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Neurocognitive Profiles in Autism Spectrum Disorder

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Neurocognitive Profiles in Autism Spectrum Disorder

by

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Abstract

Neurocognitive Profiles in Autism Spectrum Disorder

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The current research project examines the performance of a group of high functioning young adult males with autism spectrum disorders on standardized measures of neurocognitive functioning to determine whether distinct cognitive profiles of strengths and weaknesses emerge. Neuropsychological test data across various domains: general cognitive ability, visuospatial processing, verbal learning and memory, visual learning and memory, working memory, reasoning, cognitive flexibility, attention, receptive language, expressive language, social and emotional processing, and fine motor skills were examined. Data were analyzed using cluster analysis to assess for the presence and nature of unique clusters/subgroups based on neuropsychological test performance. Three unique clusters were derived from the analyses. This study highlights the well-documented heterogeneity across the spectrum of autism and suggests a method for parsing a heterogeneous sample of ASD subjects into smaller and more meaningful homogeneous groups using standardized neuropsychological assessments.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

A significant proportion of experienced professionals report difficulty distinguishing between each of the diagnostic categories subsumed under ASD in the DSM-IV TR (Happé, 2011; Howlin, 2003; Macintosh & Dissanayake, 2004; Mayes, Calhoun, & Crites, 2001; Williams et al., 2008). Additionally, other developmental disorders, such as Rett syndrome, present with clinically similar symptomology (Hagberg, Hanefeld, Percy, & Skjeldal, 2002; Percy, 2011). Due to the large amount of heterogeneity, both across the spectrum and within each diagnostic category (e.g., autistic disorder, Asperger's disorder), as well as limited research supporting a clear distinction among the various diagnostic categories, the authors of the 5th Edition of the Diagnostic and Statistical Manual (DSM-5) have eliminated these categories altogether. Clinicians will now classify all variations as autism spectrum disorder, with the option of specifying varying levels of functioning ranging from "requiring support" to "requiring very substantial support" (American Psychiatric Association, 2013).

There has been some controversy in the literature over whether or not the changes in ASD diagnostic criteria are beneficial (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013; Wiggins, Robins, Adamson, Bakeman, & Henrich, 2012; Wing, Gould, & Gillberg, 2011). Additionally, some individuals within the ASD community are upset by the changes and feel as though it is inappropriate to classify all individuals across the spectrum under one diagnostic label (Federico-O'Murchu, 2013). There is also concern that the new criteria will result in some individuals losing their diagnostic label, which would have a negative impact on eligibility for services and support (Safeminds, 2012).

SUBTYPING ASD

Researchers have argued the benefit of parsing the heterogeneity of ASD into more homogenous subtypes (Grzadzinski, Huerta, & Lord, 2013; Happé, Ronald, & Plomin, 2006). A common methodological approach has been to use cluster analysis in order to determine group membership without specifying diagnoses *a priori*, thus classifying subjects empirically based on

quantitative data. Researchers have utilized cluster analysis and other multivariate approaches in attempting to determine the number and nature of ASD subtypes based on behavioral symptoms (Bruining et al., 2010; Constantino et al., 2004; Hu & Steinberg, 2009; Lecavalier, 2006; Malvy et al., 2004; Rescorla, 1988; Ring, Woodbury-Smith, Watson, Wheelwright, & Baron-Cohen, 2008; Roux et al., 1995; Sevin et al., 1995; Szatmari, Bartolucci, & Bremner, 1989; Verté et al., 2006; Wiggins, et al., 2012), cognitive measures (Fein, Waterhouse, Lucci, & Snyder, 1985; Lewis, Murdoch, & Woodyatt, 2007; Rapin, Dunn, Allen, Stevens, & Fein, 2009), brain imaging data (Hrdlicka et al., 2005), or a mix of these data types (Ben-Sasson et al., 2008; Bitsika, Sharpley, & Orapeleng, 2008; Campbell, Shic, Macari, & Chawarska, 2013; Eagle, Romanczyk, & Lenzenweger, 2010; Eaves, Ho, & Eaves, 1994; Fein et al., 1999; Garon et al., 2008; Hameury et al., 1995; Lane, Dennis, & Geraghty, 2011; Lane, Young, Baker, & Angley, 2010; Prior et al., 1998; Ronald et al., 2006; Roux et al., 1997; Sacco et al., 2012; Shao et al., 2003; Siegel, Anders, Ciaranello, Bienenstock, & Kraemer, 1986; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002; Stevens et al., 2000).

