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Neurodevelopmental Disorders Affecting Sociability: Recent Research Advances and Future Directions in Autism Spectrum Disorder and Williams Syndrome

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Abstract

Purpose of Review In this review, we summarize current knowledge and hypotheses on the nature of social abnormalities in autism spectrum disorder (ASD) and Williams syndrome (WS).

Recent Findings Social phenotypes in ASD and WS appear to reflect analogous disruptions in *social cognition*, and distinct patterns of *social motivation*, which appears to be reduced in ASD and enhanced in WS. These abnormalities likely originate from heterogeneous vulnerabilities that disrupt the interplay between domain-general and social domain-specific cognitive and motivational processes during early development. Causal pathways remain unclear.

Summary Advances and research gaps in our understanding of the social phenotypes in ASD and WS highlight the importance of (1) parsing the construct of sociability, (2) adopting a developmental perspective, (3) including samples that are representative of the spectrum of severity within ASD and WS in neuroscientific research, and (4) adopting transdiagnostic treatment approaches to target shared areas of impairment across diagnostic boundaries.

Keywords Autism · Williams syndrome · Neurodevelopmental disorders · Social cognition · Social motivation · Early intervention

Introduction

Autism spectrum disorder (ASD) and Williams syndrome (WS) are among the most frequently contrasted disorders in cross-syndrome neurodevelopmental research. This line of research originates from the observation that social development appears to be affected along opposite trajectories in the two disorders, resulting in hyposociability in ASD and hypersociability in WS. Despite the diverging social phenotypes, recent research has pointed to shared abnormalities at the behavioral, neural, and genetic levels [1, 2]. Against this puzzling background, comparative examination of ASD and WS has become an area of increasing focus for scholars interested in biobehavioral mechanisms of human sociability in typical and atypical development [3]. In this review, we summarize recent findings and discuss the promise and caveats emerging from this area of research, with a focus on knowledge gaps, research priorities, and clinical implications.

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Current Understanding of ASD

ASD (estimated prevalence 1:59, male to female ratio 4:1 [4]) is a neurodevelopmental disorder characterized by early emerging impairments in the domains of social communication and behavioral flexibility [5]. Symptoms are expressed along a continuum (spectrum) of severity, and are affected by (and affect) the developmental level of the individual [6, 7]. Additionally, symptom presentation is affected by medical and psychiatric conditions (e.g., anxiety, tic disorders, epilepsy), which co-occur more frequently in the ASD population compared to rates in the general population [8, 9]. Cognitive profiles in the ASD population are characterized by heterogeneous patterns of strengths and weakness, with intellectual

disability observed in approximately one third of individuals with ASD (and disproportionately among females [4]).

The etiology of ASD is heterogeneous, reflecting the dynamic interplay of multiple genetic and environmental risk factors. Twin studies suggest heritability between 55 and 90% [10, 11], and over 200 genetic vulnerabilities have been identified. Importantly, many of these genes code for the production of proteins critical for early brain development and functioning. Environmental factors also play a role in autism development, with exposure to certain medications and toxins in utero linked to ASD risk [12].

Research on the ASD Social Phenotype

Research on the core impairments of ASD has documented early disruptions across multiple dimensions of social functioning, complicating the notion of "social deficit" as a unitary construct [13]. These include (a) decreased *social orienting*, i.e., a reduced attentional engagement towards faces, voices, and biological movements [14–17], (b) reduced *social motivation*, as reflected in a preference for solitary versus social activities and decreased expressions of pleasure during social interactions [18, 19], as well as (c) abnormalities in *social cognition*, i.e., the ability to "read" social information, including difficulties understanding the communicative intent of gaze [20, 21], the tendency to incorrectly interpret others' behavior based on one's knowledge, rather than others' knowledge [22, 23], as well as difficulties interpreting verbal communication when the communicative intent does not match the literal meaning of a statement (e.g., sarcasm, metaphors; [24–26]).

Differences in ability and motivation to register and interpret social information in ASD affects *social learning* (i.e., the ability to acquire knowledge from observation of and interaction with others), as suggested by recent eye-tracking studies documenting a link between atypical patterns of visual engagement with social stimuli and the ability to understand, imitate, and learn from others [27–31]; see also [32]. Disruptions in social learning, in turn, have downstream consequences and contribute to the poor adaptive functioning observed in the ASD population across cognitive functioning levels [33].

