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Is autism a biological entity?

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Is autism a biological entity?

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Editorial: Is autism a biological entity?

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Editorial on the Research Topic
Is autism a biological entity?

There has been no single cause or pathophysiology found to be unique to all those with autism, but current diagnostic criteria are linked to nearly two hundred genetic and environmental reported causes. The current DSM-5 criteria for an autism *spectrum* diagnosis (ASD) allow hundreds of varied patterns of persistent deficits in social communication and social interaction, and myriad patterns of restricted and repetitive activities and interests. This wide phenotypical heterogeneity –which appears to have markedly increased in the two last decades–has led many researchers to question the validity of the ASD diagnosis.

The papers in this special section explore varied aspects of the relationship between the many biological causes of autism and the heterogeneity of diagnostic symptoms and comorbidities. None of the twelve papers support the DSM-5 ASD criteria as defining a unitary biological entity or natural kind. Instead, the twelve papers include proposals to disentangle autism from ASD by adopting a new autism diagnosis, or by reducing the heterogeneity of causes and symptoms linked to autism, or by establishing a new causal model of autism. Taken together, all these papers assert that the heterogeneity of symptoms and causes is a core problem for autism research, and each paper views the current ASD criteria as an impediment to the discovery of meaningful categories of neurodevelopmental disorders.

Proposals for new diagnosis of autism

Crespi while underlining the issues associated with current study of autism, particularly over-inclusivity, proposed that a new autism diagnosis should be based on the recognition of a clinical pattern combining Mottron's (1) prototypical autism and Kanner's "hallmarks" of autism. Mottron outlined a new diagnosis of autism in which expert clinicians would agree on a more limited set of autism criteria in an autism sample homogeneous for comorbidity, language problems, intelligence, age, and sex. Kanner's hallmarks include extreme aloneness, severe language deficits, good cognition, intense focus on objects, repetitive behaviors, and insistence on sameness.

Like Crespi, Green argued that Mottron's model of prototypical autism should be the categorical baseline for understanding autism. However, Green proposed that 'autism states' reflect both the emergence and subsidence of the autism phenotype. There would be three ways of studying autism states: through clinical descriptions or longitudinal observations of the emergence of phenotypes in early development; through clinical descriptions or longitudinal observations of the subsidence of phenotypes of autism later in development; and through the study the emergence of autism states by means of experimental interventions in autism development. Green outlined his research program of experimental interventions, and argued that intervention studies offer the most rigorous means to test the phenomenon of emergence because they provide a controlled test of developmental change.

Fernell and Gillberg noted that early diagnoses of neurodevelopmental disorders overlap and change with time. They advocated for an umbrella category located higher in a taxonomic hierarchy, ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. ESSENCE would regroup early manifestations of childhood disorders that include impairments in motor, cognitive, neurological, communicative and social development, as well as sleep, feeding and behavioral regulation. The ESSENCE group identifies the very high rate of "comorbidities" in childhood disorders, and assumes developmental deviations or delays in speech and language and motor development are unspecific.

Hens and Van Goidsenhaven suggested that developmental diversity should be the starting point for research, rather than a static categorical autism diagnosis. They argued that interaction with environment moves the categorical boundary. A developmental diversity approach could clarify comorbidities, and enrich genes-based research without starting from diagnostic categories. They have advocated a neurodiversity-sensitive /translational perspective, wherein autism research should include children and adults who may not receive a diagnosis but who may be diverse in symptoms and causes.

Lombardo and Mandelli reviewed the history of the autism diagnostic criteria, emphasizing how the role of language level and developmental history have been gradually lessened in successive DSM criteria for autism. They asserted that the current DSM-5 criteria are only optimized to be sensitive and specific for the differentiation of autism vs. non-autism. These criteria are not valid for explaining autism biology, outcomes, and treatment response (BOT). Researchers should develop a variety of new diagnostic definitions or models of autism to address BOT. Creating varied new diagnoses does not mean the current autism diagnosis has failed, because it is still valid for maximizing clinical consensus based on autism behavior.

Phillipe maintained her confidence in a categorical diagnosis of autism. However, she claimed that studying autism should primarily identify the features that are unique to the individual. Standardized autism diagnoses should only be conducted after individual variation is identified. She asserted that syndromic autism–where a specific genetic or other specific cause is known–approaches the definition of a natural kind by means of the detection of unique sets of clinical features.

Proposals for resolving heterogeneity in autism

Eigsti and Fein argued that the heterogeneous causes can best be resolved by creating smaller homogeneous groups formed by clinical DSM 5 Specifiers: IQ, language, and outcome status. Compared to autistic and non-autistic groups, Children who had lost their autism diagnosis (LAD) have a pattern of language-related brain activations similar to that found in the autistic individuals, but also had many brain activations that were unique to LAD. Their findings demonstrate how biomarkers can be orthogonal to longitudinal trajectories.

Levy noted that neurobiological research does not support a categorical definition of ASD, and argued that a reconceptualization of ASD is needed but could only occur when there is profound dissatisfaction with the diagnosis among clinical and research communities as well as stakeholders.

Loth stated that efforts to divide autism into subgroups by biomarkers such as brain structures have not yet identified any clearly delineated diagnostic subgroups. Loth recommended that future research address the problem of the additive and interactive effects between biological and social mechanisms, while focusing on finding transdiagnostic groups of individuals across neurodiverse populations.

Waterhouse underlined the failure of iterative DSM attempts to reduce autism heterogeneity. She underlined the current inability to map biological causes to distinctly categorized phenotypes. From this, and from the variability in symptom presentation and development, she questioned the unity of autism as a *biological* entity. She argued that autism heterogeneity may be addressed by the discovery of transdiagnostic neurodevelopmental groups, grounded on endophenotypes.

Proposals for a new causal model of autism

Chawner and Owen proposed that autism is the result of two biological dimensions that combine to yield individual variation: a population-wide continuum of social and adaptive functioning resulting from multiple alleles of small effect, and a continuum of childhood-onset disorders such as intellectual disability (ID) and attention deficit/hyperactivity disorder (ADHD), and adult-onset schizophrenia and bipolar disorder linked to *de novo* genetic mutations. Commenting their proposition, Sarovic argued that varied types of disorders stem from the magnitude of rare genetic risk. He rather proposes a three-factor model of autism: natural variation in non-pathological traits, a range of neurodevelopmental risks, and adaptive behaviors that moderate the links between the first two factors.

A consensus seems to arise from these empirical and theoretical positions. The current ASD criteria are ineffective, and the

use of these criteria has not yet led to convincing discoveries. Nonetheless, whether the ASD criteria should still be used as a basis for research remains an open question. Consequently, research independent of DSM-5 ASD criteria that adopts a new autism diagnosis such as prototypes, or explores a new causal model of autism, or develops transdiagnostic endophenotypes, must be encouraged.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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PERSPECTIVE
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Rethinking Our Concepts and Assumptions About Autism

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Autism is a clinical consensus diagnosis made based on behavioral symptoms of early developmental difficulties in domains of social-communication (SC) and restricted repetitive behaviors (RRB). Many readily assume that alongside being optimal for separating individuals based on SC and RRB behavioral domains, that the label should also be highly useful for explaining differential biology, outcomes, and treatment (BOT) responses. However, we also now take for granted the fact that the autism population is vastly heterogeneous at multiple scales, from genome to phenome. In the face of such multi-scale heterogeneity, here we argue that the concept of autism along with the assumptions that surround it require some rethinking. While we should retain the diagnosis for all the good it can do in real-world circumstances, we also call for the allowance of multiple other possible definitions that are better tailored to be highly useful for other translational end goals, such as explaining differential BOT responses.

Keywords: autism, heterogeneity, precision medicine, diagnosis, subtype

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INTRODUCTION

Nearly every article on autism tends to start off in the same way. "Autism is *<insert paraphrased DSM definition, or core symptom domains here>*". Whether intended or not, this ubiquitous leading statement gives off the impression of an objective medical diagnosis. Because the diagnosis itself is automatically endowed with this face validity, it is uncommonly challenged by many. But perhaps we should heavily scrutinize and challenge it. Perhaps we need to persistently keep asking the tough questions regarding what validity it can claim to have and more importantly, whether one or many better definitions could exist. Over time, the landscape of autism has changed dramatically – from a once narrow to now wide definition, from being rare to now being common in the population, from something studied mainly in childhood to now being viewed across the lifespan, from something discrete to now something a bit more dimensional, from being one "autism" to many "autisms," from pure to complex, and from "disorder" to "neurodiversity" (1). With all of this change over time, it should be perhaps expected that we do some rethinking on the concept and challenge ourselves in terms of our assumptions. Many in the field have already begun that discussion (1–18) and the dialogue should continue until we reach a revolution or paradigm shift that radically changes the situation to improve in areas that are currently heavily lacking, and which are most important given the objectives of the community and the field. In this perspective piece, we will contribute one drop into this ocean of "rethinking autism" from a zoomed-out perspective intended to primarily promote outside-the-box thinking on the topic. If we are to "rethink autism," we should zoom out and not make many assumptions about what

should be taken as fact and start asking very basic questions about the history of the label, what the diagnostic label was/was not intended for, and whether our current focus on some features rather than others may have led us astray. We conclude with an analogy about the concept of "trees" that may be useful in illustrating similar types of thinking and how we might rethink the topic.

BACK TO THE FUTURE – THE HISTORY OF AUTISM

In moving forward, it may be useful to retrace your steps. A first way we can rethink autism is simply to look back at its history. For those who have just entered the field, this may be a difficult task, but there are several key references here which we think are essential reading on the topic (1, 19–27). We will not go through all the details here. However, to summarize one lesson that history has taught us so far, it is that "autism" is not a static concept over time, nor is it likely to be some objective "thing" out in nature waiting to be discovered and better understood. Rather, "what is autism" has changed considerably over time and will likely continue to evolve as we move forward. This notion of change in the diagnostic concept over time is important to be aware of, because we should not sit idly by assuming the current concept is necessarily more correct than past conceptions. Notions such as "prototypical autism" captured by Mottron and colleagues alongside the idea of weaning effect sizes over the years may support the idea that a previous conception of autism was more impactful (3, 4, 28). However, the sheer fact that the concept itself is non-stationarity should teach us to be highly skeptical of any current or past conception and any face validity that the diagnosis may be implicitly endowed with upon first glance. One way we might be able to evaluate whether the current situation is meeting our needs should be to question what the diagnosis is good for, but also what the diagnosis is not so good for. Certainly, we would not want to chuck out the diagnosis for all the good it does in real-world circumstances, but we should also not dogmatically hold onto it and resist change when we can all agree with its many shortcomings. Acknowledging the non-stationarity of the diagnostic concept itself, via a look back at history, should be the first step in being able to let go and allow for the possibility of new ways to characterize autism that fits the current zeitgeist and needs of the community and field.

Amongst the many notable key changes throughout the history of autism that could be commented on, here we isolate one specific change point that we believe is highly relevant for underscoring a major change in the population landscape of autism. In 1987, the DSM criteria changed from a monothetic (all criteria must be met) DSM-III to a polythetic (not all criteria need be met) DSM-III-R criteria. One of the most dramatic effects of this monothetic-to-polythetic shift was the sidelining of early language issues as a core and necessary feature. Before this point in time, influential individuals key to the construction of DSM-III criteria, such as Michael Rutter, had suggested that early language issues were a key feature of autism (29, 30). However, with the emergence of Asperger's original case studies to the English speaking world (31), notable individuals such as Lorna Wing were influential in arguing that the concept of autism be broader than that of Kanner's and DSM-III, particularly with respect to whether early language issues were essential. Wing also introduced the concept of the symptom triad (e.g., social, communication, and RRB) and the notion of a "spectrum" to further expand how social-communication difficulties might manifest in different types of individuals (e.g., aloof, passive, and active-but-odd) (32). Wing's influence for this broader view (21, 33) were important factors in the DSM-III-R changes and to a polythetic relaxation which also made early language issues non-essential. All of these changes are likely important for giving us a broader and more complete view of the heterogeneous way that social-communicative issues can arise in different individuals. However, the impact of the change regarding the non-essential nature of early language issues cannot be understated. This change substantially reshaped how the autism population could be conceptualized – from once being a large majority of individuals with substantial intellectual and early language issues, to nowadays reflecting a large majority of autistic individuals without such issues (**Figure 1**). The impact of mixing together such individuals is still a prominent and current clinical issue. For example, as recognized by a recent Lancet commission, the label currently in use (mixing together all types of individuals) does not signify the differential need for services and support that the most profoundly affected individuals require (34).

We also note that at this point in time (i.e., mid 1980's to early 1990's), modern technologies that would allow us to peek into the underlying biology (e.g., high-throughput imaging and genome sequencing) were not available. Thus, these changes were made without the opportunity for science to sufficiently put to the test whether such a change was mixing together very different underlying neurobiology. Perhaps this last point could be argued to be irrelevant if someone were to claim that the diagnostic criteria was never made in the first place to differentiate individuals by biology. This is certainly true. However, given that the diagnosis is typically implicitly endowed with a certain type of face validity that most medical diagnoses also possess (e.g., differential biology), many will still assume that the diagnosis should indeed split apart individuals with very different underlying biology behind the phenotype. Evidence has been mounting in recent years suggesting that early language issues are quite important stratifiers, both from a clinical standpoint, but also in terms of underlying biology (3, 35–49). At what point should the field reflect back on whether such changes some several decades back were warranted?

Without being aware of these changes and the biases that they may represent in different subfields within autism research, the field can be quite a confusing array of findings that may be overgeneralized to the entire population. While some autistic individuals have problems in both verbal and non-verbal cognitive abilities, higher degrees of imbalance between these domains are common in autism (50–53). This is particularly important to consider given that the subset of individuals whom are minimally verbal and intellectually disabled individuals are much harder to test. Thus, a vast majority

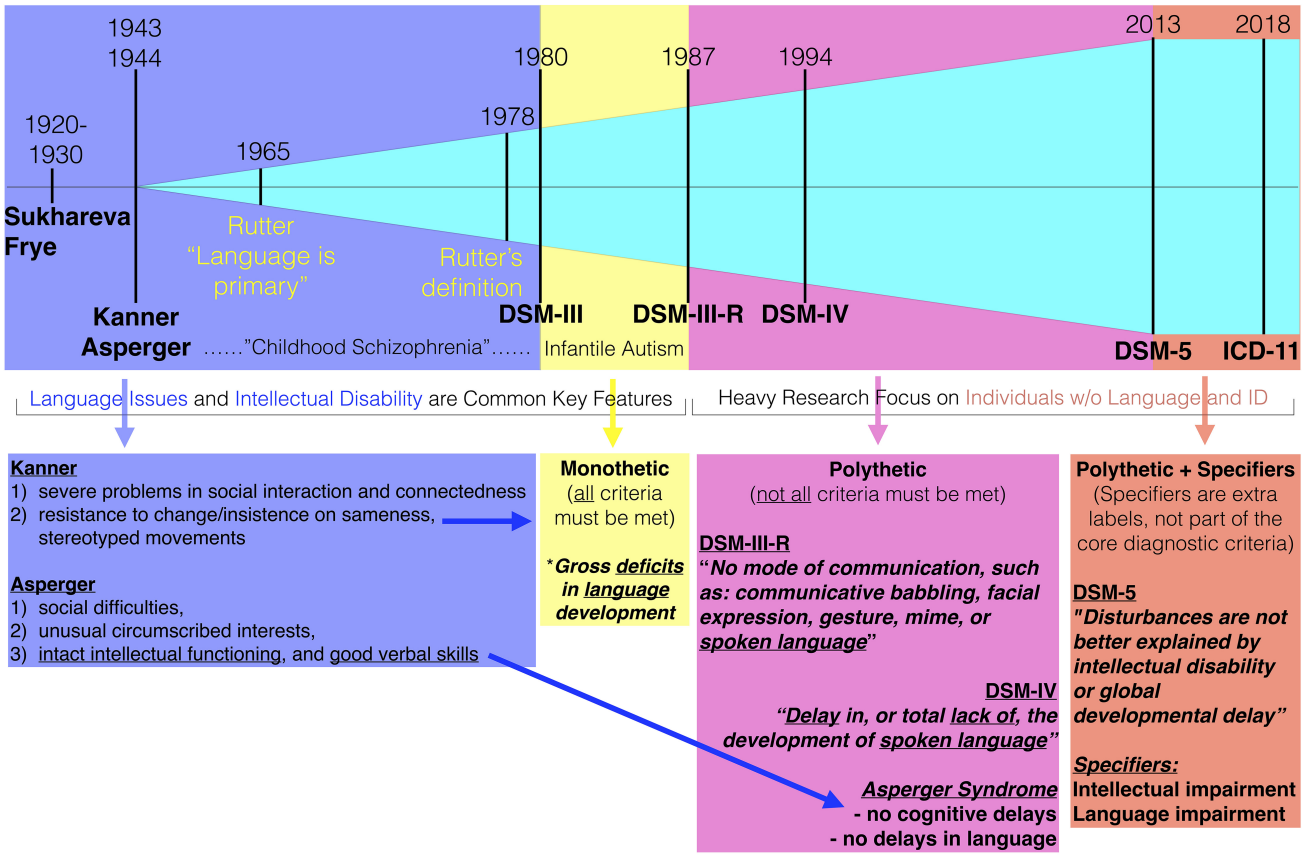

FIGURE 1 | Highlighting the 1987 breakpoint of the change to DSM-III-R criteria. Before DSM-III-R, intellectual disability and early language issues were common key features. Even Rutter's early opinions were that language was primary or core to autism. The change from monothetic to polythetic criteria in DSM-III-R changed all of this, since it allowed for individuals to be diagnosed without those kinds of issues. Over time, features such as intellectual disability and early language issues were filtered out altogether in the DSM-5 diagnostic criteria and are now used as specifiers. Star indicates one of the monothetic criteria regarding language.

of neuroimaging, behavioral, and cognitive studies heavily rely on verbal individuals with intact intellectual functioning (35, 54). Findings from such studies do not necessarily represent what may be generalized to all autistic individuals, but rather to this subset of verbal and average-to-high intelligence individuals. Many individual studies suggest this as a caveat for interpreting their results. However, such caveats can be commonly overlooked when the literature is assessed in aggregate and may thus, give off the impression that the data represents effects that generalize to the entire population as a whole. When heterogeneity in early language and intellectual ability is examined as a factor of interest, remarkable differences can be detected (37–40, 45, 46). This indicates that neglect of studying minimally verbal and intellectually disabled individuals may mask very important differences within the autism population. Conversely, blood and other biological samples that allow for DNA extraction can be collected on these "harder to test" individuals, and as such, this literature may be biased in the other direction from neuroimaging, cognitive, and behavioral research on autism. Although autism is highly heritable and much of that inherited risk may reside in a polygenic mixture of small-risk commonly occurring variants, most of the more prominent findings in the autism genetics literature are restricted to rare *de novo* variants that affect a small minority of all autistic cases, and which nearly all co-occur with intellectual or other types of developmental disabilities at the phenotypic level (47–49, 55). Thus, it appears that different research literature in autism research may be inadvertently revealing aspects that are more pertinent to subsets of the population tied to this key change point in the shift from DSM-III to DSM-III-R. Without key attention focused on this nuance, the research may come off as being over-generalized to all within the autism population.

Although some of these features regarding differences in intellectual ability and early language were attempted to be retained in DSM-IV (e.g., Asperger's Syndrome vs. autism), they have now largely been kicked to the wayside in DSM-5 (i.e., specifiers), while other features have seemed to stick. Rather than a symptom triad (pre-DSM-5), we now have a core symptom dyad of social-communication (SC) and restricted repetitive behavior (RRB) difficulties. SC and RRB tend to be the common denominators that all autistic individuals can be characterized by. However, because they are the common denominators that go into the diagnosis itself, and perhaps because they have stuck where other features have not, SC and RRB are also

endowed (either explicitly or implicitly) with extra face validity for being the most important or essential (core or hallmark) features of autism. But are these the most important and essential elements/features of interest? Whether the current conception delineates what is truly core, important/essential features is likely a debate that will continue.

"ALL MODELS ARE WRONG – BUT SOME ARE USEFUL": BEING MINDFUL OF PURPOSES, GOALS, AND OPTIMIZATION

In autism research we must be mindful that there are numerous end goals or purposes behind different types of studies. Certainly all are concerned with the diagnostic label of autism, but they may be interested in whether that diagnostic label is important for explaining a variety of very different types of things. We believe it is important to be mindful here that we are essentially building models for explaining various different phenomena of interest. These models may incorporate the diagnostic label of autism versus non-autism as one of the explanatory features (e.g., the case-control model), but may also incorporate other features. On this topic, it is important to remember the statistical aphorism that "all models are wrong, but some are useful" (56). A model's utility or usefulness is its power over explaining why variability in the phenomenon of interest occurs. Being mindful of this, we must also understand that the diagnosis itself is already an optimization for a very specific set of phenomena of interest – that is, the label of autism versus non-autism is maximally sensitive and specific for explaining variability in exemplar types of SC and RRB behaviors (57). Because of this, we can then invert the model and say that if the end purpose or goal was to predict or explain variation in the labels of autism versus non-autism, we would need a set of exemplar features of SC and RRB that are maximally useful for explaining autism versus non-autism label variation. Having specified that the label of autism already has been optimized for a specific goal or end purpose, if we turn our attention to explaining other phenomena of interest – that is, biology, outcomes, or treatment (BOT) response – then we should be fully aware of the reality that the diagnostic label of autism may not be guaranteed to explain these other phenomena very well, no matter how much we hope or assume them to be so. The diagnostic label of autism has already been optimized for a certain end goal or purpose at the level of behaviors within SC and RRB domains, and there is no guarantee that the label will also be highly useful outside of this scope.

THE BOT OBJECTIVES – BIOLOGY, OUTCOMES, AND TREATMENT

Besides explaining the behavioral phenotype of autism (e.g., SC and RRB domains), what else should we care about explaining? There are numerous directions one could go here. However, the field already has some top priorities in this realm, regarding the ability to explain variability in differential biology, outcomes and treatment responses. We would call this subset of translational research objectives the "BOT objectives." Are the BOT objectives aligned with the behavioral diagnosis of autism? If we were to assume a simple one-to-one linear mapping of biology to behavior, and vice versa, perhaps we could expect that biology exists that is indeed linked to the core hallmark SC and RRB features of autism. So far, we have not yet discovered such a mapping between biology and behavior in autism. Perhaps we haven't been looking in the right places, or perhaps we aren't yet equipped with the right tools to discover such a mapping, but perhaps we should also be prepared to accept that such an assumption is untenable as well. Thus, although the diagnosis is automatically endowed with some validity related to these BOT objectives, the reality is that the diagnosis was never designed to be optimal for explaining them. Rather, the diagnosis is optimized to explain phenomena in SC and RRB at the behavioral level. Thus, we should resist the assumption that the diagnosis should also be relevant for the BOT objectives until proven otherwise. If over time the science shows that the diagnostic label of autism may not be optimal for explaining the BOT objectives, we should then start seeking other types of models with other kinds of features that better explain the variability in differential biology, outcomes and treatment. We believe the field is already ready for this type of change (58) and we would issue a call-to-action to support the exploration of multiple other types of definitions that could be more useful for explaining BOT objectives within the autism population. However, such a call-to-action does not mean the diagnosis of autism has failed. The diagnostic label will always have the validity in being optimal for maximizing clinical consensus based on behavior. But we should be careful not to give it too much external validity with regards to other objectives that it was never optimally defined to explain in the first place.

THE TREE ANALOGY

We would like to conclude our discussion on ways to rethink autism with an analogy about the concept of "trees." We turn to this analogy not because it represents a foolproof analogy that is 100% similar in every way. There are likely many extraneous aspects of this analogy that may not be best. However, we highlight here some specific similarities in this analogy to make salient a couple of key points that may shake our deeply held assumptions about concepts like autism.

In this analogy, we will ask the simple question of "what are trees?" This is meant to be analogous to the question of "what is autism?" On the surface, we might think this is a relatively easy question to answer, because we should all have a strong common sense understanding of what trees are. Indeed this common sense understanding of the concept of "tree" is so strong that if we go back to historical roots, we can find language that describes trees in Sanskrit and ancient Greek. This indicates that our ancestors must have valued and distinguished these types of plants so much that they thought it was pertinent to give a unique word to them. Because there is such a strong commonsense understanding of "tree," could we distill an actual consensus definition as to what are the defining characteristics of trees that

set them apart from other things in the plant kingdom? Below is a layperson's consensus criteria on what is the most agreed upon definition (from Kim Coder's outreach article entitled "What is a Tree?") (59).

- Made mostly of woody substance.
- Has an erect, self-supporting, single unbranched trunk, or stem.
- Growth is perennial (throughout the year).
- Large and tall when fully mature.
- Has an elevated crown or branches.

The criteria above represent a consensus amongst a variety of dictionary, encyclopedia, botanical glossary, and ordinance/regulatory definitions of trees. This type of "consensus" definition has parallels to clinical consensus definitions based on behavior that we have about autism. The original concept behind the diagnosis was one based on observational and clinical consensus. Indeed, many experienced clinicians may have a similar strong common sense understanding of what the autism phenotype looks like, and as such, may not need much time while assessing some children to identify this autism prototype (4). While there is a difference in who makes the consensus definition (e.g., all people in the case of trees, versus specialists in the case of autism), the similarity we wish to underscore here is that both trees and autism have a consensus definition based on observable features (physical features in the example of trees, behavioral features in the example of autism).

Now that we have our consensus definition, let's take the analogy one step further and assume that our definition of "tree" has face validity and value outside of the original context where the definition was optimized (e.g., on the basis of observable physical characteristics). Could we assume that the consensus definition of "tree" has validity with regard to how botanists would taxonomically characterize plants? In other words, because we have this strong consensus definition that trees are indeed a distinct "thing" in nature, would botanical taxonomies respect that and also distinguish trees as a specific scientific grouping separated from other plants? The answer here is simply "no." Taxonomically, "trees" do not have a distinct scientific grouping. Rather, some trees are grouped into a cluster for flowering plants where seeds are encapsulated, called angiosperms (e.g., fruit trees), while the other types of trees are grouped into a class called gymnosperms, which have their seeds exposed (e.g., pine trees). Therefore, just because trees grow larger and taller than their other plant relatives in the same category, does not really matter, at least for an objective scientific definition. A blueberry bush and an apple tree come from the same angiosperm family and are not necessarily distinguished by the fact that apple trees fall within our definition of tree above, but blueberry bushes do not. Indeed, the point we are emphasizing here is that the concept of "trees" is a consensus definition historically defined in language by our human ancestors and which has carried on today. There are very good reasons to hold onto this definition, as it has value for labeling a specific type of plant that we all value culturally and wish to distinguish from other types of plants. However, although there is that consensus definition of "tree," it does not correspond well with other taxonomic classifications of plants. Other taxonomic classifications of plants are optimized in other ways that do not correspond well to optimization within the consensus model for "tree." Thus, the concept of tree is very salient to most of us and it may be very hard to shake the idea that scientifically, trees are not "one thing" that exists in nature. This point is emphasized to underscore the fact that although we might all be able to agree on a set of defining criteria, that by no means gives us license to assume that such a "thing" actually exists out in nature as an objectively defined "thing" and that all other connotations about underlying biology, etc., should follow from the initial consensus definition.

