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Heterogeneity of sensory features in autism spectrum disorder: Challenges and perspectives for future research — Source link

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Title page

Manuscript Title: Heterogeneity of Sensory Features in Autism Spectrum Disorder: A Roadmap for Future Research

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Scientific Abstract

Pronounced heterogeneity is apparent across every facet of Autism Spectrum Disorder (ASD) and it remains difficult to predict likely future potential among individuals who share a common diagnosis of ASD on the basis of early presentation. In this commentary we argue that a fine-grained understanding of individual differences in sensory features and their influence across the life span can constrain noted clinical heterogeneity in ASD. We organize our discussion around the following three critical themes: (a) considering sensory features as dimensional construct; (b) taking an "individual differences" approach; and (c) adopting a comprehensive, multidimensional and multimodal approach to measurement of sensory features. We conclude that future research will need to investigate individual differences in sensory features via: 1) multidimensional and cross-disciplinary examination, 2) prospective longitudinal designs, and 3) dimensional and developmental frameworks that emphasise the potential value of early individual variability as indicators of later outcomes, not only in relation to the categorical diagnostic outcome status but also the presence of other clinical features. This is a key time for sensory-related research and in this commentary we provide some of the steps that, in our opinion, can shape the roadmap for future research in this area.

Lay Abstract

Autism Spectrum Disorder (ASD) is a highly diverse condition and it remains difficult to predict the likely outcomes for individuals on the basis of early characteristics. In this paper we argue that a fine-grained understanding of individual differences in sensory features and their influence across the life span can assist in planning and predicting clinical pathways for individuals with ASD. We organize our discussion around the following three critical themes: (a) considering the range of sensory features in ASD and their similarities and differences to features in other developmental disorders and in typical development; (b) examining the differences in sensory features between individuals with ASD; and (c) adopting a multi-faceted approach to assessment of sensory features that includes individuals report of their experiences alongside brain imaging technologies and therapist observation. We conclude that future research will need to: 1) use interdisciplinary assessments, 2) track the development of sensory features from early childhood to adulthood, and 3) consider the interaction of sensory features with environment and other autism symptoms. This is a key time for a roadmap for future sensory-related research and in this commentary we provide some of the steps that, in our opinion, are required to increase the rigour of research in this area.

Significant advances in the effective treatment of Autism Spectrum Disorder (ASD) are limited by the heterogeneity of the behavioural presentation of the disorder. Pronounced heterogeneity is apparent across every facet of ASD, including the timing of onset, course, symptom profile, and developmental outcomes (Bryson et al., 2007; Prior et al., 1998; Vivanti et al., 2014). Although symptom severity and level of associated cognitive and language impairments are important prognostic indicators – such that individuals with milder symptom severity, higher-level cognitive functioning and better verbal skills appear more likely to have better outcomes (Magiati, Tay, & Howlin, 2014) – specific factors that may account for such heterogeneity remain poorly understood. Hence among individuals who share a common diagnosis of ASD, it remains difficult to predict likely future potential on the basis of early presentation. As such, a key imperative for the field is to identify mechanisms to understand clinical heterogeneity in ASD and in doing so, reveal new targets for customised therapy (IACC, 2011). Sensory features, characterised by behaviours such as hyper-reactivity, hypo-reactivity and unusual sensory interests, form one subset of the diagnostic criteria for ASD and subsequently, offer a potential mechanism for identifying clinically meaningful subgroups. In this paper, we discuss the state of the science in relation to the understanding of sensory features in ASD and their potential as a phenotyping tool. We conclude with a proposed roadmap for future research in this area.