Recent neuroscientific research based on the longitudinal examination of high-risk infants has generated several accounts of the social impairments listed above. One line of research has pointed to the possibility that social abnormalities in this population are the consequence of early disruptions in the reflexive, subcortically-mediated processes that bias infants' attention towards social stimuli [34]. Support for this notion comes from research showing that newborns who are at risk for ASD (by virtue of having an older sibling with ASD) show preferential looking and increased attention for inverted versus upright face-like images as well as non-biological versus biological motion compared to their low-risk newborn peers. This suggests that the neural precursors to the social abnormalities that characterize autism are present at birth, before more complex social processing networks that include cortical structures emerge.

An alternative explanatory framework proposes that core social symptoms of ASD reflect deviations in the neurocognitive mechanisms that support the developmental transition from subcortically- to cortically-mediated engagement with social stimuli [35••, 36]. Empirical research supporting this explanatory framework includes evidence that infants at high familial risk for ASD show normative attention to people's eyes in the first 2 months of life, followed by a decline in eye-looking between 2 and 6 months [15]. This suggests that reflex-like orienting to the eyes of others is initially present in newborns with ASD, but fails to give way to volitional, cortically-mediated visual social engagement during the first year of life [35••].

An additional area of debate is whether reduced visual engagement with social stimuli during infancy reflects primary deficits in social motivation (social stimuli are not experienced as rewarding) or social cognition (social stimuli are not experienced as meaningful or interpretable) and how these two dimensions (motivation and ability to engage with the social world) interact over the course of development [37].

Another line of research suggests that the core symptoms of ASD do not reflect deviations in domain-specific social processes, but rather widespread non-specific abnormalities that disrupt social processing due to the complexity and "irregularity" of social stimuli compared to other aspects of the environment [38, 39••]; see also [40]. According to this perspective, ASD reflects an early brain adaptation to compensate for widespread alterations in synaptic processing, which constrain developmental trajectories along an alternative developmental pathway [38, 39••]. Consistent with this framework, widespread network abnormalities have been identified in ASD, which are predictive of a later ASD diagnosis at 6 months of age [41], and several studies have pointed to atypical connectivity across social and non-social brain regions in older individuals, although findings in this area are mixed [42]. However, other imaging research has identified specific abnormalities within the social brain network, including atypical brain activity in response to social versus non-social rewards, and various social domain-specific processing tasks [43–45] (see [46, 47], for recent overviews).

Additional insight on the nature of social symptoms in ASD might be gained by recent prodromal intervention trials involving infants at familial risk of ASD. Such preventative intervention efforts capitalize on the "window of opportunity" of early sensitive periods to target social-communicative skills when developmental trajectories might be advantageously altered [48, 49].

Research in this area has documented substantial improvement in response to early interventions targeting prodromal social symptoms in infants and toddlers at risk for ASD, including an overall reduction of ASD symptoms [50–52], improvement in functional communication [53], gains in social engagement (e.g., eye contact, response to name, positive affect) [54], and enhancement of parent–child dynamic social engagement [51].

Additionally, research has begun to document changes in brain response to social stimuli following early intervention using electroencephalography [55] and functional magnetic resonance [56, 57] with preliminary evidence suggesting that neural response to social stimuli of children with ASD receiving intervention becomes more similar to that of typically developing children.

Summarizing, there is empirical support for different explanatory frameworks of the core social impairment in ASD, including "social-first" accounts and "multiple deficits" accounts positing different pathways from early biological constraints to symptom expressions. Regardless of causal pathways, it appears that social information is experienced as less interpretable, less rewarding, and more "noisy" by young children with ASD compared to typical peers. The resulting altered engagement with the social world during early "experience-expectant" sensitive periods (i.e., periods in which it is expected that all individuals within a species will have certain experiences that influence neural processing) [58] is likely to affect neural specialization and behavioral organization in the social domain, thus exacerbating initial abnormalities in an iterative fashion [59–61]. (See Fig. 1 for a synopsis of this conceptualization.) A corollary of this framework is that targeted intensive intervention during early sensitive periods may mitigate or prevent this escalating deviance from typical social development. Promising yet preliminary data from treatment research provide support for this notion, suggesting some degree of malleability of core social symptoms and their neural underpinnings following interventions that target social functioning in infancy and toddlerhood [50, 52, 56].

Current Understanding of WS

Williams syndrome (WS) is a rare neurodevelopmental disorder (estimated prevalence of 1:7500–1:20,000; [62]) caused by the deletion of a set of genes on chromosome 7 [63] and characterized by mild to moderate intellectual disability, profound visuospatial impairments, motor difficulties, and relative strengths in language (with remarkable heterogeneity, see [64]). Additionally, individuals with WS show an increased drive for social interactions and are noted to have atypically elevated levels of empathy and gregariousness [65, 66].

