Categorical Versus Dimensional Approaches to Autism-Associated Intermediate Phenotypes in 22q11.2 Microdeletion Syndrome

Supplemental Information

Supplemental Methods

Consensus Diagnosis of ASD

Diagnoses of autism spectrum disorder (ASD) were determined using the Autism Diagnostic Observation Schedule (ADOS (1); administered to the child), and the Autism Diagnostic Interview-Revised (ADI-R (2); administered to the subject's parent/primary caretaker) at the UCLA Autism Phenotyping Core. Raw scores from the "Social Affect" and "Restricted and Repetitive Behaviors" domains were summed. We then used the scoring algorithm created by Gotham *et al.* (3) to create an ADOS severity score (range 1-10) from the raw score. Participants were classified as having an ASD, based on the ADOS, if a severity score was above 6. Participants were classified as having ASD, based on the ADI-R, if scores were above threshold for the Reciprocal Social Interaction domain (score of 10), as well as either communication impairment (score of 8) or repetitive behaviors and stereotyped patterns (score of 3). Combined scores from the ADOS and ADI-R were used by expert clinicians at the Autism Phenotyping Core to determine a consensus diagnosis of ASD, as previously described in (4). Eight of the older 22q11DS participants were over 18 years old, and therefore, not administered the ADI-R/ADOS; instead, these subjects and their parents/primary caretakers were administered a SCID interview (5), with an additional developmental disorders module (6), as applied in (7) to determine ASD diagnostic status according to DSM-IV

diagnostic criteria (8).

Dimensional ASD Measures

Dimensional ADI-R Measures

The ADI-R questions fall into three different domains than can be split into three subscores: an ADI-R social interaction score, ADI-R communication language score, and ADI-R repetitive behavior score. For the purposes of our study, we used this information both categorically (to make an ASD diagnosis) and also examined scores from each domain as continuous variables, with higher scores indicating greater severity in all domains.

Dimensional ADOS Measure

The ADOS summary score is a sum of two different domains, Social Interaction and Communication. During the ADOS, the interviewer engages the participant in a series of standardized, interactive behaviors, which are observed and coded (0= no concern with behavior, 1= mild concern with behavior, 2= concern with behavior). For this study, we used the ADOS severity score as a continuous variable, with higher scores indicating greater severity.

Social Responsiveness Scale

The SRS is a parent-report measure of their child's ability to process social information and respond appropriately in interpersonal interactions (9; 10). Items representing all 3-criterion domains for autism (i.e., deficits in reciprocal communication, social deficits, and restricted/stereotypic behaviors or interests) are included. For this study, we used

the raw total score, with a higher score indicating greater impairment in reciprocal social behavior.

Repetitive Behavior Scale-Revised

The Repetitive Behavior Scale-Revised (RBS-R) is a 44-item questionnaire that was created to examine a variety of repetitive behaviors in individuals with an ASD diagnosis (11). The RBS-R includes six subscales: Stereotyped Behavior, Self-injurious Behavior, Compulsive Behavior, Routine Behavior, Sameness Behavior, and Restricted Behavior. The parent/caregiver is asked to respond to questions about specific behaviors and rate how severe of a problem the behavior is on a 4-point Likert Scale (0=behavior does not occur, 1=behavior occurs and is a mild problem, 2=behavior occurs and is a moderate problem, 3-behavior occurs and is a severe problem). The total raw RBS scale, the sum of all six subscales, was used as the dimensional measure of ASD symptomatology in the current study. A higher RBS-R total score indicates greater severity and impairment of repetitive behaviors.

Short Sensory Profile

The Short Sensory Profile (SSP, (12)) is a 38-item questionnaire filled out by the participant's caregiver. The SSP asks the caregiver to provide responses about how the child's sensory processing is affected by particular daily activities. Items are scores on a 5-point Likert Scale (always=1, frequently=2, occasionally=3, seldom=4, never=5). There are seven subscales: Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Under- responsive/Seeks Sensation, Auditory Filtering, Low Energy/Weak, and Visual/Auditory Sensitivity. The total SSP score is the sum of all seven subscales was used; a lower score indicates that there are higher levels of sensory dysfunction.