It has been suggested that traits that are not specific to a particular condition, but vary across typical development and clinical categorical diagnoses, may be important predictors of outcomes (Mundy, Henderson, Inge, & Coman, 2007; Trembath & Vivanti 2014). Such traits represent underlying risk for developing psychopathology depending on the interaction with characteristics of the individual, environment and treatment. These traits are identifiable from early in life, persist over time, show cross-contextual stability, a degree of heritability and association with specific brain regions and networks (Gottesman & Gould, 2003). Initiatives

such as the Research Domain Criteria (RDoC; Cuthbert & Insel, 2013) have emphasized the need to identify such fundamental traits and then study their genetic, neural and behavioural correlates, across both typical development and clinical conditions in order to enhance productivity in the quest for specific neurobiological treatment targets.

The study of temperament provides a model for research that considers individual variability in the context of both typical and atypical development. Research has suggested that temperamental variation may affect adjustment and long-term outcomes in positive as well as negative ways. Here, we argue that sensory features, like temperament characteristics, have negative downstream physiological, psychological and behavioral effects across a range of developmental conditions, including ASD. Therefore, a fine grained understanding of individual differences in sensory features and their influence across the life span has the potential to reveal clinically meaningful subtypes and inform basic behavioural, neuroscience, and genetic research into ASD. We have decided to focus here on sensory features in ASD as they are among diagnostic criteria and have been most thoroughly studied in this disorder. However, as noted they are also present in other neurodevelopmental and neuropsychiatric disorders. Therefore, in this commentary, following the RDoC approach, we will also discuss the importance of studying these features not only within groups of individuals who share the same categorical diagnosis but also across both typical development and disorders. In the following sections, we briefly review what is currently known about the variation in sensory features between individuals with ASD.

Sensory Features in ASD: Research to date

Studies of sensory features in ASD have appeared in the literature for over 40 years across the disciplines of cognitive science, experimental psychology, neuroscience and occupational therapy (see for example, Baranek et al, 2006; Happe & Frith, 1996; Ornitz,

1974; Pellicano & Burr, 2012). We now know that individuals with ASD experience difficulties in perceiving, integration and modulating their responses to daily sensory stimuli across auditory, visual, somatosensory and proprioceptive domains, and that these difficulties are present throughout the life span, including in infancy pre-diagnosis (see Marco et al, 2011; Rogers & Ozonoff, 2005; Schaaf & Lane, 2015 and Schauder & Bennetto, 2016 for reviews of this literature). The literature to date has charted these difficulties at neural, psychophysiological, behavioural, clinical and self-report levels (Schauder & Bennetto, 2016). A number of theoretical frameworks, ranging from proposals emphasising dysfunction in arousal modulation (Hutt et al., 1964; Ornitz & Ritvo, 1968), global versus local processing of stimuli (Frith, 1989; Mottron et al., 2006), to recent proposals based on Bayesian models of perception (Brock, 2012; Friston, Lawson, & Frith, 2013; Pellicano & Burr, 2012; van de Cruys et al., 2013), have been put forward in an attempt to explain existence of atypical sensory features in ASD. Furthermore, study findings suggest that individuals with ASD experience more difficulties with sensory processing than either their typically developing or non-ASD developmentally delayed peers (Baranek, David, Poe, Stone, & Watson, 2006; Tavassoli, Hoekstra, & Baron-Cohen, 2014). While it has been shown that the timing and magnitude of responses to multi-sensory inputs is different and inefficient in individuals with ASD, the neurobiology of these problems is poorly understood (Boer-Schellekens et al 2013; Cascio et al, 2012; Foss-Feig et al, 2010). In particular, it is unclear whether sensory features in ASD are a consequence of impairments in bottom-up processing (Orekhova & Stroganova, 2014), top-down processing (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Gomot, Blanc, Clery, Roux, Barthelemy, & Bruneau, 2011), or both (Green et al., 2013; Green, Hernandez, Tottenham, Krasileva, Bookheimer, & Dapretto, 2015; Donkers et al., 2014).