Results have been inconsistent, with data supporting models with two (Eagle, et al., 2010; Fein, et al., 1999; Garon, et al., 2008; Roux, et al., 1997; Stevens, et al., 2000), three (Ben-Sasson, et al., 2008; Bitsika, et al., 2008; Campbell, et al., 2013; Lane, et al., 2010; Lewis, et al., 2007; Prior, et al., 1998; Rapin, et al., 2009; Roux, et al., 1995; Spiker, et al., 2002; Szatmari, et al., 1989; Verté, et al., 2006; Wiggins, et al., 2012; Wing & Gould, 1979), four (Eaves, et al., 1994; Hameury, et al., 1995; Hrdlicka, et al., 2005; Hu & Steinberg, 2009; Malvy, et al., 2004; Ring, et al., 2008; Sacco, et al., 2012; Sevin, et al., 1995; Siegel, et al., 1986), or more subtypes (Fein, et al., 1985; Lane, et al., 2011; Lecavalier, 2006; Rescorla, 1988). Additionally, the nature of ASD subtypes has also been inconsistent, with some researchers finding support for distinct phenotypic subtypes (Bruining, et al., 2010; Campbell, et al., 2013; Eaves, et al., 1994; Fein, et al., 1985; Hameury, et al., 1995; Hrdlicka, et al., 2005; Hu & Steinberg, 2009; Lane, et al., 2011; Lane, et al., 2010; Lewis, et al., 2007; Malvy, et al., 2004; Rapin, et al., 2009; Ronald, et al., 2006; Roux, et al., 1995; Sacco, et al., 2012; Shao, et al., 2003; Siegel, et al., 1986; Silverman et

al., 2002; Wing & Gould, 1979) and others arguing that ASD clusters represent a severity gradient (Ben-Sasson, et al., 2008; Bitsika, et al., 2008; Constantino, et al., 2004; Eagle, et al., 2010; Fein, et al., 1999; Prior, et al., 1998; Ring, et al., 2008; Sevin, et al., 1995; Spiker, et al., 2002; Stevens, et al., 2000; Szatmari, et al., 1989; Verté, et al., 2006; Wiggins, et al., 2012).

Numerous studies have been dedicated to better understanding the range of behavioral, social, and communication functioning across the spectrum of ASD, yet there is a paucity of research examining variations of cognitive abilities within this population. Although the importance of assessing cognitive ability in individuals with ASD has been well documented (Frith, 2012; Happé & Frith, 1996), only a few of the studies listed above have included measures of cognitive functioning in the clustering algorithm. When these data were included, they were often limited to a few cognitive domains [e.g., general intellectual ability (IQ), measures of language functioning (Fein, et al., 1985; Lewis, et al., 2007; Rapin, et al., 2009)]. Results from studies using single broad measures of cognitive functioning (e.g., FSIQ) or only measures from one domain of functioning (e.g., language) may be somewhat misleading due to the limited scope of cognitive data included in the models.

The most comprehensive attempt to cluster ASD subjects based on unique cognitive profiles was conducted by Fein and colleagues in 1985. This study utilized a hierarchical cluster analysis to group 54 children with ASD, ages 5-17 years old, using four composite scores from the McCarthy Scales of Children's Abilities (Verbal, Perceptual Performance, Quantitative, and Memory) and the Peabody Picture Vocabulary Test (PPVT) as an additional measure of language ability. Results from this study suggested that an eight-cluster solution provided the best fit. Approximately half of the children were clustered into three groups, with peaks on perceptual-performance tests. Two clusters had peaks on verbal tests. Two clusters had more complex patterns of inter-test scatter and one cluster had minimal scatter demonstrating a profile of impairment across domains included in the analyses (Fein, et al., 1985).