Scores on this measure have previously differentiated youth with ASD from typically developing youth (13).

MRI Acquisition

Fifty percent of the participants (22q11DS=27, Controls=32) were included in a previous structural MRI publication (14) which investigated neuroanatomic measures associated with psychotic symptoms in 22q11DS. Each scan began with a 10-minute acquisition of standard images used for determining regional anatomy, including a sagittal localizer image (TR/TE=500/33ms, 192x256 matrix), a high-resolution T2-weighted axial image (TR/TE=5000/33 ms, 128x128 matrix, FOV=200x200mm), and a sagittal 1 cubic mm T1-weighted image (MPRAGE, TR/TE = 2300/2.91 ms, flip angle = 9 degrees; slice thickness = 1.20 mm, 240x256 acquisition matrix). Scans were initially obtained on 64 individuals with 22q11DS. Three participants (22q11DS-ASD+=1, 22q11DS-ASD-=2) did not pass the quality assurance protocol and were omitted from any further analyses.

sMRI Image Processing

In short, the following steps were taken in the FreeSurfer processing stream: motion correction, transformation of images to standard Talairach space, intensity normalization, removal of non-brain tissue, segmentation of white matter and subcortical structures, and final segmentation of cortical surfaces. Final segmentation is based on both a subject-independent probabilistic atlas and subject-specific measured values. Raters (MJ, AP, RJ) blind to diagnosis visually inspected the scans at several points along the processing pipeline and any errors were manually edited (details in (14)).

Using an automated computer algorithm, CT estimates were derived by taking the distance between the gray/white matter border and the pial surface at each vertex (15). Surface area was calculated by taking the sum of the area of the vertices in each parcellation. Values were extracted based on the Desikan FreeSurfer atlas (16), resulting in a total of 34 cortical regions per hemisphere. Twenty-five subcortical volumes were extracted from the automatic subcortical segmentation procedure.

Statistical Analyses

Cognition and Neuroanatomy in 22q11DS-ASD+ vs. 22q11DS-ASD-

To test for group differences in neurocognitive performance, we conducted separate univariate ANCOVAs, with each neurocognitive measure as a dependent variable, group (22q11DS-ASD+ vs. 22q11DS-ASD- vs. control) as the between-subject factor, and age and gender as covariates.

Similar procedures were followed for neuroanatomic comparisons, with brain structure as the dependent variable, group (22q11DS-ASD+ vs. 22q11DS-ASD- vs. control) as the between-subject factor, and age, gender, and scanner location as covariates. Total intracranial volume (ICV; mm^3) was an additional covariate for volumetric measures, whereas analyses of SA included ICV in mm^2 as a covariate. False discovery rate (FDR) was implemented to correct for multiple comparisons (cognitive measures: 21, brain structures: 156). Any measure/region that remained statistically significant (q<.05) after correcting for multiple comparisons was followed up with pairwise comparisons between groups. For any significant differences between

22q11DS-ASD+ and 22q11DS-ASD- partial eta squared (η_p^2) was calculated as a measure of effect size (small=.01, medium=.06, large=.14, (17)).

To address whether the relationship between age and neuroanatomic measures differed between 22q11DS-ASD+ and 22q11-ASD-, we examined any neuroanatomic region identified as statistically significant in the above analyses and conducted an ANCOVA within the 22q11DS sample, including an interaction term between ASD diagnosis and age, along with the same covariates described above.

Secondary analyses of psychotic symptoms

Finally, to ensure that psychotic symptoms were not driving any of our findings, we 1) removed all 22q11DS individuals with a psychotic disorder diagnosis (n=4) and re-ran all analyses; 2) removed all participants that had a SIPS positive symptom score above 2 and re-ran all analyses, 3) correlated the total SIPS positive symptom score with any measure that significantly differed between 22q11DS-ASD+ and 22q11DS-ASD-, and 4) correlated the total SIPS positive symptom score with ADOS and ADI-R scores.

