

Syndromic Autism: Progressing Beyond Current Levels of Description

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Abstract

Genetic syndrome groups at high risk of autism comorbidity, like Down syndrome and fragile X syndrome, have been presented as useful models for understanding risk and protective factors involved in the emergence of autistic traits. Yet despite reaching clinical thresholds, these ‘syndromic’ forms of autism appear to differ in significant ways from the idiopathic or ‘non-syndromic’ autism profile. We explore alternative mechanistic explanations for these differences and propose a developmental interpretation of syndromic autism that takes into account the character of the genetic disorder. This interpretation anticipates syndrome-specific autism phenotypes, since the neurocognitive and behavioural expression of the autism is coloured by syndromically defined atypicalities. To uncover the true nature of comorbidities and of autism per se, we argue that it is key to extend definitions of autism to include the perceptual and neurocognitive characteristics of the disorder and then apply this multilevel conceptualization to the study of syndromic autism profiles.

Key words: syndromic autism, Down syndrome, fragile X syndrome

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Abstract

Genetic syndrome groups at high risk of autism comorbidity, like Down syndrome and fragile X syndrome, have been presented as useful models for understanding risk and protective factors involved in the emergence of autistic traits. Yet despite reaching clinical thresholds, these ‘syndromic’ forms of autism appear to differ in significant ways from the idiopathic or ‘non-syndromic’ autism profile. We explore alternative mechanistic explanations for these differences and propose a developmental interpretation of syndromic autism that takes into account the character of the genetic disorder. This interpretation anticipates syndrome-specific autism phenotypes, since the neurocognitive and behavioural expression of the autism is coloured by syndromically defined atypicalities. To uncover the true nature of comorbidities and of autism per se, we argue that it is key to extend definitions of autism to include the perceptual and neurocognitive characteristics of the disorder and then apply this multilevel conceptualisation to the study of syndromic autism profiles.

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Syndromic Autism: Progressing Beyond Current Levels of Description

Autism Spectrum Disorders (henceforth *autism*) is a diagnostic umbrella term used to describe a heterogeneous collection of complex neurological disorders characterised by socio-communicative impairment and restricted, repetitive patterns of behaviour (DSM-5, American Psychiatric Association [APA], 2013; ICD-10, World Health Organization [WHO], 1994). Autism occurs in approximately 1% of the general population and is predominantly ‘non-syndromic’ or ‘idiopathic’, meaning it arises from unknown causes (Baio, 2012; Baird et al., 2006; Brugha et al., 2012). However, in 10% of cases, autism coincides with a genetic syndrome of known aetiology (Abrahams & Geschwind, 2008). These ‘syndromic’ forms of autism are so-called on account of their well-defined genetic cause and are considered by many to offer unique insights into the early risk factors that contribute to the emergence of the autism phenotype. Yet the precise nature of these comorbidities remains poorly understood.

Genetic disorders characterised by high rates of autistic symptomology include Tuberous Sclerosis complex, fragile X syndrome (FXS), Down syndrome (DS), Angelman syndrome, Rett syndrome and William syndrome (for review, see Caglayan, 2010). The most frequently occurring of these disorders, DS and FXS, receive particular attention from researchers as they offer a large empirical database in terms of neurocognitive profile and associations with autism (Moss & Howlin, 2009).

Drawing on the existing literature, we explore a number of key issues concerning syndromic autism phenotypes, with specific reference to DS and FXS populations. First, we consider current perspectives on why these two genetic syndrome groups are associated with elevated risk of autism. Second, we review what is presently known about the nature of these

syndromic forms of autism and on this basis, propose a developmental interpretation of what research would suggest are syndrome-specific autism phenotypes. Finally, we advocate for fine-grained analyses to be applied to the study of syndromic autism, with reference to clinical implications.

