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COMMENTARY

Making Research Possible: Barriers and Solutions For Those With ASD and ID

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Abstract
Participation in research can provide direct and indirect benefit to individuals with autism spectrum disorder (ASD), their caregivers, families, and society at large. Unfortunately, individuals with high support needs, including those with intellectual disability, cognitive disability or minimal verbal ability, are often systematically excluded from research on ASD. This limits the ability to generalize discoveries to all people with ASD, and results in a disparity in who benefits from research. This piece outlines the importance and extent of the problem, which is part of a broader lack of inclusivity in ASD research. It also provides examples of studies that have directly addressed issues that arise when conducting inclusive research and makes recommendations for researchers to reduce disparities in research participation.

Keywords Intellectual Disability · Research · Participation · Inclusion

Introduction

A significant source of heterogeneity in autism spectrum disorder (ASD) relates to accompanying intellectual impairment, which commonly rises to the level of intellectual disability (ID). The Centers for Disease Control estimates that 31–50% of those with an ASD diagnosis also meet criteria for ID (Christensen et al., 2019; Maenner et al., 2020), and a significant minority may be considered "minimally verbal" (Tager-Flusberg et al., 2017). People with ID (with or without ASD) are almost entirely excluded from general medical research (Spong & Bianchi, 2018), but this exclusion persists even in research on ASD, a population in which people with ID are a plurality. One meta-analysis estimated that only 6% of participants in ASD research have ID (Russell et al., 2019). While these reports have raised awareness, it still appears that this trend may be worsening over time; one meta-analysis of ASD treatment studies indicated that the rate of inclusion of severely affected children with ASD has decreased between 1991 and 2013 (Stedman et al., 2018). However, because the cognitive and verbal ability of research participants often goes unreported, these estimates—however dramatic—may still not reflect the full extent of the exclusion (Stedman et al., 2018). In this article we describe the extent and the causes of the exclusion of people with ID + ASD from research on ASD, its implications, and paths to resolving it.

Reasons for the Exclusion of People with ID from ASD Research

The exclusion of people with ID from ASD research may be through formal means – inclusion and exclusion criteria – or the incidental result of certain methodological features of the study, as described below. Often, the exclusion of people with ID + ASD is tacit; common exclusion criteria may be proxies or strong risk factors for ID, such as an identified genetic condition, a significant neurologic condition, or premature birth.

We performed a non-systematic review of actively recruiting studies registered with ClinicalTrials.gov (dates of access: August 11, 2020 and March 08, 2021; full details of the search and results are available upon request) which listed as the condition or disease "autism" (n = 224) or

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"intellectual disability" (n = 162). ASD studies were deemed exclusive of ID if exclusion criteria included cognitive impairment, comorbid developmental or learning disability, IQ in the ID range, or genetic diagnosis of a disease strongly associated with ID (e.g., fragile X syndrome). Studies which excluded any portion of the ID population, even if they allowed participants with mild ID (e.g., IQ > 50), were categorized as exclusionary. ID studies were deemed exclusive of ASD if their exclusion criteria included an ASD or developmental disability diagnosis. We found that 42% (n = 95) of ASD studies registered with ClinicalTrials.gov explicitly or implicitly exclude people with ID from participation. However, almost no current ID studies restrict participation for individuals with ASD (n = 6, 4%). This begs the question: Why do ASD research samples not include people with ID + ASD?

Many studies stratify or ensure representativeness on the basis of age and sex, and the complexity of achieving this balance across intellectual ability or other neurodevelopmental features would require larger sample sizes than are feasible in a field that already contends with sample size limitations. Methodological aspects of a study may prevent people with ID + ASD from participating; people with ID + ASD may have limited ability to read, write, communicate, process directions, and attend for long periods of time, which may make certain procedures less feasible (Jack & Pelphrey, 2017). The neuropsychological tools that researchers use to assess research participants often have limited validity for use in ID + ASD (Havdahl et al., 2016). Even tools designed to measure IQ, a core feature of ID, contain floor effects and often lack standardization beyond four standard deviations from the population mean. In fact, people with severe-to-profound ID are not represented at all in the standardization samples of many commonly used research measures (Soorya et al., 2018). Thus, in an effort to maintain the internal validity of a study, researchers may restrict participation to those who can successfully complete a task or measure. This choice differentially affects people with ID and adversely affects the generalizability of the results.