Results of secondary analyses of psychotic symptoms

The majority of the results remained when we removed all participants with a SIPS positive symptom score above 2, although effects between 22q11Ds-ASD+ and 22q11DS-ASD- were attenuated for right amygdala volume, processing speed performance, and visuospatial memory performance (Supplementary Table S6B). Finally, no measures that statistically differed between 22q11DS-ASD+ and 22q11DS-ASD- were correlated with SIPS total positive symptoms (Supplementary Table S7A), and there were not any significant relationships between SIPS total positive symptom scores and ADOS or ADI-R scores (Supplementary Table S7B).

Description of Quality Assurance and Manual Editing Carried Out in FreeSurfer

Manual edits were carried out as follows below, as previously reported in (14). If any of these steps failed to produce an image in which the white matter and pial boundaries were not correctly identified, the scan was omitted from all analyses.

1. Recon-all was run on each subject.
2. For each subject, the orig.mgz file was examined in tkmedit for ringing, increased signal-to-noise ratio, or inhomogeneity. The scan was also examined to ensure that full coverage was acquired during the scan.
3. Each scan was manually examined to make sure that intensity normalization and the Talaraich transformation were performed successfully.
4. If necessary, pial edits were then made in brainmask.mgz for each scan in tkmedit. Areas of focus included: removal of dura matter, cerebellum, tentorium cerebelli, and/or optic nerve. If these areas were misclassified as gray matter, then pial edits were made to remove these areas from the gray matter classification.
5. If necessary, white matter and control point edits were conducted in tkmedit. White matter and control points were used if white matter regions were not appropriately specified as white matter.
6. The scan was re-submitted through the appropriate point in recon-all (i.e., recon-all autorecon2-cp –autorecon3).
7. Final quality assurance was then conducted on the scan in Freeview. The inflated and pial views were examined for any errors. Cortical parcellations were also viewed to ensure accuracy.

Table S1. List of neurocognitive measures administered, the construct under examination, and the primary citation for each measure.

Measure	**Construct**	**Citations**
Vocabulary	Verbal knowledge	WASI; (18)
Matrix Reasoning	Nonverbal abstract reasoning	WASI; (18)
Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding	Speed of processing	(19)
Trails A	Speed of processing	(20)
Trails B	Set-switching	(20)
California Verbal Learning Test	Verbal memory	(21)
Delis-Kaplan Executive Function System	Verbal fluency	(22)
Children's Memory Scale: Dots Location Task	Visuospatial memory (immediate and delayed)	(23)
Children's Memory Scale: Faces Recall Task	Facial recognition memory (immediate and delayed)	(23)
Penn Emotion Recognition Test (ER40)	Emotion recognition	(24)
Penn Emotion Differentiation Test (EMO-DIFF)	Emotion differentiation	(25)
The Awareness of Social Inference Task	Social perception abilities	(26)

Table S2. Mean ADI-R and ADOS scores in 22q11DS-ASD+ vs. 22q11DS-ASD-.

	22q11DS-ASD+ (N=24)	**22q11DS-ASD- (N=27)**	**Effect Size (Cohen's d')**	***p*-value**
Mean ADI Social Interaction Score (SD)	15.0 (7.1)	6.4 (6.1)	-1.35	0.000029
Mean ADI Communication & Language Score (SD)	13.3 (5.8)	5.9 (5.2)	-1.35	0.000021
Mean ADI Repetitive Behaviors Score (SD)	3.9 (3.1)	2.0 (2.3)	-0.70	0.01
Mean Total ADOS Severity Score (SD)	9.8 (4.1)	3.9 (3.4)	-1.58	0.000001
Mean SRS T-score (SD)	74.0 (16.6)	61.5 (13.1)	-0.84	0.002
Mean SSP Total Raw Score (SD)	129.4 (29.1)	152.3 (34.5)	0.71	0.01
Mean RBS-R Total Raw Score (SD)	16.8 (13.6)	8.8 (19.1)	0.48	0.08

Table S3. There were no significant between-scanner differences in subcortical regions.