Towards an Understanding of Syndromic Autism Risk

Fragile X syndrome (FXS) is the leading known genetic cause of autism, with comorbidity rates estimated to fall between 20-50% (Hagerman & Harris, 2008; Hatton et al., 2006; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004). This single-gene disorder is caused by a CGG repeat polymorphism that represses the expression of the Fragile X mental retardation 1 (FMR1) gene on the X chromosome (Jin & Warren, 2000; Verterk et al., 1991). Subsequent deficient levels of Fragile X mental retardation protein (FMRP) yield irregularities in protein synthesis and dendritic morphology, with negative implications for synaptic functioning, regulation and overall neural connectivity (e.g., Irwin et al., 2001; Weiler et al., 2004; also for review, see Santoro, Bray, & Warren, 2012).

Similarly, Down syndrome (DS) offers an interesting association with autism, with approximately 19% of individuals exhibiting socio-communicative deficits that warrant a secondary autism diagnosis (DiGuseppi et al., 2010; Lowenthal, Paula, Schwartzman, Brunoni, & Mercadante, 2007; Warner, Moss, Smith, & Howlin, 2014). Caused by the presence of a full or partial trisomy of chromosome 21, DS is associated with widespread neuropsychological dysfunction and subsequently high rates of intellectual disability (ID; Beacher et al., 2005; Belichenko et al., 2015; Galdzicki & Siarey, 2003; Yu et al., 2010).

It is not yet known why these genetic syndrome groups are at elevated risk of autism relative to the general population and other neurodevelopmental disorders. Skuse (2007) postulates that syndromic autism risk is largely a matter of ID, as it diminishes the brains

capacity to compensate for the presence of independently inherited autistic-like traits. Indeed, individuals with DS and autism are reported to have a greater intellectual impairment than those with DS in isolation (DiGuseppi et al., 2010; Molloy et al., 2009). Similarly, autism in FXS is more likely to be identified in individuals with a greater degree of ID (Lewis et al., 2006; Loesch et al., 2007). However, while ID plays a clear role in the development and presentation of autistic-like traits in individuals at high syndromic risk, research has shown that it cannot account in full for the heightened prevalence of autistic characteristics in such genetic syndrome groups (Capone, Grados, Kaufmann, Bernad-Ripoll, & Jewell, 2005; Lee, Martin, Berry-Kravis, & Losh, 2016; for review, see Moss & Howlin, 2009).

Despite high heritability estimates, the precise genetic architecture of autism remains unclear, with each idiopathic or ‘non-syndromic’ presentation representing a complex collage of multiple genetic risk factors (Betancur, 2011; Robinson, Neale, & Hyman, 2015). Johnson (in press) accounts for this aetiological complexity by proposing that autism is the product of an adaptive brain response to early synaptic dysfunction, in which a wide variety of genes are implicated. This conceptualisation may be applied to syndromic forms of autism also.

Despite their distinct genetic origins, both FXS and DS phenotypes are characterised by neural irregularity at the level of the synapse (Huber, Gallagher, Warren & Bear, 2002; Weick et al., 2013; Weiler & Greenough, 1999; Weitzdoerfer, Dierssen, Fountoulakis, & Lubec, 2001). It may be the case, then, that regardless of aetiology, sub-optimal signal processing in early life triggers compensatory or adaptive brain processes, the developmental consequence of which is an autism-like phenotype.

Still the question remains: what differentiates individuals with syndromic autism from those with FXS or DS in isolation? Additional genetic risk factors are likely to play a role. In the case of DS, a number of genes implicated in autism are located on chromosome 21

(Molloy, Keddache, & Martin, 2005). Thus, individual variability in the overexpression of these genes may account for syndromic autism presentations in some individuals with DS (Reeves et al., 1995; Reymond et al., 2002). Moreover, the severity of neurocognitive impairment that accompanies a FXS or DS diagnosis may influence the development and expression of autistic symptomology. For instance, auditory inattention has been found to shape subsequent socio-communicative outcomes in boys with FXS (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012). Attentional impairment in the auditory modality may therefore be an important risk factor for autism in this clinical population.

