Biological Psychiatry: CNNI

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

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ABSTRACT

BACKGROUND: Individuals with 22q11.2 microdeletion syndrome (22q11DS) have elevated rates of autism spectrum disorder (ASD), although the diagnosis is controversial. To determine whether there is a biological substrate of ASD in patients with 22q11DS, we examined neurocognitive and structural neuroanatomic differences between those with 22q11DS and an ASD diagnosis (22q11DS-ASD$^+$) and those with 22q11DS without ASD (22q11DS-ASD$^-$). We then determined whether these differences were better characterized within a categorical or dimensional framework.

METHODS: We collected multiple neurocognitive measures and high-resolution T1-weighted magnetic resonance imaging scans from 116 individuals (29 patients who were 22q11DS-ASD$^+$, 32 patients who were 22q11DS-ASD$^-$, and 55 typically developing controls) who were between 6 and 26 years of age. Measures of subcortical volume, cortical thickness (CT), and surface area were extracted using the FreeSurfer image analysis software. Group differences in neurocognitive and neuroanatomic measures were assessed; regression analyses were then performed to determine whether a categorical or dimensional measure of ASD was a better predictor of neurocognitive impairment or neuroanatomic abnormalities observed in patients with 22q11DS-ASD$^+$.

RESULTS: In comparison to 22q11DS-ASD$^-$ individuals, 22q11DS-ASD$^+$ participants had decreased bilateral parahippocampal CT and decreased right amygdala volumes. Those with 22q11DS-ASD$^+$ also showed slowed processing speed and impairments in visuospatial and facial memory. Neurocognitive impairments fit a dimensional model of ASD, whereas reductions in parahippocampal CT were best explained by a categorical measure of ASD.

CONCLUSIONS: A combination of categorical and dimensional measures of ASD may provide the most comprehensive understanding of ASDs in individuals with 22q11DS.

Keywords: Amygdala, Cortical thickness, Dimensional measures, Parahippocampus, Social behavior, Velocardiofacial syndrome

http://dx.doi.org/10.1016/j.bpsc.2016.06.007

Autism spectrum disorders (ASDs) are characterized by marked impairments in social interactions and both verbal and nonverbal communication, as well as repetitive behaviors or restricted interests. However, ASD is also associated with remarkable heterogeneity at both the phenotypic (1) and genetic levels (2–4), which may be why it has been so difficult to identify replicable cognitive and biological substrates of the disorder. Given that multiple rare copy number variants have been found to play a significant role in the pathogenesis of ASD (5–10), an alternative strategy is to focus on highly penetrant genetic subtypes of the disorder. Indeed, up to 25% of individuals diagnosed with ASD have an identifiable genetic etiology (11). Examination of cognition and neuroanatomy in a homogenous subgroup with a well-known etiology may provide us with insights that are otherwise obscured by both genetic and phenotypic heterogeneity in patients with ASD.

22q11.2 Microdeletion syndrome (22q11DS) offers one potential model disorder in which to investigate this question because rates of ASD are substantially elevated in this syndrome; a recent meta-analysis concluded that 22q11DS is associated with more than an eightfold increase in risk for ASD (12). However, the reported prevalence of categorical ASD diagnosis in 22q11DS is highly variable across studies, ranging from 0% to 50% (13–18).

Some argue that this variability is attributable to methodological differences across studies (18); others speculate that ASD diagnosis in patients with 22q11DS is actually a misdiagnosis of prodromal psychosis, given that 25% to 30% of patients with 22q11DS develop psychotic illness in adolescence or adulthood (19). Still others have suggested that ASD diagnosis in patients with 22q11DS is capturing a generalized social impairment that differs from idiopathic autism (20).

ISSN: 2451-9022

On the other hand, core autism behaviors, such as impairments in joint attention, gestural communication, initiating conversation, and circumscribed interests, are recognized as characteristic phenotypes in individuals with 22q11DS independent of ASD diagnosis (21). These findings suggest that a dimensional explanation of ASD, or a "broader autism phenotype," may be more applicable to the 22q11DS population.

This concept is not specific to 22q11DS. Population twin and family studies support a dimensional view of autistic-like behaviors, suggesting that autism is at the extreme tail of a continuous distribution (22–25). In addition, studies have found that empirically derived clusters are more likely to map onto severity of ASD symptoms (26–28), rather than the classification approach used by the DSM-IV and ICD-10. However, no studies have yet addressed the question of whether neurocognitive and neuroanatomic abnormalities in 22q11DS are better explained by a categorical versus a dimensional approach to ASD-relevant traits. This question is highly relevant to the Research Domain Criteria (RDoC) framework (29), which posits that to accelerate progress in identifying disease mechanisms underlying ASD, it may be more informative to examine autistic symptoms based on dimensions and observable behaviors (30,31).