Sensory features in ASD: a roadmap for future research

Despite the significant progress made, there are still a number of unanswered questions relating to sensory features in ASD. One of the most important of these relates to understanding the sources of variability in sensory features between individuals. This involves the consideration of three critical themes: (a) considering sensory features as dimensional constructs; (b) taking an "individual differences" approach; and (c) adopting a comprehensive, multidimensional and multimodal approach to measurement of sensory features. Although discussed independently below, these themes are nevertheless inter-related and part of the same research agenda. It is particularly important to emphasise that individual differences and dimensional approaches should be seen as complementary rather than mutually exclusive.

a. Sensory functioning as a dimensional construct

The multidimensional construct of "sensory features" could be viewed as a heuristic to consider the extent to which symptoms associated with one disorder, such as ASD, exist on a continuum of typical to atypical development, and cut across numerous childhood psychopathologies. A dimensional approach has utility in quantifying the level or severity of traits along a continuum (Constantino & Todd, 2003; Moreno-De-Luca, Myers, Challman, Moreno-De-Luca, Evans, & Ledbetter, 2013), rather than just indicating presence or absence of a disorder. Potential interactions among two or more dimensional traits may allow us to better characterize complex multidimensional constructs and thereby explain heterogeneous symptom profiles within a single diagnostic group or disorder.

The study of temperament as a multidimensional construct can further illustrate this point. Early research by Thomas and Chess (1977) proposed nine dimensions of temperament, which were used to classify children into one of three categories (i.e., easy, slow to warm-up, difficult). More recently, Rothbart (2007) proposed three dimensions of

temperament -- surgency/extraversion, negative affect, and effortful control -- that reflect innate individual differences in reactivity and self-regulation. Although maturational processes, experiences, and environmental variables (e.g., parent-child temperament fit; cultural values) may impact the course of development for individual children, these enduring and stable temperamental traits are the substrates of later personality development and supported by basic biological processes that are shared across cultures. Such nuanced dimensional conceptualizations of temperament have spurred tremendous research elucidating predictors of later psychopathology (e.g., externalizing versus internalizing symptoms) as well as neurophysiological and genetic biomarkers (Rothbart, Sheese & Posner, 2007). Moreover, this research has stimulated theoretical critiques that continue to drive scientific discoveries in developmental science and social psychology (DePauw & Mervielde, 2010).

Returning to sensory features, we re-emphasize that symptoms reflecting the possible dimensions of hyporeactivity, hyperreactivity, and sensory preoccupations are evident not only in ASD, but are shared across a myriad of neurodevelopmental disorders including Fragile X syndrome (Baranek, Chin, Hess, Yankee, Hatton, & Hooper, 2008), ADHD (Ghanizadeh, 2011), Anxiety Disorders (Hoffman & Bitran, 2007), and Sensory Processing Disorder (Schaaf & Davies, 2010). This suggests that early neurodevelopmental disruptions affecting sensory processes (e.g., arousal modulation, sensory gating, multisensory integration) may pose vulnerabilities for the development of psychopathological outcomes (i.e., concept of multi-finality), rather than leading specifically to a single disorder, such as ASD. Furthermore, young, typically-developing children may evidence some unusual sensory features (e.g., sound sensitivities, picky eating, preoccupations), albeit in milder or transient forms (Ahn, Miller, Milberger, & McIntosh, 2004), underscoring the importance of a neurodevelopmental perspective for unraveling the pathogenesis and course of these

perplexing behaviors (Cascio, Woynaroski, Baranek, & Wallace, 2016). We propose, therefore, that the next generation of sensory research should track the emergence of sensory traits in early infancy and their relationship to later development of childhood disorders. Consideration of the interactions between sensory traits and early environment, neurobiology, genetic markers and other behavioural traits such as temperament will also be a productive course of inquiry.

b. Sensory features: taking an individual differences approach

It is necessary for future research to move beyond the purely descriptive models of sensory features in ASD towards an individual differences perspective that emphasizes the need to understand the variability that occurs between people with ASD.