Finally, syndromic autism risk may be mediated to some extent by environmental factors. For instance, in typical development, early parent interaction style has been found to influence the rate at which infants reach cognitive milestones (Karmiloff-Smith et al., 2010). Sensitive and responsive parenting is considered optimal as it promotes self-directed learning behaviour. Critically, infants with a diagnosed genetic syndrome are less likely to encounter this optimal interaction style. Rather, they tend to experience a more directive and less responsive parenting style, as caregivers endeavour to compensate for the child's cognitive and behavioural difficulties (Soukup-Ascençao, D'Souza, D'Souza, & Karmiloff-Smith, 2016). The potential size of this environmental mediation is as yet unknown. Nevertheless, it is clear that understanding why certain individuals at syndromic risk of autism proceed to a secondary diagnosis and others do not demands consideration of environmental factors including, but not limited to, early parenting style.

Syndrome-Specific Autism Phenotypes

Phenotypic heterogeneity is a key feature of autism. Formal diagnostic systems are designed to allow for this variability in that only a proportion of the behaviours implicated in the phenotype are necessary for a diagnosis to be given (DSM-5, APA, 2013; ICD-10, WHO,

1994). Still, it is becoming increasingly apparent in the literature that despite reaching clinical diagnostic thresholds, individuals with syndromic forms of autism present with distinct patterns or profiles of autistic symptomology in comparison to non-syndromic reference groups. Autism profiles in individuals with DS, for instance, are associated with less environmental withdrawal, greater social reciprocity, and reduced impairment in several aspects of non-verbal communication including use of gesture and imitation (DiGuseppi et al., 2010; Moss et al., 2013). Interpretations of these findings include the possibility that relative strengths in terms of sociability in DS provide protection against some of the social deficits associated with non-syndromic autism (DiGuseppi et al., 2010; Rosner, Hodapp, Fidler, Sagun, & Dykens, 2004).

Comparative behavioural analyses support a distinct profile of autistic symptomology in individuals with FXS also, with increased social responsivity, greater emotional sensitivity and less idiosyncratic speech (e.g., pronoun reversal) differentiating this form of autism from the non-syndromic phenotype (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010; McDuffie, Thurman, Hagerman, & Abbeduto, 2015; Turk & Cornish, 1998). Of note, these profile differences continue to hold when autism symptom severity and intellectual ability are accounted for (McDuffie et al., 2015). Moreover, an atypical trajectory of symptomatic expression has been documented in FXS, with socially avoidant behaviours becoming progressively more severe over time (Hatton et al., 2006; Roberts et al., 2007). Non-syndromic autism, conversely, is generally associated with improvements in core symptomatology with age (Charman et al., 2005; Moss, Magiati, Charman, & Howlin, 2008).

In terms of interpreting these symptomatic profile differences, disparate mechanistic explanations warrant consideration. First, autistic-like traits may arise as a consequence of the phenotypic expression of the genetic syndrome. For instance, empirical support has been

found for the claim that autism symptoms in FXS arise on account of anxiety, as opposed to diminished social motivation, with Thurman and colleagues documenting a significant positive correlation between general anxiety scores and autism symptom severity in boys with FXS (Thurman, McDuffie, Hagerman, & Abbeduto, 2014). According to the authors, these children struggle to partake in, and subsequently acquire knowledge from, social interactions due to an inattentive, hyperactive and anxious predisposition, with these psychiatric factors playing a cumulative role over developmental time in the emergence of the social impairments that lead to a comorbid autism diagnosis. For example, eye gaze avoidance in children with FXS has been hypothesised to occur as a direct result of these behaviours (Cohen, Vietze, Sudhalter, Jenkins, & Brown, 1989). In non-syndromic ASD, conversely, diminished eye gaze is considered an expression of reduced interest and motivation in attending to social stimuli. Thus, the evidence appears to be consistent with the possibility that different neurocognitive processes underlie autism diagnoses in this syndromic population (for review, see Cornish, Turk, & Levitas, 2007).