Previous studies have not observed differences in overall cognitive abilities (full-scale IQ [FSIQ]) between patients with 22q11DS and an ASD diagnosis (22q11DS-ASD$^+$) compared to those who do not have ASD (22q11DS-ASD$^-$) (13,21,32). However, greater ASD symptom severity was associated with poorer performance on measures of verbal knowledge (i.e., vocabulary) and processing speed (i.e., digit symbol coding) in patients with 22q11DS (32). In addition, a previous investigation from our group did not find differences in a theory of mind measure (Animations task) between patients who were 22q11DS-ASD$^+$ versus those without ASD (33); nevertheless, poorer performance was associated with greater impairment on a dimensional measure of reciprocal social behavior, the Social Responsiveness Scale (34). These findings suggest that dimensional measures may yield more precision and power when testing hypotheses regarding ASD-related neurocognitive deficits in 22q11DS.

In addition, given increasing recognition of mental disorders as biological disorders of the brain (29), there may be distinct structural neuroanatomic alterations that characterize patients with 22q11DS-ASD$^+$. To our knowledge, there is only one published study to investigate this (14); these authors found increased amygdala volumes in 22q11DS-ASD$^+$ children versus 22q11DS-ASD$^-$, with all other regions of interest being statistically similar between the two groups. However, it is important to examine cortical volume in its constituent parts, cortical thickness (CT) and surface area (SA), given that these two measures are believed to have distinct neurodevelopmental origins (35).

We sought to determine whether there are distinct neurocognitive or biological substrates associated with categorically defined ASD diagnosis in patients with 22q11DS or, alternatively, whether a dimensional approach better characterizes the findings. Specifically, we investigated whether 1) 22q11DS-ASD$^+$ and 22q11DS-ASD$^-$ patients differ in terms of social and nonsocial cognition measures; 2) we could identify patterns of neuroanatomic alteration specific to 22q11DS-ASD$^+$ patients; and 3) any observed categorical differences could be better explained by dimensional measures of autism-associated symptomatology in patients with 22q11DS.

Given the central role of facial recognition and social cognition deficits in patients with idiopathic ASD (36–40), we hypothesized that those with 22q11DS-ASD$^+$ would show poorer performance on measures of emotion recognition and face memory. In addition, based on findings in patients with idiopathic ASD, we hypothesized that those with 22q11DS-ASD$^+$ would show increased CT relative to 22q11DS-ASD$^-$ patients in brain regions associated with social cognition, including the orbitofrontal cortex and fusiform gyrus (41,42), as well as alterations in amygdala volume (43). Finally, based on the premise that dimensional, quantitative traits may map more closely to disease biology than categorical diagnoses, we hypothesized that dimensional measures would account for more variance in the neurocognitive and neuroanatomic measures than categorical ASD diagnosis in patients with 22q11DS.

METHODS AND MATERIALS

Participants

The overall sample consisted of 116 individuals (29 patients who were 22q11DS-ASD$^+$, 32 patients with 22q11DS-ASD$^-$, and 55 typically developing controls) who were between 6 and 26 years of age (Table 1) and who were recruited from an ongoing longitudinal study. Fifty percent of the participants (22q11DS, n = 27; controls, n = 32) were included in a previous publication regarding structural magnetic resonance imaging (MRI) scans (5) that investigated neuroanatomic

Table 1. Demographic and Clinical Characteristics of the Study Participants

	22q11DS-ASD$^+$ Participants (n = 29)	22q11DS-ASD$^-$ Participants (n = 32)	Typically Developing Controls (n = 55)	p Value[a]
Age, Years, Mean (SD) [Range]	14.34 (5.70) [6–26]	13.78 (5.35) [6–25]	12.87 (4.93) [6–26]	.45
Participant Education, Years, Mean (SD)	6.72 (4.41)	6.47 (4.72)	7.15 (5.16)	.81
Sex, Female, n (%)	11 (38)	18 (56)	26 (47)	.36
WAIS IQ, Mean (SD)	76.7 (11.8)	81.5 (14.0)	110.2 (20.4)	9.0121E-15

22q11DS, 22q11.2 microdeletion syndrome; 22q11DS-ASD$^+$, patients with 22q11DS and an autism spectrum diagnosis; 22q11DS-ASD$^-$, patients with 22q11DS without an autism spectrum diagnosis; WAIS, Wechsler Adult Intelligence Scale.

[a]The 22q11DS-ASD$^+$ and 22q11DS-ASD$^-$ groups did not significantly differ on measures of WASI IQ (t = 1.5, p = .2).