The WS hypersociable profile has been historically defined as the "polar opposite" of ASD (e.g., [67]). Subsequent research, however, has challenged this notion, documenting how hypersociability in WS co-exists with several social cognitive impairments that are analogous to those observed in ASD. For example, cross-syndrome studies of spontaneous social behavior during semi-structured observational protocols documented fewer and less severe social abnormalities in WS compared to ASD; however, difficulties in joint attention and reduced rates of social behaviors such as giving and showing objects to others were reported across both syndromes, although with larger heterogeneity in the WS group [68, 69]. Vivanti and colleagues [27] documented similar joint attention difficulties in age and IQ matched preschoolers with ASD and WS, with both groups showing reduced visual engagement with the focus of others' attention. Furthermore, a recent study reported that preschoolers with WS and ASD showed a similar pattern of reduced motor interference (i.e., the decrease in motor performance that occurs when one executes an action while observing an incongruent action), suggesting that action execution in both syndromes is less affected by the observation of others' behavior. Additional research [70] has documented cross-syndrome difficulties in social reasoning (understanding why an agent acts in a certain way) in school-age children with ASD and WS (see also [71]) as well as shared difficulties across several aspects of pragmatic language such as appropriateness of initiations and use of context in communication ([72]; see also [73]). Difficulties in emotion recognition have also been reported across syndromes [74], with one study showing greater deficits in WS compared to ASD in

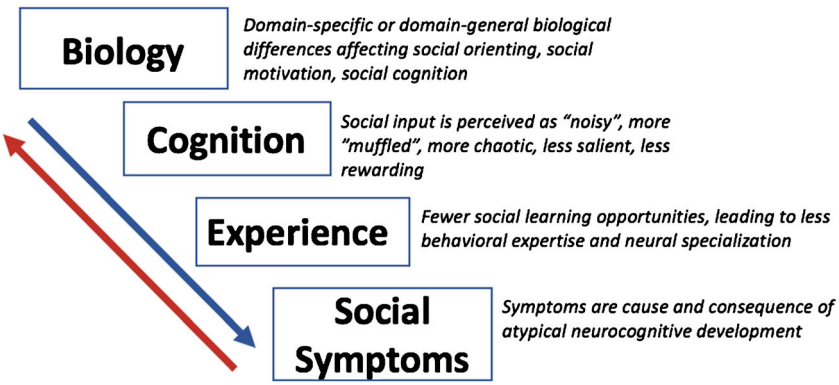

Fig. 1 Iterative processes in the social manifestations of ASD

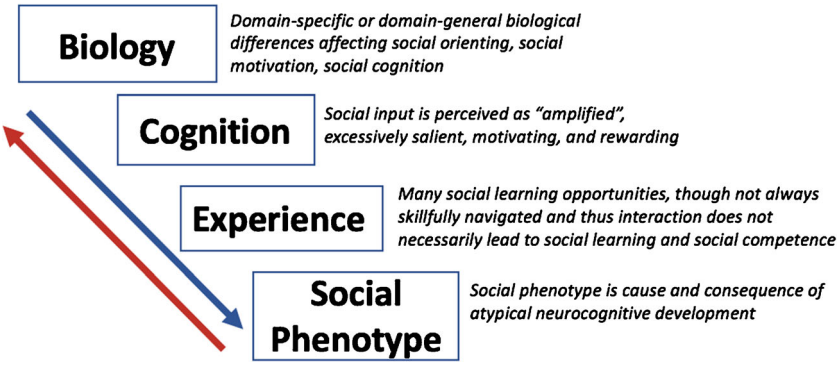

Fig. 2 Iterative processes in the social manifestations of WS

processing complex and neutral facial expressions [75]. Conversely, syndrome-specific strengths in WS versus ASD have been documented in studies evaluating attention to social stimuli [27, 74, 76, 77] and responsivity to social-communicative cues, such as paying special attention to objects that are verbally labeled by an adult and imitating adults who act in a socially engaging versus neutral manner [28, 78]; see also [79].