THE COGNITIVE PROFILE OF ASD

The heterogeneity of cognitive abilities within ASD has been well documented. Just as the etiology of ASD is unknown, it is also unclear *when* abnormality associated with ASD initially develops. Some researchers have found evidence for markers as early as 20 weeks gestation (Allen, et al., *in preparation*) while others report normal development until the second year of life (Ozonoff, et al., 2010); therefore, the course of individual brain development and developmental dysfunction is likely variable. Variability in etiology and/or the course of brain development may play a role in the variability of cognitive functioning within this population. Individuals with an ASD have a diverse range of cognitive abilities and disabilities and thus, attempting to define one single cognitive profile of ASD may not be realistic.

Numerous attempts have been made to describe *the* neurocognitive profile of ASD; however no single model that has been put forth has successfully captured the range of heterogeneity in the population. The "Theory of Mind" cognitive model is an attempt to explain impairments in social communication (Baron-Cohen, Leslie, & Frith, 1985), yet this model fails to account for stereotypical movements and repetitive interests. The "Executive Dysfunction" cognitive model is used to explain repetitive interests and lack of generativity (Ozonoff, Pennington, & Rogers, 1991), yet not all individuals with ASD demonstrate cognitive impairments in executive functioning. Some researchers have described ASD as being defined by a "weak central coherence" (Happé & Frith, 2006), though this explanatory model is limited to non-social deficits in ASD. Attempts at finding a unitary cognitive model to explain the heterogeneous range of impairment in ASD have been largely unsuccessful (For Review: Charman, et al., 2010). This difficulty may be partially attributed to the fact that these unitary models of cognitive profiles have often been described by mean deficits across a heterogeneous sample, thus obscuring different patterns of spared/impaired cognitive functioning that may exist in subgroups of individuals with ASD.

In summary, there is support for continued research aimed at defining homogenous subtypes of ASD. However, previous attempts to define these subtypes based on behavioral

symptomology, limited cognitive measures, brain-imaging data, or an assortment of these variables have been inconsistent. Researchers have also emphasized the importance of defining a cognitive profile of strengths and weakness in ASD, yet capturing the cognitive variability of ASD in one model may be unrealistic. To our knowledge, no studies to date have attempted to define distinct cognitive profiles/subtypes based on performance across a comprehensive battery of neuropsychological tests.

This exploratory study aims to determine whether distinct homogenous neurocognitive profiles/subtypes exist among a small group of young adult males with high functioning ASD by examining performance on standardized measures of neurocognitive functioning across twelve domains: general cognitive ability, visuospatial processing, verbal learning and memory, visual learning and memory, working memory, reasoning, cognitive flexibility, attention, receptive language, expressive language, social and emotional processing, and fine motor skills.

Chapter 2: Methods

Participants and Procedures

Data were previously collected as part of a larger study examining the anatomical and functional connectivity of the cerebellum in autism spectrum disorder (ASD). All data were de-identified prior to the current study. Participants were 20 young adult males between the ages of 18 and 24 years old (M = 21.140, SD = 2.197). Subjects were recruited into the larger study via professional recommendation and self-referral as well as advertising through various agencies, conferences, schools, and websites. Each subject was administered a standardized neuropsychological battery by a trained administrator. All subjects gave informed consent prior to testing, and were compensated for their time. The University of Texas at Austin Institutional Review Board approved all procedures.

Inclusion criteria required that subjects be between 18 and 26 years old and speak English as their primary language. Participants were excluded if they had an IQ (as measured by the Wechsler Abbreviated Scales of Intelligence [WASI]) of <70, a known history of epilepsy, mental retardation, fragile X syndrome, or other psychiatric or neurologic diagnosis, experienced a significant head injury that involved loss of consciousness for greater than 30 minutes, or had any significant physical or psychiatric disability that prevented involvement in the study.