Self-exclusion may also be a factor, and studies are beginning to document reasons why individuals and their families may choose not to participate in research (Cleaver et al., 2010; Haas et al., 2016). One reason is the societal stigma associated with ID, which may prevent participation in many community activities (Werner & Roth, 2014) and lead to a justified fear of unequal treatment. Even if they are interested in research participation, individuals with ID + ASD or their families may have concerns about the amount of time it takes to prepare for or complete the study, alternative approaches or coaching required to facilitate research participation, and general burden in relation to the potential for benefit (Haas et al., 2016). Individuals with ID + ASD and their caregivers/families may experience frustration as a result of psychometric limitations, as the assessments may not seem appropriate for the participant (Kelleher et al., 2020). As a result, caregivers and people with ID + ASD who elect to participate in research may experience isolation, which is likely to prohibit future participation.

The potential for ethical issues—real or presumed—can also limit participation by people with ID + ASD or limited verbal ability, especially adults (Biros, 2018). The additional effort required to adapt existing consent materials may be onerous to investigators, and capacity assessments may be necessary for adults if guardianship is not established. Parents or siblings may have legal guardianship, and while consenting of guardians is legal in most places under most circumstances, there are limitations (Horner-Johnson & Bailey, 2013). Some researchers and review boards have expressed concern about the ethics of enrolling adults with ASD who cannot consent, which may not necessarily reflect the views of the potential participants themselves (McDonald et al., 2018). As discussed below, the extreme stance that safeguards to such vulnerable populations should prohibit research participation altogether carries its own ethical burden. Researchers are therefore working to standardize methods for and educate those in best practice of consenting individuals who may not have capacity to consent (Biros, 2018).

Ethical and Scientific Implications of the Exclusion of People with ID + ASD from ASD Research.

It is useful to explicitly establish why the exclusion of people with ID from ASD research is unacceptable. There is a relevant ethical imperative conferred by the fact that people with ID are a vulnerable population, especially given the historical maleficence towards them (Iacono & Carling-Jenkins, 2012). However, when people with ID are excluded from research, they do not benefit from research; "seeking to protect people from harm in the context of research may itself therefore give rise to harm" (Northway, 2014). The assumption that scientific knowledge generated in the absence of individuals with ID + ASD may be simply generalized to all people with ASD runs counter to the basic tenets of the scientific method. Moreover, excluding people with ID + ASD from ASD research adversely affects the validity of the results in ways that may be difficult to predict. Recent studies highlight the impact of this selection bias on treatment research (Stedman et al., 2018), neuroimaging research (Jack & Pelphrey, 2017), and on ASD research in general (Russell et al., 2019).

The lack of representation of ID in research exploring the neurobiology and etiology of ASD is particularly problematic, because both within ASD and in the general population, people with ID are more likely than others to have an identifiable genetic condition (Myers et al., 2020). Recent research also implicates unique neurobiological mechanisms for

individuals with minimal verbal ability, even compared to those without low cognitive or verbal performance, including differences in functional connectivity (Gabrielsen et al., 2018) and auditory processing (Roberts et al., 2019).

Because ID + ASD is associated with greater ASD symptom severity and a greater likelihood of behavior problems (Maskey et al., 2013; Soorya et al., 2018), criteria which exclude people with ID + ASD may truncate the phenotypic range represented within a study. As a result, existing research has limited applicability to people who may need the most support. An understanding of the true prevalence of comorbidities and the impact of the unique behavioral phenotype on treatment efficacy is limited (Stedman et al., 2018), which complicates efforts to ensure personalized and individualized approaches to treatments. If clinical trials do not include people with ID + ASD, regulatory bodies may exclude them from clinical indications for approved treatments (Yazdani et al., 2020); this may in turn result in the exclusion of people with ID + ASD from guidelines published by governmental agencies or reimbursement payers. The seriousness of these potential outcomes prompted the American Academy of Child and Adolescent Psychiatry to advocate for the inclusion of people with ID + ASD in both natural history and treatment studies of psychiatric comorbidity (American Academy of Child & Adolescent Psychiatry, 2013).

