finger oscillation tasks showed significant group differences. ASD had slower performances in all three tasks than the TD group. All three of these reductions in performance are indicative of reduced processing speed and may be related to reduced white matter integrity of several tracts throughout the brain. It has previously been noted that FA directly relates to processing speed [55]. Notably, the ASD group did not show impairments on cognitive tasks subserved by more posterior brain regions, such as visual search or semantic memory, nor did they show differences in brain activity during a visual search task. Taken together, the results support our hypothesis that older adults with ASD show cognitive and brain differences within the frontal lobe.

Hippocampus

The hippocampus is commonly associated with memory, specifically long-term memory. The ASD cohort had smaller hippocampi, as compared to the TD cohort. These results were similar to another study conducted by Herbert et al., (2003) which found trends of disproportionately smaller hippocampi volumes in ASD boys [50]. Further, white matter integrity data revealed reduced FA in ASD participants for the cingulum fibers supporting the hippocampus. This data extends findings from other research which found reduced integrity of the cingulum in children and adolescents with ASD, as compared to TD peers [46]. For the cognitive testing, groups did not differ in long-term memory abilities, as measured by the AVLT, a task that is commonly associated with hippocampal functioning [51]. Therefore, it will be

interesting to see if the structural brain changes in the hippocampus we observed are predictive of functional memory changes as we follow these participants as they age. The differences in the hippocampal regions are concerning that the ASD group may undergo steeper age-related memory decline.

Cerebellum

The cerebellum is recognized for its role in motor skills and movement of the body, as well its importance for language and cognition [52]. Reduced white matter integrity was found in the ASD group within the bilateral cortico-ponto-cerebellar white matter tracts. Further, the white matter volumes showed a trend for being smaller in ASD individuals in both the left and right cerebellum [47]. Noriuchi et al. (2010) and Chung et al. (2009), also found reduced sizes of the white matter in the cerebellum of ASD children and young adults, indicating a disruption in white matter development [47, 48]. The DMN resting state results also point to altered cerebellum functioning, where the ASD group showed greater connectivity within the left cerebellum. To our knowledge, there are no other findings regarding altered cerebellum connectivity to the DMN in children or young-adults with ASD, indicating that it could be a brain region that shows greater changes as a function of age. Behaviorally, differences in cerebellum structure and function are in accordance with the slower finger tapping we observed in the ASD group.

Conclusion

The main goal of this study was to determine whether older adults with ASD, show reduced cognitive functioning and increased brain degeneration particularly concerning the FL, as compared to age-matched TD. Our hypothesis was supported in that the ASD individuals showed reduced EF but intact cognitive abilities such as semantic memory and visual search. By complementing this with multiple neuroimaging modalities, we show a window on the complex

changes that can occur in the brain as a result of aging in the ASD group. These changes included reduced gray and white matter structural integrity.

Due to the lack of research in older adults with ASD, this study provides some of the first insights in this increasingly important area of knowledge. However it is noteworthy that the findings from this study make logical connections to the previous literature in young adults with ASD and normal aging. The critical next step is to continue to follow this cohort over time and to implement multimodal analyses that take advantage of longitudinal designs to determine if aging affects the ASD brain to a greater extent. We would aim to achieve this by two ways: 1) evaluating multivariate brain-behavior relationship differences between young-adult and middle-aged ASD and TD cohorts, and 2) using multi-task regression to identify structural and functional brain measures that predict the longitudinal cognitive decline in ASD versus TD individuals. With this knowledge, we will be better equipped to help these individuals maintain as much independence as possible for as long as possible.

