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Re-conceptualizing ASD Within a Dimensional Framework: Positive, Negative, and Cognitive Feature Clusters

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Abstract

Introduction of the National Institute of Mental Health's Research Domain Criteria and revision of diagnostic classification for Autism Spectrum Disorder in the latest diagnostic manual call for a new way of conceptualizing heterogeneous ASD features. We propose a novel conceptualization of ASD, borrowing from the schizophrenia literature in clustering ASD features along positive, negative, and cognitive dimensions. We argue that this dimensional conceptualization can offer improved ability to classify, diagnose, and treat, to apply and predict response to treatment, and to explore underlying neural and genetic alterations that may contribute to particular feature clusters. We suggest the proposed conceptualization can advance the field in a manner that may prove clinically and biologically useful for understanding and addressing heterogeneity within ASD.

Keywords

Autism spectrum disorder; Symptoms; Heterogeneity; Classification; Diagnosis; RDoC

The introduction of the National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) initiative, in conjunction with the recently revised diagnostic classification of a broad Autism Spectrum Disorder (ASD) category, calls for novel ways of conceptualizing and clustering heterogeneity among ASD features. In this paper, we borrow from the schizophrenia literature in proposing a conceptualization of ASD on the basis of positive, negative, and cognitive features. We propose that this novel dimensional conceptualization may be informative for researchers and clinicians alike, offering: (1) a new lens on viewing symptomatology that could better capture heterogeneity, improve diagnostic precision, and allow more targeted consideration of dimensional symptom overlap with other disorders; (2) an opportunity to apply treatment approaches best suited to the dimensional disturbances evident in a given individual; and (3) a new perspective from which to explore underlying disruptions in neural and genetic pathways that may contribute to particular clusters of symptoms or features. In so doing, the proposed conceptualization attempts to move the field of ASD research forward in a manner that may prove clinically and biologically useful for contending with heterogeneity within the autism spectrum.

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The Fifth Edition of the Diagnostic and Statistical Manual (DSM-5) refined diagnostic criteria and classification for autism spectrum disorder (ASD), moving from related subdiagnoses to a single, spectrum diagnosis (APA 2013). This change reflected the limited validity and reliability of DSM-IV diagnostic categories (Mahjouri and Lord 2012; Volkmar and McPartland 2014). For example, clinician, clinic location, IQ, age, and comorbid symptoms predicted DSM-IV diagnosis better than did the core features differentiating among them in the diagnostic rubric (Lord et al. 2012). The clinical relevance of former subcategories was also challenged, with treatment selection and response reflecting specific features (e.g., language delays), comorbidities (e.g., hyperactivity, anxiety), and developmental and cognitive level, rather than particular diagnosis (Happe 2011). The shift to a new, broader ASD category in the DSM-5 was intended to conceptualize the disorder at a level that more accurately corresponds to clinical correlates and the existing state of limited scientific knowledge regarding valid, replicable subtypes, while simultaneously opening new freedom for exploring novel ways to parse heterogeneity (Grzadzinski et al. 2013).

Though ASD is now conceptualized as an umbrella category, it is widely acknowledged that ASD is not a single biological entity (Geschwind and Levitt 2007; Happe et al. 2006). Instead, ASD likely reflects a ‘dimensional’ disturbance (Happe et al. 2006; Insel et al. 2010), with great phenotypic heterogeneity (e.g., in spoken language and social interest) that represents extreme values on multiple functional continua that extend into the normative range. Efforts to parse this heterogeneity have focused on both feature expression (Willemsen-Swinkels and Buitelaar 2002) and neural and genetic mechanisms underlying distinct phenotypic dimensions (Jeste and Geschwind 2014). Nevertheless, despite promising advances (e.g., specific genetic subtypes; Bernier et al. 2014), the field as yet has failed to characterize subtypes in ways that (a) are biologically and prognostically meaningful and reliable, and (b) explain the range of phenotypic expression. This goal is critical for the identification of etiological mechanisms and development of individualized treatment strategies. Novel ways of conceptualizing feature clusters may be helpful in driving research to better understand the etiology of various phenotypic presentations of ASD. Here we propose that development of a dimensional understanding of ASD may benefit from insights derived in the context of clinical research in schizophrenia.