We can take a final step further in this analogy by considering the defining core or non-core characteristics of "trees" and drawing parallels to the diagnosis of autism. For example, let us say that the feature of growing large and tall when fully mature is akin to the RRB domain in autism, while the trunk or stem of a tree might be akin to the SC domain in autism. Here are two central defining features of trees and autism that are very well evident. Now let us take the seeds trees produce, along with the encapsulating tissue around it (e.g., fruit) and let us say that this is analogous to early language issues. Not all individuals with autism have early language issues, but some do. Not all trees bear fruit, but some do. A characteristic such as bearing fruit is not a core characteristic of a tree, because not all trees bear fruit, and also because many non-tree plants can bear fruit as well. Similarly, early language issues are no longer a core feature of autism (as they were in DSM-III) because the rationale is that not all individuals with the other core features have early language issues, and most crucially, because many non-autistic individuals can have substantial early language issues. By drawing this analogy, we would like to point out a distinction of importance. Fruit bearing trees are indeed a different class of plant altogether (i.e., an angiosperm) and such plants are so heavily differentiated from other trees falling into the gymnosperm category as to not be considered together, even despite the fact that, for example, a pine tree and an apple tree meet all the other core features of being a "tree." By focusing on the core elements that are characteristic of autism, and marginalizing the importance of other non-core features, are we missing important aspects that would help us to derive a different definition or set of labels that is more tailored to elucidating differences that are considered to be of high-importance (e.g., BOT objectives)? This example is one of many that could be drawn in this type of "tree" analogy, and we offer it up as a potential thought experiment to help readers challenge their assumptions about autism and what is held to be of most importance, given a specific end goal/purpose/objective.

CONCLUSION

In conclusion, we think the time is ripe to actively have the field reconsider or rethink their assumptions and strongly held core beliefs about autism. In doing such a "rethink," we should consider that the single diagnostic definition we currently possess need not be the only or most important way of defining

the autisms. Indeed, we may need multiple different types of definitions or classification structures (i.e., models) that are tailored to different end goals/objectives. We hope that we have been able to make more salient that the diagnostic model currently in place is there to be optimal for a specific type of phenomena and end goal and that for other purposes or objectives, other models may be needed. As we consider other models, we may need to let go of what we believe are the core versus non-core features of the current diagnostic model, and think about other ways to optimally explain autism in terms of a variety of alternative, yet important objectives (e.g., BOT objectives).

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Alternatives to Gold Standard Diagnostic Tools for Distinguishing "Natural Kinds" on the Autism Spectrum

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Next-generation sequencing techniques have accelerated the discovery of rare mutations responsible for autism spectrum disorder (ASD) in genes involved in a large number of physiological processes, including the control of gene expression, chromatin remodeling, signaling pathways, synaptic scaffolding, neurotransmitter receptors, and lipid metabolism. Genetic diagnosis provides subjects with an explanation of the cause of their disorder. However, it does not, or at least does not yet, shed light on the psychopathological phenomena specific to the individual. It could be hypothesized that each physiological impact of a mutation corresponds to a specific psychopathological phenomenon of ASD, i.e., "a psychopathological natural kind". We discuss here the difficulties identifying this specificity of underlying psychopathology in individuals with ASD due to a rare mutation with a major effect. A comparison of Newson's *pathological demand avoidance* and Wing's *Asperger's syndrome* with Asperger's *autistic psychopathy* highlights different ways of approaching psychopathological descriptions and diagnosis, by focusing on either common or unusual features. Such a comparison calls into question the principles of clinical research recommended by Falret for characterizing "disease individuality" of ASD due to a rare mutation.

Keywords: autism spectrum disorder, rare single-nucleotide variants, rare copy-number variants, psychopathological phenomenon, Asperger, Newson, Wing, Falret

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INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous condition, with many etiologies, characterized by impaired social communication, repetitive behaviors, and highly restricted interests and/or sensory behaviors beginning early in life (1).

In the era of next-generation sequencing, the use of a *genotype-first* approach combined with *reverse phenotyping* has led to the identification of pathogenic genetic variants underlying ASD in more than a hundred genes over the last decade. Pathogenic variants are individually rare, but collectively, they allow genetic diagnosis in 10–30% of individuals with ASD (2).

This strategy involves grouping individuals with a *rare* potentially damaging variant of the same gene together (genotype-first step) and then comparing their phenotypes *a posteriori* (reverse phenotyping step), in greater detail, to determine whether the individuals in the same group share the same specific phenotype (2, 3). If the *specific* phenotype appears to be consistent in at least three unrelated individuals, variants of this gene can be considered pathogenic, allowing the description of a novel "natural kind" (4).

This recognition of a *specific* phenotype is facilitated when the cognitive affective behavioral disturbances are associated with specific somatic or paraclinical signs, such as dysmorphic facial features (5), macrocephaly (6), or abnormal cerebellar foliation (7). In these cases, ASD is considered syndromic (8).

In the absence of objective signs (non-syndromic ASD), the recognition of a specific cognitive affective behavioral phenotype is more difficult, requiring intersubjective methods, such as observation, scales and questionnaires, interviews with the individual and their relatives, or psychological tests, resulting in a greater divergence of points of view between clinicians.

In this article, we discuss how best to investigate the specific psychopathology of ASD subjects with rare pathogenic variants, assuming that each physiological impact of a mutation corresponds to a specific psychopathology.

Elizabeth Newson's *Pathological Demand Avoidance Syndrome*

Identification of the specific "psychopathological natural kind" of ASD subjects with a rare pathogenic variant requires an extensive knowledge of normal child development and of the various clinical entities described within and beyond ASD, such as *autism* (9, 10), *schizoid/autistic psychopathy* (11, 12), *multiple complex developmental disorder* (13), and *schizoid personality* (14), neuropsychological syndromes, such as *nonverbal learning disabilities syndrome* (15), *semantic-pragmatic disorder* (16), *developmental prosopagnosia* (17), *cerebellar cognitive affective syndrome* (18), and *executive dysfunction* (19), and differential diagnoses, such as *Landau-Kleffner syndrome* (20), *early-onset schizophrenia* (21), *early-onset catatonias* (22), and *attachment disorders* (23).

It is within this context that we are discussing the clinical entity proposed by Elizabeth Newson, "pathological demand avoidance syndrome", which she described as a necessary distinction within the pervasive developmental disorders, but which is little known outside of Great Britain (24).

In the 1980s Elizabeth Newson (1929–2014), a professor of developmental psychology at the University of Nottingham, described a particular behavioral pattern in a subgroup of children some of whom had been referred to her for suspected autism or Asperger's syndrome. However, these diagnoses were not confirmed by her own diagnostic assessment, and she considered these children to have what she called "pathological demand avoidance" (PDA) (24).

The key characteristics of these children were: (1) feeling intolerable pressure when faced with the most ordinary of everyday demands, and using various manipulative strategies to avoid most of the requests they encountered, (2) a superficial sociability that was invested in a self-centered manner, (3) mood swings or impulsivity in response to a request or for no apparent reason, and (4) a marked interest in an imaginary world.

Newson showed PDA to be different from both classical autism and Asperger's syndrome in a functional analysis on 90 children (50 with PDA, 20 with classical autism, 20 with Asperger's syndrome). She considered PDA to be a *specific* pervasive developmental disorder (24). However, the validity of her results was limited by several methodological flaws: the diagnostic criteria for the three groups compared were not defined, Autism Diagnostic Interview-Revised (ADI-R) testing was not used to ensure that none of the children with PDA also met the criteria for ASD, etc.

Close to Hans Asperger's *Autistic Psychopathy*?

Given the seeming convergence, it is odd that Newson did not draw parallels between her syndrome and that of the four autistic psychopathy cases, Fritz, Harro, Ernst and Helmut described by Asperger (11). Indeed, as described by Asperger:

"from the earliest age Fritz never did what he was told. He did just what he wanted to, or the opposite of what he was told. He was utterly indifferent to the authority of adults, he called everybody 'Du'. As one would expect, the conduct disorders were particularly gross when demands were made on him. In fact, it is typical of children such as Fritz that they do not comply with requests or orders that are affectively charged with anger, kindness, persuasion or flattery. Instead, they respond with negativistic, naughty and aggressive behavior" (11).

Harro presented similar discipline problems: "[He] often refused to co-operate, sometimes using bad language. He rarely did what he was told but answered back and with such cheek that the teacher had given up asking him. He was said to be an inveterate 'liar'. He did not lie in order to get out of something that he had done - this was certainly not the problem, as he always told the truth very brazenly - but he told long, fantastic stories" (11).

The article "*Die Austitischen Psychopathen im Kindesalter*" (1944) remained almost unknown for many years, probably because it was originally written in German. An unabridged English translation did not become available until 1991 (11), so Newson may have been unaware of it when she developed the PDA concept in the 1980s. In any case, she did not mention it in the references of her 2003 article (24).

Different From Lorna Wing's *Asperger's Syndrome*?

Lorna Wing (1928–2014) introduced Hans Asperger's article to the scientific community in an article published in 1981, entitled "Asperger's syndrome: a clinical account", in which she redefined the syndrome starting from the original description, but with alterations drawn from her own experience. Indeed, Wing disagreed with Asperger, disputing the "highly sophisticated linguistic skills" of these children and any creativity and originality that they may have displayed, instead focusing on their absence of social imagination (25).

Her search for severe impairments of social interaction and repetitive stereotyped behaviors, initially in disabled children and then among children without intellectual deficiency, revealed that these children shared many abnormalities. This led her to propose a "continuum" between Kanner's autism and other related entities, such as Asperger's autistic psychopathy or PDA (26, 27), which greatly influenced the current concept of "autism." This view diverged from former representations, such

as Folstein and Rutter's first twins' study (1977), in which they regarded a pair of monozygotic twins as discordant because one presented autistic disorder and the other, Asperger's autistic psychopathy (28). Wing also contributed to the introduction of Asperger's syndrome into the DSM-IV. Nevertheless, the difference between Asperger's original description and the definition in the DSM-IV generated confusion among clinicians. Asperger's syndrome was, therefore, removed from the DSM-5, instead included, though a dimensional approach, in a diagnostic classification within a new category -autism spectrum disorder- along with autism and pervasive developmental disorder-not otherwise specified.

So, were Newson and Wing talking about the same children? Do these children display clinical variability or clinical heterogeneity? Are their *socio-communicative deficits* and *pathological demand avoidance* two facets of the same disorder?

To answer these questions, we encourage clinicians to read the translation of the original article by Asperger ("Die autistischen Psychopathen im Kindesalter"), from the book by Uta Frith (11), in its entirety so that they can judge for themselves whether the Asperger's original description is identical to or different from PDA and Wing's Asperger's syndrome.

DISCUSSION

The difficulty of directly accessing the mental state underlying the signs and symptoms of a subject makes it difficult to develop nosographies in psychiatry.

The DSM and its successive versions marked a turning point in the history of psychiatry, by proposing a classification widely used in applied research for constituting groups of patients. This has improved inter-rater agreement, and, thus, the reliability of diagnosis, with the use of a common language facilitating exchanges in clinical practice (29). There occasionally are disagreements between clinicians, as illustrated by the case report of "An 8-year-old boy with school difficulties and "odd behavior" (30). The behavior of this boy suggested a diagnosis of Asperger's syndrome ("happy to play alone") but his teacher found "[his] social skills were a notable strength", which led to several other potential diagnoses, such as ADHD and obsessive-compulsive disorder, and diverse suggestions for therapeutic strategies ranging from "wait and see" to treatment with methylphenidate (30).

In basic research, the validity of the DSM has been called into question (31), including for ASD (32), due to a lack of knowledge of the underlying etiopathological mechanisms.

The identification, in recent years, of rare pathogenic variants [single-nucleotide variants (SNVs) or copy-number variants (CNVs)] in individuals with ASD has made it possible to develop a taxonomy, based on an etiological approach (33). Each type of physiological impact of a mutation, resulting, for example, in a decrease or increase in gene expression or a loss-of-function or a gain-of-function in protein, may correspond to a specific psychopathological form of ASD that can be seen as a "psychopathological natural kind".

These discoveries provided some initial insight into physiological mechanisms, through explorations of the impact of these pathogenic variants in functional studies *in vitro* and *in vivo* (34). They made it possible to group subjects with the same rare pathogenic genomic abnormality together, in a way that current clinical assessment cannot, either because clinical manifestations are not very specific or because they differ too much between subjects according to contemporary classifications. This grouping together of small numbers of subjects makes it possible to evaluate the *principle of specificity* defended by Bretonneau in the field of infectious diseases at the start of the nineteenth century, by assessing the correspondence between genetic and psychopathological diagnoses (35).

This principle of specificity often initially appears not to be respected in ASD, particularly in non-syndromic forms, whether for SNVs or CNVs. Partial deletions of the *SHANK3* gene, for example, can manifest in ASD subjects with and without intellectual deficiencies (36), and proximal 16p11.2 duplication (BP4–BP5) may arise *de novo* in an ASD subject or be inherited from a "healthy" parent, highlighting the incomplete penetrance and/or variable expressivity (37).

Before studying the influence of background factors, including "concrete" variables, such as environmental factors (exposure *in utero* to toxic substances, neonatal distress, psychosocial environment), epigenetic and stochastic factors (monoallelic or allele-biased gene expression), and genetic background, on *phenotypic heterogeneity* in subjects carrying a given pathogenic variant, it is important to describe the *phenotypic variability* of the "natural kind" associated with the variant in question.

From a fundamental research perspective, ASD lies at the frontier between life sciences, supported by a naturalist framework for studying objects with a "concrete" reality (signs, mutations, dysembryoplastic neuroepithelial tumor, tubers, etc.), and human sciences, which function within a normative framework, exploring complex objects often constructed in a more abstract manner (symptoms, idiosyncratic interests, psychiatric diagnosis, etc.) (38).

Improvements in our knowledge of ASD require continual switching between these two types of science. For example, studies of the expression of mutated genes have improved our understanding of the reasons for which only a subgroup of patients suffering from neuromuscular diseases (e.g., the Duchenne and Becker dystrophies linked to the *DMD* gene, dyneinopathies linked to the *DYNC1H1* gene) present cognitive, emotional, and/or behavioral problems (including ASD). Such studies have identified mutations located in particular domains of the gene that lead to specific physiological alterations to the resulting transcripts in the brain (e.g., the Dp71 transcript of the *DMD* gene) (39, 40).

The *reverse phenotyping* approach has drawn attention to certain behavioral peculiarities, such as obsessive-compulsive disorder in Prader-Willi syndrome and social anxiety disorder in fragile X syndrome (41). However, the nature of these disorders remains to be understood, and a methodological reflection is required to describe the underlying psychopathology of "natural kinds." Indeed, it is not a question of confirming or rejecting a known psychiatric diagnosis, but of identifying

psychopathological consequences with, *a priori,* signs that are new or have rarely been taken into account.

The DSM is not particularly suitable for identifying the unusual clinical manifestations corresponding to rare mutations. This tool is based on the findings of epidemiological studies on large samples, which favor frequently occurring symptoms over rare, often more specific, signs or symptoms. It consists of diagnostic categories defined by the presence of sufficient symptoms from a specific list, but it does not take the context into account, which is essential to understand the psychopathological value of the manifestations. Finally, for therapeutic purposes, the DSM concerns only "clinically significant" manifestations, whereas basic research is equally interested in the "silent side of the spectrum" (42, 43).

In addition, the DSM, with its operational criteria defining each clinical category, has profoundly modified the psychiatric semiological approach of an entire generation of clinicians, by structuring the representation of disorders around these criteria, which are sometimes abusively considered to be exhaustive (44). The recognition of signs and symptoms is, thus, strongly influenced by the category of the suspected diagnosis, and this may constitute an epistemological obstacle to the psychiatric observation of unusual clinical manifestations (45).

So, how can we discover the "psychopathological natural kind", given that "what is observed is often neither relevant nor significant, and what is relevant and significant is often difficult to observe" (46)?

We can now return to the starting point, the principles recorded by Falret in his *Clinical Lessons* in 1864, which enabled him to identify "circular insanity" (1854), now known as bipolar disorder, which he considered, along with general paralysis, to be a model of "natural forms" (47–49).

The *first principle* is "do not reduce your responsibility as an observer to the passive role of the patient's secretary" (47, 48). Careful clinical observation is the cornerstone of the clinical method, but clinicians must also play an active role in "bringing out manifestations that would not arise spontaneously", just as neurologists look for imbalance in Romberg's test by asking the patients to close their eyes.

Clinicians can, for example, explore psychomotricity by examining the reaction of the subject to stimuli (verbal request, exaggerated gesture), making it possible to observe the tendency to initiate a bizarre automatic response (echolalia/ echomimia /echopraxia) or increased response latency, or even automatic resistance to verbal or non-verbal requests (50). For subjects with spontaneous fluid speech, they can propose more restrictive conditions, for example, by asking the subject to explain the differences between pairs of words relating to tangible (box/basket) or abstract (error/lie) entities, to reveal small logical or conceptual difficulties (51).

The *second principle* is to characterize "disease individuality," "describing the subject observed and what distinguishes that subject individually, rather than describing the phenomena common to this and other subjects according to existing classifications" (49).

Finding differences between subjects with ASD of different etiologies obviously requires us to look for their singularities rather than the features they have in common. The information collected by the ADI-R or the Autism Diagnostic Observation Schedule (ADOS) (52), which seek common manifestations of ASD, should not, therefore, *initially* be taken into account.

Alongside the most salient symptoms, the identification of "negative findings" defined as "the absence of certain findings under conditions in which they should necessarily occur," can also be discriminating in the differential clinical approach. Such findings may correspond not only to developmental delays (e.g., lack of protodeclarative pointing at 18 months), with a reference framework of normal development, but also to the absence of certain typical "autistic traits" in ASD subjects of a given etiology relative to prototypical autism (9). For example, deviant language development (delayed echolalia, pronoun reversal) or atypical visual exploratory behavior is regularly absent from the "autistic traits" of subjects with *SHANK3* abnormalities (53).

Finally, close longitudinal observation to assess the temporal dynamics of the natural course also contributes to the characterization of "disease individuality" (47, 48).

The *third principle* is "never to separate a finding from the condition from which it arises, or from the circumstances that precede or follow its occurrence" (47). Detached from their context, the signs or symptoms lose their significance; it is the context that allows its clinical value to be assessed (54). "It is not enough to note the odd and extraordinary words pronounced by the insane patient, and the eccentric and muddled actions he committed; one must, above all, assess and carefully analyze the internal psychic state that gives birth to these words and actions" (47, 49). "When faced with an agitated patient, it is therefore important to search carefully for the cause of such agitation, to determine whether it is automatic and muscular, or voluntary, driven by an idea" (47). Returning to the clinical case of "An 8-year-old boy with "odd behavior"' taking the context into account makes it possible to understand the differences in the diagnostic process. This boy seemed to be very comfortable in interactions involving a mediated activity (class presentations, speaking through a microphone) and when he took the initiative for the exchange, whereas he seemed more troubled when he was solicited or had to interact directly with his peers (30).

Understanding ASD requires symbiosis between the life sciences and the sciences of the mind, two disciplines that differ in their objectives, methods, and experimental design. They often see each other as rivals, each tending to claim a monopoly on explanation or understanding, whereas here, in the specific case of ASD caused by a rare variants, it is precisely their differences in approach that make it possible to validate results reciprocally, demonstrating the pathogenicity of the variant and the specificity of the psychopathological profile.

Studies of subjects carrying rare mutations provide an opportunity to understand the physiological and developmental functions of the genes concerned, but, above all, they also provide unique access to the psychopathological impact of each mutation.

Indeed, the grouping together of subjects carrying the same rare mutation makes it possible, by taking into account both chronological and development age, to perceive the underlying psychopathological prototype beyond the background noise of temperament, individual history, and sociocultural influences,

provided that we do not get cling to our stereotypes and that we systematically verify our perceptions. An awareness of these psychopathological profiles will open up new perspectives for research, diagnostic genomic testing and clinical practice.

In the field of research, this will make it possible to examine the functional relationships linking psychopathological phenotypes and physiological dysfunctions through *in vivo* studies (functional imaging, electrophysiology, animal models, etc.) or *in vitro* studies (cell models based on cells directly derived from patients, etc.). In diagnostic genomic testing, a knowledge of psychopathological characteristics will facilitate clinical interpretation, by biologists, of genetic variants that have not been encountered before. In the clinical setting, disentangling psychopathological profiles on the autism spectrum will improve our understanding of the mental state of patients, making it possible to provide more personalized treatment.

Finally, although monogenic forms represent a small fraction of ASD cases, this change in perspective concerning the way we view the signs and symptoms of ASD with rare etiologies may provide insight to improve clinical judgments for more prevalent idiopathic forms of ASD, and may facilitate the identification of mutations in the subjects described by Asperger, Newson, or Wing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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ASD–Time for a paradigm shift

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Problems with the diagnosis of ASD have been acknowledged by clinicians and researchers alike. In a seminal paper in 2006, Happe et al. (1) called for the fractionation of autism arguing that the parameters by which autism was diagnosed at the time could not have a single explanation. Although the evidence has been there (2), side by side with worries expressed by clinicians, it took years for the implications of this work and many that followed to be digested and brought to the center of attention of research on ASD. Since Waterhouse and Gillberg (3) in which concerns about the categorical diagnosis of ASD were clearly expressed, the discussion took a more radical turn and a call to abandon the diagnosis of autism has been on the table. Finally, the last few years have seen more intensive work arguing for a reconceptualization of ASD, although still somewhat hesitantly. It seems we are still far from a consensus on the need for a paradigm shift with respect to ASD (4–6).

Of relevance to the current discussion on the status of ASD as a biological entity are writings of philosophers of science that concern the epistemological standing of psychiatric disorders, among them ASD. It is of course beyond the scope of this paper to do full justice to this topic. However, framing our discussion in reference to the terminology used by philosophers could help us see what is being claimed with respect to psychiatric disorders and whether the way ASD is defined in DSM V respects these conceptual boundaries.

Zachar and Kendler (7) review the history of psychiatric nosology tracing today's "crisis of confidence" (Ibid p. 50) to attempts in the 17th and 18th centuries to classify medical conditions and define their nature. They identify two positions in current day debate. The first involves gradual iterative improvement of DSM nosology. DSM-V has adopted this approach and has implemented a hybrid model of dimensions and categories in a number of psychiatric disorders including ASD (8). The second approach involves a paradigm shift, as exemplified in the RDoC initiative (9). RDoC severs ties between clinical and research constructs, organizing research around symptoms, not syndromes. Research domains in the RDoC model are anchored in behavioral neuroscience and cognitive theory, with the hope of increasing chances of discovering etiologies of psychiatric symptoms.

Kendler (10) discusses three theories about the nature of psychiatric disorders that can be placed on a scale of "realness," namely, realism, pragmatism and constructivism. The latter are also referred to as "practical kinds" (7). Realism assumes that the content that comes under a diagnosis exists in the world independent of scientists' conceptions and activities. Natural kinds are "real"–they are bounded, stable and unified by virtue of a causal explanation. Much like a biological species, a "real" psychiatric disorder needs to be discovered, not created. Pragmatism sees psychiatric categories as a way of organizing practical aspects such as interventions, support systems and developmental predictions. To the pragmatist, reality is not a major concern. If an invented diagnostic category

does the work, so be it. Constructivism does not give up realism, yet it accepts the fact that social-pragmatic concerns crucially affect the reality of psychiatric disorders. Thus, constructivism does not disjoin research and clinic. It welcomes the impact of social and cultural elements on the nosology, while aspiring to discover its biological essence.

Ongoing work in psychiatry has shown that realism as it is defined in the biological sciences sets prerequisites that cannot be met by psychiatric diagnoses. Still, giving up on the claim to "existence in the world" is a move likely to encounter objections from professionals in the field. Kemder's (10) limited view of realisms offers a working hypothesis that fits with the science of psychiatry, as well as with its clinical practices. In Kendler's words, a limited form of realism suggests that "a diagnosis is real to the degree that it coheres well with what we know empirically and feel comfortable about" (Ibid, p. 9). This is a narrower sense of realism that the field can and should adopt.

Genetic makeup, brain imaging, pathophysiology, developmental course, behavioral characteristics and treatment effects are parameters that provide the empirical basis of psychiatry. In line with the above suggestion of a limited version of realism, results related to these fields of study are expected to cohere as they relate to a given diagnostic category. If they do, they will confer a sense of reality on the projected entity. Does ASD as it is defined in DSM-V pass the test? and if it does not, is the field ready to reconceptualize ASD?

There seem to be three inter-dependent conditions that, if satisfied will lead to a reconceptualization of ASD. The first concerns a profound dissatisfaction among clinical and research communities as well as stakeholders with respect to the existing diagnosis of ASD. The second is the need to offer an alternative conceptualization that will get us closer to an understanding of the phenomena currently diagnosed as ASD and will meet patients' needs. The third involves the crosstalk among stakeholders. Few psychiatric diagnoses have had as much public impact as has been the case with ASD. For a new conceptualization to replace ASD, families, patients' associations, government support systems, social services, educators and funding agencies need to come to terms with a new way of thinking about ASD.

Is dissatisfaction with the current definition of ASD deep enough? The answer seems to be–Yes. Despite impressive technological progress and a growing understanding of brain structure and function, as well as the genetics of various developmental conditions, neurobiological research has not provided definitive answers that support a categorical definition of ASD. Our current understanding of genetic risk factors of neurodevelopmental disorders among them ASD suggests that they are polygenic, pleiotropic and are on a continuum with typical behavior (11). Polygenic variations seen on a large number of alleles jointly and probabilistically increased risk for a neurodevelopmental disorder. Beside risk alleles there are protective alleles as well as variations that improve performance, as is not rarely seen among people diagnosed with ASD (12, 13).

The genetic architecture of neurodevelopmental disorders overlaps. Risk alleles but also protective alleles have additive and overlapping effects that, in many cases can contribute to more than a single unique phenotype (11). Of particular relevance is recent evidence of a common factor, labeled the factor p, underlying diagnostically **diverse** developmental disorders, among them ASD (14). A recent study examined whether polygenic risk scores in school age children are associated with a general propensity for psychopathology or with specific disorder. The results suggest that phenotypes are more often associated with general pathology, rather than with one specific domain (15). In other words, questions about the validity of ASD as an independent category concern not only the heterogeneity within ASD but also the similarities across neurodevelopmental disorders. This conclusion is reinforced by neuroimaging studies of people with ASD, which present mixed results with few unique patterns that can be attributed to the diagnosis (16).

The message from neurobiological results as of now is the following: An individual's ultimate behavioral profile is a function of his/her genetic architecture, internal and external environmental effects, developmental history as well as stochastic events that interact to produce a behavioral phenotype. There seems to be no evidence for a DSM-type system of discrete categories that map onto psychiatric disorders, ASD included.

As for behavioral research, as early as 1971, acknowledging similarities and differences between children with different diagnoses, among them children with autism, Wing and Wing (2) stated that "a combination of language, perceptual, motor and autonomic impairments underlies autistic behavior... Such a combination could have a single or multiple etiologies. Isolated fragments of the full picture often occur, either alone or in combination with different syndromes" (Ibid p. 256). Fifty years of behavioral research confirmed this account.

Current diagnosis of ASD allows extreme within-category heterogeneity and lacks category-specific developmental course. Attempts to define sub-groups within the spectrum failed. Similar to studies in the biology of ASD, behavioral research typically fails to reproduce and the study population does not cover the entire spectrum. In particular, it fails to cover low functioning individuals as well as those without speech (17, 18). The phenomenon of regression is poorly defined, girls have been less studied than boys probably due to stereotyping and to biases in the diagnostic tools (19). Children in low-income countries are poorly represented in the studied populations (20) and this is the case with respect to adults with ASD as well (21). Finally, there is little predictive power relating to intervention effects on ASD symptomatology (22).

An extension of the problems inherent in the attempt to enclose the behaviors that characterize ASD within the boundaries of a labeled category is evident in the new category

SCD (Social Communication Disorder). SCD is characterized in DSM-V as a communication disorder but is considered by some as a mild form of ASD (23, 24), as identical to what has been known in the literature as pragmatic language impairment (25), as a version of the BAP (26) or as providing motivation for an independent RRB category (27). Similar to ASD, SCD is framed in a DSM-type language. Much like ASD, the dimensional characteristics of SCD extending to typical children and adults, difficulties in its definition and its overlap with other language disorders (28) does not lend validity to SCD as a category.