Similar to current directions in the field of ASD, it is debated whether the WS social phenotype reflects specific abnormalities in the social domain or non-social cognitive deficits with downstream consequences affecting sociability. One prominent "social-first" account is the "amygdala hypothesis," which points to the behavioral similarities in those with WS to patients with focal amygdala damage, including increased approach behavior [80] and violations of personal space [81], as well as findings of atypical amygdala morphology and functioning in WS [82–84]. These include relative increases in amygdala volume in WS relative to typically developing controls [82, 85] as well as associations between right amygdala volume and approachability ratings for negative faces [84]. Additionally, functional neuroimaging studies have documented that adults with WS, compared to neurotypical peers show lower amygdala reactivity in response to social stimuli, but heightened reactivity to non-social stimuli [44], as well as reduced amygdala reactivity to threatening faces and heightened arousal in response to happy faces [83]. Another "social-first" account of the WS social phenotype is the "social salience" hypothesis; [86, 87], suggesting that increased social approach in WS is the result of experiencing facial stimuli as excessively salient or rewarding. Consistent with this notion, Frigerio, Burt [88] documented increased approachability ratings for happy faces in individuals with WS compared to typical peers, but no group differences when viewing angry or sad faces, and more recently Järvinen et al. documented greater autonomic arousal in response to happy faces in those with WS compared to typically developing peers [75].

Other research suggests that the atypical WS social phenotype originates from non-social specific deficits, such as domain-general frontal lobe impairments. This perspective is supported by research documenting impaired response inhibition in WS (an index of frontal lobe impairment) relative to mental-age expectations, despite mental age appropriate emotion recognition skills [89]. Additionally, recent research shows similar behavioral presentations in individuals with WS and ADHD on ADHD rating scales [90], suggesting that core frontal lobe dysfunction in ADHD may also be shared by those with WS. While additional research is needed to evaluate the merits of these different explanatory accounts, a plausible model deriving from existing knowledge is that social information in children with WS is experienced as "amplified" and highly motivating from a very early age, due to either domain-specific or domain-general initial abnormalities. Atypical processing of social information and decreased social inhibition might result in increased approach as well as social cognitive abnormalities, giving rise to atypical engagement with the social world that might exacerbate initial abnormalities in an iterative fashion (see Fig. 2).

Despite the challenges experienced by those with WS, and in contrast with the growing body of early intervention literature on ASD, rigorous research on targeted early intervention programs for young children with WS is currently lacking, and knowledge in the area is limited to medical treatment for comorbid conditions (e.g., anxiety) or social skills training for adults [91]. Future efforts should focus on the development and examination of early interventions informed by the successful randomized trials in ASD, as positive outcomes for deficits shared across syndromes have been documented (e.g., joint attention deficits [92]).

Conclusions and Future Directions

The research reviewed in this article highlight the importance of parsing the construct of sociability to gain insight on the nature of social abnormalities in WS and ASD. Knowledge on the constellation of shared and distinct social impairments in these syndromes and their underlying biology, in turn, can help identify key neurocognitive processes and structures involved in human sociability. Overall, recent research suggests that social abnormalities in ASD and WS can be characterized in terms of analogous difficulties in social cognition (the ability to read others' behavior), and distinct patterns of social

motivation (the propensity for social approach/engagement) which appears to be reduced in ASD and enhanced in WS [93, 94]. These abnormalities, rather than reflecting static patterns of intact and impaired "cognitive modules" in the two conditions, likely originate from heterogeneous vulnerabilities that disrupt the interplay between domain-general and domain-specific social-motivational and social-cognitive processes during early development. While causal directionality is unclear, it is possible that difficulties understanding others' intentions and misreading "threatening" cues such as angry facial expressions leads children with WS to experience the social world as excessively friendly, thus producing hypersociability. Conversely, more severe social cognitive difficulties might lead children with ASD to experience the social world as chaotic and undecipherable, thus leading to hyposociability. Alternatively, impaired social cognition might be caused by excessive social motivation in WS (with extreme emotional arousal in response to social situations disorganizing the ability to process social information) and decreased social motivation in ASD (with reduced reward associated with social stimuli leading to diminished social expertise, and, consequently impaired social cognition). As summarized above, additional models have also been proposed, and more research is needed to gain a fine-grained understanding of the processes leading to the atypical social phenotypes observed in ASD and WS.

In particular, the following research gaps should be addressed to move the field forward. First, additional efforts are needed to clarify the conceptual taxonomy, developmental pathways, and neurobiological underpinnings of social behaviors and processes in typical development [95]. A fine-grained, dynamic account of social development from infancy to adulthood would provide a more solid background against which social disruptions observed in ASD and WS may be examined. Research in typical and atypical social development is characterized by many constructs (e.g., social reciprocity, social competence, social orienting, social reward social motivation, social cognition etc.), but few formal theories that parsimoniously articulate the elemental structure of competent social functioning exist. Imprecision in the definition of relevant constructs in different social domains is a barrier to the identification of causal factors, developmental sequelae, and treatment targets in neurodevelopmental disorders affecting social functioning such as ASD and WS [96].