Several recent studies have attempted to move beyond group-level descriptions and proposed that the presentation of sensory features in ASD are best characterised as a set of distinct sensory subtypes (Ausderau et al, 2014; Lane et al, 2014). To date, two sensory subtype schemas have been proposed utilising differing sensory measurement tools and cluster analysis techniques (Ausderau et al, 2014; Lane et al, 2014). Both classification models identify four distinct sensory subtypes including one that is characterised by mild sensory features that are unlikely to impact function, and another where sensory features are frequent and range across sensory modalities. The remaining two subtypes in both models can be distinguished by more or less reactivity to sensory stimuli (Lane & Philpott-Robinson, 2015). Further, researchers have identified behavioural patterns associated with each sensory subtype, and are therefore starting to identify clusters of sensory features that might predict positive and negative aspects of development. For example, Uljarević, Lane, Kelly, and Leekam (2016) reported that children with ASD who fell into the mild sensory subtype had significantly lower levels of anxiety when compared to more severe sensory subtypes. Ausderau and colleagues observed that a subgroup of children with ASD with the most

extreme and mixed sensory features (17.2% of a national sample) had the highest levels of ASD symptom severity (Ausderau et al., 2014), maldaptive behaviour (Ausderau et al., 2016), and parenting stress (Ausderau et al., 2016). In contrast, children with ASD in a subgroup with low sensory reactivity combined with high sensory preoccupations (16.9% of a national sample) were younger (Ausderau et al., 2014), had lower IQ (Ausderau et al, 2014), and the lowest adaptive behaviour in communication, socialization, and daily living skills (Ausderau et al., 2016).

This recent work identifying distinct sensory subtypes supports the potential utility of sensory features as a method of identifying clinically meaningful subgroups in ASD (Ausderau et al., 2014; Lane et al, 2014; Uljarević et al., 2016). A clustering approach (as used in the sensory subtype research) allows for the elucidation of specific sensory-based phenotypes that might direct customised evaluation and treatment for individuals. As such, it represents a significant step forward towards personalised intervention. Earlier sensory models facilitated treatment planning on the basis of discrete behaviours rather than individual case-based profiles (Miller et al, 2007). Furthermore, this approach has the potential to inform research on the neurobiological basis of sensory features. The utility of this approach is illustrated by Green et al. (2015) who observed different patterns of brain responses to mildly aversive sensory stimuli between two subgroups with ASD, one with and one without sensory over-responsivity. While ASD individuals who were also behaviourally sensory over-responsive showed decreased neural habituation in sensory cortices and the amygdala, individuals with ASD and without sensory over-responsivity showed negative connectivity between amygdala and orbitofrontal cortex, suggestive of more efficient downregulation. Further research is needed to consolidate sensory subtype models and link these to specific neural and physiological profiles.

In addition to the subtyping work, a promising approach is to explore the interactions of sensory features and other variables in predicting outcomes, especially using longitudinal design. For example, a study by Green, Ben-Sasson, Soto, and Carter (2012) explored the emergence of anxiety and sensory hyper-reactivity in a sample of 149 toddlers with PDD-NOS as well as the extent to which sensory hyper-reactivity might predict changes in anxiety and vice versa over a 12-month time period. A cross-lag analysis showed that while sensory hyper-reactivity positively predicted changes in anxiety (over and above the contribution of chronological and mental age and ASD symptom severity), anxiety did not predict changes in sensory hyper-reactivity.

Further examples of an individual differences approach come from intervention research. In fact, some of the earliest treatment models for ASD were informed by an understanding of how sensory processing abnormalities affect learning in ASD. Early work by Lovaas and colleagues suggested that children with ASD responded normally to specific sensory input across modalities, but had difficulties with processing multiple sensory stimuli delivered simultaneously (Lovaas, Litrownik, & Mann, 1971). Discrete Trial Teaching procedures emphasised a simplified instruction delivery format to facilitate processing of instructional cues. Similarly, one of the rationales underlying the structured approach used in the TEACCH model is based on the idea (first detailed in Schopler & Reichler, 1968; see also Mesibov & Shea, 2010) that abnormally high threshold or avoidance across sensory modalities was one source of confusion and a barrier to learning in ASD. The strategies of modifying and structuring the environment (e.g., tall shelves facing away from the rest of the room in a visually stimulating classroom, noise-reducing headphones for a loud environment) were developed to accommodate these sensory challenges in order to optimize learning. Further, Naturalistic Developmental Behavioral Interventions (Schreibman et al., 2015; Rogers & Dawson, 2010; Baranek et al., 2015) emphasize the role of early social engagement