In sum, results coming from diverse areas of study, all intensely researched in children and adolescents that have received a diagnosis of ASD, do not fulfill the limited sense of realism suggested by Kendler (10). That is, they fail to present a coherent picture that could convincingly define an entity. Rather, the observed phenomena are on continua with the distribution of similar behaviors in the typical population. In Hayman's (11) words, ASD, as well as other neurodevelopmental disorders. are "grounded in nature, but they are not natural kinds" (Ibid p. 21).

There is undoubtedly a sense of disappointment in the clinical and the research communities in having to admit that decades of work within a categorical framework of ASD, have resulted in "many insights, but few answers," as stated in a recent review article on neuroscience research on ASD (16) (Ibid p. 4344). Nevertheless, many are reluctant to re-consider the categorical status of ASD. The reasons refer primarily to the worry that a re-conceptualization could affect patients' welfare on a variety of levels. Even more so, since there is no acceptable alternative against which the risks of such a move could be weighed (6). The second condition listed above, namely, the need to sketch a blueprint of a re-conceptualization of ASD, is therefore a most urgent task.

A new way of thinking about ASD may be inspired by the conceptualization of other neurodevelopmental disorders. Consider the following: the continuous nature of the behaviors diagnosed as ASD with behaviors seen in typical individuals, the overlap in the genetics of neurodevelopmental disorders, the frequent "comorbidity" with childhood syndromes, the potential for considering diagnosed individuals as diverse, not disordered–all of these characterize neurodevelopmental disorders, such as cognitive impairment or language impairment as well as ASD. Yet, neither cognitive impairment nor language disorders denote a diagnostic category. They are viewed as meta-terms, and are referred to in relation to DSM terminology as specifiers of a DSM diagnosis.

Are the defining parameters of ASD inherently and developmentally different from cognitive impairment or language impairment? Behavioral work tells us that this is not the case. In fact, they too are better described as meta-terms, on the same theoretical level as the currently-noted specifiers, such as cognitive level or language.

Note that dismantling ASD and reconceptualising each of its defining parameters as a meta-term that can have multiple behavioral manifestations and is not tied to a single diagnosis is not a semantic issue. This change gets us closer to the scientific truth, namely, to the picture that emerges out of the neurobiological, genetic and behavioral studies conducted on ASD in the past 50 years. It coheres well with what we know empirically and thus maintains a sense of realism (10).

Importantly, redefining ASD along these lines does not dissociate it from clinical terminology. Rather, it is a bottom-up approach, based on behavior and attentive to practical considerations, that has clinical advantages a well. In considering social-communication behavior, routine-repetitive behavior, cognitive impairment and language development, along with perceptual sensitivities, attention deficits and temperament as characterizing a child's profile relative to age and background, the within category dimensional approach is turned from vertical to horizontal, encompassing typical as well as atypical behavior. By adopting this approach, developmental science and the science of pathology may acquire a road map to variability, with respect to which it can resolve questions related to comorbidities and evaluate decisions as to needs and types of intervention. The lab and the clinic will definitely have a common language.

What about the prototypical cases of "pure" autism, described by Mottron (29)? I believe it is an open question whether such "pure" cases are instances of a diagnostic category. Assuming a consensus can be reached among expert clinicians with respect to a sufficiently large group of children who will be considered exemplars of "pure" autism, the existence of biological underpinnings of such a group could be tested. The possibility exists however, that "pure" autism, just like less prototypical cases, is the outcome of interactions among the polygenic factors and environmental effects that are involved in these set of behaviors. Note however, that the logic behind Mottron's hypothesis suggests that even if a unique causal, biological basis for the symptomatology that characterizes "pure" autism is found, it will not generalize to ASD as it is defined in DSM V. Thus, the need to reconceptualize ASD will remain.

Perhaps the major obstacle to an open discussion relating to the status of ASD is the third condition listed above, namely, the crosstalk among stakeholders. In the case of ASD it involves not only the clinic and the laboratory but the media, the public, the educational system, welfare and research funding. In the case of ASD, these are powerful social-political institutions whose position with respect to the controversy within academic and clinical quarters has not been heard yet. Constructivism tells us that nosology, formulated by the professional community, affects social organizations, resources and trends and is affected by them (10). Given this mutual dependency, the question whether we should reconceptualize ASD, must take into consideration these social factors as well.

In conclusion, despite concerns and difficulties, I believe it is the duty of the professional community to revolutionize ASD definition, aspiring for a conceptualization that will cohere with what research in relevant domains has taught us. We owe it to our patients and to the public. Given the current advancement in technological solutions, opportunities for big data analyses, network perspectives (30) machine learning methods (31), it seems that reliance on categories as systematizers of our knowledge base could become more relaxed, perhaps even obsolete. Medicine and psychology may face real-world considerations, such as suitable interventions, educational placement, and welfare without the aid of categorical labels. Such an approach will better connect clinical work and scientific research. Developmental psychiatry may be able to more effectively join other areas of medicine and apply personalized medicine successfully.

True, in the absence of a label, ASD may lose its public prominence, but hopefully, this will open up opportunities for children with other neurodevelopmental disorders or monogenic syndromes. Perhaps the public will turn its attention to them as well.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The hallmarks of autism

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I suggest that the current study of autism is problematic, due to: (1) its failure to pursue a medical model of disease causation, with protocols for differential diagnoses of causes; (2) a notable incidence of unrecognized false positive diagnoses in children; (3) the conceptual equating of autism with sets of traits that have been shown to be genetically and phenotypically unrelated to one another; and (4) the expansion of use of the terms "autism" and "autism traits" to psychiatric conditions that have no substantive etiological or symptomatic overlap with autism. These problems can be alleviated by, like Kanner, considering autism as a syndrome, a constellation of traits, conceptualized as differences rather than deficits, some set of which is found in each affected individual to some degree. The original, prototypical form of autism can be delineated based on the "hallmarks" of autism: a set of core traits, originally explicated by Kanner, that defines a relatively-homogeneous group, and that connects with the larger set of autism symptoms. The hallmarks of autism provide a touchstone for research that is unambiguous, historically continuous to the present, and linked with major theories for explaining the causes and symptoms of autism. Use of the hallmarks of autism does not impact recognition and treatment of individuals with DSM diagnosed autism, or individuals with the many disorders that involve social deficits. This perspective is compatible with the research domain criteria approach to studying autism, *via* analyses of autism's constituent traits and the differential diagnosis of its individual-specific causes.

KEYWORDS

autism, syndrome, Kanner, prototypes, diagnosis

Introduction

The purpose of this article is to suggest that the current conceptualization and study of autism are highly problematic, with notable deleterious impacts on the efficacy of empirical research and the development of better clinical protocols and applications. A simple solution is proposed, based on ideas developed by Mottron (1, 2) and on what I call Kanner's "hallmarks" of autism.

I first describe the standard medical model of human disease, and show how it does not apply to the main, current psychiatric model for mental disorders in general and autism in particular. Second, I discuss salient findings on the genetic and phenotypic heterogeneity of autism, in the context of the history of its diagnostic criteria. This heterogeneity has led to conceptual expansion of the "autism spectrum" and "autism traits" such that they have become largely synonymous with social deficits and lose meaning as psychological-psychiatric constructs with any useful specificity. These changes have also apparently led to a substantial incidence of false positive autism

diagnoses in childhood. Third, I provide specific suggestions for surmounting these problems, in the context of autism as originally described by Kanner (3), and centered on his "hallmarks" of autism, described below, as currently conceived.

The standard medical model

The standard medical model of disease focuses on diagnosing what adaptive biological system has become maladaptive and dysfunctional in what way (4). Diseases are thus inextricably connected, conceptually and mechanistically, with specific adaptations. For example, lymphoma represents excessive lymphocyte replication, osteoporosis is defined as bone density that has become notably reduced, and type 1 diabetes is triggered by insufficient production of insulin. The causes of such diseases are discerned by studying the normal biological functioning of the adaptations, to understand how and why different dysfunctions occur and manifest in a disease and its symptoms. For each patient presenting initially with some set of symptoms, some process of implicit or explicit differential diagnosis is typically followed to determine the biological causes, which determine the optimal treatment.

In contrast to this model, mental disorders are considered predominantly in terms of symptomatic deficits in cognition, mood, and behavior, and the presence of some pattern or patterns of dysfunctional or distorted cognition, mood or behavior. Diagnostic procedures are used, in DSM or ICD frameworks, to determine what named disorder best fits a particular subject. Subjects are then provided some category of psychological or pharmacological treatment, based on their diagnosis. This approach is pragmatic in a societal framework but it is also becoming more and more limited, scientifically and clinically, as the genetic and biological bases of mental disorders have become better understood.

The primary difficulties with the psychiatric model of disease are two-fold. First, nominal disorders are commonly reified (considered as "real" when they are not, because the relevant adaptations and specific biological dysfunctions have not been defined or delineated), despite the fact that their descriptions and categories have changed, sometimes profoundly, every five, ten or fifteen years (5). Reification implies truth that does not exist, and promotes use of broad, formalized, and inflexible categories without questioning their scientific bases. It also encourages people to believe that diagnoses of autism by clinicians are not only biologically real (having biological coherence in terms of dysregulated adaptations) but also necessarily always correct, rather than representing hypotheses that may turn out to be false positives. Most generally, and in keeping with the standard medical model described above, mental disorders such as autism can more usefully be considered as "harmful dysfunctions" (6, 7), where "dysfunction" represents a scientific criterion that refers to specific mental traits that are not performing their evolved, adaptive functions, and "harmful" represents a cultural, value-based criterion determining whether or not a set of mental traits (a putative disorder) are considered as problematic for the individual or individuals concerned (6, 7). In the context of human neurodiversity, and subjective experiential wellbeing, many "autistic" individuals indeed consider their "disorder" to be nothing of the kind [e.g., (8)].

Second, because the differential diagnostic process aims at DSM or ICD diagnoses, it usually stops there. As such, psychiatrists, and other medical professionals, normally do not attempt to ascertain the biological causes of a person's psychiatric problems, by gathering data on known causes and correlates, aside from rare genetic risk factors. In this framework, the causes of autism can be depicted as tracings from genes, through development, to different levels of phenotypes. Every individual diagnosed with autism can be represented as expressing a different trajectory to a similar endpoint: some set of diagnostic traits. Most importantly, there have been virtually no attempts to develop efficient protocols for differential diagnosis of the biological causes of autism, to recover this trajectory as best possible. Presumably, the absence of such efforts stems in part from the known high heterogeneity of autism as regards symptom profiles, intelligence, genetic and environmental bases, and ultimately causes. How can such heterogeneity be addressed?

The heterogeneity of autism

Autism was once considered to be a unitary disorder, with a single cause. Happé et al. (9) showed, using twin data, that the three main characteristics of autism as then conceived, (a) social impairment, (b) communication difficulties, and (c) repetitive and rigid behaviors and interests, were mainly independent of one another genetically and phenotypically. Autism was thus "fractionable" into these domains, and did not, by this evidence, exist as a clearly, coherent entity. Mandy and Skuse (10) similarly reported a lack of evidence for association of social with restricted-interests, repetitive behavior dimensions of autism, in a review of evidence available to date, and Robinson et al. (11) found notably low genetic and environmental correlations between these two domains. Comparable supporting results, at the genomic level for the first time, were recently reported by Warrier et al. (12), who found that genetic risk for a non-social autism-related trait ("systemizing") was independent of genetic risk for social autism traits. Taken together, these studies suggest that current studies of autism often confound its social and non-social aspects. How can genomic architecture and causes be analyzed for a psychiatric construct that may not, as a unitary phenomenon, even exist?

The approach taken by most geneticists is to retain the term "autism" as the focus for their analyses, and to continue

searching for "core" autism genes, perhaps also taking account of apparent heterogeneity in causes by seeking to identify autism "subtypes" (13), or by expanding analyses to include additional "neurodevelopmental disorders" (as a higher-level diagnostic category itself), like schizophrenia [e.g., (14)]. The degree to which autism subtypes exist as any sort of distinct "types," and how they might be identified, remains an open question. A broader issue is that, given high levels of both genetic and phenotypic heterogeneity in the psychological traits found among people diagnosed with autism, what exactly GWAS studies of autism are measuring, and how their findings can ever be made useful for diagnoses, causal understanding or treatment. Ultimately, and as suggested originally by Rutter (15), what we may need is GWAS, and other analyses, of variation in each of the adaptive neurological and cognitive systems that may be altered in people diagnosed with autism. After all, we need to understand how adaptive systems actually develop and work before we can understand the many ways that they vary and can become problematic. And a key adaptive system, in autism as well as many other disorders including, especially, schizophrenia, is normally considered to be social cognition.

Social deficits, autism, and schizophrenia

Autism-related social traits were reconceptualized in terms of cognitive and social impairments by Wing and Gould [see (5, 16)]; before that, description of autistic phenotypes could be traced to Kanner (3) who did not discuss social or cognitive deficits or impairments at all (5). As described by Evans (5), Wing and Gould acted from a desire to expand the pool of children who could be recognized as "autistic" and thereby helped by medical systems. From 1980 until now, characterization and measurement of social and cognitive deficits have dominated the diagnosis and study of autism. Throughout most of this period, an autism spectrum disorder could indeed be diagnosed based on social impairments alone (e.g., as PDD-NOS). The autism spectrum broadened in other ways, through the adoption of such concepts and metrics as the "broad autism phenotype," the "Autism Quotient," and use of the term "autism traits" to refer to social deficits (17, 18). The equating or conflating of autism with various forms of social and cognitive deficits has led, for example, to studies finding high levels of "autism traits," or diagnoses of autism, by Autism Quotient scores or other metrics, among subjects with anorexia (19), suicide attempts (20), borderline personality (21), and schizophrenia spectrum disorders (22). Such findings are interpreted as indicating that each of these conditions overlaps with, and is often comorbid with, autism, and also includes so-called "autism traits." Other studies, such as those that apply questionnaires to quantify "autistic features" among individuals with schizophrenia [e.g., (23, 24)], are based in Bleuler's century-old characterization of schizophrenia, and ignore the fact that Bleuler's view of "autistic" cognition was profoundly different, and in some ways opposite, to that described by Kanner (5, 25) and Crespi (26).

An alternative explanation for reports of "autism" or "autism traits" in non-autistic populations, from Rutter (15), is that "almost any mental disorder will impinge on social functioning to some degree or other." The conceptual "explosion" of autism and "autism traits" to include social deficits has indeed apparently driven, in substantial part, the increases in autism diagnoses over time, and the decreases in effect sizes found among studies that compare "autistic" with "control" groups (1). It has also, as described below, essentially obliterated Kanner's view of autism.

Conflation of autism with social impairments is especially problematic given that social difficulties are common and pronounced in many children who are premorbid for schizophrenia (27, 28), (or with other disorders), but whose only option for diagnosis, during most of the periods of GWAS and CNV (copy-number variation) studies, has been the autism spectrum, including PDD-NOS. False positive diagnoses of schizophrenia premorbidity as autism spectrum, due in large part to the considered primacy of social-cognitive deficits in child psychiatry, may, by the views presented here, have systematically misled a generation of researchers, as detailed by Crespi et al. (27), Crespi and Crofts (28), and Crespi (29). Such conflation may also have resulted in the weak positive genetic correlation between schizophrenia and autism found in some studies (30), and the belief that reciprocal CNVs, which involve opposite deviations from typical average values for diverse neurological and anatomical traits, cause the same deviation as regards psychiatric diagnosis of autism (29). There is indeed no unambiguous or substantive neurological evidence for causal, etiological overlap of autism with schizophrenia (31), and overlap in "social deficits" (e.g., of "autism traits" with negative symptoms of schizophrenia) is irrelevant without data on their causes and biological bases.

If autism, then, is neither social and cognitive deficits, nor social deficits combined with restricted interests and repetitive behaviors, nor an overlapping facet of schizophrenia, what is it? I would suggest: what Kanner (3) said it is: a "syndrome." In medicine and psychiatry, a "syndrome" can be conceptualized simply as a constellation of phenotypic traits and differences that shows some tendency to be found together in sets of individuals or that, when found together, causes particular sorts of problems. A syndrome may thus comprise a set of morphological, neurological, physiological, behavioral and developmental traits, each of which shows some level of difference from the age- and gender-typical average. Any given individual exhibits some degree of expression of each trait that, taken across them, is individual-specific. The traits that comprise a syndrome are thus discrete, but their levels of expression are continuous. Some sets of traits may tend to be found together, statistically, and one or more traits may be found at some level in all individuals considered to exhibit the syndrome. High

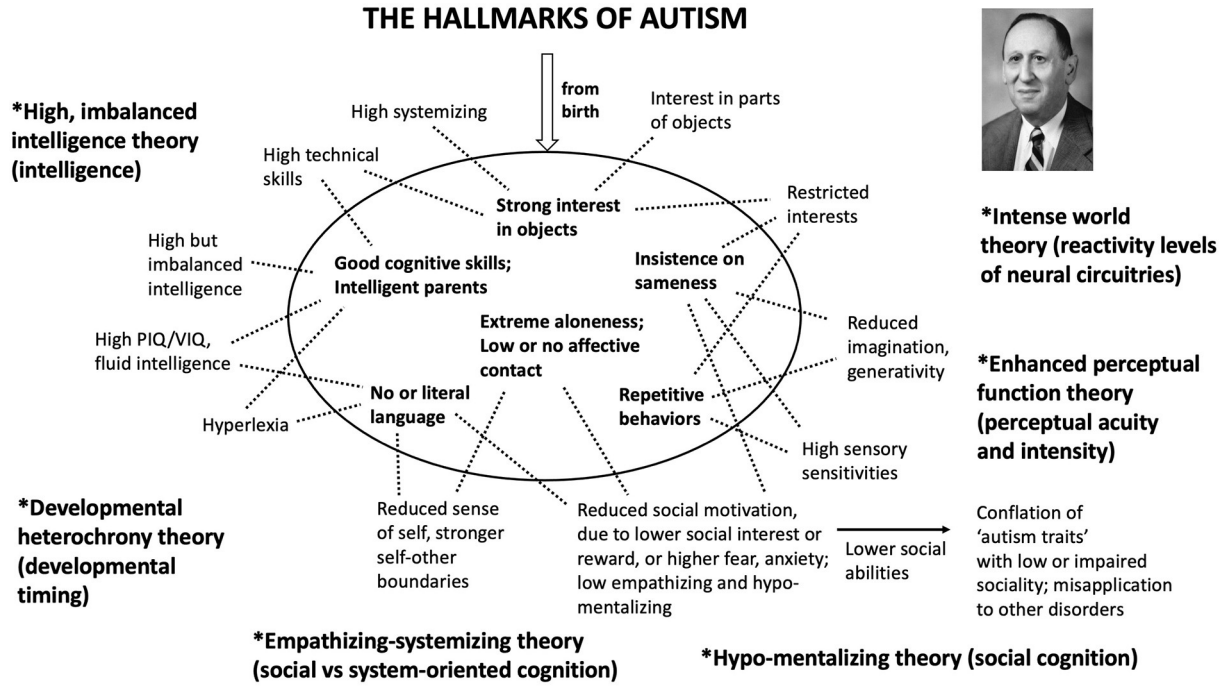

FIGURE 1
The six main "hallmarks of autism" described by Kanner in his 1943 paper. These hallmarks represent the core phenotypes that Kanner used to define and describe the syndrome of autism. Each of them has since been connected (here, by the dotted lines) with additional traits that are associated with autism. They are also linked with the main theories set forth for understanding autism (here, in boldface); these theories include systemizing and empathizing (34), enhanced perceptual function and veridical mapping (35, 36), neuronal hyper-excitability and plasticity (37), and high but imbalanced intelligence, hyperdeveloped patternistic cognition, developmental heterochrony, and hypo-developed mentalizing (38–40). Each theory is followed in parentheses by the adaptation(s) that, by the theory, are altered in autism. These theories show evidence of strong connections with one another, especially as regards intelligence with high perceptual function and neural reactivity, and low empathizing with hypo-mentalism; relatively or absolutely enhanced non-social cognitive abilities and interests are also prominent in all of them.

expression of particular traits or sets of them may be indicative of specific psychological difficulties and expected benefits from particular forms of care and treatment. Van Os (32) described schizophrenia as exhibiting such a structure, and he referred to it as "salience syndrome." The term "syndrome" as used here applies to idiopathic (cause-unknown) conditions, such as autism or schizophrenia, not to genetic syndromes, such as Fragile X syndrome or Down syndrome, which involve a known genetic cause for their particular sets of associated phenotypes. As applied here, recognition of the syndrome of autism is not linked to its causal mechanisms, which will vary notably from person to person.

Syndromes are characterized by a set of traits, and they exhibit four key properties. First, syndromes constitute multiple dimensions (their constituent phenotypes), each of which varies in degree of expression. As such, considering autism as a one-dimensional spectrum *per se,* such as along a line from low to high functioning or severity, is incompatible with their structure (33). This consideration means that the term autism "spectrum" may itself be misleading, because the term means unidimensionality of a singular construct between two points. Autism is, by contrast, multidimensional.

Second, syndromes are, or should be, made up of traits that are associated with adaptation in some way. As such, each trait characteristic of a syndrome is expected to be causally connected with one or more neurological structures or functions. Differences from typical or average function can thus be analyzed in the context of the standard medical model and the research domain criteria approaches. As such, the components of a syndrome are "real," in the sense that they represent alterations to, or variation in, evolved adaptations (e. g., specific aspects of human cognition with neurological bases) that have become more or less maladapted, and might also be considered as harmful or problematic. Most importantly, such components need not be based on, or defined by, deficits *per se*, just differences. Indeed, social and communicative deficits as measured among individuals with autism may well represent secondary effects of the primary differences described by Kanner.

Third, the boundaries of syndromes, in terms of the specific collection of traits that comprises them, can be "fuzzy": some such traits are found in all or most affected individuals, but other traits are less common. As a result, delineation of a set of traits characteristic of a syndrome is necessarily arbitrary to some

degree, once one moves beyond any traits that are considered necessary for the syndrome to be recognized. Figure 1 thus depicts one delineation of "hallmarks" for autism, drawn directly from Kanner. There could be others, derived empirically (2), and equally or more useful in terms of guiding research and, ultimately, helping individuals.

Fourth, syndromes naturally promote protocols for finding individual-specific etiology, because they dictate measurement across a suite of syndrome-associated traits. Individual etiology is real, and its diagnoses lead to understanding of causes that may be more or less general, or specific. Such precision diagnostic medicine can lead directly to personalized optimization of therapies.

Kanner's description of autism as a syndrome centers on a set of traits that were characteristic across the eleven individuals who he originally studied. These traits, extracted from his 1943 article and depicted in Figure 1, represent his main "hallmarks" of autism: the primary distinguishing features that he used to recognize it as a psychiatric entity in the first place. Each of Kanner's hallmarks can be connected with one or more specific autism-associated traits from more-recent studies, and, taken together, these can all be linked with core theories for understanding autism (Figure 1). In principle, Kanner's hallmarks should also be underlain by differences, between individuals with and without autism, in neurological traits that jointly subserve human abilities in the domains that are shared by these theories, especially as regards enhanced motivation toward, and recognition and processing of, non-social information as found in patterns, systems, and integrated structures (34, 39, 41, 42).

Of his six hallmarks, Kanner considered the construct of "aloneness" as being characteristic, most broadly, of autism as he conceived it. His hallmarks remain useful for research insights, in that, for example, "aloneness," "interest in objects" and "insistence on sameness" are all central aspects of autism that have been largely ignored as regards their neurological and genetically-based causes. Kanner's collection of autism-diagnostic traits also overlaps substantially with the of Asperger (43), excepting Asperger's increased focus on individuals with relatively developed language abilities and less-developed repetitive behavior. Perhaps most importantly, by Kanner's hallmarks of autism, social and communicative deficits may represent secondary effects of autistic development, and not primary, causal, or usefully diagnostic manifestations of the condition itself.

Considering autism as a syndrome, as Kanner did, need have little or no impact upon current diagnostic criteria, which serve a variety of goals in communication and flagging of individuals who may benefit from support. However, as regards the conduct of research, a syndromic view of autism, and differential diagnosis of autism's diverse manifestations and causes, are likely to be considerably more productive than current alternatives. In particular, focusing research studies on individuals with "prototypical" autism, and on the collecting of data to better-define autism prototypes (1, 2), as well as autism defined by criteria compatible with Kanner's hallmarks, will help to better ensure that autism researchers are all studying a closely-similar condition, and will help to connect the "harmful dysfunctions" involved in autism with the relevant underlying adaptations. As such, clinical and research strategies for scientific studies of autism become partially dissociated, with clinical work focusing on individualized diagnoses in the syndrome context as well as the DSM or ICD frameworks, research work characterizing and quantifying heterogeneity in study populations as an integral and essential part of every study, and treatments following from protocols designed to indicate more or less individualized causes and correlates. Such a framework will, at very least, help to prevent further untoward and misleading expansion of the concept of autism away from its well-founded roots.

Data availability statement

No datasets were generated for this study.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Insights from losing the autism diagnosis: Autism spectrum disorder as a biological entity

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loss of autism diagnosis (LAD), developmental trajectories and cascades, response to intervention, outcomes, autism spectrum disorder

Introduction

There is an explosion of interest in the question of whether autism spectrum disorder (ASD) is a coherent entity, and further, whether this entity maps onto some biological substrate. We propose that much can be learned by studying symptom remission in ASD.

Defining a syndrome

Disorders are defined by the characteristics of *impaired functioning*, *distress*, and *atypicality*. These characteristics are polythetic; one can have atypicality and impairment, but not distress (e.g., in personality disorders). Further, syndromes (which may not meet criteria for a disorder) are defined by the fact that symptoms co-occur more than would be expected by chance and have presumed common etiologies. For example, many neurologists and neuropsychologists believe firmly in the reality of the Gerstmann syndrome (1, 2), a cluster of three to five symptoms associated with angular gyrus lesions, but Arthur Benton was a skeptic (3). Similarly, while some eminent neurologists believe a specific behavioral syndrome occurs interictally with temporal lobe epilepsy (4), others [e.g., (5)] propose a "simple" elevation of non-specific psychopathology, rather than this personality profile. Thus, even when syndromes have a clear anatomical substrate, and have been studied for decades, the presence of a resulting clinical syndrome can remain controversial. The diagnostic challenges are heightened when one starts with a clinical syndrome and attempts to uncover a biological physiology or etiology, as with autism.

Categories vs. dimensions

Disorders are generally defined as categorical entities, in which each category member shares the characteristics of that category. The DSM generally has a categorical structure, with the caveat that DSM-5 diagnoses also have specifiers that allow category members to differ on important dimensions such as language impairment and degree of support needed. In the DSM approach, diagnoses consist of complex clusters

of symptoms; these complex clusters are difficult to connect to underlying physiology and neurobiology. Rapin (6) eloquently described the challenges associated with mapping a syndrome defined at one level of description (e.g., behavior) onto characteristics at other levels [pathophysiology, etiology (such as, genetics)]; she held that given our current state of knowledge, such mapping was impossible. NIH's Research Domain Criteria [RDoC; (7)] offer an alternative structure, which provides a strategy for discovering lawful relationships linking basic biological processes to behaviors. By decoupling the symptom clusters, RDoC promotes treating each symptom as a continuum and linking individual differences in those symptoms to causal mechanisms.

This continuum approach holds great appeal, in part because it maps well onto our intuitions about many symptoms; there does not appear to be a qualitative difference between momentary anxiety experienced under threat, vs. the daily anxiety experienced in an anxiety disorder. The continuum approach also facilitates access to clinical services and financial supports for those individuals who do not meet full diagnostic criteria under the categorical medical model but might still benefit from services. Another strength of the continuum approach is that its advocates promote a focus on the societal structures that serve to impede or promote autonomy, health, and success, rather than individual-level symptoms (8).