Symptom Dimensions in Schizophrenia—Defining an Illness Spectrum

Schizophrenia shares a long history with ASD (Ornitz 1969) and, prior to 1980, autism was considered a subtype of early-emerging schizophrenia (APA 1968). Like ASD, schizophrenia is a heterogeneous clinical syndrome characterized by a diverse array of signs and symptoms that exhibit a highly variable presentation across patients (Jablensky 2006; Tamminga and Holcomb 2005). While there are ‘canonical’ symptoms of the illness, such as disturbances in belief (delusions) and perception (hallucinations), no one sign or symptom is sufficient to establish a formal schizophrenia diagnosis. Like ASD (Happe et al. 2006), schizophrenia is conceptualized as a group of disorders, or “schizophrenias” (Bleuler 1950; Siever et al. 1993), varying across symptom dimensions (Barch et al. 2013). In line with this view, as with ASD, in the transition to the DSM-5, schizophrenia subtypes (e.g., disorganized, paranoid, catatonic) were removed due to their having limited reliability for

parsing heterogeneity (Linscott and van Os 2010), as well as limited utility for informing treatment or predicting course of illness (Tandon 2012; Tandon et al. 2013).

Although reliable subtypes for schizophrenia have not been validated, subsets of schizophrenia characteristics have been effectively parsed in terms of “positive” versus “negative” symptoms (N. C. Andreasen and Olsen 1982) that occur alongside reliable patterns of cognitive deficits (Barch 2005; Reichenberg et al. 2009). Positive symptoms of schizophrenia include hallucinations, delusions, and bizarre and disorganized speech and behaviors—characteristics that are absent in typical adults. Negative symptoms, in contrast, are those that represent a deficit of function, or a lack of behaviors that are normally present in typical adults. In schizophrenia, these features include blunted affect, anhedonia, avolition, and alogia. Finally, cognitive deficits in schizophrenia are quite diffuse and include impairments in processing speed, problem solving and reasoning, verbal and non-verbal learning and memory, attention, working memory, and executive functioning (Fatouros-Bergman et al. 2014; Nuechterlein et al. 2004).

Classifying schizophrenia symptoms along positive, negative, and cognitive dimensions has not been important just with regard to nosology and classification. Rather, this conceptualization has led to improved ability to diagnose and treat, to predict and track course of illness, response to treatment, and functional outcomes in affected patients (Chen et al. 2013; Mohr et al. 2004), and to begin to understand the universality versus specificity of underlying neural abnormalities and genetic alterations in driving clusters of symptoms within and across individuals (Barch and Ceaser 2012). Positive symptoms are often more acute and transient and respond most reliably to anti-psychotic medications (Angrist et al. 1980; Chien and Yip 2013; Leucht et al. 2009). Negative symptoms, on the other hand, are more stable, are associated with worse premorbid functioning as well as poorer psychosocial adjustment and functional outcomes (Rabinowitz et al. 2012), and have only recently been more effectively targeted by interventions (Brunelin et al. 2012; Goff et al. 2001a, b; Levkovitz et al. 2010). Finally, cognitive features are unique in preceding onset of acute illness (Bora and Murray 2014), are most treatment refractory (Harvey and Keefe 2001), and have led to organized, NIMH-funded efforts in the research community to assess and develop interventions particularly targeting this dimension (Marder 2011). With regard to underlying genetics and neurobiology, while many have proposed common pathways and neural abnormalities in schizophrenia (Coyle 2006; Krystal et al. 2003; Uhlhaas and Singer 2010), it is also likely there are at least some more specific or localized differences in brain development and functioning driving subsets of abnormalities associated with this disorder (Lisman 2012). To this end, the schizophrenia research community has found it fruitful to consider symptom dimensions in understanding pathways and circuitry by which underlying mechanisms lead to specific disease manifestations.