Strategies to Improve Inclusivity

In recent years, increased attention to the lack of generalizability of ASD research has led to several attempts to ensure that people with ID + ASD are studied. Such approaches fall into two areas: one reflects the need to improve inclusion of people with ID + ASD in the existing ASD research portfolio, while the other involves modifying the research portfolio to fill research gaps for people with ID + ASD by over-enriching or even exclusively recruiting individuals with ID + ASD into studies. The latter approach is especially relevant for clinical phenomena that are specific to people with ID + ASD, including the evaluation of treatments already studied in individuals without ID.

Some researchers have modified modalities in which it is traditionally difficult for people with ID to participate, such as neuroimaging. Alternative procedures, such as scanning during sleep or sedation, have been used (Jack & Pelphrey, 2017), and behavioral techniques to optimize EEG cap placement and stillness in the MRI have been developed (Nordahl et al., 2016; Tager-Flusberg et al., 2017). These approaches include using a trained behavioral specialist, mock scanner sessions, and additional scans to ensure acceptable resolution. While some success has been documented (Nordahl et al., 2016), the additional staff, equipment, and time required by this approach may require increased budgets, staff members, and continued development to increase success. All of these elements, including developing manuals for such adaptations, should be built into projects.

Researchers can use the principles of inclusive or participatory action research (Werner & Roth, 2014) to develop study protocols that enroll individuals with ID + ASD. This could even include training people with ID to be part of the research process (e.g., Tuffrey-Wijne et al., 2020). While this may require additional and alternative methods for certain types of data acquisition (e.g., visual instructions) (Boxall & Ralph, 2011), the systematic piecewise introduction of new methods will be essential to help clarify how findings are affected by methodological differences. Likewise, new methods may require even further modification to include those in the severe and profound range of ID (see Maes et al., 2021 for a description of such recommendations).

Researchers should explicitly justify inclusion/exclusion criteria that may affect the ability of individuals with ID + ASD to participate in ASD research; this practice may highlight areas where the wholesale exclusion of people with any level of ID is not necessary. The inclusion/exclusion criteria should be tailored to the specific demands of the study, to avoid excluding more people than necessary. For example, rather than excluding generally based on ID, a study may include participants who can achieve a score above the floor of a given IQ test, but who also have a mental age of at least 18 months to comply with the demands of autism diagnostic testing. Finally, researchers should carefully discuss how the explicit or implicit exclusion of people with ID + ASD may impact the validity and generalization of their findings.

Studies which recruit based on genetic etiology, or otherwise do not specify any particular neurodevelopmental presentation and may therefore reflect a wide range of phenotypic expression, should use a tiered approach to tests and procedures to accommodate all levels of cognitive ability (Soorya et al., 2018). For instance, a developmental or IQ test may be selected from a hierarchy based on the ability level of the participant, following systematic guidelines described in a study protocol. While different tests are not fully exchangeable, a consistent test hierarchy employed across studies would allow for broad estimation of cognitive level. Where possible, measures that span a wide age and developmental range should be employed, to allow for successful measurement across the entire sample.

The Future of Inclusive Research on ASD

Given the strides made in research on understanding and treating ASD over the past 75 + years, we are well-poised to address the persistent exclusion of people with ID + ASD from future work as we aim to learn more about how the

condition affects all of those who are diagnosed with it. We must focus on ways to be more inclusive in studies that aim to be generalizable to all people with ASD, which must include people with ID. However, we must also remember that people with ID + ASD may require focused study, particularly around etiology and treatment. To achieve these goals, a comprehensive approach is required, including a) increased flexibility for study engagement to reduce participant and family burden, b) increased workforce training, including clinical training around ID for professionals (e.g., pediatricians, psychologists and psychiatrists), research staff, community liaisons, and others who may work directly on improving research methods for this population, c) new methods to increase the participation, compliance, and success of individuals with ID in clinical research (e.g., mobile technology, telehealth, telemetric assessments, use of alternative and augmentative communication), including both standardized and non-standardized measures, and most importantly, d) an overall goal of research that is relevant and useful for people with ID + ASD. This is to ensure there is better inclusion of, and more rigorous reporting of, cognitive abilities in study participants.

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Consent to Publish There were no human subject's data used in the creation of this commentary. This was the report from a meeting. No ethical approval is required, and no informed consent was needed to discuss these issues and report them in this commentary. Meeting participants consented to the submission of this commentary in the journal and their names to be included in the acknowledgements.

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