However, the continuum approach masks some important practical advantages of the categorical medical model. Most important, in our view, is the notion of impairment and distress; while everyone experiences feelings of anxiety on occasion, those individuals with anxiety disorders are so affected by their symptoms that they struggle to function; their anxiety prevents them from performing everyday life tasks, impacts their social relationships, and prevents them from performing as successfully as they could in academic and vocational domains. Treating a condition as a set of dimensions makes it more difficult to allocate scarce treatment resources; in contrast, the DSM model helps to identify those who most require treatment or support in order to function. While the precise threshold for treatment is arbitrary, its location can be data-driven, based on long-term outcomes and experiences. Based on our clinical experience, we also fear that, in jettisoning the medical model, we risk ignoring important variance in cognitive and linguistic barriers, which will lead to neglect or harm to some individuals.

Is autism a syndrome?

Doubts about the coherence of autism as a behavioral syndrome are legion, despite the fact that most research still generally follows the case-control method, where cases of autism are examined as a group. Indeed, the 2014 special issue of *Autism the International Journal of Research and Practice* was devoted to discussions of this question [e.g., (9, 10)]. Waterhouse (11–14) has argued that autism must be "taken apart" in order to map clinical features onto possible etiologies. Waterhouse and Gillberg (12) suggest that very narrowly defined subgroups, both at the phenotypic and biological levels, will increase the probability of being able to link the two domains. In addition, Waterhouse (11) reviews the heterogeneity in all domains of symptomatology and the failure to identify causes and effective treatments, and suggests that examining possible biology of specific, clearly defined symptoms will be more productive than trying to uncover the biology of a "syndrome" that does not really exist.

One would think that the sheer volume of research in the last 50 years would have settled the question of syndrome coherence, but since almost all studies with an autism group require both social communication deficits and repetitive and restricted behaviors, the existence of one without the other cannot be examined in these samples. Whether there is a strong link in the general population between the presence of these two general deficits (suggesting a continuum of an "autism trait") or in their genetic liability has been argued positively (15) and negatively (16). Fein and Helt (17) argue that lack of co-occurrence or genetic linkage between the two autism domains in the *general population* does not bear directly on their relationship in a *neurodevelopmental syndrome*. This formidable problem echoes difficulties identified in other fields, such as the challenges of mapping from cognitive levels of analysis to neurobiology, to explain fundamental psychological processes such as language or vision (18). Developmental and clinical processes can help shed light on this mapping. Marr proposed that we gain explanatory power by describing problems or systems (or in the current case, syndromes) at three levels: the computational, the algorithmic, and the physical (19); addressing these levels will likely strengthen our theories of clinical phenomena.

An additional difficulty in considering the coherence of autism as a syndrome is the tremendous heterogeneity within each domain (11). Social impairment can range from aloofness and disinterest in other people, sometimes including parents, to a desire to socialize but with limited and inflexible social judgment. Language can range from complete lack of spoken language with very impaired language comprehension, to structural language that is within the normal range but affected by impaired social judgment. Intellectual ability can range from severe intellectual disability to superior cognitive functioning. The biological underpinnings of such a diverse set of abilities are also likely to be diverse.

Prototypical autism

One approach to defining a more homogeneous syndrome rests with the idea of "prototypical" or "frank" autism, posited to be obvious to experienced clinicians within a few minutes

(20, 21). Wieckowski et al. (21) found that clinicians were generally correct (high specificity) if they confidently detected autism in the first few minutes of observing very young children; their impressions of non-autism were less accurate (lower sensitivity). Mottron et al. (22, 23) suggest focusing on prototypical autism as a means of increasing the homogeneity of possible etiologies. Several issues limit the utility of this approach, including the difficulty of deciding who is expert enough to define prototypical autism, and the lack of success in aligning prototypical cases to underlying biology (17, 24).

Non-biological causes of autism as a classifier

If "biological" refers to factors inherent to the development of the brain or other systems, usually genetic, then the overwhelming majority of autism cases are no doubt biological in origin. Although it may not be clear exactly where to draw the line, there is a fundamental distinction between causes inherent in the developing fetus vs. environmental causes (from intrauterine to early childhood environments), which might include toxic exposure, disease exposure, injury, preterm birth, or extreme deprivation. There is evidence that environmental deprivation can result in syndromes that would meet criteria for autism, as seen in children reared in neglectful institutions (25, 26) or those with severe congenital blindness (27). Although the relationship of blindness to autism remains controversial (28, 29), Jure et al. make a strong argument for blindness leading to true autistic behavior (27). Note that both situations involve sensory deprivation, which may impact early attachment and social communication (e.g., the development of infant-mother attachment). In cases where a non-biological factor is a prominent element, relatively good prognoses are likely if environmental change including sensory stimulation occurs early in development (28), validating severe environmental/sensory deprivation as a classifier.

Individuals who lose the autism diagnosis (LAD)

Autism is characterized by distinct behavioral trajectories, demonstrated in longitudinal studies (30, 31). Uher and Rutter (32) suggest that developmental trajectory and outcome are relevant to reducing heterogeneity at the phenotypic level. One informative group is composed of individuals who amply met criteria for autism in earlier life and no longer do. Our published and ongoing studies of these individuals include only individuals with clear diagnoses of autism by the age of 5 years, who currently function within typical parameters, excluding borderline cases. We have described this group in detail (33), documenting their good social and adaptive skills (33, 34), typical academic abilities including reading comprehension (35), ability to focus on gestalt rather than overfocus on detail (36), and correct use of subtle dysfluency fillers (37). They received significantly more early behavioral intervention between ages 2 and 3 years than the still-autistic group (38), and were left with higher rates of ADHD than the control group (30). On observed and parent-reported measures of executive functioning, scores for the LAD group were within the average range, though scores on impulsivity, set-shifting, working memory, and planning were lower than scores in non-autistic controls (31). Other research groups have also reported on this subgroup whose symptoms remit with intervention (39–41).

In addition to advancing basic understanding of the biology of subgroups, treatment is another fundamental motivation for identifying autism syndromes and their underlying anatomy or physiology. By analogy, the best designs for bridges are informed by an understanding mechanical force. While it is possible to construct some bridges, such as timber-fall bridges, without this knowledge, bridges last longer, and withstand greater stress, when builders have explicit or implicit knowledge of these forces. Similarly, understanding the mechanisms that contribute to a syndrome at either the biological or behavioral level can be a potent contributor to effective treatment. For example, if individuals differ in patterns of activation in a reading task, one might hypothesize that those with prominent right hemisphere (likely compensatory) activation might benefit from approaches that incorporate strong visual and orthographic training components, while individuals with left hemisphere activation in areas similar to good readers, but with abnormalities (e.g., less connectivity, lower amplitude, slower response) might have phonological processing deficits that would benefit from intensive reading practice (42, 43).

Learning about causal mechanisms from studying outcome status

Most autism studies, sensibly, include participants who meet diagnostic criteria for ASD; by definition, they have deficits in both DSM domains of (1) social communication and (2) the presence of repetitive and restricted behaviors (RRBs), making it nearly impossible to evaluate how these domains cluster. Another solution is to study individuals experiencing social disabilities, and then explore the presence, type, and extent of their RRBs, and also to do the opposite, taking a sample of individuals with significant RRBs and studying their social functioning. Such an enterprise could examine the interdependence of the two domains of impairment and the coherent syndrome status of autism. Certainly, looking at the emergence of earliest symptoms, and following how individual children respond to treatment—provides a critically

important window into causal mechanisms. We further argue that understanding the forces that contribute to the steep developmental trajectory that characterizes LAD individuals provides a useful lens through which to conceptualize the mechanisms that underlie the symptoms of ASD. We can examine which specific features remit together in LAD, to understand more about which how symptoms of ASD "lawfully" co-occur and cluster; this approach offers a pathway to understanding the coherence of autism as a syndrome (13). Examining significant symptom remission in LAD, with a detailed and comprehensive evaluation of subclinical behaviors in both domains, and assessing brain anatomy and physiology, provide a pathway for understanding the coherence of ASD.

Biology of LAD individuals

Is there any evidence that individuals whose autism symptoms remit have a distinctive biological underpinning of their autism, either anatomical or functional? One study examined head circumference growth in early childhood from medical records and found *no* differences between individuals whose autism later remitted and those who still met autism criteria, disappointing any hope of a straightforward anatomical marker (44). Following the example of examining brain activation in successfully remediated adult dyslexics (43), which found both increased activation in the usual reading areas plus compensatory activation in right hemisphere areas, we examined language-related brain activation in LAD, autistic, and non-autistic individuals. Eigsti et al. (45) found that LAD individuals showed a distinctive pattern of such brain activation, compared to autistic and non-autistic groups. Specifically, the LAD individuals had a small set of language-related activations similar to that found in the autistic individuals, and a large set of (likely compensatory) activations that was unique to LAD; there were *no* activation areas that were more like the typically developing controls than the autistic group. They concluded that, unlike the brain changes in improved dyslexia as reported by Eden et al. (41), LAD individuals showed some residual ASD patterns and extensive compensation, but little or no evidence of normalization of brain activations. Follow-up work indicated unique patterns of language-related neural specialization as it related to language abilities in these groups (46).

Positive and negative aspects of LAD

While from one perspective, losing the diagnosis (and thus having fewer difficulties with social communication and fewer RRBs) is a positive outcome, it is not unambiguously so. Autistic self-advocates and others have raised concerns about one's identity as a member of the autism community and about the loss of the diagnosis which can be a helpful explanation of preferences (e.g., vocations that involve fewer social interactions with strangers) and abilities (e.g., efficient attention to detail). Prior changes in diagnostic entities, as in the removal of the Asperger's Disorder diagnosis in DSM-5 (47), led many to feel robbed of an important aspect of their identities. Additionally, "officially" losing the diagnosis may entail losing beneficial supports. More broadly, describing the loss of the diagnosis as a positive outcome implies that meeting criteria for autism is necessarily negative, a position vigorously rejected by many autism advocates (8). In response, our group has adopted the more neutral "loss of autism diagnosis, LAD" terminology (48).

Conclusions

We have discussed the nature of syndromes, and whether it is possible to characterize autism in this way; approaches to defining autism, including prototypicality, non-biological causes of ASD and, especially, trajectories of change and outcomes (particularly focusing on LAD); the relevance of studying the neural circuitry associated with the steep developmental trajectories in LAD; and the pros and cons of losing the ASD diagnosis. Clearly, there has been slow and limited progress to date in understanding ASD via the medical model. Our group aims to better understand the causal mechanisms of ASD—(the underlying forces of tension, compression, and shear, in the bridge analogy)—by focusing on homogeneous groups that are subtyped by important clinical characteristics such as IQ, language level, and outcome status. While the strategy of studying smaller, more homogeneous subgroups in order to find links between phenotype and biology has not succeeded to date, this lack of success, which also characterizes research in schizophrenia, depression, and other conditions, reflects the enormity of the theoretical problem. In the long run, it seems to us that the slow but steady work of discovering and describing biological causes and then exploring the phenotypes associated with them is likely to yield the most solid long-range results. The parallel approach of defining more homogeneous subgroups, focusing on variables outlined here, offers the most effective path to specifying subgroups that will be useful in basic biological studies, and can help inform any needed treatment strategies.

Author contributions

I-ME: conceptualization, data curation, funding acquisition, methodology, project administration, resources, and writing—original and editing. DF: conceptualization, funding acquisition, methodology, resources, and writing—original and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Autism: A model of neurodevelopmental diversity informed by genomics

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Definitions of autism are constantly in flux and the validity and utility of diagnostic criteria remain hotly debated. The boundaries of autism are unclear and there is considerable heterogeneity within autistic individuals. Autistic individuals experience a range of co-occurring conditions notably including other childhood onset neurodevelopmental conditions such as intellectual disability, epilepsy and ADHD, but also other neuropsychiatric conditions. Recently, the neurodiversity movement has challenged the conception of autism as a medical syndrome defined by functional deficits. Whereas others have argued that autistic individuals with the highest support needs, including those with intellectual disability and limited functional communication, are better represented by a medical model. Genomic research indicates that, rather than being a circumscribed biological entity, autism can be understood in relation to two continua. On the one hand, it can be conceived as lying on a continuum of population variation in social and adaptive functioning traits, reflecting in large part the combination of multiple alleles of small effect. On the other, it can be viewed as lying on a broader neurodevelopmental continuum whereby rare genetic mutations and environmental risk factors impact the developing brain, resulting in a diverse spectrum of outcomes including childhood-onset neurodevelopmental conditions as well as adult-onset psychiatric conditions such as schizophrenia. This model helps us understand heterogeneity within autism and to reconcile the view that autism is a part of natural variability, as advocated by the neurodiversity movement, with the presence of co-occurring disabilities and impairments of function in some autistic individuals.

KEYWORDS

autism, genomics, co-occurring disorders, neurodiversity, neurodevelopmental outcome

The shifting sands of autism diagnosis

The diagnostic features of autism have been in constant flux since early descriptions by Sukhareva (1, 2) and later Kanner (3). Definitions have been altered six times (2) across the history of DSM and ICD (4), reflecting ongoing debates about the essential characteristics of autism and how it should be diagnosed (2). The following is not an exhaustive summary, but highlights some of the important changes in diagnostic criteria and definitions. Currently, in DSM-5, autism is defined by two key domains; atypical social communication and interaction; and restricted, repetitive behavior and interests (5). Prior to DSM-5, these two domains were conceptualized as a triad of impairments by Wing and Gould (6), with social function and communication being considered separately. Moreover, in DSM-5, Asperger syndrome and autism spectrum disorder were subsumed into a single category of autism. Previously, a diagnosis of autism spectrum disorder required delays in language development to be present in addition to social, communication and repetitive behaviors, whereas developmental delays were required to be absent for a diagnosis of Asperger syndrome.

These changes have resulted in the DSM-5 definition of autism being more inclusive, with greater phenomenological heterogeneity (2). In response to this, terminology outside the DSM-5 diagnostic framework has been developed, to delineate autism subgroups. For instance, The Lancet Commission recently introduced the term "profound autism" to indicate autistic individuals who have higher support needs (7). An important shift in our perspective of autism has come from the neurodiversity movement, pioneered by autistic activists. Neurodiversity challenges the conception of autism as a medical syndrome defined by functional deficits. Under neurodiversity, autism is seen as one form of variation within a diversity of minds (8–10). This has the potential to radically change how autism is researched and how autistic people are valued and supported (9). However not all people with autism and stakeholders identify with the neurodiversity movement (11), and concerns remain about how autistic individuals with the highest support needs, including those with intellectual disability and limited functional communication, are represented in a non-medical model (7).

These shifts in diagnosis and conceptualization have caused debate, but also reflect the inherent phenomenological basis of diagnosis. Autism is still diagnosed based on observation and reported behavior in relation to societal norms. However, if we are to move beyond behavioral definitions, there is a need for new perspectives, and, in this article, we discuss the insights genomics has provided to our understanding of autism as a diagnostic entity.

Genetic epidemiology

Genetic epidemiological studies have shown that genetics plays a major role in the etiology of autism and have yielded high heritability estimates. Interest in the genetics of autism was initiated by a small twin study, published in 1977, which included 10 dizygotic (DZ) and 11 monozygotic (MZ) pairs and found that four out of the 11 MZ pairs (36%) but none of the DZ pairs were concordant for autism (12). A subsequent meta-analysis of seven primary twin studies yielded heritability estimates ranging from 64 to 93% (13). The emerging data from early twin studies provided important evidence challenging stigmatizing theories that autism is caused by maternal coldness or emotionless parenting styles (14). The role of maternal warmth and attachment in the etiology of autism was first proposed by Kanner and then popularized by Bruno Bettleheim's book—The Empty Fortress (1967), which introduced and promoted the "refrigerator mother hypothesis" (15) of autism, which although now largely rejected was influential in its time.

Alongside twin studies, family studies also highlighted the high heritability of autism, indicating that the probability of a child having autism corresponds to their degree of relatedness to autistic relatives (16–19). Family studies also found that relatives of autistic individuals were more likely to exhibit behaviors consistent with a "broader autism phenotype"—consisting of sub-threshold difficulties with social skills and communication, and the presence of autistic-like personality features (20). Whereas the presence of broader autism features in parents had often been interpreted as being causative of childhood autism in line with the refrigerator hypothesis (21), the application of genetic study designs provided an important lesson that genetic correlation might underlie the relationship between parental and childhood behavior. Increased broader autism-related strengths have also been reported in the relatives of autistic individuals; many autistic individuals evince superior folk physics ability (the ability to spontaneously perceive the workings of the physical world), and fathers and grandfathers of autistic children have been found to be more than twice than likely to work in the field of engineering (22). A study of undergraduate students of physics, engineering and mathematics found they were more likely to have an autistic relative than undergraduate students studying arts subjects (23). These findings are a reminder of the potential evolutionary benefit of autistic traits in the population.

Research into the priorities of the autistic community has identified co-occurring neurodevelopmental and mental health conditions as key issues impacting wellbeing in autistic individuals (7, 24). A meta-analysis incorporating clinical, population and registry based cohorts found increased prevalence of psychiatric conditions in autistic individuals; 28% for attention-deficit hyperactivity disorder (ADHD); 20% for anxiety disorders; 13% for sleep–wake disorders;

12% for disruptive, impulse-control, and conduct disorders; 11% for depressive disorders; 9% for obsessive-compulsive disorder; 5% for bipolar disorders; and 4% for schizophrenia spectrum disorders (25). Further studies highlight increased prevalence of intellectual disability (ID) (26) and eating disorders (27). For some co-occurring conditions, the stigma faced by autistic individuals in society is likely to be an important contributing factor, but twin studies have also indicated a substantial genetic overlap between autistic traits and symptoms of other psychiatric conditions, including ID (28), ADHD (29), anxiety (30), and psychotic experiences (31). Studies of relatives of autistic individuals also find increased prevalence of co-occurring neurodevelopmental and mental health conditions (32).

Genomics

Genomics allows genetic risk factors to be identified and measured at the molecular level of DNA variation. Its reach is limited by the technologies that can currently be feasibly applied to large samples. Most of the informative data on autism obtained to date come from genome-wide association studies (GWAS), which use genotyping arrays to identify common (>1%) single nucleotide polymorphisms (SNPs) that typically have small effects on individual risk, and rare copy number variants (CNVs), which are large deletions and duplications of DNA typically affecting multiple genes. Sequencing studies have been used successfully to detect rare single nucleotide variants (SNVs) that have large effects on individual risk and, for reasons of cost, to date most have been based on whole exome, rather than whole genome, sequencing. The identification of rare high-risk SNVs, as well as small structural variants and other mutation classes, outside of genes, and rare mutations that have small effects on risk will require whole genome sequencing in large samples (33). However, while as a consequence much genetic risk remains unaccounted for at the DNA level (34), genomic studies have yielded findings with important implications for our understanding of autism as a biological entity.

Genomic studies have revealed that autism has a complex polygenic architecture, involving risk alleles across the frequency spectrum (16). In other words, an individual's genetic risk of developing autism is determined by a constellation of genetic risk factors some of which are rare and some common in the general population. Approximately 4–5% of individuals with autism have a recognized syndrome consisting of a clinically defined pattern of somatic abnormalities and a neurobehavioral phenotype which may include autism (35). Most of these are associated with a known genetic cause, often rare mutations or CNVs, and examples include tuberous sclerosis and fragile X syndrome. Recent genomic research has focused on large samples of individuals with autism, the great majority of whom do not have syndromic autism. This has identified rare SNVs in over 100 genes that confer large effects on individual risk (36). These mutations are defined as "damaging" in the biological sense that that they disrupt protein quantity or structure, and they tend to be found in genes that are "constrained" in that they rarely contain damaging mutations in the general population. They also frequently, but not exclusively, occur *de novo*, i.e., as new mutations not present in either parent. Large, rare CNVs are also associated with a high risk of autism and occur in 4–10% of autistic individuals (37–39). These are also frequently *de novo* but can be transmitted from affected or unaffected parents and found in unaffected relatives.

Although rare risk alleles confer large effects on individual risk, it appears that the great majority of the identified genetic risk at a population level is conferred by the *en masse* effects of a very large number, probably thousands, of common risk alleles each of which has a very small effect on individual risk (40). It also seems that in those with rare mutations, the burden of common risk alleles combines additively with the risk conferred by the rare mutations to determine individual risk (34, 41).

As well as beginning to reveal, in broad terms, the genetic architecture of autism, genomic findings also help us understand the possible relationships between autism and other conditions and traits by revealing a lack of specificity of genetic risk to autism. Notably, genetic variants associated with autism also increase risk for conditions that frequently co-occur in autistic people and to which their relatives are at increased risk. Thus, common variant genetic risk is at least modestly correlated with that for other neurodevelopmental and psychiatric conditions such as ADHD, depression and schizophrenia (40). Moreover, rare risk variants, both SNVs and CNVs, overlap with those that confer risk to other childhood neurodevelopmental conditions such as ID, ADHD, as well as schizophrenia, a neurodevelopmental condition that typically has its onset in adolescence or early adulthood (42, 43).

Interestingly, the enrichment of rare risk mutations is not equal across neurodevelopmental conditions, but is greatest in ID, followed respectively by autism, ADHD, and schizophrenia (42). These findings suggest that neurodevelopmental conditions, including autism, rather than being etiologically discrete entities, are better conceptualized as lying on a neurodevelopmental continuum, with the major clinical conditions reflecting in part the magnitude of the impact on brain development and resulting functional outcomes (42, 44). Thus, within this continuum, neurodevelopmental conditions occupy a gradient of decreasing neurodevelopmental impact as follows: ID, autism, ADHD, schizophrenia (42) (**Figure 1**).

Recent genomic data suggest that the notion of a neurodevelopmental continuum can also be extended to help understand heterogeneity and the large variability in cognitive and functional ability within autism. Autistic children

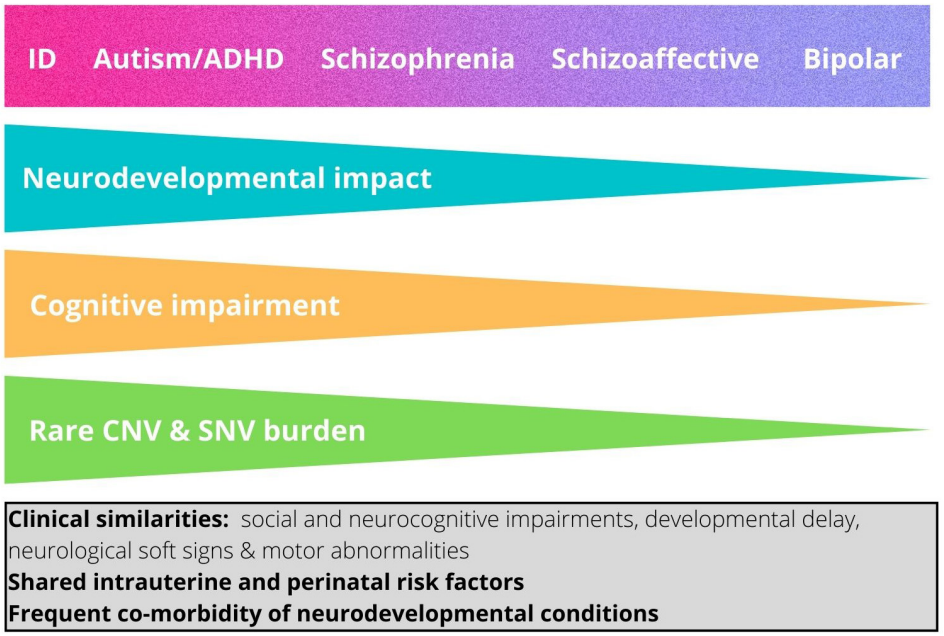

FIGURE 1
The neurodevelopmental continuum. This shows the hypothesized relationship between magnitude of neurodevelopmental impact and categorical neurodevelopmental and psychiatric diagnoses (42). The relative impact of copy number variants and damaging point mutations and the degree of associated cognitive impairment typically associated with each diagnosis are also shown. ID, intellectual disability; ADHD, attention-deficit/hyperactivity disorder. The box shows features that are shared by the different neurodevelopmental diagnostic categories.

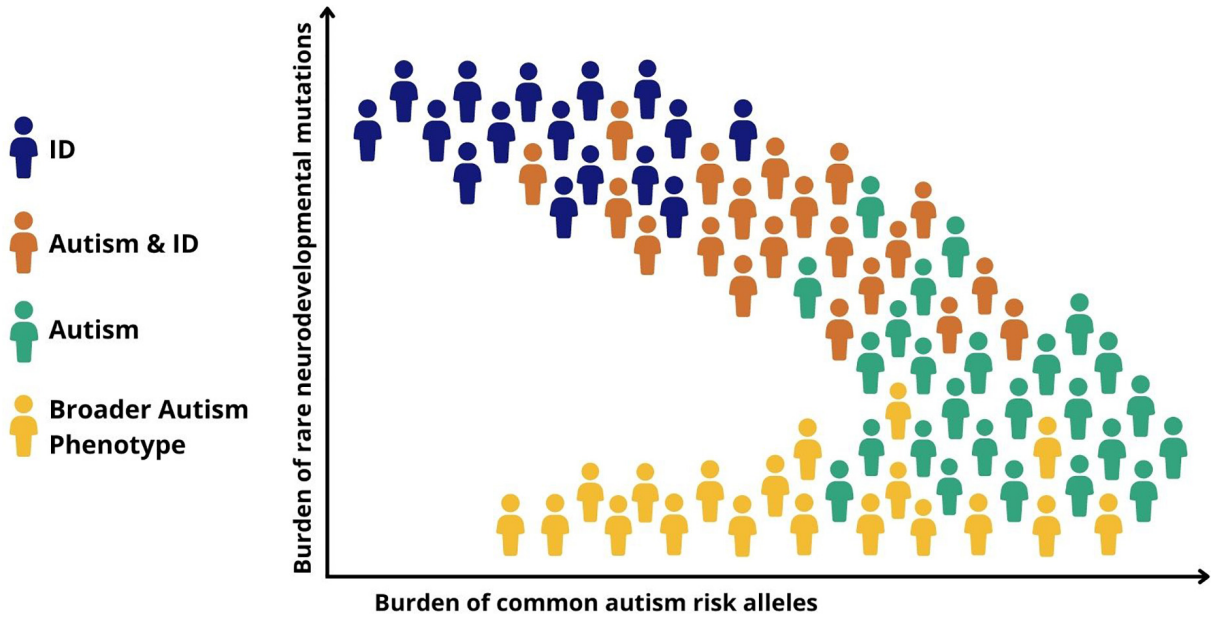

FIGURE 2
Genomic and symptomatic heterogeneity in autism. Simplified schematic representation of the relationship between different classes of genetic risk factors and neurodevelopmental outcomes. ID, intellectual disability; Autism + ID, autism and co-occurring ID; Autism, childhood autism with moderate language delays; Broader autism phenotype, variation in social behavior and adaptive functioning seen in the general population.

with high support needs and particularly those with co-occurring ID are more likely to have rare risk mutations, particularly those that have occurred *de novo,* compared to autistic individuals without ID (45). This is congruent with a gradient of decreasing neurodevelopmental impact from autism and co-occurring ID, through childhood autism with moderate language delays, to autism without ID or language delays (**Figure 2**). Common variants, on the other hand, appear to play a relatively larger role in autistic individuals without ID (40, 46). This helps to explain why autism without co-occurring ID is more heritable than autism with co-occurring ID, which has a prominent contribution from *de novo* rare mutations, which are, by definition, not carried by parents.

As we have seen, family studies suggest that there may be a genetic relationship between diagnosed autism and autistic traits in the general population. This has been confirmed by genomic studies showing that genetic risk for autistic traits varies across the population with contributions from both common and rare risk variants, with those carrying a greater burden of risk alleles being more likely to meet diagnostic criteria (44, 47). As well as suggesting a continuous risk landscape among neurodevelopmental conditions including autism, genomic findings also point to a second continuum of genetic risk between autism and typical variation in social behavior and adaptive functioning (communication and daily living skills) seen in the population (**Figure 2**). Regarding the genetic etiology of repetitive and restricted behaviors (RRB) in the population, a twin study has demonstrated high heritability for RRBs, but that RRBs have low genetic covariation with social traits, indicating potentially different genetic etiologies for different autism domains (48).