Application to Autism Spectrum Disorder

We propose that considering symptoms of ASD along positive, negative, and cognitive dimensions may represent a meaningful strategy for parsing heterogeneity, paralleling the work that has been done in schizophrenia. We do not intend to suggest that positive and negative dimensions of ASD are the same as those in schizophrenia, but rather that

conceptualizing existing features of ASD as those that are atypical (not present in typical development, but present in ASD), deficient (those that are present in typical development, but delayed, deficient, or absent in ASD), or cognitively-driven may open new avenues for scientific discourse, research, and clinical practice. In this framework, positive features of ASD include behaviors that are not often seen in typical individuals, such as stereotypic motor behaviors, echolalia, and circumscribed interests. In contrast, negative features reflect the absence of behaviors expected in typical individuals, and include reduction in eye contact, facial expression, social engagement, and spoken language. Finally, the cognitive dimension could include patterns of thinking, behavior, and relating that are most clearly cognitively-driven and common among individuals with ASD, such as rigidity of thinking, deficits with set shifting and broader executive functioning, impaired theory of mind, and commonly detected neuropsychological deficits (e.g., in processing speed, verbal IQ, working memory, episodic memory, sustained attention) (Brunsdon and Happé 2014). Table 1 reflects additional examples of framing hallmark ASD features, as currently represented in the DSM-5 rubric, along positive, negative, and cognitive dimensions. In the paragraphs that follow, we demonstrate how clustering ASD features in this manner can be an informative conceptual framework for making diagnostic distinctions, applying treatments, and understanding etiology.

Existing knowledge of ASD phenotypic profiles and developmental course points to the possibility that conceptualizing features along positive, negative, and cognitive dimensions could have utility with regard to diagnosis and prognosis. For example, in toddlers, the presence of positive motor stereotypy behaviors does not differentiate children with ASD from those with typical development or developmental delay (Baranek 1999; Lord 1995), as many of these behaviors are normative at this young age. As such, negative signs, characterized by the absence or delay in development of more typical social behaviors (e.g., response to name) are the best predictors of ASD diagnosis in young children (Barton et al. 2012).

At later ages, the persistence and emergence of positive signs may be more diagnostic, as some positive features, such as circumscribed interests, become more pronounced and impairing at older ages (South et al. 2005). Similarly, with age, stereotypies increasingly differentiate ASD from typical development (MacDonald et al. 2007). On the other hand, negative features, while fairly diagnostic in young children with ASD, increasingly overlap with other disorders in later childhood and adolescence, leading to challenges in differential diagnosis in individuals with exclusively negative symptoms. For example, symptoms of anxiety, depression, and schizophrenia (e.g., blunted affect, reduced eye contact, social isolation or avoidance; Blanchard and Cohen 2006) overlap with ASD negative features, making this cluster of features less helpful for differential diagnosis in older children, adolescents, and adults. Thus, when older children are presenting for a first time diagnosis with a question of ASD and display primarily negative features within the proposed framework, it may be important to consider whether their presentation is better explained by an alternative primary diagnosis, particularly if no positive features of ASD have ever been present. On the other hand, when an older child with a past diagnosis of ASD displays both positive and negative features of ASD but negative features have become increasingly

prominent with age, clinicians should continue to consider whether a comorbid anxiety or mood disorder is occurring alongside the primary ASD diagnosis.

Finally, though perhaps least specific to ASD versus other neurodevelopmental disorders, common cognitive styles and features can often lead to specific patterns of behaviors that cause significant functional impairment for individuals with ASD when navigating educational, social, domestic, and vocational challenges. As such, cognitive features may underlie significant behavioral challenges and require intervention for subsets of patients, thus warranting intentional attention to salient features along this dimension. As a guiding principle, we suggest that clinicians could benefit from considering ASD features along our proposed dimensions in making their initial diagnosis, in considering what alternative diagnoses might better explain the individual's presentation and/or what comorbidity the patient might currently be experiencing, in forecasting which future behaviors or difficulties a child might be at more or less at risk for, and in considering which treatment approaches to recommend. Thus, we believe that this framework could be quite helpful for improving current diagnostic thinking and practices.