to promote sensory-motor skill acquisition within a naturalistic environment. In this framework, the adult optimizes the child's arousal and sensory responsivity through choice of play material, tone of voice and level of adult activity. It is thought this optimises the child's participation in naturalistic social learning activities during everyday play-based routines. Given that children with ASD vary in their sensory features, it is plausible that some children will be more responsive to a particular treatment approach because of the compatibility between their sensory features and the procedures involved in the specific intervention. Suboptimal fit between sensory features and intervention strategies might contribute to the substantial individual differences in treatment response documented in the ASD literature across approaches (e.g., Vivanti et al., 2014). However, in order to test hypotheses on how sensory features might interact with treatment components to produce different treatment responses, an individual differences approach to the analysis of sensory features in ASD is needed.

c. Multidimensional and Multimodal Measurement of sensory features

A further step that is necessary to advance knowledge in the field concerns the measurement of sensory features. There is no universally accepted method of clinically evaluating sensory features in ASD (Schaaf & Lane, 2015). Tools used currently for sensory measurement in the clinic are based mainly on parent or proxy report – for example, the Sensory Profile (Dunn & Westman, 1997) or the Sensory Experiences Questionnaire (Baranek et al, 2006) - and in fewer cases on direct observation – for example, the Sensory Integration and Praxis Tests (Ayres, 1989). Questionnaire measures have numerous advantages over observational and experimental measures, such as the ability to sample behaviours over time and across different contexts, and to generate rich data that lend themselves easily to group comparison, factor analysis and also to person-centred statistical approaches (e.g., cluster analysis). However, there are several limitations related to the

exclusive use of parental/proxy report. Caregiver factors, such as stress, anxiety and depression, and Broader Autism Phenotype traits, known to be prevalent among parents of individuals with ASD, can significantly bias the reporting of child characteristics. Furthermore, and particularly relevant for high-risk infant sibling designs, are parental tendencies to either exaggerate (i.e., contrasting effect) or under-estimate (i.e., assimilation effect) differences between children by evaluating them relative to one another (Eaves, Rutter, Silberg, Shillady, Maes, & Pickles, 2000; Majandzic, van den Boom, & Heesbeen, 2008).

Although structured and semi-structured observational protocols do not suffer from issues inherent in the use of questionnaire measures, they also have their own limitations such as potential lack of ecological validity, temporal and contextual restrictedness, and influence of "noise" variables, for example, the child's temporary mood or somatic health issues (Zentner & Bates, 2008). Instruments to assess the physiological components of sensory features include electroencephalogram (EEG), magnetic resonance imaging (MRI & fMRI) and magnetocephalogram (MEG; Marco et al, 2011; Schauder & Bennetto, 2016). While these assessments provide a more precise measurement of neural function associated with sensory processing, the protocols are not yet clinic-ready. Further, it is recognised that these tools, on their own, are insufficient to fully characterise the functional implications of sensory alterations for individuals with ASD in their daily lives (Schauder & Bennetto, 2016).