Second, research on ASD and WS can benefit from additional research that adopts a true developmental perspective. As Karmiloff-Smith [97••] argued, developmental research entails more than studying infants and children. Most of today's research on ASD and WS, particularly neuroimaging studies, utilize case-control research designs. Such studies often include individuals of heterogeneous ages and compare clinical groups to typically developing controls without regard for developmental processes. As suggested by Johnson [39••], Karmiloff-Smith [98] and others, small deviations in early neural and cognitive processing may lead to large scale deviations in multiple domains of functioning in children with neurodevelopmental disorders, such as ASD and WS. Thus, more developmentally focused research is needed to identify behavioral and neural precursors to different aspects of the ASD and WS phenotypes to inform early intervention and even prevention efforts. The power of such research is evident from the growing corpus of behavioral (e.g., [99, 100] and neuroimaging investigations (e.g., [101, 102]) that have adopted developmentally-focused longitudinal investigations. However, there is still much to be done.

Third, the existing neuroimaging research literature has tended to focus on subsets of the ASD and WS population. For example, as reviewed by Jack and Pelphrey [103•], most neuroimaging studies of individuals with ASD have focused on those with typical intellectual and language functioning. They illustrated this by noting that at the time of their review, only about 1% of the participants in the National Database for Autism Research [104] with neuroimaging data had verbal and non-verbal IQ scores less than 85. However, research indicates that over 50% of children with ASD are thought to have IQ scores that fall below 85 [4, 105]. A similar trend was noted in early functional neuroimaging research on WS. As reviewed by Pryweller, Avery [106], 33% of functional neuroimaging studies at that time excluded participants with intellectual abilities below approximately 85. However, they noted that approximately 95% of people with WS have IQs below 85. Thus, a sizeable portion of what the field knew about brain functioning in WS was based on investigations that described a very small, non-representative portion of the WS population.

There are important methodological issues that have likely limited inclusion of a wide range of individuals who present with ASD and WS in neuroimaging investigations. Most notable among these is the need for individuals to remain still to capture accurate images of the brain when completing magnetic resonance imaging. However, recent advances in neuroscientific data collection and design allow for inclusion of children who have previously been considered "untestable" or neglected from such studies. Best practices for pediatric neuroimaging have been outlined by Raschle, Zuk [107], which provide solutions for both methodological (e.g., child appropriate equipment and analyses) and practical (e.g., anxiety) challenges. Similarly, use of functional near-infrared spectroscopy (fNIRS) allows for greater motor freedom during data collection as it is generally robust to motion artifact [108]. Given the low incidence of WS, it will also be necessary for future studies to include multi-site designs in order to reach a greater number of individuals than one could achieve in a given region (a design also helpful for intervention research), allowing for implementation of more advanced neuroimaging analyses. Use of data harmonization techniques as outlined by the Enhancing

NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium [109] will allow for pooling of data across sites.

Finally, understanding the developmental pathways that shape the social phenotype of individuals with ASD and WS is critical to the development of research-informed treatment strategies and intervention targets. Rigorous research on intervention outcomes and mechanisms, in turn, holds the potential to generate knowledge relevant to practice while also feeding back to basic science. In the WS field, however, intervention research is nearly non-existent. In the ASD field, cross-fertilization between basic science and intervention research in the past few years has started to provide novel insight on the malleability of social impairments in ASD [110, 111••]. As ASD and WS share analogous difficulties in social cognitive processes that are modifiable by treatment, such as joint attention, the field would benefit from transdiagnostic treatment approaches to target shared areas of impairment across diagnostic boundaries. Additionally, more research efforts are needed to clarify the mechanisms of treatment-related changes in the social domain and their biological underpinnings in neurodevelopmental conditions affecting sociability. A related goal for future research is the investigation of heterogeneity in response to intervention, with a particular focus on individuals with ASD and co-occurring genetic syndromes associated with cognitive and social abnormalities, including WS and Down syndrome, who are often excluded by intervention trials. Advances along these research fronts hold the potential to provide critical insight into the nature of human sociability and its derailment in ASD and WS, thus informing the development of targeted interventions for neurodevelopmental disorders that affect the social domain.

Compliance with Ethical Standards

Conflict of Interest Giacomo Vivanti, Taralee Hamner, and Nancy Raitano Lee each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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