At present, existing assessment measures for ASD do not lend themselves to conceptualizing relevant features along positive, negative, and cognitive dimensions. As most were derived to match DSM categories (social, communication, repetitive behaviors) in their existing format and with their existing scales, these measures offer little support for clinicians or researchers wishing to conceptualize features along our proposed dimensions. On some scales, it may be possible to derive positive, negative, and cognitive factors for existing subsets of items that have not previously been grouped together. On other measures, however, existing items lump both positive and negative expressions of a given feature (e.g., a single item for inappropriate affect, which does not differentiate exaggerated from flat affect), and additional measure development and refinement would be necessary. In schizophrenia, the most widely used rating scales (i.e., Positive and Negative Syndrome Scale, Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms; Andreasen 1984, 1989; Kay et al. 1987) divide features along positive and negative dimensions, which has been useful in the clinical context for characterizing an individual's diagnostic presentation and for measuring the response of subsets of features to treatment. In research, these dimensional rating scales have been useful for measuring efficacy in clinical trials as well as for evaluating onto which aspects of the clinical phenotype particular behavioral or neurological findings map. Given the utility of these dimensional measures in schizophrenia, it may be worthwhile for the autism community to consider whether development of analogous scales for ASD would be a fruitful investment.

Similarly, the DSM-5 rubric for ASD diagnosis includes only severity ratings for social communication and restricted/repetitive behaviors, whereas for schizophrenia, an optional severity rating scale (the "Clinician-Rated Dimensions of Psychosis Symptom Severity") is available for rating various positive, negative, and cognitive features in patients with this disorder (APA 2013). In line with our proposal, it may be meaningful to develop a parallel optional rating scale for the positive, negative, and cognitive features of ASD in order provide a richer clinical picture of the patient's functioning and to inform treatment planning. Such severity ratings could be useful for capturing the most prominent features

affecting an individual at a given point in time, as the relative expression and impact of features along dimensions will certainly vary both across individuals as well as within individuals over the course of development, as settings change, and as treatments yield effects.

Consideration of existing interventions suggests that many may be differentially useful for treating positive, negative, and cognitive features of ASD, though they have not previously been conceptualized or applied within this framework. For example, some medications are effective in treating stereotyped behaviors (a positive feature; McPheeters et al. 2011), whereas other novel approaches, such as oxytocin, aim to increase social approach (decrease a negative feature; Andari et al. 2010). Likewise, different behavioral interventions may be indicated for positive versus negative features. Whereas extinction procedures may be used to eliminate undesirable or atypical behaviors (positive features; Wolff et al. 2013), behavioral reinforcement protocols might be best suited to shape typical behaviors that are reduced or absent (negative features; Koegel et al. 2009). The treatment of prominent negative features of ASD could also be informed and enhanced by drawing upon both psychosocial and medical interventions that have been validated for treating related symptoms in other disorders, such as anxiety, depression, and schizophrenia. Finally, executive functioning interventions (Kenworthy et al. 2014) may be best suited to target underlying cognitive impairments in ASD. Thus, describing an individual's difficulties in terms of positive, negative, and cognitive features may be informative in selecting which treatment approaches are best suited to address their particular set of difficulties and in considering novel ways in which existing interventions could be applied to features for which they are not currently targeted. Moreover, as ASD presentation often changes with age and with successful treatment, tracking developmental trajectories and monitoring the most prominent and disabling features across time and settings along positive, negative, and cognitive axes may inform dynamic implementation of treatments in response to the most pressing features at a given point in time.

Increased research into the particular neural and genetic etiology of positive, negative, and cognitive features of ASD may pave the way for more precise diagnosis and targeted treatments. As with schizophrenia, several broad mechanisms, including an imbalance in excitatory and inhibitory neurotransmission and atypical neural synchrony, have been proposed to be at the core of ASD (Rubenstein and Merzenich 2003; Uhlhaas and Singer 2006). However, these models do not clearly articulate why the hallmark pattern of features associated with ASD result from the proposed underlying neural abnormalities, while other signs and symptoms do not. The ability to test the likelihood of these mechanisms underlying ASD may benefit from more clearly articulating specific feature clusters and dimensions within the ASD phenotype. To date, though not previously discussed in this manner, specific brain regions have been associated with negative features, such as deficits in social perception (McPartland et al. 2011), whereas others have been associated with cognitive impairments (Schmitz et al. 2006), and still others have been linked to different positive features, including circumscribed interests (Cascio et al. 2014). While certainly some underlying neurobiological abnormalities may link to features that span positive, negative, and cognitive dimensions, exploring them along these dimensions may offer opportunity to identify other specific biological alterations that may map more directly onto

one feature dimension than another, whereas this link may have previously been obscured by the search for brain-behavior mappings to explain ASD features clustered within existing DSM domains.