Alternatively, it may be that the genes for autism are present in a proportion of individuals with DS and FXS but their expression is altered in some way by the neurophysiological and cognitive properties of the genetic syndrome itself. Inherent in this assumption are neuroconstructivist principles of progressive neural specialisation and emergent cognitive outcomes (Karmiloff-Smith, 2009). From this dynamic developmental perspective, autism is considered an emergent phenotype vulnerable to the impact of syndromic factors, as opposed to a predetermined phenotype immune to the character of the genetic syndrome. As such, it is intuitive to anticipate that syndrome-specific autism profiles, in terms of the neurocognitive and behavioural expression of the 'classic' autism phenotype, will be coloured by the nature of the genetic disorder.

This notion of syndrome-specific autism phenotypes gives rise to novel hypotheses. First, it is important to note that beyond formal diagnostic classification, non-syndromic autism is associated with a unique visuo-attentional and perceptual profile. This includes a local or featural processing bias, on account of which individuals with autism have difficulty processing complex social information, like faces (Behrmann et al., 2006; Gauthier, Klaiman, & Schultz, 2009; Scherf, Elbich, Minshew, & Behrmann, 2014). This is substantiated by brain imaging research documenting atypical neural responses to eye gaze and diminished face inversion effects in individuals with autism (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; Tye et al., 2013). Now, consider that, as stated previously, relative social competency in DS is considered to be a protective factor against certain elements of the autism phenotype, including diminished social reciprocity and environmental withdrawal (DiGuseppi et al., 2010). If the expression of autism in DS is indeed coloured in this way, it should be evident across multiple levels of description. Beyond overt phenotypic characteristics, then, individuals with DS and autism may be expected to demonstrate less of a visuo-perceptual preference for local detail and subsequently fewer face processing deficits than individuals with non-syndromic autism.

Clinical and Diagnostic Implications

When faced with the challenge of discerning whether a child with a genetic disorder is presenting with autism, clinicians deliberate on the extent to which the behavioural, symptomatic profile exhibited by the child resembles that of non-syndromic autism. However, the autism encountered in individuals with genetic disorders like FXS or DS does not appear to reflect the ‘classic’ phenotype, with subtle deviations in terms of cognitive strengths and weaknesses distinguishing syndromic from non-syndromic presentations. Consequent clinical uncertainty surrounding the nature and validity of syndromic forms of

autism often leads to prolonged diagnostic decision making and delayed access to intervention services. The significance of this is apparent in research documenting poorer prognostic outcomes in individuals presenting with syndromic autism, relative to those with stand-alone diagnoses (Carter, Capone, Gray, Cox, & Kaufmann, 2007; Hatton et al., 2003; Molloy et al., 2009; Philofsky et al., 2004; Warner et al., 2014).

Clinical uncertainty is aggravated further by the insensitivity of current assessment measures to detect cases of secondary autism from genetic syndrome groups characterised by distinct, yet nuanced, socio-communicative impairment. While there is some preliminary support for the clinical incorporation of eye tracking paradigms as objective means of identifying risk markers for autism (Frazier et al., 2016; Pierce et al., 2016), diagnostic utility in the context of syndromic autism has yet to be explored. First, future research will need to ascertain whether syndrome-specific autism phenotypes exist and can be documented across multiple levels of analyses. Empirical insights gained may ultimately benefit clinical practice by facilitating more timely and accurate diagnoses, and by minimizing the risk of diagnostic overshadowing (i.e., the clinical tendency to attribute symptoms of a co-occurring disorder to the primary diagnosis).