Subjects in the ASD group were evaluated by a psychologist with expertise in autism diagnosis prior to further testing. Confirmation of ASD diagnosis, using DSM-IV diagnostic criteria (American Psychiatric Association, 2013), was determined using the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989).

Measures

Participants were evaluated using standardized assessments and administration procedures across 12 domains of neurocognitive functioning: general cognitive ability, visuospatial processing, verbal learning and memory, visual learning and memory, working

memory, reasoning, cognitive flexibility, attention, receptive language, expressive language, social and emotional processing, and fine motor skills. For information on tests included within each domain, see **Table 1**. All tests are considered to have high reliability and validity (Strauss, Sherman, & Spreen, 2006).

STATISTICAL ANALYSES

Data from all neuropsychological measures were transformed into z-scores based on published test norms when available or on norms derived from the sample when test norms were not available. These z-scores were then combined into composite scores reflecting each domain of interest, resulting in 12 composite mean z-scores. Within each domain, correlations between z-scores ranged from moderate to high (r = .408 to .912). To determine whether unique profiles of neuropsychological functioning exist among individuals with ASD, as well as the nature of these potential subgroups, *k*–means cluster analysis was performed.

Although the *k*–means procedure is commonly used in this type of analysis, as it is less susceptible to outliers and the inclusion of potentially non-relevant variables, one limitation is the requirement to indicate the number of clusters (*k*) to be extracted *a priori* (Aldenderfer, 1985). Because this study is exploratory in nature in that the intent is to identify the presence and nature of *potential* subtypes based on neuropsychological test performance, the appropriate number of clusters was unknown. Therefore, an initial agglomerative hierarchical clustering algorithm was run using Ward's minimum variance method and squared Euclidean distance as the measure of difference between clusters. The dendrogram resulting from this initial analysis was examined for gaps in distance measurements between clusters, using procedures outlined in the SPSS manual (SPSS, 2010), to determine the number of clusters to be extracted during the *k*–means clustering procedure. Finally, the nature of the clusters identified during the *k*–means cluster analysis was defined by examining the means of the final cluster centers for each of the 12 domains. The relative importance of each domain score in the final cluster solution was

determined using analysis of variance (ANOVA) techniques. SPSS statistical software package version 19.0 was used for all statistical analyses (SPSS, 2010).

Chapter 3: Results

The dendrogram resulting from the hierarchical cluster analysis was examined and the three-cluster solution was selected as providing the best separation between clusters. A *k*–means cluster analysis was then run with initial cluster centers randomly generated and up to 20 iterations allowed. Final cluster centers were achieved with convergence after three iterations. See **Table 2** for distances between final cluster centers. Mean domain scores for each cluster are illustrated in **Figure 1**. Of the total sample of 20 participants, 9 (45%) belonged to Cluster 1 (C1); 9 (45%) belonged to Cluster 2 (C2); and 2 (10%) belonged to Cluster 3 (C3).

Clusters are described by their profile of apparent strengths and weakness, defined as mean domain scores greater than .67 standard deviations above or below the mean. This cutoff score was selected to correspond to standard scores above 110 or below 90, which is a commonly used criterion in clinical assessments to differentiate between average and above average or below average performance (Guilmette, Hagan, & Giuliano, 2007). Analysis of variance (ANOVA) on domain scores for each cluster provides additional information about the relative importance of each domain score to the final cluster solution by comparing the *F* statistics. Importantly, however, significance values are useful for descriptive purposes only and cannot be used to extrapolate to population differences, as they are derived from a clustering algorithm designed to optimize differences between clusters.

C1 denoted subjects with strengths in general intellectual ability (FSIQ) and reasoning, high average receptive and expressive language, and a weakness in fine-motor skills. C2 was defined by subjects with high FSIQ scores and low scores on measures of verbal learning and memory, visual learning and memory, and fine-motor skills. Generally, performance across domains appeared more varied in this cluster. C3 was comprised of 2 subjects with relatively low performance on tests of reasoning ability, cognitive flexibility, working memory, verbal learning and memory, expressive and receptive language, and visuospatial processing. While these 2 subjects may appear to be outliers, the small sample size precluded us from making

determinations about their representativeness to the population and therefore they were not removed from these analyses. Percentages of subjects in each cluster meeting criteria for autism versus autism spectrum disorders is described in **Table 3**.