Work also has identified links between known genetic risk factors for ASD and feature clusters. For example, in some genetic disorders that result in ASD, the phenotypic presentation is more homogenous across individuals and features appear to be more negative, such as failure to initiate conversation, than positive (Bruining et al. 2010). Whether specific genes map to positive versus negative versus cognitive features is yet unknown as we are limited by how the field has been looking for them. For example, mouse models of ASD are developed and evaluated based on the extent to which their phenotypic expression is analogous to the social, communication, and restricted/ repetitive symptoms of ASD (Silverman et al. 2010). If the mouse models were instead evaluated based on their expression of positive vs. negative features, we might find differences in genes underlying positive vs. negative feature expression. Likewise, underlying mechanisms may not be uncovered if researchers are lumping across positive and negative expressions of an attribute (e.g. exaggerated vs. restricted affect) in describing and attempting to identify the biological basis of the broader attribute (i.e., atypical facial expressions). This point is well illustrated in the context of mood disorders, where mania (i.e., elevated mood) and depression (i.e., low mood) have different biological correlates (Delvecchio et al. 2012; Kempton et al. 2011). If researchers had lumped the positive and negative manifestations of altered mood together as a single construct of “atypical mood expression,” these different mechanisms might not have been uncovered, and our diagnosis and treatment of affected individuals would be well behind where it is today. Thus, conceptualization of ASD symptomatology along positive, negative, and cognitive dimensions holds promise to inform and build upon existing neuroimaging and genetic findings attempting to parse clinical heterogeneity in biologically meaningful ways.

Summary

The introduction of RDoC and the revised diagnostic classification of ASD in DSM-5 call for a new way of conceptualizing heterogeneous ASD features. Here we have suggested a novel conceptualization of ASD on the basis of positive, negative, and cognitive dimensions, paralleling the dimensional symptom framework already recognized in schizophrenia. We argue that this conceptualization will provide three vital research opportunities: (1) a new means of capturing the heterogeneity of feature presentation in ASD, (2) more precise identification of common etiologies and neural abnormalities underlying feature dimensions, and (3) dimension-specific treatment approaches across disorders. Collectively, we posit that both researchers and clinicians in the ASD field would benefit substantially by leveraging the dimensional feature understanding that has been advanced through schizophrenia research. Ultimately, this cross-fertilization has the potential to improve our mechanistic understanding of links from genes and cells, to neural systems, and ultimately to specific patterns of behavioral impairments that exist within and across currently defined diagnostic categories.

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Table 1

Examples of ASD symptoms, grouped as delineated in the DSM-5 criteria, then classified along positive, negative, and cognitive dimensions

Positive symptoms	Negative symptoms	Cognitive symptoms
A1. Deficits in social-emotional reciprocity		
Abnormal social approach • Intrusive initiations • Use of others as tools • Excessive verbosity		
Failure of normal back and forth conversation • One-sided conversations • Monologues • Tangential speech	• Failure to respond when name is called or when spoken to directly • Failure to initiate conversation	• Failure to understand humor, sarcasm, and non-literal language
Reduced sharing of interests	• Lack of bringing, showing, pointing • Lack of initiating or responding to joint attention	
Reduced sharing of emotion • Aversive reaction to physical contact and affection	• Lack of social smile • Failure to share enjoyment • Failure to offer comfort	
Lack of initiation of or response to social interaction	• Failure to initiate interactions with others	
A2. Deficits in nonverbal communicative behaviors		
Abnormalities in eye contact • Prolonged or overly intense eye contact	• Reduced eye contact • Gaze avoidance	
Impairment in use and understanding of body language • Standing too close to interaction partners	• Facing away from a listener	
Abnormal volume, pitch, intonation, rate, rhythm, stress, prosody, or volume in speech • “Sing-song” or exaggerated intonation	• Mechanical intonation	
Deficits in understanding and use of gestures	• Reduced nodding or shaking head • Lack of descriptive gestures	
Abnormalities in use and understanding of facial expressions • Exaggerated facial expressions	• Limited range of facial expressions	