Autism as a diagnostic entity

How do genetic findings inform our understanding of autism as a diagnostic entity? There is strong evidence that susceptibility has a genetic, and therefore a biological basis, but genetics does not support the notion that autism is a biological entity that is distinct from other clinical conditions or neurotypical variation. Instead, the data suggest that autism can best be understood in relation its position in two continua. On the one hand, it can be conceived as lying at one end of continuous population variation in social and adaptive functioning, underpinned by a combination of multiple alleles of small effect. On the other, it can be seen as part of a broader neurodevelopmental continuum whereby rare, frequently *de novo*, genetic mutations that confer high individual risk impact the developing brain, resulting in a spectrum of outcomes including other childhood-onset neurodevelopmental conditions such as ID and ADHD as well as adult-onset psychiatric conditions such as schizophrenia and bipolar disorder (42) (**Figure 1**). We do not propose that these two continua underlie two distinct types of autism, rather they represent biological dimensions that combine to different extents in autistic individuals. Indeed, recent research has highlighted the importance of the combined effects of common polygenic variability and rare variants in conferring risk to autism (34, 41, 46).

Genetic findings also shine a light on heterogeneity within autism. Although the evidence does not support the existence of a simple dichotomy between the effects of rare and common genetic variation, it seems that *de novo* rare high-risk mutations play a relatively greater role in more severely impaired cases such as those with childhood onset autism or autism and co-occurring ID, whereas less impaired individuals reflect a greater contribution from common genetic variants that underlie variation in autistic traits in the population (**Figure 2**) (46). It is important to stress that these genetic mechanisms are not discrete, with rare and common risk variants combining to determine both an individual's risk of autism and whether, and if so to what extent, co-occurring disabilities and impairments of function might be present (34).

The overlap between neurodevelopmental conditions indicates that there are likely to be biological dimensions that transcend current diagnoses, and these may provide a more useful system of characterizing neurodevelopmental diversity. Indeed, this mirrors findings from neuroimaging and neuropsychology studies of neurodivergent individuals which have identified a range of transdiagnostic dimensions, examples include global measures of brain connectivity, hyperactivity and impulsivity, inattention, social communication, executive functioning, and phonological processing (49, 50).

Implications

Our model helps us understand how to reconcile that autism is a part of the natural variability within human brains and minds as advocated by the neurodiversity movement, with the fact that disability is a reality for some autistic people and their families (7). It provides a basis for the idea that a medical model may be appropriate in some instances, where needs are high, alongside a social model of understanding and supporting autistic individuals.

Genomic research does not indicate that autism is a discrete biological entity. Rather it supports a dimensional approach both to heterogeneity within autism and to the relationship between autism and other neurodevelopmental and psychiatric conditions. This in turn supports calls for transdiagnostic approaches to both research and clinical practice (50). Ill-fitting diagnostic criteria will impede progress toward identifying the barriers that neurodivergent individuals encounter,

understanding underpinning mechanisms and finding the best route to supporting them (50). Current diagnostic categories fail to capture the extensive symptom heterogeneity within categories, or to accommodate the extensive overlap across supposedly distinct diagnostic entities. Current diagnoses also fail to capture the needs of many children who require additional support in the broad areas of learning, behavior or social functioning, and many children whose symptoms do not reach arbitrary thresholds but who nevertheless have significant difficulties cannot access support or care.

Prospects

Autism genomics is still at an early stage and much genetic risk remains unaccounted for at the DNA level. We can expect to learn a great deal more from the application of new and emerging approaches (16) that will refine our approach to diagnosis, illuminate the underlying biology, identify novel treatment and early intervention targets for co-occurring conditions. However, genomics is already changing the lives of some families with an autistic child. Children with signs of early neurodevelopmental delay are increasingly being referred for genetic testing within clinical services to detect rare variants (51). For many families a genetic diagnosis can be the end of a diagnostic odyssey and can help explain the presence of co-occurring conditions, which can then inform tailored clinical care (51). A study of a US healthcare service that screened adults for rare neurodevelopmental CNVs explored the reactions of adults receiving a genetic diagnosis. 95% of these were positive or neutral and many individuals experienced emotionally poignant responses to learning a medical reason for lifelong cognitive and psychiatric disabilities (52). However important ethical concerns have been raised by the autistic community concerning the potential misuse of genetic research findings for eugenics (53). It is therefore important that genetic research is coproduced with the autistic community and stakeholders, and that data sharing from genetic studies is regulated appropriately. Working in partnership with the autistic community on identifying which aspects of their healthcare can most benefit from genomic insights will be crucial to ensuring success.

Author contributions

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Commentary: Autism: A model of neurodevelopmental diversity informed by genomics

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A Commentary on
Autism: A model of neurodevelopmental diversity informed by genomics

by Chawner, S. J. R. A., and Owen, M. J. (2022). *Front. Psychiatry* 13:981691. doi: 10.3389/fpsyt.2022.981691

In their paper, Chawner and Owen (1) present a genetic model for autism that outlines two contributory factors: (1) a social and adaptive continuum due to common genetic variation; and (2) a neurodevelopmental continuum due to rare genetic variation that presents itself as a continuum of impairment spanning from intellectual disability, through autism and ADHD, to schizophrenia and bipolar disorder.

I applaud the authors on relating the main mechanisms of the model to the differing views between the neurodiversity community and that of the medical model regarding the nature of autism, as they pertain to different aspects of the phenotype and both being important for explaining variability in clinical presentations. The model itself is very similar to part of a more comprehensive model I previously proposed (2, 3) and although there are many similarities between the papers, it is worth noting some empirical differences with important ramifications. I will argue that their conceptualization is not supported by the current literature and that it contains an issue that limits its practical usefulness. I will conclude by presenting testable postulates arising from the two models which will allow future studies to empirically validate them.

They write that the "neurodevelopmental continuum [...] results in a diverse spectrum of outcomes," referring to individual diagnoses under the neurodevelopmental umbrella. It does that through the effects of rare genetic mutations and environmental risk factors. As they operationalize it, the magnitude of the rare genetic burden determines which phenotype develops, and ultimately which diagnosis is received [see Figure 1 in (1)]. Conceptually, greater impairment is more closely associated with intellectual disability and autism than with schizophrenia and bipolar disorder.

Although the apparent statistical associations of these features appear in the literature, there is an issue with this operationalization that can be illustrated with an example. Consider an individual with a rare genetic burden of a given magnitude ($X_{inherited}$) and a diagnosis of bipolar disorder. If that individual were to have a child with inherited said burden, but with additional *de novo* variants ($X_{inherited} + X_{de\ novo}$) that child should be more likely to develop autism or ADHD than bipolar disorder. The idea that the type of condition one develops is contingent

TABLE 1 Testable postulates for differences between the operationalizations.

	Genomic neurodevelopmental model (1)	Pathogenetic triad (2, 3)
Specificity of diagnosis	Which diagnosis one receives depends on the individual rare variant genomic profile. Individuals are less likely to have conditions or endo-/phenotypes that are further from each other along the neurodevelopmental continuum [e.g., unlikely co-occurrence of BD and ID; (10, 11)].	Which diagnoses one receives depends on the individual common variant genomic profile.
The presence of multiple diagnoses	Individuals should only be able to get one diagnosis (although they write "frequent co-morbidity," one cannot be located in two positions along a single continuum and simultaneously have a high and low rare genetic burden). The main clinical difficulty lies in ascertaining between those that are close to each other along the neurodevelopmental continuum.	A higher neuropathological burden is positively associated with the risk of any one diagnosis, and the number of co-occurring diagnoses. The higher the burden, the more of the different disorder-specific traits/personality types (autistic, schizotypal etc.) become maladaptive and fulfill diagnostic criteria (12, 13).
Transgenerational inheritance pattern	Which condition(s) one develops is less related to the traits or conditions of the parents, and instead depends on the magnitude of rare genetic burden and risk factors.	The condition(s) one develops depends on which common variants, traits and conditions the parents have. Parents that have a higher magnitude of rare genetic variants and risk factors are more likely to have children with any, and multiple condition(s).
Distribution of traits in the population	[See Figure 2 in (1)] An intermediate rare and common burden do not additively give rise to an autistic-like phenotype (due to empty area of plot), implying a non-continuous distribution and a strictly non-linear additivity for common and rare variants.	[See Figure 2 in (3); Y-axis conceptually inverted compared with (1)] The first and second factor are both continuously distributed in the population (14), with additivity for common and rare variants.

BD, Bipolar Disorder; ID, Intellectual Disability.

on the magnitude of rare genetic risk is not supported by empirical evidence. The conditions have partly independent genotypic (4–7), and neuroendophenotypic signatures (8, 9), suggesting that they also have partly different biological backgrounds, rather than them being part of a single continuum. A person with bipolar disorder can certainly have a lower IQ and greater "cognitive impairment" than someone with an autism diagnosis. The operationalization of the neurodevelopmental continuum alludes to a causative mechanism by which the magnitude of the rare genetic burden impacts specificity of diagnosis. This is empirically unlikely given the state of the literature, unless the continuum is a pseudo-unidimensional manifold rather than linear, and it therefore probably represents a statistical artifact.

Furthermore, following the conceptualization of a neurodevelopmental continuum, the addition of a social-adaptive factor to the model is not without issues since the autistic phenotype (which also encompasses such traits) is already conceptualized along the first factor. Clearly, the second factor is conceptualized in order to accommodate the literature on the association between autism and common genetic variation. However, within the proposed model one cannot dissociate the autistic phenotypes residing within each of the factors (whether an autistic trait belongs to the social-adaptive or the neurodevelopmental continuum), greatly limiting the practical utility of the proposed model.

Their operationalization can be contrasted with that of the pathogenetic triad (2, 3), which previously suggested that there is (1) natural variation in non-pathological traits (such as autistic or schizotypal) due to common genetic variation, and (2) a range of neurodevelopmental risk factors including, but not limited to, rare genetic variation. These risk factors negatively influence brain and cognitive development, and limit adaptive behaviors. Notably, adaptive behavior is conceptualized within a third factor that moderates the association between the first two factors in giving rise to a diagnosis. This is an important distinction since Chawner and Owen seem to conceptualize adaptive behavior within the first factor as "social-adaptive traits" (although, they do not formally operationalize it). These two factors additively influence the risk, and crucially, the first factor provides the model with disorder specificity (through common variant burden for each condition, not rare burden). Also, rather than the magnitude of neurodevelopmental risk factors affecting which condition develops (as in their model), it non-specifically determines the probability of fulfilling criteria for any one diagnosis (or multiple).

Although the models are similar, there are subtle differences that give rise to different empirical predictions, each with testable postulates. In Table 1 present a few of these predictions, and the patterns in the existing and future literature that would favor one model or the other (some of which are already supported or undermined).

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The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Autism as emergent and transactional

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The current epistemology of autism as a phenotype derives from the consistency of historical accounts and decades of work within the tradition of descriptive epidemiology, culminating in current categorical descriptions within DSM and ICD nosologies and the concept of "prototypical autism." The demonstrated high heritability of this phenotype has led to an essentialist theory of autism as a biological entity and the concerted search within the developmental brain and genetic science for discrete biological markers. This search has not revealed simple markers explaining autistic outcomes and has led to moves towards a more dimensional account. This article proposes an alternative transactional approach. It proposes to understand autistic states as an emergent property within a complex developmental system; as the neurodivergent brain, and mind and body, encounter their social and physical environment within early development. Key evidence in support of this approach comes from random allocation intervention trials based on such transactional development theory, both in the infancy pre-diagnostic prodrome and the early post-diagnostic period. In replicated evidence, these intervention trials show that a targeted alteration in the quality of social transactional environment available for the child leads to significant, predictable, and sustained alterations in the outcome dimensional autistic phenotype over time; and further, in one prodromal trial, to a significant reduction in later categorical classification status. The inference from this evidence is that the prototypical autistic phenotype is to a degree malleable with a changed experienced social environment and that it is emergent from its constituent traits. Such a transactional approach enlarges our notion of the phenotype and brings the study of autism within mainstream individual difference developmental science. It challenges essentialist views, for instance as to intrinsic autistic "social avoidance" or theory of mind empathy deficits, integrates dimensional and categorical perspectives, and is consistent with the lived experience of autistic people and their advocacy for improved understanding within a social model.

KEYWORDS

autism, transaction, emergence, neurodiversity, intervention, autism spectrum conditions, clinical trials, neurodivergence

Introduction

Dimensional and categorical autism

One of the original tenets behind the National Institutes of Health Research Domain Criteria project (RDoC),[1] an initiative in relation to neurodevelopmental conditions, well-advocated by Insel (1, 2), was the aspiration to replace current nosological behavioural phenotypes with the antecedent neurodevelopmental trajectories underpinning them (3). However, this impetus finds additional weight from different sources too; for instance, from many in the developmental psychology and research community who instinctively lean towards "dimensional" approaches to development and psychopathology, and in recent advocacy from many in the autistic community. The idea of categorical autism has sometimes come to be equated negatively with what can be felt as a reductive "medical model," with implicit associations to the experience of unequal power relationships in clinical practice, academia, and social life. These are delicate waters. On the one hand, there are key strengths in the dimensional approach, which is in many ways fundamental to what I will be arguing in this article in terms of a transactional account of neurodiversity development within the social sphere. On the other hand, I wish to argue that opposing dimensional and categorical accounts in this way sets up a false binary. The dimensional and the categorical lenses have always been present in our developmental thinking—and both are crucial. It is intrinsic to our perceptual and cognitive functioning that we look at both process *and* entity as complimentary; it is the wood *and* the trees. The term "medical model" can sometimes underplay the sophisticated underpinnings of developmental psychopathology and psychiatry, not to mention good clinical work. This article is written from that clinical science tradition—indeed, aspiring to update that tradition into the current context.

There are also paradoxes in a purely "dimensional" approach. One of the immediate paradoxes is sure that the very term "autism" is categorical; a term that has been used historically to name something, and has also more recently become a term naming a valued social identity. The history and evolution of this naming is in itself a valuable subject for reflection (4); from the earliest highly theory-driven accounts of Bleuler and others, the more considered clinical descriptions of Sukhareva (5), Binswanger, and Kanner; into the tradition of empirical description and nosology elaborated in the last 60 years, which morphed into the developmental science and neurodevelopmental account of the current paradigm. The rise of the social advocacy and the pressing forward of social identity in relation to autism introduces a new note into this progression; a lived-subject assertion of experience which results in a rather different idea of autism as an "identity"—giving, in Levi-Strauss's formulation, "every individual . . . his own (identity) as . . .a signifier of his signified being" (6). An easy momentum from now could be towards the term "autism" fragmenting, and becoming applied quite differently to a prototypical phenotypic description for researchers, a diagnostic construct for clinicians and health service administrators (for instance as a ticket to a service support), and a social identity signifier within the community. Lack of mutual understanding across these domains would inevitably grow. Some may feel such fragmentation is inevitable or indeed desirable, and there are, indeed, deep differences between some of these perspectives. However, the implicit aim of clinical science towards evidence-based practice over decades has been to bridge these domains; working with research and in dialogue towards a stable descriptive language that could integrate science, evidence-based clinical practice, and social understanding. There are opportunities within current challenges and debates to enrich and develop this common language with new insights, and to reduce misunderstanding; this article is part of trying to do just that.

Further, in scientific terms, replacing categorical autism with a neurodiversity dimension just replaces one complex paradox with another. Decades of neurodevelopmental science have not yet succeeded in defining a commonly accepted neurodevelopmental trajectory unique to autism (7, 8), and in this context, the RDoC project is far from realising success (9). An alternative strategy has been to replace the notion of an autism phenotype altogether with a series of RDoC-inspired "transdiagnostic" trait phenomena (such as impulsivity, executive function) and to make these targets for attention and intervention as "needs" rather than autism itself (10, 11). But this deconstruction of the autistic phenotype has been criticised by Mottron et al. (12) as potentially leading to a series of false equivalents or homologues; those specific phenomena may appear superficially similar but actually be very different in different contexts. Without care and accurate demonstration of real equivalence, such an approach would threaten to collapse nuance and discrimination in developmental science. Advanced machine learning and deep learning paradigms *may* provide a route into an alternative empirical way of moving from observed traits to an autism entity (10); however, there are no reproducible outcomes from this as yet. The strategy will also depend, just as previous research has done, on the quality of the basic measurements that are undertaken. In many ways, the proposed path to automation will need to parallel the methodological efforts from previous decades of clinical observation, clinical practice, and developmental science research; it will also itself have to wrestle with these same paradoxes of dimension vs. category in development.

1 www.nimh.nih.gov/research-priorities/rdoc/index.shtml

Combining categorical and dimensional accounts: Autism as "emergent"

In sum, the pitting of dimensional against categorical remains, as it always has been, a false binary. This article proposes to cleave, for historical, linguistic, conceptual, and pragmatic reasons at this point, to the notion of a prototypic autism entity articulated by Mottron (12), but to avoid false binaries by seeing the autism entity of this kind as an *emergent property* within complex-system neurodevelopment—where "emergent" is stringently defined as referring to "arising phenomena that are novel and that differ in type and quality from the interacting components" (13, 14). This is a more dynamic model which defines autistic "states" arising out of dimensional variation, rather than pre-formed entities. It combines constitutional difference, transactional experience, and phenotypic entity into a mutually informing whole (15–17). There is an acknowledged challenge (13) in translating such appealing metaphor and theory into the operational description and the investigative strategies necessary to do science, for instance, to formulate testable and refutable hypotheses (18); empirical success to date with dynamic system modelling has largely been restricted to motor development in children, with analogies made to wider aspects of development (17). The strategy I will take towards this is to focus on the key moments of emergence and subsidence of the phenotype as points of entry for understanding; particularly focusing on the insights that can be gained from investigative experimental clinical trials; using the classic approach that a good way towards the understanding of a complex system is by trying to change it.

Approaching autism emergence and epistemology through empirical trials

There are three ways of addressing empirically a notional property of emergence: (i) constructing an observational account of phenotypic emergence within early development (12), (ii) observation of any possible phenotype subsidence later in development (19), and (iii) the effects of an experimental intervention into developmental processes through randomised allocation clinical trials. The first two can only essentially be approached through clinical description or longitudinal observational paradigms. These can be highly informative but are subject to a range of confounds that can limit the strength of inferences. The third, however, because it is the result of a controlled test of the results of a discrete and well-characterised developmental change, provides the most robust way into causal inference for the phenomenon of emergence, and that is what I focus on here.

Outcome measurement

In a series of investigative randomised controlled clinical trials, myself and colleagues have been able to address questions of emergence in this "experimental" sense. This was possible because we included in the initial design of these trials from 2000, as our pre-specified primary outcome, a specific measure of the autism phenotype [Autism Diagnostic Observation Schedule (ADOS; 20) or Autism Observation Scale for Infants (AOSI; 21)]. This was done at that time from an assertion that any intervention that wished to claim effect on "autism" should have as its outcome some measure of the actuality of "autism" itself, rather than solely some proxy or parallel measure of adaption or other functioning. This choice in itself is a deep issue for epistemology; it implies that a scientific understanding of the phenotype is only possible through measurement and that the form of measure chosen needs both accurately to reflect the richness of the phenomenon or phenotype in question and to be fit for the purpose for which it is being used. Measures of a complex reality like autism have a hard challenge to translate the complexity into quantifiable data for analysis. For our use, the ADOS, in particular, had the strong advantage of being the best-validated proxy for the full range and richness of the formal phenotype, with extensive psychometric and longitudinal cohort work behind it (20); and also being objectively and reliably codable from videotape, thus allowing blinded ascertainment and reduced bias for a trial. Further, the development of developmentally specific ADOS modules (22) facilitated the comparability of measurement over development and time, crucial in facilitating the longitudinal study of the clinical phenotype through the differing presentations as development proceeds and allowing our follow-up studies of trial outcomes.

Much has changed in the dialogue around autism in recent years and, within that, ADOS has been criticised (along with related nosological phenotypic definitions) for its normative and "deficit-focused" assumptions (23). Alternative measurement innovations have been proposed that aim to make less normative assumptions (24). These new approaches are in their early stages and may, indeed, prove transformative as they develop, but in the meantime, we need to address the concerns around the ADOS and the value of the corpus of results from it. I acknowledge the concerns but point to the roots of ADOS as a distillation of the clinical encounter; in good hands, it is sensitive to the autistic child and can bring out their ability across a range of social contexts, allowing the manifestation of both strengths and difficulties within autistic difference. When I administer it I feel I am able to engage deeply with a key part of the child's personhood and development. The language used in the coding may now seem over-medicalised and deficit-focused and this could be usefully updated without affecting the essence of what it does. No measurement is perfect but the ADOS I would say remains

the best current consensus means of measuring the observed behavioural phenotype and I hope to be able to demonstrate below the richness and power of what it can tell us. A particular unknown when we started was whether we would be able to show any intervention-related change in an instrument that was essentially designed as a stable phenotypic measure. In the event, throughout the programme to be described, both ADOS and AOSI have proved informative measures that are sensitive to intervention-related change. In a later discussion of these results, I will discuss more fully the nuances and caveats as to what we can learn from this measurement and try to address potential misunderstandings. I also note a key part of what is missing in current measurement—phenomenology—and point the way forward to a key new area of measurement practice.

Post-diagnostic intervention

The intervention used in this programme, called the Paediatric Autism Communication Therapy (PACT), was specifically designed to address the early developmental precursors of social communication, social engagement, and language relevant to the autistic phenotype and its emergence. The therapy was initially designed for the pre-school period. It works with parents in a naturalistic context aided by video-feedback techniques to help their awareness and understanding of the particularities of the communication style and intent of their neurodivergent child; in consequence improving the accuracy, sensitivity, and contingency of their dyadic responses. The model is that the young autistic child will then respond in turn with increased social response and communication initiation. What emerges is a powerful "coupling" of social interaction (25) of a kind that is central to naturalistic social learning in development (26). In this approach, there is no direct therapeutic work with the child, the focus is on the surrounding interpersonal and communication context. Any alteration in child behaviour, social orientation, and motivation comes naturalistically as a by-product of the altered dyadic response from the parent in real-time. Such an approach can be distinguished from traditional behavioural learning models of therapy such as EIBI or ESDM, either delivered by the therapist or the parent, which target specific behaviours to change in a specified direction through operant conditioning with rewards and contingency reinforcers. PACT therapy is manualised and developmentally staged to build on this early dyadic synchrony towards further social and communication engagement. In the trial testing, the extent to which the parent is able successfully to understand and respond to the child in this way is measured through an assessor-blinded coding of the proportion of parental "synchronous responses" within a video-sample of parent–child free play taken separately to the therapy context. Similarly, the extent to which the child responds is coded through the proportion of their behaviours that are "social communication initiations" to the parent. These alterations in the dyadic interaction between parent and child are the proximal target of the therapy, with the developmentally based hypothesis that such change will translate through a developmental cascade into more "distal" generalised improvement in child functioning in different contexts and through time as they grow. In our trials, this more generalised improvement later in time is measured with another adult in the context of the ADOS assessment, as well as more functional parent and teacher-rated outcomes. Such style of measurement thus allows a precise mechanism testing of the logic model of the therapy, since the developmental hypothesis predicts a cascade of effects from parent synchrony to child initiation to generalised enhancement of the child's social engagement and communication beyond the dyadic context. The "distal" effect on the phenotypic expression, measured by the ADOS, is thus the pre-specified primary outcome test in the trial.

The first randomised controlled trial (RCT) of this intervention compared to usual care (27) found a substantial treatment effect on the outcome child ADOS total score [$F_{(1,25)} = 7.30$; $p = 0.01$], a result particularly carried by therapy effect to increase function in the "social communication" domain as it was then called. In the subsequent larger PACT RCT (28), we found at the treatment endpoint point a trend for positive intervention effect on both social communication and "restricted repetitive behaviour" including sensory (RRB) domains of ADOS considered separately, and when these were considered together as the full autistic phenotype (29), they showed a significant endpoint treatment effect to reduce the (dimensional) ADOS "combined severity score" (CSS) (OR −6.4; −1.22, −0.06, $p = 0.02$). This endpoint treatment effect was then shown to be sustained; in follow-up intention to treat analysis 6 years after treatment end, 80% of the original cohort of children were assessed at a mean age of 10.5 years, with the assessors remaining blinded to the originally allocated groups. The analysis showed that the between-groups treatment effect on ADOS scores continued all through this time (OR −8.2; −1.53, −0.12, $p = 0.02$), giving a highly significant cumulative effect of the therapy [marginal log-odds effect size of 0.55 (95% CI 0.14–0.91; $p = 0.009$)] (29; see **Figure 1**). This kind of cumulative analysis is important in giving insight into the ongoing impact of an intervention on development. While these ADOS outcomes were the nominated primary outcome of the trial, effects supporting this change were also seen in parent-reported outcomes in relation to communication, adaptation, and family functioning; teacher ratings of adaptive function in school. One area not showing change was objectively measured "structural" language (vocabulary and grammar) despite parent accounts of vocabulary and communication increasing.

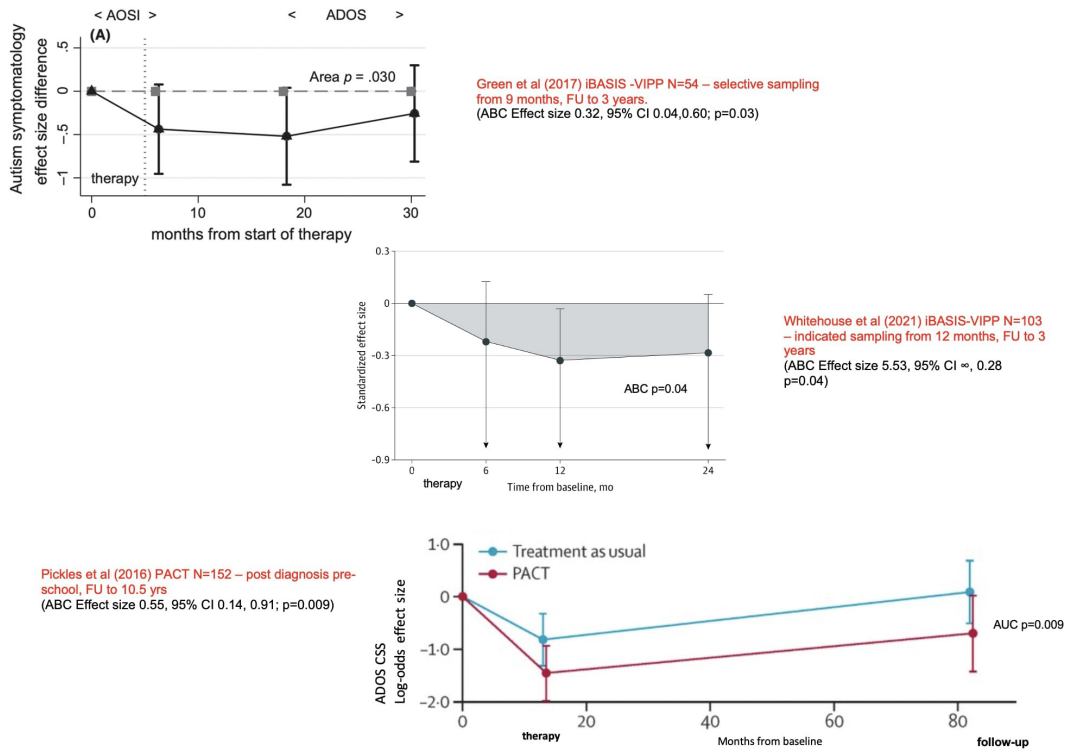

FIGURE 1
Long term developmental outcomes from three parent-mediated intervention trials. Showing replicated effects at different stages in early development to improve a combination of social communication skills, behavioural rigidity, and sensory sensitivities; improvements sustained after the end of therapy. Reproduced from Green et al. (43), Whitehouse et al. (44), Pickles et al. (29)–see main text. ABC/AUC, Area between curves estimation over time. These estimates provide a principled basis for an overall mean effect for unequally spaced measures that summarise treatment effect over the whole trial from baseline to follow-up.