Examination of the resulting ANOVA table (see **Table 4**) suggests the reasoning domain scores provided the greatest separation between clusters and thus contributed most heavily to the final cluster solution, followed by performance on tests of receptive language and verbal learning and memory. Interestingly, performance on measures of social and emotional processing was less useful for determining the final cluster solution and subjects tended to perform in the average range across the clusters in this domain.

Chapter 4: Discussion

This study highlights the well-documented heterogeneity across the spectrum of autism and related disorders and suggests a method for parsing a heterogeneous sample of ASD subjects into smaller and more meaningful homogeneous groups using standardized neuropsychological assessments.

Clusters 1 and 2 both demonstrated above average general intellectual functioning and reasoning abilities combined with below average fine-motor coordination. C1 was also characterized by high average expressive and receptive language while C2 had low scores on tests of verbal and visual learning and memory. The two subjects in C3 performed poorly across seven of the twelve domains included in the analyses, yet, in contrast to C2, they demonstrated intact visual learning and memory. Additionally, although fine-motor coordination was well below average in both C1 and C2, this function appears to be intact in C3. Thus, classifications of individuals across the spectrum of ASD that are based on broad measures of general cognitive functioning or on scores from only one domain (e.g., language) may be flawed or incomplete. Examination of performance across a wide range of domains may provide a more appropriate assessment of functioning, not just at the individual level, but also at the group level within research studies.

Although the sample consisted of only high functioning individuals with ASD, the heterogeneity of cognitive ability was readily apparent. While in the DSM-IV TR, the subcategories of ASD were based on different diagnostic criteria, in the DSM-5 a finer-grained picture of individual functioning is provided only by the use of certain specifiers (i.e., requires support, requires substantial support, or requires very substantial support). Additionally, clinicians can specify either with or without intellectual disability. Interpretation of these specifiers and of what constitutes classification into one versus another is somewhat ambiguous. In order to provide a more rich and accurate portrayal of individual strengths and weaknesses

and level of support required, diagnostic specifiers should be reflective of functioning across multiple cognitive domains.

Additionally, it will be important for treatment and intervention efforts to take into account the variability of cognitive ability and disability in ASD. Treatments may need to be tailored to specific sub-groups of individuals with ASD. Also, it will be important for researchers to consider and document variation in ability levels and adequately describe study samples in order for potentially effective interventions to gain sufficient empirical support. Otherwise, studies may inadvertently include more individuals with one cognitive profile than another, and doing so may make replications of findings particularly difficult.

Finally, neuropsychological theories of brain-behavior relationships allow us to make inferences about structural or functional impairment based on performance on behavioral neuropsychological tests, and vice versa. Knowledge of differences in brain function, structure, or connectivity may eventually help elucidate the etiologies of different cognitive subtypes of ASD. Hrdlicka and colleagues (2005) found four unique clusters of children with ASD using structural magnetic resonance imaging (MRI) of the brain. While potential ASD subtypes based on structural neuroimaging data is an exciting next step in uncovering more information about this population, research has shown that much of the underlying brain dysfunction in ASD may be more closely tied to differences in brain functioning/activation (i.e., fMRI) and altered structural and functional connectivity (i.e., DTI and fcMRI), rather than regional volumetric structural differences (Frank & Pavlakis, 2001; Minshew & Williams, 2007; Pina-Camacho et al., 2012; M. C. Stevens, 2005). Thus, variations in cognitive ability among the three clusters obtained from this study may be related to differences in underlying brain functioning and/or connectivity. We hypothesize the greatest differences in regions associated with the cognitive domains that contributed most heavily to our final cluster solutions. To assess for these differences in underlying brain function, the next step in our research will include comparison of previously collected structural, functional, and connectivity brain measures (e.g., MRI, fMRI, DTI, and fcMRI) among the different clusters.