Region of Interest	Hemisphere	F	FDR q-value
Cerebellum (white matter)	L	3.2	0.50
	R	3.4	0.50
Cerebellum (cortex)	L	0.12	1.00
	R	1.3	0.83
Caudate	L	7.6	0.20
	R	7.1	0.20
Putamen	L	4.2	0.42
	R	4.8	0.42
Hippocampus	L	0.05	1.00
	R	0.63	1.00
Amygdala	L	2.2	0.64
	R	0.19	1.00
Nucleus accumbens area	L	1.98	0.71
	R	6.2	0.20
Ventral diencephalon	L	0.02	1.00
	R	0.02	1.00
Thalamus	L	1.0	0.90
	R	1.6	0.82
Pallidum	L	1.5	0.85
Pallidum	R	2.9	0.52

Table S4. There were no significant between-scanner differences in cortical thickness (CT) and surface area (SA) in cortical regions.

		Cortical Thickness		Surface Area	
Region of Interest	**Hemisphere**	**F**	**q-value**	**F**	**q-value**
Banks of Superior Temporal Sulcus	L	0.08	1.00	0.07	1.00
	R	0.00	1.00	0.21	1.00
Caudal Anterior Cingulate	L	1.1	0.90	0.002	1.00
	R	0.4	1.00	0.07	1.00
Caudal Middle Frontal	L	3.6	0.50	7.8	0.20
	R	6.3	0.20	3.1	0.50
Cuneus	L	0.0	1.00	0.64	1.00
	R	0.0	1.00	0.24	1.00
Entorhinal	L	1.1	0.90	0.14	1.00
	R	2.6	0.57	10.4	0.20
Fusiform	L	0.5	1.00	0.06	1.00
	R	0.1	1.00	0.13	1.00
Inferior Parietal	L	1.6	0.82	0.003	1.00
	R	1.4	0.83	3.1	0.50
Inferior Temporal	L	0.63	1.00	0.05	1.00
	R	0.02	1.00	3.0	0.52
Isthmus Cingulate	L	3.9	0.49	0.34	1.00
	R	9.3	0.20	0.88	0.94
Lateral Occipital	L	7.3	0.20	0.55	1.00
	R	2.3	0.61	0.04	1.00
Lateral Orbitofrontal	L	1.9	0.78	4.3	0.42
	R	0.36	1.00	0.55	1.00

		Cortical Thickness		Surface Area	
Region of Interest	**Hemisphere**	**F**	**q-value**	**F**	**q-value**
Lingual	L	4.5	0.42	0.08	1.00
	R	0.78	1.00	0.60	1.00
Medial Orbitofrontal	L	0.001	1.00	2.7	0.54
	R	0.27	1.00	4.8	0.42
Middle Temporal	L	0.29	1.00	0.001	1.00
	R	3.5	0.50	0.68	1.00
Parahippocampal	L	0.01	1.00	1.6	0.82
	R	0.01	1.00	0.91	0.93
Paracentral	L	0.02	1.00	0.11	1.00
	R	0.06	1.00	0.18	1.00
Pars Opercularis	L	0.26	1.00	0.40	1.00
	R	0.03	1.00	0.04	1.00
Pars Orbitalis	L	1.4	0.83	0.007	1.00
	R	0.98	0.92	0.96	0.92
Pars Triangularis	L	0.40	1.00	0.16	1.00
	R	0.55	1.00	0.05	1.00
Pericalcarine	L	0.53	1.00	0.00	1.00
	R	0.08	1.00	0.41	1.00
Postcentral	L	0.70	1.00	1.2	0.87
	R	0.17	1.00	0.4	1.00
Posterior Cingulate	L	0.09	1.00	0.56	1.00
	R	3.1	0.50	0.24	1.00
Precentral	L	1.4	0.83	0.08	1.00
	R	0.09	1.00	0.38	1.00
Precuneus	L	0.01	1.00	4.9	0.42