Process of intervention effect

Mechanistic analysis of both these trials identified the mediating (or "active") processes at different stages of the therapy towards achieving these outcomes. In the first trial, the increased parental synchrony from treatment mediated the ADOS change at the end of therapy (30). In the second larger trial, a two-stage process was identified (31): in the *first step* within the immediate "proximal" parent–child dyad, increased parental synchrony strongly mediated the improvement in child communication initiation with a parent. Then in a *second step*, that improvement in child dyadic communication in turn strongly mediates the later improvement in ADOS generalised outcome. In a further result, it was these same improvements in child dyadic communication initiation during the intervention period that also strongly mediated the sustained reduction in ADOS severity score from endpoint through to 6-year follow-up in middle childhood (32; **Figure 2**). We thus here identify two stages also in the timing of effects: The first immediate short-term effect on the dyadic interaction of increased parental understanding, responsivity, and "synchronous" communication is to increase the child's spontaneous social initiation and engagement. This evidences the intended emergent "coupling" of social interaction (25), which is also marked by an increase in manifest shared enjoyment and parent reports of "light-bulb" moments of connectedness (often for the first time) with their child (33). Such a finding is consistent with much of what we know about how dyadic interaction works in neurotypical social development: but what is new here [and consistent with some other intervention research (34)] is to find that neurodivergent children also respond in a similar way, with increased social engagement. This crucial discovery gives empirical evidence counter to an "essentialist" notion of innate unchangeable social avoidance or disinterest in autistic development, suggesting that it is more contextual than that; consistent with a position increasingly advocated in the theoretical literature (35). Then secondly over a longer timescale, we see a "within-child" process that allows the generalisation of the short-term change into longer-term impact on child social communication, behavioural, and adaptive outcomes in development. These longer-term improvements are not so much in formal "structural language" (extent of vocabulary, etc.), which does not change in objective tests, but rather in the pragmatics of

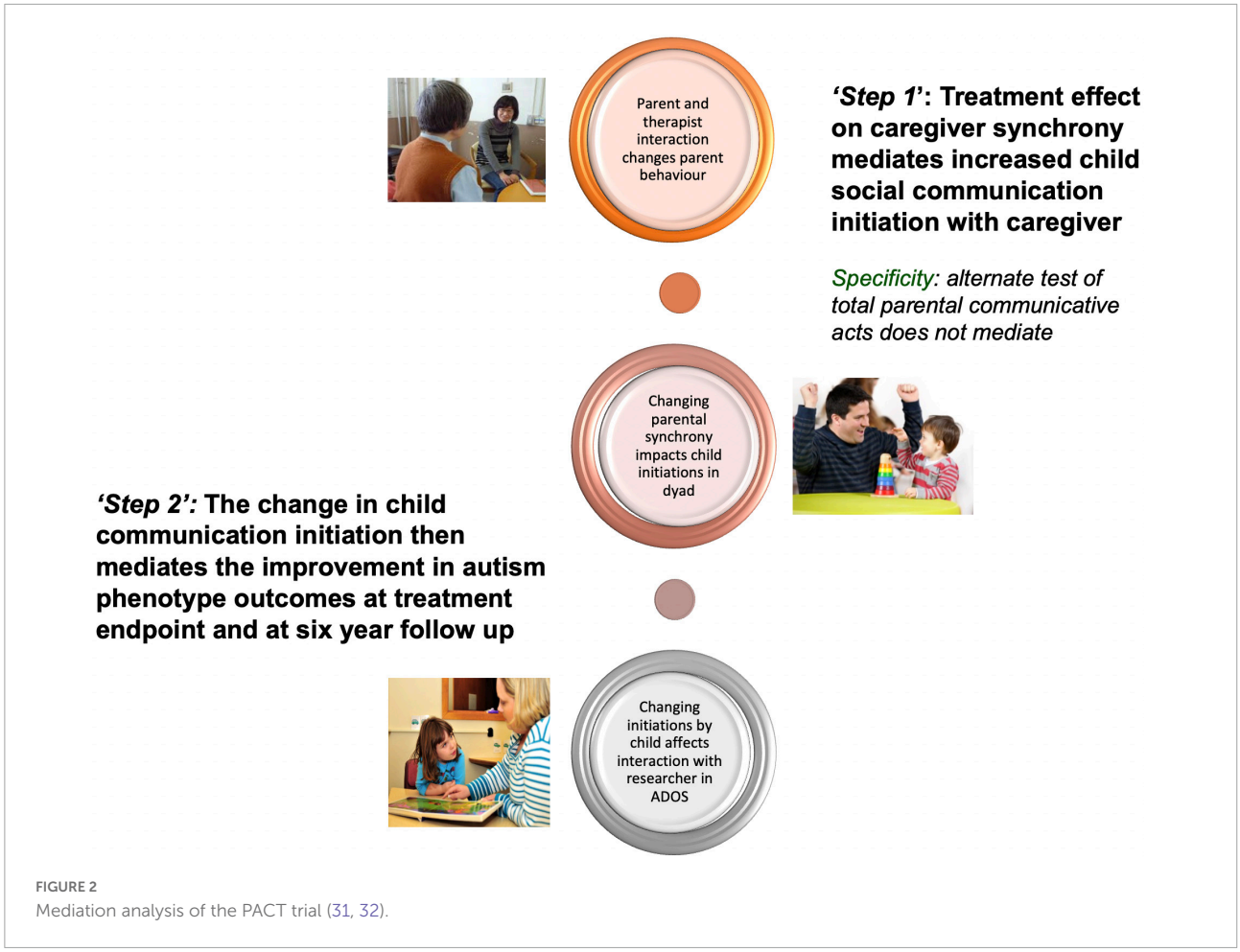

FIGURE 2
Mediation analysis of the PACT trial (31, 32).

social discourse, which does show objective improvement—and this later can be seen as of the key importance, acting as an interactional accomplishment for the child and increasing their connectedness (36). Parent reports of wider development and family effects also suggest broader improvements (37). These mediation results support the logic model of the PACT parent-mediated intervention, as to how it is intended to work. They have further developmental implications for a wider transactional model of autism development, as I will develop further below.

A more recently published trial tested an adaptation of this original clinic-based PACT therapy into a multicomponent intervention simultaneously at home with a parent and in education/school with learning support assistants (PACT-G, 38). This shows both similar and different effects: similar in the significant "proximal" effects of an intervention to improve parental synchrony and child communication in dyadic interaction across all contexts (albeit at a reduced effect size to the original clinic-based PACT trial), different in the lack of transmission and generalisation of these dyadic effects into independent ADOS change. Mechanistic analysis of this PACT-G trial (38) shows a replication of the first stage PACT mediation from parental synchrony to child dyadic communication, but there was a lack of the second stage generalisation process. We put this lack down to the reduced dosage in each context in the PACT-G model, the complexities of implementation in education and also at home, evidence by reduced model fidelity, and possibly the effect of a substantial proportion of online therapy in this iteration. The important learning from this trial is around dosage thresholds and implementation context methods.

Pre-diagnosis intervention in the autism prodrome

Myself and colleagues then developed a related style of parent-mediated video-aided therapy specifically designed to address the very early infant precursors of prodromal autism. The theory and hypotheses behind this work were similar to that in the post-diagnostic PACT, but the method was adapted to what we knew of early-emerging developmental differences in some infants with a high likelihood of developing later autism, and the empirically observed interaction changes in such

TABLE 1 Clinical best estimate ascertainment against categorical DSM5 criteria at 3 years of age, comparing groups receiving iBASIS-VIPP intervention at 1 year and usual care; showing treatment effects on social reciprocity, restricted repetitive behaviours and sensory symptoms (see text).

	No. (%)		Fisher exact test		Binary logistic regression analysis[a]	
Variable	**iBASIS-VIPP group (n = 45)**	**Usual care group (n = 44)**	**Odds ratio (95% CI)**	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
DSM-5 criterion						
A1: deficits in social-emotional reciprocity	9 (20.0)	16 (36.4)	0.44 (0–1.08)	0.07	0.35 (0–0.82)	0.02
A2: deficits in non-verbal communicative behaviours used for social interaction	13 (28.9)	17 (38.6)	0.65 (0–1.49)	0.23	0.47 (0–1.08)	0.07
A3: deficits in developing, maintaining, and understanding relationships	13 (28.9)	16 (36.4)	0.71 (0–1.65)	0.3	0.60 (0–1.31)	0.14
B1: stereotyped or repetitive motor movements, use of objects, or speech	7 (15.6)	14 (31.8)	0.40 (0–1.04)	0.06	0.29 (0–0.73)	0.02
B2: insistence on sameness, inflexible adherence to routines, or ritualized behaviour	2 (4.4)	2 (4.5)	0.98 (0–9.40)	0.49	1.03 (0–6.21)	0.51
B3: highly restricted fixated interests that are abnormal in intensity or focus	3 (6.7)	2 (4.5)	1.49 (0–12.57)	0.67	1.16 (0–6.50)	0.56
B4: hyperreactivity or hyporeactivity sensory input or unusual sensory interests	2 (4.4)	8 (18.2)	0.21 (0–0.94)	0.04	0.13 (0–0.53)	0.02
Diagnosis						
ASD	3 (6.7)	9 (20.5)	NA	0.07	0.18 (0–0.68)[b]	0.02
Atypical development	37 (82.2)	27 (61.4)	NA	NA	NA	NA
Typical development	5 (11.1)	8 (18.2)	NA	NA	NA	NA

Reproduced from Whitehouse et al. (44).
ASD, autism spectrum disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders (Fifth edition); iBASIS-VIPP, iBASIS-Video Interaction to Promote Positive Parenting; NA, not applicable.
[a]The binary logistic regression analysis incorporated the following covariates: infant age at the 24-month postbaseline assessment, baseline score on the Autism Observation Scale for infants, and infant sex.
[b]The binary logistic regression analysis comparing ASD vs. no ASD incorporated the following covariates: infant age at the 24-month postbaseline assessment, baseline score on the Autism Observation Scale for infants, and infant sex.

groups the first year (39). The therapy manual was adapted from work with neurotypical infants into the briefer 5-month iBASIS-VIPP manualised home-based intervention (40). It is important to note that, as with PACT, there is no intention in this therapy to "change" unwanted child behaviours (concerns that have been expressed in relation to some early intervention strategies). Rather the aim is to increase parental awareness of and sensitivity to neurodivergence in their baby, increasing by this the infant's experience of being attended to, understood, and responded to by others; and through that to support and nurture the neurodivergent infant's development and outcomes (41). This is an important point of difference that speaks to the need for promoting autonomous outcomes in early intervention outcome work (42). Results are available from two clinical trials of this parent-mediated intervention on two different populations of infants with an increased likelihood of autistic development. One ascertained through familial incidence (infant siblings of an autistic child) and intervention initiated from mean age 10 months (43), the other with babies identified in community health services at mean age 13 months as having early developmental features suggestive of the raised likelihood of later autism (44). In both these trials, the distal autism phenotypic outcomes were measured as developmentally appropriate using AOSI and ADOS instruments. Both trials showed the sustained impact of intervention on AOSI and then ADOS scores over the 2 years following intervention until diagnostic evaluation at 3 years (see **Figure 1**). The latter trial (44) additionally had a large enough sample to enable results on a diagnostic evaluation at 3 years, conducted by blinded independent experienced clinicians using clinical best-estimate algorithms from all available information against DSM categorical criteria. This showed a treatment difference across

the three categorical autism domains in favour of iBASIS-VIPP therapy (Table 1); amounting to a 60% reduction in emergent autism overall diagnosis at 3 years after intervention (20.5% emergence in TAU against 6.7% in the iBASIS-VIPP group); an odds ratio of 0.18 (0–0.68; $p = 0.02$) or a "number needed to treat" of 7.2 interventions to reduce one autism classification (44). It is important to note here and will be discussed further below, that the children in the therapy group not developing above an autism threshold still did show evidence of other developmental differences of various kinds.

Autism as emergent

In sum, there is through this programme, testing a model of intervention targeting developmental precursors of social functioning and autistic development, a consistent replicated pattern of treatment effect across trials on the nosological phenotype as reflected in the ADOS score, sustained in development for several years subsequent to treatment end (Figures 1, 3, 4). Effects are seen at different developmental ages but with the same basic characteristics in response to essentially the same kind of intervention. These effects are seen in relation to the ADOS considered dimensionally, notably across *all* components of the phenotype, both social communication and restricted, repetitive and sensory behaviours. Additionally, in the latest pre-diagnosis trial (44), for the first time, effects are also seen in terms of reducing the incidence of the categorical diagnostic phenotype, as assessed by independent clinicians (Table 1).

The results of these trials taken together represent, therefore, for the first time, a replicated experimental change in autism phenotype emergence/submergence in a way that links together dimensional and categorical approaches. The fact of this replicated effect on dimensional ADOS at different developmental ages makes unsurprising the fact that the intervention also, in the pre-diagnosis trial powered to show this, systematically alters the relation of children to clinical thresholds, such that they no longer meet "autism" criteria (i.e., a prototypical autism description) on best-estimate clinical diagnosis (although they remain neurodivergent). The *threshold categorical* effect (Table 1) is thus directly related to critical changes in *dimensional components* seen in both pre-diagnostic and post-diagnostic cohorts (Figures 1, 3, 4). This is an illustration of the traditional relationship between dimensional change and threshold-related categorical shifts within a complex system. The intervention experiment causes critical planned alterations in the dimensional components, which are linked in turn to whether or not the categorical phenotype emerges. The logical inference from this must be that the categorical phenotype itself is an "emergent" phenomenon; altered threshold effects on ADOS reflect the emergence of a prototypical phenotype from a combination of constituent traits acting within a complex system; a strict definition of emergence (13, 14). Emergent autism in this sense has a particular "quality" that is not manifesting in the constituent traits in children with neurodivergence below the autism threshold. This is in line with the traditional view that the autistic phenotype historically described and evolved does have internal coherence and a predictive and face validity. The described phenotype is not perfect and contains inherent complexity and contradictions, especially as its boundaries have been flexible to changing perceptions; the complexities underlying Mottron's prototypical suggestion (12). However, it has the virtue of utility and predictability. Efforts to identify an autism-equivalent inductively from constituent traits using for instance machine learning techniques have not so far shown replicable success. The fact remains that, in approaching complex systems, the level of analysis is always crucial—and a level of analysis that includes the historically determined prototypical autistic form has proven its longevity and utility.

What are we to learn then from this about the autism phenotype as measured in this way? I have argued above, with acknowledged caveats, for the veracity of ADOS measurement in reflecting the characteristic breadth and richness of the presentation of autism as behaviour. Our clinical trials data suggest that a consistent, reproducible long-term change in this presentation is possible with targeted early intervention that focuses on the quality of interpersonal and communication environment around the child. The change involves an increase in the child's social orientation and ability within interaction and communication; also in a reduction in the amount of sensory-related and repetitive behaviours, a "cross-domain" effect across all aspects of the phenotype that is very salient from a theoretical perspective. Equally, however, I would not want to overemphasise the extent of this phenotypic malleability: the amount of difference that we show in these trials is statistically significant but not massive or magical; children in middle childhood after pre-school intervention generally remained autistic and those after infancy intervention who did not develop the emergent phenotype still showed neurodivergent development of other kinds. ADOS results can be confounded sometimes by cognitive ability (45) or clinical heterogeneity (46); although there is no evidence in the trials described above that either of these factors modifies the intervention results reported here. However, these intervention studies do show that the autistic phenotype understood like this is neither fully predetermined nor inviolable; it has empirical malleability to intervention. Nor is it the case that this malleability is confined to "higher functioning" autistic states; the trials described above apply to a range of core (27, 29)

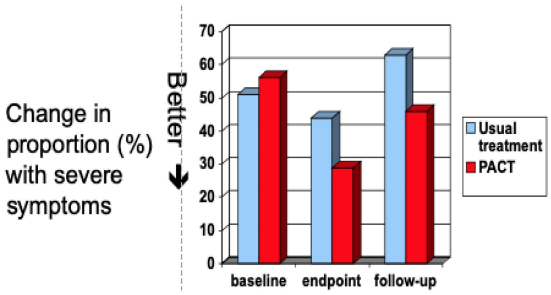

FIGURE 3
Distribution on dimensional ADOS CSS after post-diagnostic PACT intervention through to 6 year follow up, compared to treatment as usual. Data from Pickles et al (29).

to "spectrum" (43, 44) autistic development and a similar range across DQ.

A possible explanation for these results is that the intervention simply reduces arousal or anxiety and that this might affect ADOS scores. This may well partly be the case (for instance with the level of sensory and repetitive behaviours, that are sensitive to arousal states); but this is insufficient to explain the long-term sustained effects, and anyway begs the question of *why* the arousal reduces. More profoundly I would argue that if we change the fundamental and early sense of the child's connection, acceptance, belonging, and being, within and accepting neurodiversity, then outcomes related to social motivation, engagement, and communication will predictably be altered. And since these latter aspects constitute core aspects of the phenotype as we currently understand and define it, then, to that extent, the phenotype is changed. This malleability then suggests something about the autistic phenotype as a "*state*" phenomenon—a state that is emergent under certain conditions and that can subside under others. This is not to imply an absence of other difficulties (47) but it points to something in the epistemology of the condition. Another inference could be that the autistic phenotype as measured like this is not actually the irreducible core "difference" experienced within neurodiversity—that the core phenotype lies somewhere else behind. I would be very open to this account, which I explore further below. But the relative malleability of part of the phenotype as measured here (and as encoded in the current nosology) opens up to another profound re-framing, that of autistic states within a transactional context—to which I now turn.

Autism as transactional

With this evidence, we can now do something new to enlarge the nature of the complex system that we are describing within autism. Whereas traditionally within developmental science, the object of description has been the individual developmental trajectory (autism as an individual condition), and these dyadic intervention studies, along with the developmental theory that underpins them, enlarge this to include *both the individual and the immediate social environment in transactional relation*. This is not a new idea in developmental science generally; in both Winnicott's famous formulation that "there is no such thing as a baby" (48), and Bowlby's theory of the "goal-directed partnership" within early relatedness (49), there is an implicit recognition of the interpersonal context within which any individual development operates—an idea formalised in Sameroff's transactional theory (50). However, traditionally autism, partly because of its high heritability, has been considered more from an essentialist rather than a transactional position. My aim is here to bring autism/neurodiversity into this transactional/developmental domain; a paradigm shift in the context of much previous theory and research.

In our intervention model above, we are essentially perturbing this *interpersonal dyadic early relational system around the child*; we make the perturbation by initiating a change in adult responsiveness to child communications, finding that perturbing the interpersonal system in this way has predictable effects on the child dyadic response according to well-described transactional dynamics within developmental science in neurotypical development. We show that such transactional dynamics are as applicable to neurodivergence and neurodifference as to neurotypicality. Further, in a way that seems consonant to that described in normative developmental theory, the child appears to internalise that dyadic experience into an acquired ability and *intra*personal dynamic that allows generalisation out into other interpersonal contexts. This is the dynamic underpinning social development in neurotypical children and the generalisation of acquired social skills into social abilities across contexts independent of immediate contingencies. In our work, we show that *intra*personal dynamic is also seen within autistic development (in contra-distinction to frequent assumptions that autistic children find it hard to generalise acquired skills across context).

Such a transactional framing of autism is consistent with normative social development and social development theory. The prototypical autism phenotype is in this sense not solely within-child phenomena, it is also partly a transactional phenomenon, which is in itself emergent in development depending on the characteristics of the child's neurodivergence and immediate relational and physical environment. Not only is the course of brain maturation itself likely influenced by such an experienced environment (51); but development and identity are co-constructed, not only interpersonally but also socially. Here this developmental account converges with the autistic community's advocacy around social adaptation and the social model of autism (52); although for a complete transactional model one needs to articulate both poles—the particular quality and characteristics of the neurodivergence as well as the characteristics of the environment, whether interpersonal or social.

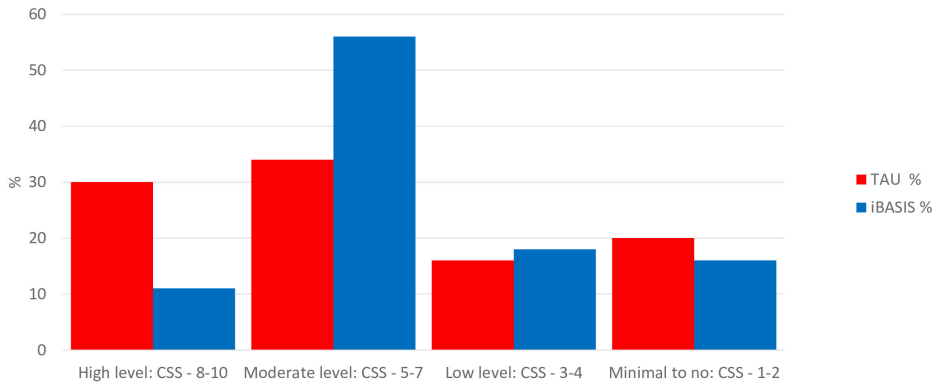

FIGURE 4
Distribution on dimensional ADOS CSS at 3 years, comparing pre-emptive iBASIS intervention from 1 year with treatment as usual. Data from Whitehouse et al (44).

This element of malleability in the outcome of autism phenotype is sufficient to show that it is not simply pre-formed or a mechanical translation of heritable probability or brain development; to an important extent, it is the developmental outcome of the neurodivergent brain, mind, and body as it grows in the transaction within its inter-personal and material environment. (An extreme case for the effects of environmental perturbation is also well-made from the results of investigations into the "natural experiment" of environmental perturbation consequent on extreme social deprivation within institutions. As it is now well-attested, such environmental conditions, if prolonged beyond 6 months in early infancy/childhood, can result in a social development homologous with autism (53), and indeed meet current criteria for the phenotype) (54).

Steps towards a transactional model of autism and its development

For a developed transactional model of autistic development, therefore, I see no reason to discard the value and utility of a categorical behavioural phenotype. However, we can reframe the dimensional processes that go into its formation by adding the *inter*personal processes of the environmental transaction to the *intra*personal processes around heritable brain development, interactive specialisation, and neurodivergence. Two decades of "babysibs" longitudinal neuroscience work have not identified specific discrete markers of autism emergence, but rather more general perturbations in many aspects of the developing brain system that are linked to later autism (7, 8). In such a complex system, experimental perturbation of this kind through intervention can be a royal road to understanding specificity and causation in the developmental process.

The tradition of individual difference psychology (55) investigated the nature of variation in distributed biological (including neural), physical, and psychological traits, and the interplay between such trait variation and consequent environmental transactions and adjustments in producing developmental outcomes. From early temperament theory and research (56) came the related notion of "goodness of fit"; developmental outcomes were found to be crucially impacted by the quality of these observed and experienced transactions rather than simply the intrinsic properties of trait or biological variation—a theory elaborated in the transactional model (50). The developmental model proposed here applies these transactional theory ideas to neurodiversity—making it an extension, or special case, of individual difference theory, but stretching its envelope and explanatory power.

Logically from this, the constituent elements of such a transactional developmental model would need to include the identification of: (i) the specific characteristics of neurodiversity/neurodifference in the first few years of life; (ii) the interactional consequences and experiential responses of such specific neurodivergence; (iii) the consequent evolution of an outcome behavioural phenotype through early development; (iv) establishing causal influence between these reciprocal elements through experimental perturbation studies; (v) building and testing a developmental model by integrating (i)–(iv). **Table 2** outlines some theory and current evidence for each of these steps.

Autistic states and irreducible difference—The role of phenomenology

I hope the evidence will be clear from the above account that there is an element of malleability in the early emergent phenotype of autism. This is important at the practical level of providing early evidenced support for diagnosed autistic children and those infants who are at increased likelihood of

TABLE 2 Elements of a proposed transactional theory transactional model of autism.

Model element	Current theory and evidence	Comments
1. Early neurodivergence	Difference in visual response to eye gaze from 2 months (57), to speech sounds from 4 months (58), altered trajectories of social engagement with preserved attention to faces but reduced triadic attention to objects from 2 to 3 months, predicting social—communication skills at 2 years (59). These differences in perceptual organisation noted in different modalities later in the first year (60).	Preliminary evidence and these changes are subtle. No intervention experiments yet accomplished at this age to identify causal influence or potential for change.
2. Interaction consequences of early neurodivergence	High autism likelihood (HL; siblings of autism probands) show relative increase in parent directiveness from 7 months compared to low likelihood (LL) infant-parent dyads, associated with altered visually evoked potentials in the infant (61). By 14 months the parent differences joined by observed infants alterations in social engagement and affect sharing with the adult; these infant observations predict autism emergence at 3 years in the cohort (39).	Since this dyadic interaction is itself a dynamic system, it can in some dyads re-organise into something itself less mutual and self-correcting, experienced often by parents' account as despair or disengagement on the one hand or anxiously directive on the other. This interaction dynamic is the proximal target of early dyadic intervention (28, 40, 43).
3. Phenotypic outcome trajectories	Emerging group differences in behaviour between HL and LL infants in the latter part of the first year, involving dyadic social engagement, flexibility of attention, and integration between verbal and non-verbal communication, vocalisation and gesture, predict later autism development and suggest gradually emergent autistic trajectories (7, 8).	In the second year, Mottron et al. (12) postulate a more definitive threshold (bifurcation) event often signalled by abrupt skills regression, which they link to a decisive shift in the infant from a social to a non-social perceptual bias and resulting developmental disruption. This is postulated to further re-organise over into the (prototypical) pattern of phenotypic autism seen by the later 2nd and 3rd years.
4. Evidence from perturbation (intervention) experiments about causal influence	Re-orientation of parental focus and response to the child in therapy re-establishes reciprocal social interchange, with increased child social initiations and engagement [evidenced by video coding (27, 28, 43, 44)]. This mitigates the interaction consequences in section 2 above and is causally associated with improved social functioning beyond the dyad (30, 31) as well as increased reported connectedness and relatedness in parent's experience of the child (33). This increased social orientation and engagement is sustained after the intervention period in subsequent development (43, 44)—and sufficiently in Whitehouse et al (44) to reduce outcome developmental characteristics below a prototypical autism threshold. Increased child social engagement and communication initiation is also the origin of the sustained intervention effect on outcome symptoms from pre-school to mid-childhood (29, 32).	Neurodivergent infant and child social engagement is a function of transactional experience, rather than "social avoidance" being an intrinsic part of the phenotype. The therapy arguably results in an internal rebalancing of social and object focus with increased social behaviours and decreased object focused routines. The child retains neurodifference but arguably to a less distressing and impairing degree and better able to take advantage of social life. This evidence thus supports a *relative* malleability of processes within autistic development—and the idea that the prototypic phenotype can both emerge and relatively "sub-merge." While "bifurcation" suggests a linear and irreversible process, emergence has something more of a state quality: a combination of distributed dimensional dynamics induces a state change with emergent characteristics, which can reverse.

an autistic trajectory. The intervention science suggests that this support will benefit these children and their families, not just at a phenotype level but in terms of wellbeing and confidence, and we are now in a position as this intervention science has proceeded, to advocate now for a practical and evidenced integrated early care pathway within health systems (62).