	Positive symptoms	Negative symptoms	Cognitive symptoms
		• Limited communication of own affect • Inability to recognize others' nonverbal expressions	
Lack of coordinated verbal and non-verbal communication		• Failure to integrate multiple modes of communication	
A3. Deficits in developing, maintaining, and understanding relationships			
Difficulties in making friends	• Excessive overtures that are off-putting to others • Breaching conventions of social interactions, such as by being extremely directive or rigid	• Inability to make and maintain relationships with developmentally matched peers • Lack of friendships • Lack of cooperative play • Failure to respond to social approaches of other children	• Lack of Theory of Mind or ability to take another's perspective
Difficulties adjusting behavior to suit various social contexts	• Inappropriate expressions of emotion, such as laughing or smiling out of context • Socially inappropriate statements and questions	• Failure to notice others' lack of interest • Lack of response to contextual cues • Failure to notice other's distress • Failure to recognize when not welcome in play or conversation • Limited recognition of social emotion	
Difficulties in sharing imaginative play		• Lack of imaginative play with peers	
Absence of interest in peers		• Lack of interest in peers • Withdrawal and aloofness • Preference for solitary activities	
B1. Stereotyped or repetitive motor movements, use of objects, or speech			
Stereotyped or repetitive speech	• Pedantic speech • Echolalia • Idiosyncratic language	• Failure to develop functional language	

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	Positive symptoms	Negative symptoms	Cognitive symptoms
	• Pronoun reversal • Perseverative language		
Stereotyped or repetitive motor movements	• Repetitive hand movements • Complex whole body movements • Body tensing • Abnormal postures, such as toe walking		
Stereotyped or repetitive use of objects	• Lining up toys or objects • Repetitively turning lights on and off	• Non-functional play with toys	
B2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal and nonverbal behavior			
Adherence to routine	• Specific sequences of behavior • Insistence on rigidity in following specific routines		• Cognitive inflexibility • Black and white thinking • Rigid adherence to rules, rituals, and routines
Excessive resistant to change	• Difficulty with transitions • Overreaction to trivial changes in environment or appearances		• Insistence on sameness
Rigid thinking			• Inability to understand humor • Inability to understand nonliteral aspects of speech • Excessively rigid, inflexibility, or rule-bound thought
B3. Highly restricted, fixated interests that are abnormal in intensity or focus			
Preoccupations and obsessions	• Preoccupation with particular, narrow, or unusual topics of interest to an excessive degree	• Narrow range of interests	• Perseverative thinking patterns • Preoccupation with numbers, letters, symbols • Splinter skills, such as hyperlexia

	Positive symptoms		Negative symptoms		Cognitive symptoms	
					•	Overly perfectionistic cognitive style
Excessively circumscribed or perseverative interest	•	Persistent focus on same few objects, topics, or activities				
Excessive focus on non-relevant or non-functional parts of objects	•	Focus on parts of objects, such as wheels on cars	•	Failure to use toys or objects as intended		
			•	Lack of imagination		
Attachment to unusual objects	•	Unusual attachment to specific objects				
B4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment						
Unusual visual exploration	•	Close visual inspections of objects				
	•	Peering out of the corner of one's eyes				
	•	Extreme fascination with watching movement				
Apparent indifference to pain	•	Self-injurious behavior	•	Failure to show pain response to stimuli typically considered painful		
In all domains of sensory stimuli, odd response to sensory input	•	Extreme distress to loud noises or particular clothing or food textures	•	Lack of response to sound, sight, or touch		
	•	Persistent focus on sensory input, such as fans spinning or water running	•	Under-responsiveness to sensory stimuli		
Unusual sensory exploration with objects	•	Licking or sniffing objects				