		Cortical Thickness		Surface Area	
Region of Interest	**Hemisphere**	**F**	**q-value**	**F**	**q-value**
	R	0.001	1.00	2.3	0.61
Rostral Anterior Cingulate	L	0.006	1.00	2.5	0.60
	R	0.34	1.00	0.37	1.00
Rostral Middle Frontal	L	0.02	1.00	1.6	0.82
	R	0.19	1.00	0.31	1.00
Superior Frontal	L	2.7	0.54	0.002	1.00
	R	4.3	0.42	0.26	1.00
Superior Parietal	L	0.33	1.00	0.01	1.00
	R	0.42	1.00	0.008	1.00
Superior Temporal	L	0.11	1.00	0.28	1.00
	R	0.01	1.00	0.27	1.00
Supramarginal	L	0.37	1.00	0.11	1.00
	R	0.17	1.00	3.5	0.50
Frontal Pole	L	1.0	0.90	1.5	0.83
	R	0.07	1.00	0.00	1.00
Temporal Pole	L	0.39	1.00	0.29	1.00
	R	3.1	0.50	0.06	1.00
Transverse Temporal	L	0.02	1.00	0.43	1.00
	R	0.001	1.00	0.52	1.00
Insula	L	1.4	0.83	0.14	1.00
	R	1.5	0.83	1.5	0.86

Table S5. Global neuroanatomic measures in 22q11DS-ASD+ vs. 22q11DS-ASD- vs. controls. There were no significant differences in any global neuroanatomic measures between those with 22q11DS-ASD+ vs. 22q11DS-ASD-.

	22q11DS-ASD+ (N=29)	**22q11DS-ASD- (N=32)**	**Controls (N=55)**	**Overall Univariate ANOVA**		**Pairwise comparison between 22q11DS-ASD+ vs. 22q11ASD-**	
	Mean (SE)	**Mean (SE)**	**Mean (SE)**	**F**	***p*-value**	**t**	***p*-value**
Total Intracranial Volume (mm^3)	1411813 (174164)	1337226 (157367)	1446999 (16612)	6.7	0.002	1.8	0.09
Total Cortical Volume (mm^3)	500702 (55367)	486965 (62044)	553154 (6851)	12.3	0.000015	0.9	0.37
Total Cortical Surface Area (mm^2)	160511 (15868)	157895 (34563)	175755 (2847)	9.6	0.0001	0.4	0.71
Overall Mean Cortical Thickness (mm)	2.79 (0.02)	2.81 (0.02)	2.71 (0.01)	13.69	0.000005	-0.4	0.70

Table S6. Regression statistics for best-fitting ASD predictor for neurocognitive and neuroanatomic measures that were significantly different between 22q11DS-ASD+ and 22q11DS-ASD-.

Neurocognitive and neuroanatomic measures	***Best-Fitting ASD Predictor***	***F***	***p-value***	***R^2***	***Standardized b-value***
Processing speed	ADI-R Communication Language Score	11.3	0.00001	0.42	-0.62
Immediate face memory	ADI-R Communication Language Score	13.4	0.000002	0.46	-0.36
Delayed face memory	ADI-R Communication Language Score	9.1	0.00007	0.37	-0.36
Delayed visuospatial memory	ADOS Summary Score	8.2	0.0001	0.34	-0.43
R parahippocampal cortical thickness	Categorical dx of ASD	3.8	0.01	0.17	-0.23
L parahippocampal cortical thickness	Categorical dx of ASD	8.3	0.0001	0.3	-0.27
R amygdala volume	ADI-R Communication Language Score	3.7	0.02	0.19	-0.53

Table S7. Akaike's criterion for the regression analyses comparing fit of a categorical vs. a dimensional predictor. The smaller the AIC value in reference to other models, the better the fit. The smallest AIC value for each measure (in bold) indicates the best model fit.