At a more epistemological level, a transactional approach identifies some phenotypic malleability, but there remains behind these undoubtedly irreducible aspects of neurodiversity and experience; about which there is no evidence for or intention here to "remove" or "eradicate" through intervention or support. Further progress towards refining understanding of this more irreducible part of the phenotype will require new strategies and complimentary measurement. This will entail centrally at this point in my view an approach to the phenotype from the "inside-out" through phenomenology. It is an extraordinary lacuna to date in mainstream autism science that there is no *systematic autistic phenomenology*. The prototypical autism phenotype measured and analysed above has always been characterised externally from observed behaviour (in common with many developmental conditions from early childhood)—a fact that has certainly limited theorising and has naturally led to criticism from those with lived experience and others that much about the current phenotypic description objectifies them. While sympathetic observation and careful neuroscience can still increase empathic understanding, the time has come for this to be complimented by phenomenology and systematic data from lived experience. This is partly an ethical imperative, but it will also fill in a key gap scientifically in understanding autism and a dynamic systems perspective on its emergence. We have much narrative information already from the often extraordinary and rich accounts that have been written by autistic people and parents of autistic children. But a systematic exploration of such phenomenology using shared qualitative and quantitative methods will add much more generalisability to this existing information and allow

comparison with other areas, for instance, of neurotypical experience. There have been increasing calls for more systematic attention to the lived phenomenology of autism (63, 64), and some early work has begun (65). The perspective of the development of the experiencing mind if systematically done will clarify much in developmental science and direct the focus of research going forward. For instance, gaining a richer and more general understanding of the experienced autistic sensorium within different environments, the experience of space and time and attentional focus, will all be central to a fuller phenotype description and potentially valuable for the direction of approach in autism neuroscience. Systematic work by and with autistic people will be core to this approach; they would be at the centre of a phenomenologically informed phenotype—and the new measures needed to describe it. Such joint work joint work may act as a further practical bridge through action between neurodiversity, clinical and research perspectives on "what is autism."

I have argued that, for further evolution of the developmental science of autism at this point, we will need to elaborate a more nuanced and transactional account of what it means to be autistic and how autism becomes itself; and I have evidenced how information from clinical trials can contribute to that. Moreover, in doing so, we may not wish to dispense with autism as an entity, despite its paradoxes; and may want to consider the prototypical version that Mottron advocated as one pole of thought and action. I intend this article to outline one way to do this.

Ethics statement

The studies involving human participants were reviewed and approved by Greater Manchester Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

Author JG declares director fees for a not-for-profit community interest company IMPACT (number: 10902031) to deliver/disseminate training on the PACT intervention method. He is an NIHR Senior Investigator NF-SI-0617-10168.

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Heterogeneity thwarts autism explanatory power: A proposal for endophenotypes

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Many researchers now believe that autism heterogeneity is likely to include many disorders, but most research is based on samples defined by the DSM-5 Autism Spectrum Disorder (ASD) criteria. However, individuals diagnosed with autism have complex and varied biological causes for their symptoms. Therefore, autism is not a unitary biological entity. And although autism is significantly different from typical development, autism is not a unitary clinical disorder because diagnosed individuals vary in symptom patterns, comorbidities, biomarkers, and gene variants. The DSM-5 ASD criteria were designed to reduce heterogeneity, and there have been many other efforts to reduce autism heterogeneity including using more stringent clinical criteria, dividing autism into low and high functioning groups, creating subgroups, and by studying larger samples. However, to date these efforts have not been successful. Heterogeneity is extensive and remains unexplained, and no autism pathophysiology has been discovered. Most importantly, heterogeneity has hindered the explanatory power of the autism diagnosis to discover drug regimens and effective behavioral treatments. The paper proposes that possible transdiagnostic endophenotypes may reduce autism heterogeneity. Searching for transdiagnostic endophenotypes requires exploring autism symptoms outside of the framework of the DSM-5 autism diagnosis. This paper proposes that researchers relax diagnostic criteria to increase the range of phenotypes to support the search for transdiagnostic endophenotypes. The paper proposes possible candidates for transdiagnostic endophenotypes. These candidates are taken from DSM-5 ASD criteria, from concepts that have resulted from researched theories, and from symptoms that are the result of subtyping. The paper then sketches a possible basis for a future transdiagnostic endophenotypes screening tool that includes symptoms of autism and other neurodevelopmental disorders.

KEYWORDS

autism, heterogeneity, diagnosis, paradigm, DSM-5, subgroups, transdiagnostic

Introduction: Heterogeneity thwarts autism explanatory power: Can transdiagnostic behavioral endophenotypes help?

Morris et al. (1) stated that psychiatric diagnoses "have been reified—seen as "real entities" —when in reality they are not natural kinds" (p. 2). Autism is not a unitary biological entity or natural kind (2) because individuals diagnosed with autism have many varied and complex biological causes for their symptoms, and vary in symptom

patterns, comorbidities, and biomarkers (3–7). Casanova et al. (8) asserted that, "The diagnostic boundaries of the behavioral phenotype that define ASD are fairly broad due to the large variability that is observed in symptom types, onset, and severity. This variability serves as an index of etiological heterogeneity for a group of complex conditions" (p. 1).

Given this heterogeneity, it is unclear whether or not DSM-5 Autism Spectrum Disorder (ASD) (9) is a unitary clinical entity. Lai et al. (10) argued that DSM-5 ASD *was* a unitary clinical disorder because the field had agreed on unifying elements: the diagnostic criteria; increased prevalence; early presentation; clinical assessments; interventions; cognitive processes; and links to multiple causal agents. However, Tunç et al. (11) reported evidence for a fuzzy boundary between ASD and non-ASD that did not result from misdiagnosis, and they stated that an "ASD or a non-ASD diagnosis at a given time should then be seen as a 'current' state of a child within the phenotypic and developmental continuum" (p. 1237). Moreover, Hyman (2) argued that no psychiatric diagnostic categories can be unitary entities because they all include heterogeneous symptoms, gene variants, significant comorbidity and varied biomarkers "accompanied by a large variability of other symptoms" (p. 3).

Importantly, heterogeneity has hobbled the explanatory power of the autism diagnosis. In 2021, McCracken et al. (12) reported that "Two decades of increases in intervention research funding with advances in the basic neuroscience understanding of ASD has not produced progress in pharmacological interventions for ASD core deficits" (p. 4). In 2021, the Lancet Commission Report (13) asserted that research has yet to discover behavioral treatments for the "heterogeneity of manifestations of autism" (p. 300). However, because autism heterogeneity is so extensive, if the Lancet Commission Report's goal is finding behavioral treatments for each of the heterogenous "manifestations of autism" then hundreds of studies will be needed to discover unique behavioral treatments for each manifestation of autism. Moreover, Shic et al. (4) noted that "Progress in developing interventions for ASD has been hindered by a lack of measures that can, within this heterogeneity, provide objective quantification of intrinsic features of ASD with sensitivity, reliability, and mechanistic relationship to core symptoms" (p. 2).

Borsboom et al. theorized heterogeneity would be resolved by one large network encompassing all symptoms and causes for all childhood and adult DSM-5 psychiatric disorders (14). By contrast, Wolfers et al. (15) noted that autism should be best understood "at the level of the individual" (p. 250). This paper argues that because autism heterogeneity, including comorbidities, is so extensive, it is likely that transdiagnostic neurodevelopmental social impairment endophenotypes may be found within and across the current diagnostic boundaries of autism and other neurodevelopmental disorders (5, 6, 8, 11, 16, 17).

The paper proposes that transdiagnostic social impairment endophenotypes may address heterogeneity by discovering meaningful transdiagnostic social impairment neurodevelopmental groups. Although social impairment is just one of the two diagnostic criteria for DSM-5 ASD, the other being restrictive/repetitive behaviors (RRB), social impairment has remained the core feature of all those diagnosed with autism, and therefore is a good candidate for establishing concepts that can yield productive transdiagnostic endophenotypes.

Of course, transdiagnostic behavioral social impairment endophenotypes may not exist or may not be of value, but they cannot be proven valueless if researchers continue to study samples defined by the DSM5 ASD diagnosis. As Hyman (2) noted, studying samples based on DSM diagnoses reflects the "dogged persistence of the *DSM* categorical approach, notwithstanding a large, convincing, and still growing body of negative evidence" (p. 21).

This paper has six sections. The first section, Transdiagnostic endophenotypes, (a) defines endophenotypes, (b) provides examples of the transdiagnostic endophenotype approach, and (c) discusses the relationship of transdiagnostic endophenotypes to diagnoses. The second section, The DSM-5 ASD, explains how the DSM-5 spectrum diagnosis (a) was designed to reduce heterogeneity in autism by creating a single diagnostic category, (b) but has excluded many individuals from diagnosis, and (c) still allows a wide range of heterogeneity. The third section, The extent of autism heterogeneity, that occurs along with DSM-5 ASD outlines current evidence for autism heterogeneity. The fourth section, Efforts to reduce autism heterogeneity, outlines current efforts to reduce autism heterogeneity. The fifth section, Finding transdiagnostic endophenotypes, explores possible constructs for transdiagnostic behavioral endophenotypes (a) from DSM-5 ASD and ADOS (18), (b) from theories of the causes for social impairment, and (c) from autism subgrouping. The sixth section, Pro tem sketch for a future transdiagnostic endophenotype symptom screening, proposes sets of autism symptoms and comorbid disorder symptoms that could provide a basis for items on a screening tool to discover transdiagnostic endophenotypes.

Transdiagnostic endophenotypes

Definitions of endophenotypes and transdiagnostic endophenotypes

An endophenotype aggregates a group of phenotypes of affected individuals, for which a specific behavioral trait, gene variant or biomarker exists with explanatory power across the affected individuals' diagnostic category. Endophenotypes were first defined as gene variants used to explore behavioral traits or biological markers, but endophenotypes now include using behavioral traits or biological markers to explore possible

links between other features of a disorder (19). An autism biomarker endophenotype, such as abnormal brain white matter (20), could be used to search for a narrowed set of gene variants, or narrowed set of symptoms and behaviors. And a behavioral endophenotype can also be used to index other behavioral endophenotypes. For example, The Autism Biomarkers Consortium for Clinical Trials (ABC-CT) is using a behavioral measure, Oculomotor Index of Gaze to Human Faces (OMI), to explore three attention behavior patterns: Activity Monitoring, Social Interactive, and Static Scenes (4).

Transdiagnostic endophenotypes are endophenotypes that explore behavioral traits, gene variants or biomarkers that cross diagnostic boundaries. For example, Rommelse et al. (17) argued for the use of autism gene variant endophenotypes that might link ASD with Attention Deficit Hyperactivity Disorder (ADHD).

Examples of transdiagnostic endophenotypes

The Research Domain Criteria (RDoC) project (1), initiated by the National Institute of Mental Health, is designed to find transdiagnostic pathophysiologies by means of functional behavioral constructs. RDoC is one of two large projects studying transdiagnostic behavioral endophenotypes in adult disorders, the other is the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project (20, 21). Both projects use transdiagnostic endophenotypes as devices for exploring the possible shared biological bases of psychiatric disorders and symptoms. Currently, the PRISM project is using the transdiagnostic behavioral endophenotype of social withdrawal as a means to explore brain regions that are impaired across psychiatric disorders.

The ESSENCE model, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (16), is a transdiagnostic umbrella that addresses the problem that many children with neurodevelopmental diagnoses such as ASD and ADHD have symptoms that cross diagnostic boundaries. Gillberg proposed "There is good evidence that ASD and ADHD can be separate and recognizable 'disorders', but, equally, there is mounting evidence that they often overlap, constitute amalgams of problems, and that in some families they separate together and probably represent different aspects of the same underlying disorder" (p. 1544).

Other diagnoses included under the ESSENCE umbrella include Specific Language Impairment, Oppositional Defiant Disorder, Developmental Coordination Disorder, Tic disorders including Tourette syndrome, Bipolar Disorder, behavioral phenotype syndromes, rare epilepsy syndromes, and Reactive Attachment Disorder. The main behaviors of these disorders are impaired motor skills, social interaction, speech and language, attention, sleep, activity levels, and general developmental delay. Gillberg (16) stated that "a reasonable estimate would be that about 5–7% of children under age 6 years would meet 'criteria' for ESSENCE (i.e., have clinical symptoms of a syndrome and have presented at a clinic with a view to diagnosis and intervention)" (p. 1545).

Endophenotypes and diagnostic categories

RDoC, PRISM, and ESSENCE preserve diagnostic boundaries while simultaneously searching for transdiagnostic endophenotypic commonalities across diagnoses. None of these three approaches is designed to form a new diagnosis from an endophenotype. Like RDoC, PRISM, and ESSENCE, the goal of the transdiagnostic endophenotypes proposed here is to discover groups with commonalities across autism and comorbid diagnoses. If, however, a transdiagnostic neurodevelopmental endophenotype of social impairment can identify a group of affected individuals who share a significant number of symptoms and causes, there may be meaningful transdiagnostic social impairment neurodevelopmental diagnostic groups.

The DSM-5 ASD

Unifying autism through the DSM-5 ASD diagnosis

Rosen et al. (22) claimed that prior to the DSM-5 ASD diagnosis, research was "a history of largely unsuccessful attempts to categorize the heterogeneity of autism into empirically-defined subcategories" (p. 13), and they argued that having just one DSM-5 autism diagnosis addressed heterogeneity by eliminating these subcategories. The researchers noted that the previous five diagnoses were abandoned because those five disorders [autistic disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), Rett's disorder, and childhood disintegrative disorder] did not have distinct symptom profiles and the five failed to be differentially predictive.

The DSM-5 ASD includes two core diagnostic symptom groups, social deficits and RRBs. These criteria are understood as dimensional, on a continuum of typical to atypical behaviors. These symptoms must be present in early development, and must cause significant impairment in current functioning. Moreover, and when symptoms of ASD and intellectual disability (ID) occur together, social communication should be below that expected for general developmental level. Within social deficits and RRBs there are three specified levels of support (requires support, requires substantial support, and requires

very substantial support). Also, in DSM-5 ASD, language is a separate non-diagnostic dimension, defined as a specifier. In DSM-5 ASD impaired conversation became a symptom of impaired social-emotional reciprocity within social deficits, and stereotyped language became a symptom within the RRBs. Vivanti and Messinger (23) asserted the dimensional model moved away from "grand theories focused on autism as a unitary and monolithic entity to the examination of specific phenomena and processes" (p. 13). Grzadzinski et al. (24) claimed that the dimensions approach would reduce heterogeneity by allowing "the identification of subgroups within ASD that will be important for understanding the biological mechanisms, clinical outcomes, and treatment responses" (p. 4).

Exclusion of individuals from a DSM-5 ASD diagnosis

Although Lai et al. (10) argued, "DSM-5 ASD criteria should be commended" (p. 3) for their effectiveness in diagnosing individuals, Kulage et al. (25) reviewed studies of the effect of DSM-5 criteria on autism diagnoses and reported that "More than half of the studies included in this systematic review and meta-analysis demonstrated ASD reduction rates between 25 and 68% when applying DSM-5 criteria" (p. 1930). Thus, there are now many who previously had an autism diagnosis but do not meet the DSM-5 ASD criteria, and therefore "have fallen outside of DSM-5 thresholds for receiving state-funded, school-supported, and/or insurance-covered services for their developmental, social, and communication deficiencies" (p. 1930).

DSM-5 ASD heterogeneity

Although DSM-5 ASD reduced the heterogeneity of five diagnostic categories to one, nonetheless the two DSM-5 ASD core diagnostic dimensions, social deficits and RRBs, allow for a wide range of diagnostic symptom patterns. Moreover, the DSM-5 criteria for ASD require the specification of whether ASD occurs with intellectual disability (ID), language impairment, other neurodevelopmental, mental, or behavioral disorder, or with a known medical or genetic condition or environmental factor. Although these specifiers exist outside the core diagnosis, the wide range of specifiers means that there will be heterogeneity in any ASD sample studied.

Wiggins et al. (7) found that one ASD heterogeneity factor—symptoms of dysregulation including anxiety, depression, aggression, and sleep problems—was responsible for 49–65% of the variance in an ASD sample. They also reported that expressive and receptive language skills were responsible for an additional 15–30% of the variance. The presence of sensory dysfunction was the only symptom that defined homogeneity for ASD, and they recommended that sensory dysfunction should be added as a core diagnostic symptom.

The extent of autism heterogeneity

Researchers have identified heterogeneity in many aspects of autism. Here are some recent studies that report heterogeneity.

Gene variant heterogeneity

A review of gene variants reported that autism has been found with multiple single nucleotide polymorphisms (SNPs) for all major synapse types, serotonergic, dopaminergic, GABAergic, and glutamatergic, as well as with many copy number variants (CNVs)–deletions or duplications of DNA (26).

Comorbidity heterogeneity

McCormick et al. reviewed comorbidities in autism and noted that 47% of those with autism had another neurodevelopmental disorder, 44% had a psychiatric disorder, 43% had a neurological condition, and 93% had a medical condition that was not neurological or psychiatric (27).

Biomarker heterogeneity

Girault et al. (28) noted that there are many varied forms of brain disorder in autism. These include aberrant white matter integrity, aberrant connectivity, altered morphology of the corpus callosum, increased extra-axial CSF volumes, cortical surface area hyperexpansion, and greater total cerebral volume. However, Martinez-Murcia et al. found no difference between neuroimages of individuals with autism and typically developing controls (29). Although many autism biomarkers have been identified (30), no autism-specific set of biomarkers has been found (31). However, The European Autism Interventions - A Multicentre Study for Developing New Medications is currently searching for a comprehensive set of significant biomarkers (32).

Subgroup heterogeneity

Many subgroups of autism have been proposed (5–8, 16, 17, 24). A wide range of subgroups was discovered in thirty studies from the Autism Phenome Project (33). Across the thirty studies they identified nine endophenotypic subgroups of autism: (a) disproportionate megalocephaly; (b) external hydrocephalus; (c) distress at noise with good cognition; (d) mothers with maternal IgG autoantibodies that bind to fetal brain tissue; (e) significant

GI problems; (f) anxiety disorders; (g) IQ variation across development; (h) high levels of atypical sensory behavior; and, (i) higher IQ females with decreasing autism symptoms over time (33).

Increased heterogeneity generated by increasing prevalence

Changes over time in the autism diagnostic criteria and autism research findings have resulted in an ever-increasing autism prevalence. This increasing prevalence has added to autism heterogeneity. In 1967, Wing et al. reported a U.K regional prevalence of core autism as 2.1 in 10,000 or 0.00021% (34). The U.S. prevalence was recently reported to be 1.85% (35), and a 2022 study of data from the National Health Interview Survey (36) reported that the prevalence of ASD was 2.79% in 2019, 3.49% in 2020 and 3.14% for both years combined. A 2022 U.S. survey found a 2.6% prevalence rate among Spanish-speaking families (37). Saito et al. reported a prevalence of 3.22% for Japan (38), and Schendel et al. reported that a lifetime incidence of autism in a Danish cohort ranged from 3.52 to 4.28% (39). By contrast, schizophrenia prevalence was 0.33% before 1990, and 0.51% after 2013 (40). Thus, the prevalence of schizophrenia was 2,429 times that of autism before 1970, and currently the prevalence of schizophrenia is between one-third and one-sixth that of autism.

Heterogeneity of the wide range of ASD high and low symptom severity

The severity of autism impairment has changed significantly over time. Wing et al.'s (34) autism criteria combined low functioning which was significant intellectual disability with the absence of speech, along with high functioning which was islands of normal intelligence. Currently, the DSM-5 ASD diagnosis includes severity of symptoms ranging from needing complete support to needing very little or no support. For example, within the DSM-5 ASD diagnosis, there are very high functioning individuals identified as "on the autism spectrum" who can speak their minds and publish articles criticizing the DSM-5 for missing crucial subtypes and having criteria that are outdated (41). And Roman-Urrestarazou et al. (42) have proposed many with autism could be a socio-political force. They argued that "it's time for a change, and we should start by asking autistic people how they would like to be called and recognizing the long civil rights struggle that they have endured to be recognized and validated in their lived-in experience" (p. 634).

However, in contrast to very high functioning individuals with autism who can form a lobbying group, there is evidence for an increased number of low functioning individuals with autism. An analysis of change in impairment levels over time in 27,240 individuals in the Child and Adolescent Twin Study in Sweden found that level of autism impairment increased with consecutively later birth cohorts (43). The authors suggested that the autism diagnosis was expanding and raised doubt that a clinically relevant syndrome was formed by social communication deficits with RRBs.

Heterogeneity of life course in ASD

Tunç et al. (11) reported that "children with ASD have heterogeneous developmental trajectories" (p. 1236). Steinhausen et al. (44) conducted a meta-analysis of studies of ASD outcomes. They reported that "Across the various studies an estimated percentage of 19.7% demonstrated a good outcome, close to 31.1% had a fair outcome, whereas close to half (47.7%) of the participants had either a poor or even a very poor outcome in adulthood" (p. 450). Elias and Lord (45) studied four outcome groups, Retained ASD, Lost ASD, Never Had ASD and Gained ASD Diagnosis, and the researchers concluded that diagnoses of autism can shift across development.

Heterogeneity of treatments

A recent report outlined the current lack of effective drug treatment regimens for autism: "Dozens of clinical trials… have so far failed to identify any pharmacologic treatments for the core symptom domains of social deficits and restricted/repetitive behavior" (46). However, a new drug development platform, the Autism Spectrum POC (proof of concept) Initiative (ASPI) (47) is working to create effective treatment regimens. It remains a problem, though, that the ASPI project relies on biomarkers, because a set of significant biomarkers has not yet been established (30–32). And the effectiveness of behavioral interventions remains unclear. Sandbank et al. (48) and Bottema-Beutel et al. (49) reported that studies of behavioral interventions are not sufficiently well-designed, thus we do not yet know the effectiveness of autism behavioral interventions. Moreover, as noted in the Introduction, The Lancet Commission Report (13) asserted that varied behavioral treatments for the "heterogeneity of manifestations of autism" (p. 300) need to be discovered.

Efforts to reduce autism heterogeneity

In addition to establishing the DSM-5 ASD diagnosis as a means to reduce autism heterogeneity, other ways to reduce autism heterogeneity have been proposed, including the use of

more stringent clinical criteria; excluding moderate-to-severe autism symptoms; creating subgroups; and increasing study sample sizes.

Reducing heterogeneity by determining prototypical autism

Mottron proposed prototypical autism, a new diagnosis that would reduce ASD heterogeneity by requiring two clinicians to agree on a more circumscribed set of autism criteria (50). Mottron posited that in an autism sample homogeneous for comorbidity, language problems, intelligence, age and sex, prototypicality would be determined by two experts based on their clinical knowledge of autism, and their speed of clinical identification. One difficulty for this proposal is that DSM-5 ASD criteria have already significantly reduced the number of affected individuals being diagnosed with autism (25), and prototypical autism would further reduce the number of DSM-5 ASD diagnosed individuals.

Reducing heterogeneity by dividing levels of functioning

Wiggins et al. found that excluding moderate-to-severe autism symptoms reduced autism heterogeneity (7). Lord et al. created a new administrative classification, profound autism, to better provide care for the lowest functioning individuals (13). This, de facto, formed two categories: "autism-profound" defined by an IQ below 50 and an inability to use comprehensible sentences; and "autism-not profound".

Reducing heterogeneity by creating subgroups

As noted above, Grzadzinski et al. (24) claimed that forming subgroups would reduce heterogeneity, and Nordahl et al. outlined nine unique subgroups within autism (33). In addition, many different subgroups of autism have been proposed (51–54) to reduce heterogeneity by finding factors and clusters defining grouping symptoms.

Reducing heterogeneity by using larger samples

Many researchers have argued that very large sample sizes would reduce heterogeneity. Chen et al. claimed that mammoth data sets would resolve heterogeneity (55), and Vivanti and Messinger (23) argued that studying "vast quantities of behavior" (p. 4316) would explain autism phenotype heterogeneity.

Happé and Frith (56) optimistically predicted, "As sample sizes in autism genetic consortia rise, polygenic scores for autism may begin to explain a meaningful proportion of variance in autistic traits" (p. 224). There are polygenic risk scores for autism, however, as gene study sample size has increased, explaining autism variance has gotten more difficult and not less difficult, because larger samples have revealed more associations with ID, ADHD, anxiety disorders, schizophrenia, and other non-autism disorders and symptoms (57). Moreover, increasingly larger samples have led to the discovery of more CNVs and SNPs that converge on one autism behavior, and to the discovery of subsets of gene variants linked to subsets of autism behaviors (58). Overall, larger samples have increased genetic heterogeneity, and have identified many forms of syndromic autism, but have not untangled gene-behavior causal complexities in idiopathic autism as was predicted by Happé and Frith (56).

Lombardo et al. (59) asserted that, "Small samples cannot adequately cover heterogeneity in the autism population in a highly generalizable fashion, and hence there is a need for 'big data' when studying heterogeneity. Big data should be both broad and deep, to not only sample adequately across different strata from the population but also to examine how strata defined at one level may be relevant for explaining variability at other levels" (p. 1446–1447).

Summary of efforts to reduce heterogeneity

The efforts for reducing autism heterogeneity—creating prototypical autism, excluding moderate-to-severe autism symptoms, creating subgroups, and increasing sample sizes–have not yet been effective in reducing heterogeneity. Thus, heterogeneity remains an unresolved problem (2–17, 26–49). Moreover, as discussed previously, establishing the unitary DSM-5 ASD diagnosis has not reduced autism heterogeneity.

Finding transdiagnostic endophenotypes

There are two crucial steps for finding transdiagnostic endophenotypes. The first step is to relax DSM-5 ASD criteria in order to increase the range of phenotypes to include many individuals with subthreshold ASD. The second step is to find constructs for endophenotypes in DSM-5 ASD criteria, in theories of autism, and in autism subgroups.

Step one: Relaxing DSM-5 ASD criteria to create a large sample of phenotypes

Relaxing DSM-5 ASD criteria is the first step toward discovering transdiagnostic endophenotypes because having a large pool of phenotypes that includes those diagnosed with DSM-5 ASD, and those with autism symptoms who do not fully meet the criteria for ASD, provides the best chance for discovering transdiagnostic endophenotypes. For example, relaxing the DSM-5 ASD criteria will likely allow the inclusion of the 25–68% of affected individuals that Kulage et al. (25) found were excluded by the DSM-5 ASD criteria.

Relaxing the DSM-5 ASD criteria will also include affected individuals at the ASD fuzzy boundaries with comorbidities. Wiggins et al. (7) stated that "phenotypic diversity in preschool children with ASD symptoms extends beyond diagnostic boundaries" (p. 548), Tunç et al. (11) reported evidence for a fuzzy boundary between ASD and non-ASD that did not result from misdiagnosis, and Gillberg (16) noted that there are significant overlaps between autism and many other neurodevelopmental disorders. And as noted earlier, there is a very high level of comorbidities for autism: McCormick et al. reported (27) that in those diagnosed with DSM-5 ASD 47% had another neurodevelopmental disorder, 44% had a psychiatric disorder, 43% had a neurological condition, and 93% had a medical condition that was not neurological or psychiatric.

The existence of syndromic autism argues for relaxing the DSM-5 ASD criteria

Although research has found many forms of syndromic autism, Waye and Cheng pointed out that no treatments for syndromic autism have been discovered (60). Eighty-five percent of autism is idiopathic, i.e., of unknown cause, and 15% is syndromic autism, for which a cause has been identified. Syndromic autism includes Rett's disorder, tuberous sclerosis, Down syndrome, Fragile X syndrome (FXS), and congenital infections such as cytomegalovirus. Ziats et al. (61) conducted a comprehensive review of syndromic autism and found 180 autism syndromes. Of the 180 syndromes, 59 syndromes were unique to autism and included loci and chromosome duplication and deletion syndromes, six were chromosomal aneuploidy disorders, and 115 were single gene disorders. Notably, in only 17 of the 115 monogenic syndromes did most patients meet DSM autism criteria.

Because many with syndromic autism do not meet the full DSM-5 criteria, and because many with idiopathic autism have links to gene variants, if the DSM-5 criteria were relaxed, then it is likely that many partial idiopathic autism phenotypes would be found. As noted above, this would be of significant value, because having more phenotypes would improve the chance to discover transdiagnostic endophenotypes.

Co-occurring autism with ID argues for relaxing autism criteria

ID is variably expressed with autism symptoms. Approximately forty percent of those with autism are non-verbal, and roughly thirty percent of those who can be tested have IQs below 70. Nordahl et al. (33) reported three patterns of ID in autism: a large majority with persistent ID; a minority with no ID; and some with ID improving to the normal range by age 6–7.