In summary, a neuropsychological evaluation to provide individuals and their families with additional diagnostic information is an invaluable part of the assessment process. Diagnostic clarification in the form of a "neurocognitive subtype" could give the client and family useful information about cognitive strengths and weaknesses, and provide other service providers with direction for treatment and intervention planning. In addition, it will be helpful for future researchers to provide information about the cognitive profiles of subjects included in their studies, to allow for more accurate comparisons among other research samples. Future directions should include comparisons of functional imaging (fMRI) and brain connectivity (DTI, fcMRI) among cognitive subtypes of ASD.

LIMITATIONS

While the small sample size and nature of the statistical methods employed in these exploratory analyses preclude us from making many conclusions regarding the significance of our results or generalizations to the ASD population as a whole, these results do suggests a few important considerations. It will be important for future studies to replicate these analyses with larger sample sizes, including individuals with various levels of functioning across various age ranges and of both sexes. Additionally, verification of potential cognitive subtypes/clusters will be needed and should include external validation procedures, such as comparing clusters on data not included in the cluster analysis (Aldenderfer, 1985).

There are likely additional cognitive profiles within the ASD spectrum, however because this study only included high functioning ASD subjects recruited largely from UT, we were unlikely to capture subtypes existing at the lower end of the spectrum. This is a common limitation for studies that include an imaging component, as lower functioning individuals may have difficulty remaining still during the scans or may find the loud noises from the machine intolerable. Additionally, the level of overall cognitive ability of our sample was particularly high. Therefore, it should be noted that, although our subjects are characterized as being "high

functioning" there might be qualitative differences between our sample and samples consisting of high functioning individuals.

Appendix

Domain / Composite	Test	Score
Attention	Conner's Continuous Performance Test, Second Edition (CPT II V.5)	Percent commissions raw score
		Percent omissions raw score
Reasoning	Woodcock Johnson Tests of Cognitive Abilities, Third Edition (WJ Cog III)	Analysis-Synthesis raw score
		Concept Formation raw score
	Wechsler Abbreviated Scales of Intelligence (WASI)	Matrix Reasoning total raw score
Cognitive Flexibility	Wisconsin Card Sort Test (WCST)	Perseverative Errors
		Nonperseverative Errors
Working Memory	Wechsler Adult Intelligence Scale (WAIS-IV)	Digit Span Backwards raw score
		Digit Span Sequencing raw score
Visual Learning and Memory	Brief Visuospatial Memory Test-Revised (BVMT-R)	Total recall raw score
		Delayed recall raw score
Verbal Learning and Memory	Hopkins Verbal Learning Test-Revised (HVLT-R)	Total recall raw score
		Delayed recall raw score
Expressive Language	Wechsler Abbreviated Scales of Intelligence (WASI)	Vocabulary total raw score
	Boston Naming Test, Second Edition (BNT)	Total raw score
Receptive Language	Token Test	Total raw score
	Peabody Picture Vocabulary Test, Fourth Edition (PPVT)	Total raw score
Visuospatial	Judgment of Line Orientation (JLO)	Total number correct
Fine Motor Coordination	Grooved Peg Board	Dominant hand completion time
		Non-dominant hand completion time
Social and Emotion Processing	Wechsler Advanced Clinical Solutions-Social Cognition (ACS-Social Cog) Social Perception	Total raw score
General Cognitive Ability	Wechsler Abbreviated Scales of Intelligence (WASI)	Full-scale IQ (FSIQ)

Table 1. Neuropsychological tests and scores included in the analyses.

Cluster	1	2	3
1		3.052	6.648
2	3.052		4.970
3	6.648	4.970	

Table 2. Distances between final cluster centers.