	Categorical Diagnosis of Autism Spectrum Disorder	ADI-R Communication-Language Score	ADI-R Repetitive Behavior Score	ADI-R Social Interaction Score	ADOS Summary Score	Total SRS Raw Score	Total SSP Score	Total RBS Score
Neurocognitive measures								
Processing speed	457.9	**393.57**	398	401.2	396.5	461.2	446.6	432.5
Immediate face memory	385.4	**331**	338	341.7	333.4	380.7	363.6	351.1
Delayed face memory	395.5	**338.6**	344.2	348.95	340.5	389.4	370.7	360.9
Delayed visuospatial memory	364.6	319.4	322.7	328.2	**316.2**	363.7	345.4	338.6
Neuroanatomic Measures								
R parahippocampal cortical thickness	**20.9**	29.3	32.5	30.49	30.3	33.7	29.0	31.0
L parahippocampal cortical thickness	**25.5**	28.39	29.6	28.22	30.5	32.6	35.9	34.6
R amygdala volume	830.9	**696.9**	698.3	709.5	697.2	817	778.4	742.5

Table S8A. Re-analysis of measures that were statistically different between 22q11DS-ASD+ and 22q11DS-ASD-, after removing 22q11DS individuals with a psychotic disorder diagnosis.

Measure	**F**	**Overall *p*-value**	**á or â in 22q11DS-ASD+ vs. 22q11DS-ASD- (*p*-value)**	**á or â in 22q11DS-ASD+ vs. CTL (*p*-value)**
Processing speed (BACS Symbol Coding)	17.6	2.6e-07	â (0.003)	â (4.6e-10)
Visuospatial Memory (Delayed)	9.1	0.0002	â (0.02)	â (1.0e-05)
Facial Memory: Immediate	23.5	3.7e-09	â (0.009)	â (3.6e-11)
Facial Memory: Delayed	21.2	1.8e-08	â (0.01)	â (4.3e-10)
Right Amygdala volume	6.9	0.002	â (0.04)	â (0.0003)
Left Parahippocampal cortical thickness	12.8	0.00001	â (0.003)	â (2.0e-06)
Right Parahippocampal cortical thickness	7.5	0.001	â (0.0002)	â (0.01)

Table S8B. Re-analysis of measures that were statistically different between 22q11DS-ASD+ (N=17) and 22q11DS-ASD- (n=28), excluding 22q11DS individuals with sub-threshold and fully psychotic symptoms.

Measure	**F**	**Overall *p*-value**	**á or â in 22q11DS-ASD+ vs. 22q11DS-ASD- (*p*-value)**	**á or â in 22q11DS-ASD+ vs. CTL (*p*-value)**
Processing speed (BACS Symbol Coding)	15.5	0.000002	0.11	â (0.000004)
Visuospatial Memory (Delayed)	7.7	0.001	0.43	â (0.001)
Facial Memory: Immediate	36.0	3.0152e-12	â (0.01)	â (1.8762E-11)
Facial Memory: Delayed	25.4	1.6527e-9	â (0.03)	â (4.8257e-9)
Right Amygdala volume	6.7	0.002	0.43	â (0.002)
Left Parahippocampal cortical thickness	12.6	0.000014	â (0.001)	â (0.000002)
Right Parahippocampal cortical thickness	7.1	0.001	â (0.0003)	â (0.02)

Table S9A. Pearson correlations between SIPS total positive symptom scores and measures that statistically differed between 22q11DS-ASD+ and 22q11DS-ASD-.

	***r* (Pearson)**	***p*-value**	**N**
Right amygdala volume	-0.05	0.78	41
LH parahippocampal CT	0.08	0.62	41
RH parahippocampal CT	-0.04	0.82	41
BACS symbol coding	-0.28	0.08	40
Dots Delayed	-0.97	0.55	41
Faces Immediate	-0.033	0.84	41
Faces Delayed	-0.006	0.97	41

Table S9B. Pearson correlations between SIPS total positive symptom scores and ADI-R and ADOS measures.

	***r* (Pearson)**	***p*-value**	**N**
ADI-R Social Interaction Score	0.197	0.28	32
ADI-R Communication Language Score	0.180	0.32	32
ADI-R Repetitive Behavior Score	0.195	0.28	32
ADOS Summary Score	0.013	0.94	33

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