Illustrations

Figure 1

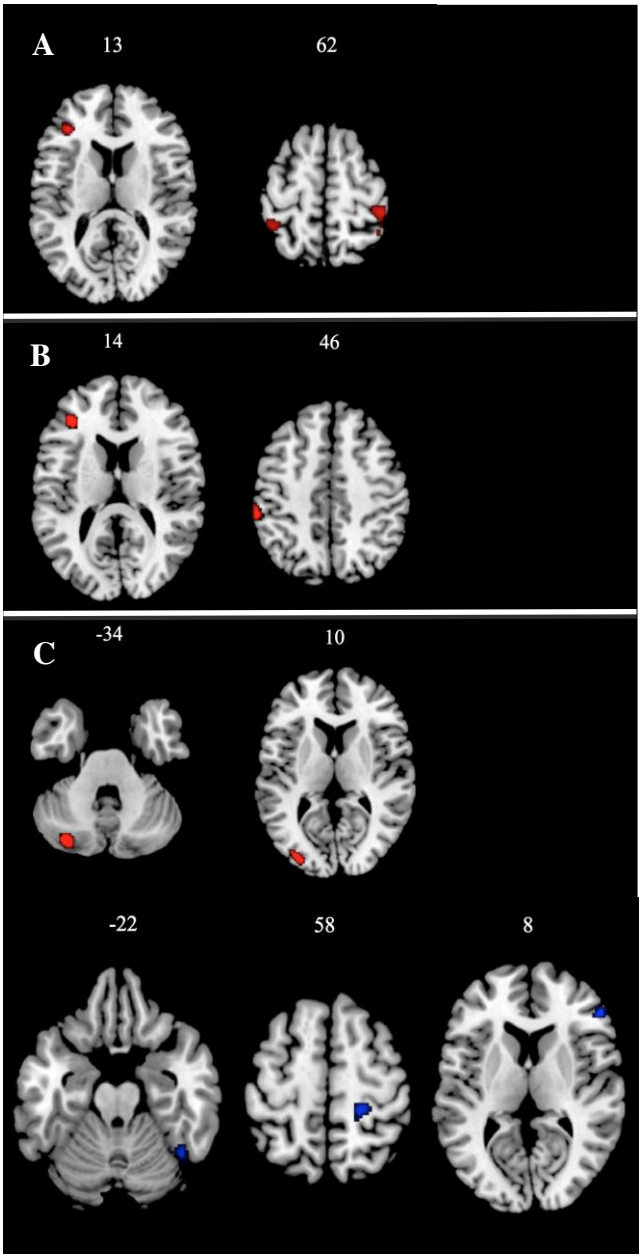

Figure 1: fMRI BOLD and Resting State Results. A) N-Back task ASD>TD. B) Fluency task ASD>TD. C) DMN ASD>TD (red), TD>ASD (blue)

Figure 2

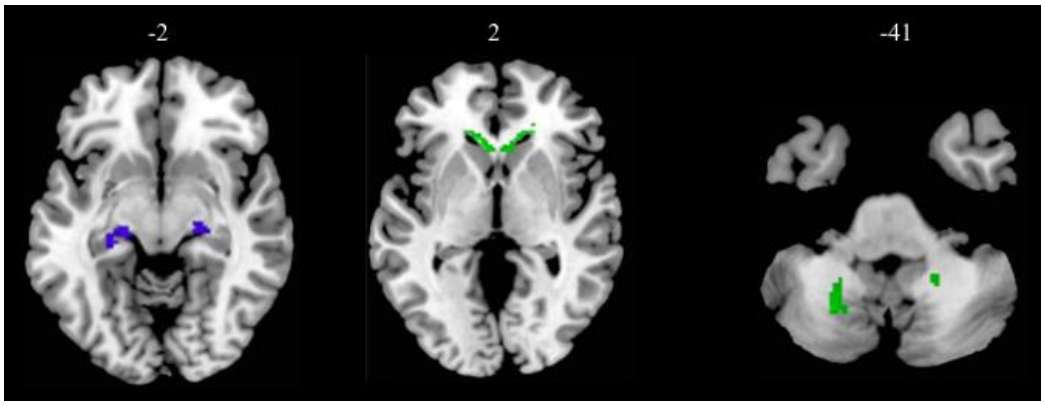

Figure 2: FA Results. ASD>TD P<0.001 (blue), ASD>TD P<0.005 (green)