Finally, the issue of measurement confounding in developmental psychology and psychopathology research is well known (Lengua, West, & Sandler, 1998; Lemery, Essex, & Smider, 2002; Sanson, Prior, & Kyrios, 1990) and the research on sensory features is certainly not the exception. The potential item overlap between sensory features and other measures of interest represents a significant limitation of the existing research as, in order to understand the nature of associations between constructs, it is essential to ensure that

measures provide unique rather than overlapping information, lest the strength of the association be artificially inflated. In summary, it is difficult to reconcile information gained from questionnaire, observational and physiological measures since these different modes of assessments sample different contexts and different levels of information. As recently identified, the optimal way to assess sensory features is one that is comprehensive, multidimensional and multimodal, combining observational, physiological and questionnaire-based measures (Schauder & Bennetto, 2016). Good examples of this line of work are previous studies that have combined the use of questionnaires with observational (Watson et al., 2012) and physiological laboratory protocols (Schoen, Miller, Brett-Green, & Nielsen, 2009) as well as new measures designed to assess perceived performance on basic sensory perception abilities rather than experience of sensory stimuli (Tavassoli, Hoekstra, & Baron-Cohen, 2014).

Despite the recent inclusion of sensory features in the DSM-5 (APA, 2013), the assessment of sensory features during diagnostic evaluations is relatively superficial. For example, only one sensory item is included in the current ADOS-2 diagnostic algorithm (i.e., unusual sensory interest in play material/person; Lord et al., 2012), and the Centers for Disease Control and Prevention recommendations for the assessment of ASD do not currently refer to specific sensory assessment at all (http://www.cdc.gov/ncbddd/autism/hcp-recommendations.html). While the Autism Treatment Network includes the Sensory Profile short form (Dunn, 1994; Kientz & Dunn, 1997) in its instrument registry (http://www.autismspeaks.org/docs/sciencedocs/atn/ATNRegistryInstruments072009.pdf), the instrument is limited to children aged 3 to 10 years. Despite the absence of sensory profiling as a recommended component of standard diagnostic practice, it may be advantageous to do so. For example, characterisation of phenotypic subtypes within the broader ASD diagnostic category may be critical for determining "what works for whom, and

why" when it comes to predicting treatment outcomes (Trembath & Vivanti, 2014; p. 58) and, furthermore, may assist in the development of individualised intervention programs. Thus, comprehensive sensory profiling during the diagnostic and assessment process may compliment the process by creating a comprehensive and individualised profile.

Conclusions

Pronounced clinical heterogeneity is a hallmark feature of ASD and limits our understanding of the prognosis of the disorder based on early presentation. The identification of mechanisms to constrain clinical heterogeneity will advance knowledge and facilitate the development of personalised interventions. We argue that a more fine-grained understanding of sensory features in ASD is one way to constrain clinical heterogeneity. As such, we propose that a roadmap for future sensory-related research is timely and in this commentary we have provided some of the steps that, in our opinion, are required to increase the rigour of research in this area. Future research will need to investigate individual differences in sensory features via multidimensional and cross-disciplinary assessments, within prospective longitudinal designs, from infancy through the toddlerhood, preschool years through to adulthood, exploring the potential value of early individual variability as indicators of later outcomes, not only in relation to the categorical diagnostic outcome status but also the presence of other clinical features. The role of sensory features in neurodevelopment will need to be explored within frameworks that emphasise the dimensional nature of clinical phenomena (such as developmental psychopathology and, more recently, RDoC) and considering direct, indirect (i.e., moderating and mediating) effects, interactional and transactional models including, for example, interactions between sensory features and other intrinsic child characteristics. Findings that among adopted children, prolonged institutional care is associated with the presence of atypical sensory features (Cermak & Groza, 1998; Lin et al., 2005; Wilbarger, Gunnar, Schneider, & Pollak, 2010) highlights the need to consider

interactions between child's characteristics, aspects of the environment (e.g., characteristics of parents and the family) and the wider sociocultural context. Longitudinal designs will be essential for our ability to make inferences about the directionality of brain-behaviour associations and understand the complex dynamics and temporal unfolding of gene-environment-brain-behaviour inter-relationship. Investment in this area of research is critical for the broader ASD field and success in this endeavour will be reliant on strong engagement between the basic, experimental and applied disciplines who study sensory features. Recent findings suggest that the close examination of sensory features may provide a unique perspective on clinical meaningful subgroups and constraining the heterogeneity within ASD, leading subsequently to the development of new customised targets for therapies.

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