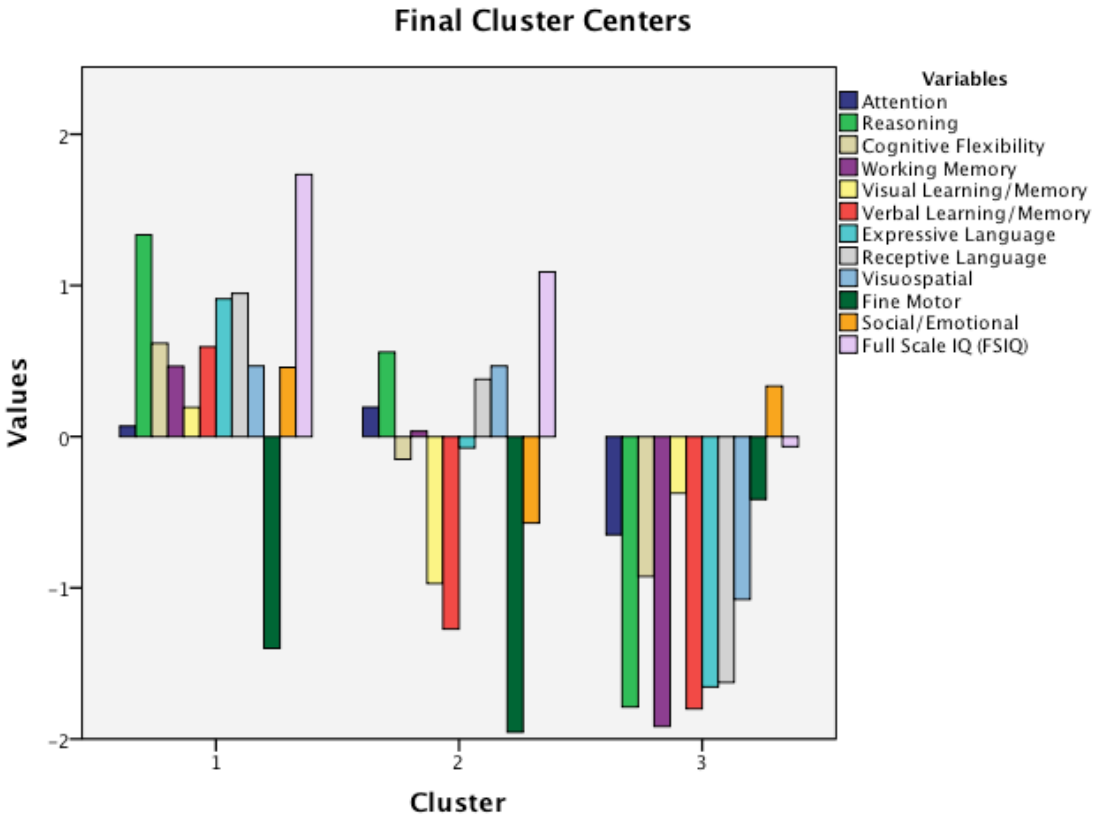

Figure 1. Mean domain z-scores for each cluster.

			Cluster Number		
			1	2	3
ADOS	Autism	N	2	4	2
Classification		% of Cluster	22.2%	57.1%	100.0%
	Autism	N	7	3	0
	Spectrum	% of Cluster	77.8%	42.9%	0%
Total		N	9	7*	2

*ADOS Classification data is missing for two subjects from Cluster 2.

Table 3. Percentages of ADOS classifications by cluster.

	Cluster Mean Square	df	Error Mean Square	df	F	Sig.
Attention	.574	2	.541	15	1.061	.371
Reasoning	8.089	2	.220	17	36.792	.000
Cognitive Flexibility	2.492	2	.606	16	4.113	.036
Working Memory	4.642	2	.395	17	11.758	.001
Visual Learning/Memory	2.682	2	1.081	15	2.481	.117
Verbal Learning/Memory	9.761	2	.636	17	15.340	.000
Expressive Language	6.057	2	.646	17	9.373	.002
Receptive Language	5.440	2	.292	17	18.613	.000
Visuospatial	2.119	2	.201	15	10.561	.001
Fine Motor	2.127	2	1.549	17	1.373	.280
Social/Emotional	2.091	2	1.185	14	1.765	.207
Full Scale IQ (FSIQ)	2.900	2	.354	17	8.192	.003

Table 4. ANOVA results

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