Table 1: Demographics, Cognitive Results, and fMRI Task Behavior

	ASD	TD
Age	50.1(±6.93)	50.1(±7.3)
Education	14.9(±2.52)	16.05(±3.3)
IQ	110.929(±12.6)	115.0(±11.86)
WCST	35.6(±28.3)	18.9(±16.08)
Trails A	35.4(±14.09)	27.1(±9.13)
Stroop 1	73.5(±21.4)	88.2(±12.6)
Finger Tap	42.9(±14.2)	54.0(±6.27)
Fluency Total Wordgen A&B Average	43.8(±8.3)	50.97(±13.6)
N-Back A&B Average	92.00(±7.3)	96.3(±3.47)

Table 2: fMRI BOLD and Resting-State Results

Brain Region	cluster size	cluster p-value	peak T-score	peak Z-score	peak p-value	coordinates
Group Differences in N-Back for ASD>TD P<0.001 K=30						
left cerebrum frontal lobe; Brodmann Area 46	58	0.192	5.51	4.50	0	-36 36 14
right cerebrum parietal lobe; Brodmann Area 2			4.63	3.96	0	44 -34 62
	254	0.012	4.45	3.84	0	16 -42 76
			4.10	3.60	0	28 -32 70
right cerebrum parietal lobe	67	0.163	4.32	3.75	0	-22 -40 74
left cerebrum parietal lobe; Brodmann Area 40	48	0.234	4.13	3.62	0	-56 -34 52
left cerebrum parietal lobe; Brodmann Area 5	45	0.249	3.99	3.52	0	-38 -44 64
Group Differences in Fluency for ASD>TD P<0.001 K=30						
left cerebrum frontal lobe; Brodmann Area 46	62	0.178	5.57	4.53	0	-36 36 14
left cerebrum parietal lobe; Brodmann Area 40	63	0.174	4.26	3.71	0	-56 -34 50
Group Differences in Resting-State for ASD>TD P<0.001 K=30						
left cerebellum	85	0.023	5.27	4.38	0	-32-78-36
left cerebrum occipital lobe; Brodmann Area 19	81	0.026	4.58	3.94	0	-32 -88 10
			3.68	3.30	0	-24 -92 18
Group Differences in Resting-State for TD>ASD P<0.001 K=30						
right cerebrum parietal lobe; Brodmann Area 3	58	0.053	4.73	4.04	0	20 -34 58
			3.62	3.26	0.001	22 -28 52
right cerebrum frontal lobe; Brodmann Area 46	35	0.124	4.44	3.85	0	52 40 12
			3.64	3.27	0.001	48 34 6
temporal lobe			4.11	3.62	0	44 -56 -20
	39	0.106	3.53	3.20	0.001	44 -64 -18
			3.53	3.19	0.001	40 -48 -24

Table 3: FA Results

Location of Regions with Decreased FA in ASD Compared to TD with a P Value<0.001						
Brain Region	**cluster size**	**cluster p-value**	**peak T-score**	**peak Z-score**	**peak p-value**	**coordinates**
left hippocampus	49	0.001	4.7	4.02	0	-26 -28 -8
			4.62	3.96	0	-20 -22 -8
right hippocampus	31	0.007	4.29	3.75	0	18 -18 -12
Location of Regions with Decreased FA in ASD Compared to TD with a P Value<0.005						
left white matter cerebellum			4.7	4.02	0	-26 -28 -8
	124	0.001	4.62	3.96	0	-20 -22 -8
			3.53	3.2	0.001	-12 -26 -18
right white matter cerebellum			4.29	3.75	0	18 -18 -12
	102	0.001	3.97	3.52	0	14 -24 -18
			3.84	3.43	0	26 -32 -4
genu corpus callosum			4.19	3.68	0	20 32 2
	144	0	4.17	3.66	0	-12 28 0
			4.13	3.63	0	10 299 2

Table 4: Cortical Thickness and Regional Volumes Results

Brain Region	ASD	TD
Left Caudal Middle Frontal	2.303(±.015)	2.39(±0.106)
Left Hippocampus	4545.04(±482.09)	4859.35(±476.28)
Right Hippocampus	4534.0(±400.89)	4884.2(±405.7)
Mid-posterior Corpus Callosum	366.67(±43.64)	432.58(±97.626)
Left Cerebellum White Matter	15229.4(±1923.70)	16500.43(±2008.18)
Right Cerebellum White Matter	15148.09(±2113.927)	16418.75(±1855.48)

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