Little is known about whether treatment programs designed to target the mechanisms underpinning socio-communicative impairment in non-syndromic autism are applicable to syndromic forms of the disorder. Founded upon a social motivational account of autism, the Early Start Denver Model (ESDM) is one intervention program for which significant improvements in autistic symptomatology have been documented (Dawson et al., 2010; Estes et al., 2015). By increasing a child's exposure to meaningful interpersonal exchange and positive affect, this practice seeks to facilitate active attention to faces, promote the development of neural reward systems specific to social interaction and consequently elevate

the child's social motivation. In addition to significant gains in socio-communicative function, long-term participation in this program has been found to normalise electrophysiological brain responses to facial stimuli in young children with autism (Dawson et al., 2012). It remains unknown, however, whether application of ESDM to syndromic forms of autism would generate similar improvements. If, as per the literature, the neurocognitive basis for autism in FXS is inattention and anxiety as opposed diminished social motivation, this kind of intervention is unlikely to be effective (Thurman et al., 2014). Rather, a remedial focus on minimising anxiety levels in infants with FXS may be preferable. Attention training, for instance, has been found to reduce anxiety in anxious individuals (Amir et al., 2008; Hazen et al., 2009; Mathews & McLeod, 2002; Schmidt et al., 2009). This may be a more promising approach to treating socio-communicative impairment in children with comorbid FXS and autism. Thus, research focused on identifying the mechanisms by which syndromic autism profiles emerge is necessary in order to direct clinical foci in the early years and improve prognostic outcomes in these populations.

Future Research: Cautions & Considerations

If we define autism strictly according to current diagnostic standards, we may conclude that a child with a genetic disorder who reaches clinical thresholds on widely used assessment measures, such as the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2000) and the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & LeCouteur, 1994), has autism. However, to address the question of whether autistic symptomology in syndromic populations represents the 'classic' autism phenotype, we advocate empirical incorporation of a broader definition of autism - one that includes the visuo-perceptual and neurophysiological markers for the disorder that have been documented in the literature. Investigating whether syndromic autism is similarly characterised by a

perceptual preference for local detail, for instance, would provide valuable insight into the mechanisms underpinning syndromic autism profiles. Empirical efforts to differentiate comorbid from non-syndromic autism phenotypes must, therefore, progress from a reliance on insensitive behavioural measures of socio-communicative function towards more fine-grained analytic frameworks incorporating sensory processing and neuroimaging modalities. Furthermore, longitudinal trajectory analyses of symptomatic change over time are necessary to build a more comprehensive understanding of the nature and development of syndromic autism profiles (Karmiloff-Smith et al., 2004; Thomas et al., 2009). Such a research foundation would then provide a basis on which to develop sensitive and robust measures of neurocognitive profile for potential clinical use.

Advances in the field of autism research are challenged by developing definitions of autism and uncertainty concerning the phenotypic specificity of autistic traits (for discussion, see Xavier, Bursztein, Stiskin, Canitano, & Cohen, 2015). Recent enquiry into what constitutes the ‘typical’ DS phenotype, for instance, has provided support for the inclusion of repetitive and restricted patterns of behaviour (Channell et al., 2015). These findings caution researchers against accepting superficial behavioural similarities or heightened scores on autism assessments that may be accounted for by syndromic factors. Clinical input is necessary for accurate differentiation of individuals with and without syndromic autism. Thus, future research should endeavour to include clinical judgement when evaluating the nature of autistic symptomology in syndromic populations.

Syndromic autism was first documented over 30 years ago (Brown et al., 1982), yet much remains to be elucidated about this comorbidity. Critically, it remains unclear whether autistic symptomology exhibited by individuals with a genetic disorder reflects the same underlying cognitive and neurobiological impairments as in non-syndromic autism. We

propose a developmental interpretation of autism comorbidity that takes into account the character of the genetic disorder and anticipates emerging syndrome-specific autism phenotypes. Clinical efforts to diagnose syndromic autism may be better served by an expectation of syndrome-specific autism phenotypes, as opposed to the ‘classic’ autism presentation. Such a distinction provides a sounder basis on which to evaluate the utility of different types of intervention for syndromic and non-syndromic forms of autism.

Compliance with Ethical Standards

The authors declare that they have no conflict of interest. No study was performed on any human or animal subjects. For this type of research, formal consent is not required.

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