Thurm et al. claimed autism and ID are two distinct disorders (62). However, ID is most likely to be evidence of additional symptoms in individuals with autism, and not evidence of an additional comorbid disorder. As Carpenter pointed out, diagnostic divisions are unlikely to divide causes for symptoms (63). ID and autism are unlikely to be separate comorbid disorders, (a) because many of those with syndromic autism express both ID and autism symptoms, and (b) because a large subset of those with idiopathic DSM-5 ASD are diagnosed with ID, and (c) because many ID and autism symptoms overlap.

Thurm et al. argued that it is crucial to determine whether autism or ID is more prominent in an individual. They asserted that "Whereas ID is associated with general deficits across developmental domains, ASD is in fact defined by the observation that social communication deficits *are particularly impairing*" (p. 2). However, ID and autism are not effectively divided by "particularly impairing" social communication because the DSM diagnosis allows for high functioning individuals who hold jobs and write articles and do not have "particularly impairing" social communication deficits (41, 42).

Because ID and autism symptoms occur together, DSM-5 criteria should be relaxed to include individuals who do not meet all DSM-5 criteria, and who may also be diagnosed with ID, ADHD, anxiety disorder, and other disorders. Opening the diagnosis will enrich the number of phenotypes, and thus will provide a greater chance for discovering possible transdiagnostic behavioral endophenotypes.

Step two: Searching DSM-5 ASD criteria, autism theories and autism subgroups for possible endophenotype constructs

Step two is to search three likely sources for symptom constructs for endophenotypes. The first source is the DSM-5 ASD criteria and the social impairment symptom groups found in diagnostic assessments. The rationale for searching here is that these diagnostic symptoms have documented significant differences between autism and typical development, and these diagnostic symptoms include symptoms that are found in other neurodevelopmental disorders. The second source is the causal autism symptoms proposed in theories of social impairment in autism. The rationale for searching here is that theories

propose specific mechanisms that might be the source of social impairment. The third source is the symptoms found in ASD subgrouping studies. The rationale for searching here is that subgrouping studies employ factor analysis and cluster analysis to discover symptoms identified in significant subgroups.

The first sources for possible transdiagnostic constructs are DSM-5 ASD and ADOS symptoms

DSM-5 ASD social impairment symptoms

Because social impairment has been the core autism symptom from past to present, social impairment constructs may be a good place to start the search for possible endophenotypes in autism. DSM-5 social impairment criteria describe both (a) the inability to engage socially, and (b) socially engaged behavior that is impaired. Inability to engage includes making little or inconsistent eye contact; appearing not to look at or listen to people who are talking; and trouble in responding to one's name or to other verbal bids for attention.

Impaired social engagement behaviors include: infrequently sharing interests, emotion, or enjoyment of objects or activities; having difficulties with the back and forth of conversation; often talking at length about a favorite subject without noticing that others are not interested or without giving others a chance to respond; displaying facial expressions, movements, and gestures that do not match what is being said; having an unusual tone of voice that may sound sing-song or flat and robot-like; having trouble understanding another person's point of view or being unable to predict or understand other people's actions; difficulties adjusting behaviors to social situations; and, difficulties sharing in imaginative play.

The simple division of autism diagnostic social impairments into two constructs, *inability to engage socially*, and *impaired socially engaged behavior*, may serve as endophenotypes.

ADOS social impairment symptoms

A study of ADOS (18, 64) social impairment items by Bishop et al. (65) discovered two subgroups: (1) basic social communication, which included eye contact, facial expression, gesture, and shared enjoyment; and (2) interaction quality, which included the amount of reciprocal social communication, conversation, and overall quality of rapport. Scores for interaction quality, but not for basic social communication, were linked to non-verbal IQ and to being male. The researchers' goal was to predict an autism diagnosis. They found that the basic social communication subgroup and RRB symptoms contributed to the prediction of an autism diagnosis, but the interaction quality subgroup did not.

Bishop et al. claimed that the basic social communication subgroup could be caused by other dysfunctions, such as hyperactivity or ID. However, as was discussed above, only if autism and ID were distinct unitary disorders with clear boundaries could ID be claimed to be the cause of autism symptoms. In fact, ID and autism are better understood as two symptom sets that occur together most often linked by gene variants, therefore it is unlikely that they are two separate disorders, one of which causes the other. Bishop et al. claimed that if ID caused basic social communication impairments, then these impairments would be poorer predictors of an autism diagnosis. Of course, the goal of transdiagnostic endophenotypes is not to predict an ASD diagnosis, nonetheless, from the Bishop et al. subgroups, *impaired social engagement*, and *poor interaction quality*, might be possible constructs.

The second source for possible transdiagnostic constructs is theories of the cause of ASD social impairment

Three influential theories of the cause of social impairment are unlikely to be a sound basis for the discovery of constructs for endophenotypes: (1) weak central coherence, (2) impaired Theory of Mind (ToM), and (3) impaired executive function. Bottema-Beutel et al. (66) conducted a meta-analysis of these three theories thought to index eight social skills: imitations; responding to and initiating joint attention; pretend play; executive functions; ToM; central coherence; and visual fixation to social stimuli. The three theorized models—central coherence, ToM, executive function—accounted for just a tiny amount of variance in the eight social skills. And notably, ToM explained just 4.5% of the variance in social functioning overall. The researchers (66) concluded that accepting and employing these three theories "may have led to false conclusions about the nature of ASD, the nature of social functioning more generally, and the intervention strategies that should be implemented to support individuals with ASD" (p. 164).

Similarly, the broken mirror neuron theory of autism social deficits is unlikely to be a sound source of transdiagnostic symptoms (67, 68). Heyes and Catmur (67) presented evidence that the mirror theory of social behavior has not been explanatory. And Hamilton's review of mirror system research (68) led him to conclude that here was "little evidence for a global dysfunction of the mirror system in autism" (p. 91).

In 1967 Wing et al. theorized that the core dysfunction of autism was "a lack of response to others" (34), and in 2012 Chevalier et al. proposed that the lack of social motivation to interact with others was the core dysfunction of autism (69). They argued that early childhood impairments in social attention result in poor learning of social interaction behaviors, which in turn impairs social cognitive development. Their rationale was that humans have psychological dispositions and biological mechanisms that bias them "to preferentially orient to the social world (social orienting), to seek and take pleasure in social interactions (social reward), and to work to foster and maintain social bonds (social maintaining)" (p. 231). Chevalier et al. proposed that individuals with autism lack social

motivation because they are not rewarded by orienting to others or maintaining social interaction as a result of disruptions of the orbitofrontal–striatal–amygdala circuitry. The Chevalier theory suggests that *impaired social motivation* could be a basis for an endophenotype.

Hornix et al. theorized that social behavior is crucially dependent on sensory processing and multisensory cue integration of the myriad social cues exhibited by others (70). Hornix et al. proposed that autism social withdrawal was a direct result of impaired sensory processing of social cues and impaired multisensory cue integration because without sensory processing and integration, social information cannot be comprehended. In addition, McCarty and Brumback (71) found evidence that repetitive movements or stereotypies are a byproduct of the brain's attempt to use rhythmic motor commands to regulate impaired sensory processing. They argued that the brain generates compensatory motor signals to entrain abnormal rhythms in the sensory system. They theorized that compensatory motor commands cause the repeated hand movements or body movements identified as stereotypies. The researchers also proposed that attention to mechanical rhythms in the environment, such as spinning fans, could entrain the brain's dysfunctional sensory processing. If so, stereotypies may be a motor byproduct of the brain's attempt to correct sensory dysfunction. *Sensory dysfunction* could be a basis for an endophenotype.

There are many theories of oxytocin abnormalities as a cause of autism symptoms. Grattrocki and Friston (72) proposed that "a dysfunction in the oxytocin system, early in life, could account for the development of autism" (p. 411). They argued that an aberrant oxytocin system led to problems in an awareness of self and impairment in attention to social features in the behavior of others. From their model, it is possible that *impaired social attention* might be an endophenotype construct.

The PRISM project theorized that social withdrawal is a feature of many psychiatric diagnoses (21). The rationale for the PRISM project using social withdrawal as a transdiagnostic endophenotype is the evidence that social withdrawal is the product of three distinct brain networks that are theorized to govern social behavior. The first network governs social stimuli detection and processing. The second network governs social affiliation and social aversion. The third network governs social imitation and mentalizing. Because evidence indicates that social withdrawal results from all three networks (21), the PRISM project argues that therefore social withdrawal should be a central transdiagnostic endophenotype used in the discovery of possible shared pathophysiologies across many psychiatric diagnoses. The PRISM project evidence suggests that *social withdrawal* could be an important construct for a transdiagnostic endophenotype that may link autism with other neurodevelopmental disorders.

The third source for possible transdiagnostic constructs is autism subgrouping studies

van Rentergem et al. (73) reviewed an exhaustive set of subgrouping studies and concluded, "there is too little evidence that the observed subtypes are valid and reliable" (p. 9). The researchers argued that future subgrouping studies must pre-register hypotheses, use follow-up data to validate subgroups, and document data that falsifies or confirms subgroup validity. However, despite these meta-analysis findings, existing subgroups may nonetheless offer clues about possible endophenotypes.

Rosello et al. reviewed several subgroup studies and reported three general subgroups: (1) severe expression of all autism diagnostic symptoms; (2) moderate social impairment with few RRBs; and (3) a low level of social impairment with a high level of RRBs (51). The three levels of social impairment—severe, moderate, low—may reflect an underlying continuous distribution of social impairment. If so, the three levels of social impairment are unlikely to generate distinctive investigatory constructs of social impairment.

Sacco et al. analyzed autism symptoms, family characteristics, and biological endophenotypes, and identified four clusters (52). The clusters were: (1) circadian and sensory dysfunctions with immune abnormalities and minimal developmental delay; (2) circadian and sensory dysfunctions without immune abnormalities; (3) stereotypies; and (4) immune abnormalities, circadian and sensory dysfunctions, disruptive behaviors, and ID. Inspection of Sacco et al.'s four clusters suggests that *sensory dysfunction* may be a possible construct for a transdiagnostic endophenotype.

As described earlier, nine autism subgroups, based on neural, biological, and clinical characteristics and developmental trajectories, were discovered by The Autism Phenome Project (33). Of these nine, only two subgroups included autism symptoms: individuals with high levels of sensory dysfunction; and females with higher IQs whose autism symptoms decreased over time. The subgroup of females may identify a variant neurodevelopmental disorder, but *sensory dysfunction* is a possible endophenotype. The Autism Phenome Project's sensory dysfunction subgroup is strengthened as a possible construct candidate because three of Sacco et al.'s four subgroups included sensory dysfunction.

Harris et al. discovered three classes of social communication symptoms and two classes of RRB symptoms in a large sample of toddlers (53). The five classes shared missing or inconsistent social communication and RRBs. Kim et al. also conducted a cluster analysis of behaviors in a sample of toddlers (54). Their first two clusters were defined by significantly delayed verbal skills, and their third and fourth clusters included more severe social impairment than the first two. However, there were many commonalities across Kim et al.'s four groups: all four had consistent levels of non-verbal

communication and daily living skills. Although clusters of symptoms in these two groups of toddlers identified nine possible groups, the nine clusters share overlapping symptoms such that they don't provide a clear basis for finding constructs. However, because all of Harris and colleagues' five classes shared missing social communication, consequently *missing social communication* may be a productive construct for the discovery of a transdiagnostic endophenotype.

Summary of candidates for endophenotypes

Examining DSM-5 ASD criteria and ADOS items suggested four possible endophenotype constructs: *inability to engage socially*; *impaired socially engaged behavior*; *impaired social engagement*; and *poor interaction quality*. These can be combined to yield two constructs: *inability to engage socially*; and *poor interaction quality*. Examining theories of social impairment in autism suggested four possible endophenotype constructs: *impaired social motivation; sensory dysfunction; impaired social attention;* and *social withdrawal.* And examining autism subgrouping studies suggested two possible endophenotype constructs: *sensory dysfunc*tion and *lack of social communication*.

Combining possible constructs from all three sources yields six social impairment constructs: *sensory dysfunction*; *impaired social motivation*; *impaired social attention*; *social withdrawal*; *lack of social communication*; and *poor interaction quality*. These six constructs have been determined by inspecting diagnostic criteria, causal theories, and the products of subtyping. An analytic approach to these same sources will likely discover different constructs. However, these six constructs are a reasonable place to start.

Pro tem sketch for a future transdiagnostic endophenotype symptom screening

The search for transdiagnostic behavioral endophenotypes requires the documentation of transdiagnostic symptoms, and thus any screening tool must include a wide range of behaviors in children referred for autism and for a range of neurodevelopmental disorders.

Six construct groups for a future transdiagnostic screening tool are sketched here. One might include *sensory dysfunction*; *impaired social motivation*; and *impaired social attention*. A second construct group might include *social withdrawal* and *lack of social communication*. And a third construct might be *poor interaction quality*. A fourth group of symptoms might include ID behaviors, a fifth might include ADHD behaviors, and a sixth might include symptoms of anxiety.

Of course, as noted, these six groups are just a pro tem sketch. Only an analysis of the relationships between transdiagnostic symptoms can determine whether there are construct groups, and what they may include. Below are some possible specific symptoms that might be included in the sketched construct groups.

The first construct group might include measures of sensory dysfunction, impaired social motivation, and impaired social attention

Possible measures for this construct group might include lack of eye contact, total lack of facial expressions, failure to express affect, and inattention to others. Other possible measures might include overly focused interest in moving objects or parts of objects, becoming upset by slight changes in a routine and having difficulty with transitions. Additional measure might include being more sensitive or less sensitive than other people to sensory input, such as light, sound, clothing, or temperature.

The second construct group might include measures of social withdrawal and lack of social communication

Possible measures might include lack of non-verbal communication, failed joint attention, and failure to initiate or respond to social interactions.

The third construct group might include measures of poor interaction quality

Measures of poor interaction quality might include infrequent sharing of interests, talking at length about a favorite subject without noticing others, expressing incongruous emotional displays, speaking in an odd tone, and having trouble understanding another person's point of view.

The fourth construct group might include measures of adaptive behaviors that include items indexing cognitive functioning

Jonkers et al. tested his measure Adaptive Ability Performance Test (ADAPT) and found it to be a valid instrument for assessing difficulties in adaptive skills (74). The researchers reported that adaptive behaviors could be divided into three domains: conceptual, social, and practical. Specific

items included brushing teeth; washing hands; maintaining relationships; taking the initiative to talk; thinking before acting; learning from mistakes; and the ability to stop an action if necessary. A wide array of behavior problems can also be indexed by the Child Behavior Checklist (CBCL), a questionnaire to assess behavioral and emotional problems (75). There are seven scales of symptoms for young children: emotional reactivity; anxious/depressed; somatic complaints; withdrawal; sleep problems; attention problems; and aggressive behavior. The CBCL was tested as a measure of autism (76) and it was discovered that "children with ASD had significantly higher scores than controls… (on) all syndrome scales" (p. 6).

The fifth construct group might include measures of ADHD behaviors

Llanes et al. identified the symptoms that predict an ADHD diagnosis (77). These include the inability to concentrate, sit still, finish a project, pay attention, follow directions, and be quiet. The Connors Parents Rating Scale-Revised (78) is another source of ADHD symptoms including items such as needs supervision to get through assignments, is easily distracted, has difficulty in engaging in tasks, and is restless.

The sixth construct group might include measures of anxiety

Muris et al. described types of anxiety in children: separation anxiety disorder; selective mutism; social anxiety disorder; panic disorder; generalized anxiety disorder; agoraphobia; and phobias (79). Muris et al. provided examples of items; I am afraid my parents will leave and never come back, I am so shy I don't speak at all, I find it scary to be with people I don't know, I feel panic, and I worry a lot, and I fear going out of my home.

Summary of transdiagnostic symptom items

A screening tool is necessary to capture the possible neurodevelopmental symptoms that might contribute to transdiagnostic behavioral endophenotypes. Building a future transdiagnostic screening tool will require research to examine the effectiveness of the sets of symptoms. The constructs and items outlined here are a pro tem sketch of a future screening tool that must include a wide range of behaviors in children referred for autism and for a range of neurodevelopmental disorders. Six possible sets of symptoms were proposed: (1) sensory dysfunction; impaired social motivation; and impaired social attention; (2) social withdrawal and lack of social communication; (3) poor interaction quality; (4) impaired adaptive behaviors that also index cognitive impairment; (5) ADHD behaviors, and (6) symptoms of anxiety.

Conclusion

DSM-5-TR will be released 72 years after DSM-1, during which time many diagnoses have come and gone. NIMH director Gordon offered the optimistic opinion that today's DSM-5 ASD studies were like May flowers (80). And he predicted there would be a "Summertime" of autism research 20 years from now, when autism heterogeneity then would have been thoroughly explained (80). Less optimistically, Miller proposed scrapping the DSM and replacing it with a diagnostic manual that simply documents complexity (81). But because the heterogeneity of autism symptoms and causes and comorbidities reflects a very complex web of relationships, it might be that only advanced artificial intelligence (82, 83) will be able to discover clearly defined significant subgroups with explanatory power for the creation of effective drug regimens and effective behavioral treatments.

DSM-5 ASD criteria are a paradigm. Researchers have adhered to this paradigm in building a body of knowledge about autism as a unitary entity. Although previous DSM autism criteria did not define just one autism diagnosis (22), the paradigm of autism as a single clinical entity now governs autism research. Despite existing heterogeneity, the DSM5 ASD diagnosis and autism diagnostic assessments such as the ADOS both assume that autism is a single disorder.

The most important problem for the DSM-5 ASD paradigm is that autism heterogeneity has impaired the explanatory power of the diagnosis (5, 6, 13, 15, 46–49). Wolfers et al. (15) stated that "it has not been possible to predict ASD to a degree that translated to clinical practice" (p. 25). Validated behavioral treatments have not yet been established (48, 49), and effective drug regimens have not been discovered (46, 47). Although the errant paradigm of an Earth-centered universe was maintained for 2,000 years, most paradigms are abandoned when there is evidence that the paradigm's explanatory power has failed. Clearly, it is crucial to abandon paradigms that fail to advance science and fail to improve public health. Believing in a fixed set of species blocked the discovery of evolution and consequently genetics. Maintaining belief in a failed paradigm has even cost lives. Many lives were lost through infections during the 90 years it took for all physicians to accept Semmelweis's paradigm of sepsis—that sepsis was caused by "ichor" (wound discharge) on unwashed physicians' hands (84).

Unfortunately, belief in autism as a single entity *has* caused harm (85). Drug regimens designed for autism as a single entity have yet to be discovered, and the effectiveness of behavioral treatments for all with ASD is uncertain. Importantly, in large part because there are no sufficiently effective treatments for

autism as a whole, bogus "drug" regimens, dubious behavioral treatments, and unfounded beliefs have caused harm. In particular, the belief that vaccines cause autism has led to illness and even death (86).

Many researchers now begin their research papers by stating that autism is many disorders. However, their papers then go on to present research based on the paradigm of autism as a unitary disorder (10, 11). This is a common "straddle position" in the process of shifting to a new paradigm (autism is many disorders) from an old paradigm (autism is one disorder). For example, Casanova et al. (8) described autism as a group of complex conditions, but defined autism as one disorder with wide boundaries. Lai et al. (10) began their paper by stating that "Autism is a set of heterogeneous neurodevelopmental conditions" (p. 896). However, in all the sections of their paper the authors discuss autism as a unitary entity (10), making claims such as that autism has a high heritability, that the brain bases of autism have been found at the neuroanatomical level, and that more males are diagnosed with autism than females. If autism is a set of heterogeneous neurodevelopmental conditions, these varied conditions cannot have one high heritability or one neuroanatomical brain dysfunction.

This paper has proposed that autism heterogeneity stands against the paradigm that autism is a single unitary clinical entity. Although DSM-5 ASD has been shown to differ from typical development, DSM-5 ASD remains a theoretical paradigm that has not been tested as a whole (87). Transdiagnostic behavioral endophenotypes may or may not form groups with more explanatory power than the single autism diagnosis. But only when researchers test the unitary autism paradigm as an unproven theory, may new paradigms with more explanatory power be found.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Developmental diversity: Putting the development back into research about developmental conditions

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The dominant discourse surrounding neurodevelopmental conditions such as autism and ADHD emphasizes biological explanations. Neurodevelopmental conditions are conceived as different types of brains, the result of different types of genes. This way of thinking is present both in medical research and in clinical practice. Indeed, it is widely acknowledged that the idea of having a biological diagnosis helps people see beyond blame and guilt. It aids acceptance. However, simplistic approaches to biology risks neglecting the experiences and stories of autistic people in favor of finding etiological causes. At the same time, there is growing awareness that risks, functioning, and resilience are not solely defined by genes and brains but have a cultural and experiential component as well. Furthermore, atypical cognitive trajectories are not straightforwardly associated with poor outcomes. In this paper we describe the concept of developmental diversity as an alternative to more categorical approaches to neurodevelopmental conditions. We explore how dynamic models of life offer possibilities to look at neurodevelopmental conditions differently: rather than seeing autistic people as people with fundamental flaws in their genes or software faults in their brains that have to be explained, autism appears as a phenomenon that exists in interaction with the context, as a meaningful reaction to the environment. We explore what it would mean for research to go from a diagnosis-based approach to a developmental diversity approach that will define wellbeing and functioning in a more granular way across developmental trajectories. We argue that this would mean incorporating lived experiences into biological research and going beyond genes-environment dichotomies. Next to yielding a more complete picture on the phenomenon of autism, we describe how an approach that takes developmental diversity as a starting point offers a new way to look at existing challenges of autism research, such as how to deal with the significant overlap between diagnosis. Our hypothesis is that thinking with developmental diversity rather than categorical difference both represents an opportunity for a more inclusive society, and fundamentally can alter the way we perform research. As such, it is in line with requests of neurodiversity and disability movements.

KEYWORDS

autism, ethics, development, diversity, humanities and social science, neurodiversity

Introduction: Autism and biology

The dominant discourse surrounding neurodevelopmental disabilities, such as autism and ADHD, emphasizes straightforward biological explanations. Neurodevelopmental disabilities are conceived as different types of brains resulting from different genes. In the case of autism, often, explanatory models are presented as composed of different layers, influencing each other downstream. In autism research, clinical practice and the general public, it is accepted that genes cause brain differences, which cause different modes of cognitive functioning. Such cognitive functioning is then reflected in behavior, which in its turn forms the basis of formal diagnosis, done through behavioral assessment and assessment of functioning (1). At the same time, autism is considered heterogeneous, meaning different people can exhibit other behaviors more or less (2).[1] This heterogeneity is not only present at the level of the behavior but also at the level of the genes (3). Nevertheless, after decades of genetic research on autism, the one conclusion that researchers have drawn is that the idea of a "gene for autism" should be given up. Many different genes seem to play a role, and the genes associated with autism are also associated with other conditions such as ADHD—as the adage goes: genes do not think in DSM terms (4).[2] At the same time, *heterogeneity* suggests that there is at least a factor that binds different manifestations together.

There have been various explanatory models for autistic behavior (7, 8). For example, some older models, such as deficit in Theory of Mind, focused on the social and communicative atypicalities in the behavior of autistic people. These models explained autism primarily as a social deficit (9). Other models focus on differences in information processing, such as the Enhanced Perceptual Functioning hypothesis or the High Inflexible Precision of Prediction Errors (HIPPEA) hypothesis (10, 11), or increased sensory perception (12). These explanatory models are not easily reduced to one another: it is one thing to say that specific autistic behavior that some would call "socially awkward" is due to a lack of social insight or of "theory of mind," and it is another thing to state that it is due to the effort it takes for autistic people to deal with incoming sensory and informational stimuli. There is also a fundamental difference between claiming, for instance, that autistic people have atypical eye contact because they do not understand that the eyes are mirrors of the soul or do not understand that other people have such things as minds and saying that autistic people have atypical eye contact because other people's gaze is too intense, borderline insupportable (13). As we have argued elsewhere, the explanatory model one chooses is not without its therapeutic and normative consequences (1, 14, 15). If one thinks autism is due to a deficit of social cognition, therapy will focus on teaching social skills and scripts rather than avoiding too intense stimuli. For research as well, this has far-reaching implications, as one's idea about autism will guide the choice of experiments and brain regions to investigate.

Nevertheless, despite this heterogeneity, these genetic and cognitive explanatory models of autism suggest that autism is a relatively stable given (2, 16). The idea that there is a stable core to autism is not only present in research. Also in clinical contexts, it is often assumed that we can delineate and define autism and that it has an essence that we can pin down. The underlying idea is that it may be so that we do not wholly understand what autism is at the moment, but we do know that it has a biological underpinning that can be discovered. This assumption has, of course, several implications. First, it is widely acknowledged that the idea of having a precise biological diagnosis helps people see beyond blame and guilt (17): it aids acceptance and offers parents of autistic children and autistic people themselves a handhold, a name with which to identify (18). However, the role that this aspect of biological certainty plays in (self-)acceptance and the factual lack of that biological certainty puts clinicians and diagnosticians in a dilemma (19–21). For instance, in informal conversations with the authors of this paper, they often acknowledge that little is known about the autistic brain or the brain in general. Still, they admit that presenting autism as a different kind of brain, with scientific and biological certainty, is helpful for people in diagnostic processes.

This sentiment (the idea of using the narrative of a different kind of brain, biological certainty and cause clarity) keeps explanatory research into the causes of autism very much alive. Clinicians still often express their hope for biomarkers that would help diagnose autism with biological certainty. They feel that this would give some confidence and some gist to what is now a diagnosis based on behavior. Also, autistic people themselves often welcome this certainty (18). As such, a *raison-d-être* is provided to the search for (somewhat reductionist) biological explanations for autism (20, 22). At the same time, we may wonder what biology's unique role is in providing such certainty.

Approaches to autism that start from a reductionist view on biology, for example, because they claim that autism is straightforwardly caused by "genes" or is a "differently wired

1 On the basis of interviews with scientists, Hollin connects the heterogeneity of autism to uncertainty and states that we need to reflect more on the concept of uncertainty in autism research as uncertainty can mean many things, e.g., epistemic uncertainty and ontological uncertainty (2).

2 The DSM is the Diagnostic and Statistical Manual of Mental Disorders which provides the standard language by which clinicians, public health officials and researchers in the United States and most European countries as well communicate about mental disorders. The current edition is the fifth edition (DSM-5) and was published in 2013 (5). There are of course also other classification systems, like the one of the World Health Organization (WHO), which is the International Classification of Diseases (ICD) (6).

brain" risk neglecting, among others, the experiences and stories of autistic people in favor of finding etiological causes. It also does not sufficiently engage with the neurodiversity-affirmative paradigm—which is increasingly acknowledged as relevant for autism research (23–25). We, therefore, assert that the idea that "genes cause behaviour" is naive at best and dangerous at worst. In line with that, we notice a growing awareness that risks, functioning, and resilience are not solely defined by genes and brains but are situated and thus have a cultural and experiential component (26, 27). Furthermore, atypical cognitive trajectories are not straightforwardly associated with poor outcomes in terms of wellbeing (28, 29). Integrating this knowledge and insights into new research and the autism discourse is essential (30). Nevertheless, we do not suggest that biological approaches to autism are wrong *per se* or that research into the biological underpinnings of autism is not interesting anymore. Instead, we are critical of reductionist approaches to biology. We want to point out that research incorporating systemic approaches (also called integrative approaches) to biology, and thus incorporating culture, experience, dynamics and development, will benefit autistic people, their kin and autism science in general. *In this article, we suggest that developmental diversity as the starting point for research, rather than categorical diagnosis, helps conceptualize what such research might entail.* We proceed as follows: we will first describe the concept of neurodiversity and its relation to developmental diversity, stressing that neither term aims to romanticize autism or minimize challenges that people with diagnoses may encounter. We then situate the concept of development in philosophy and the history of science and autism. We end with giving some suggestions as to what a developmental diversity approach in autism research could entail.

Developmental diversity and neurodiversity

Developmental diversity is, of course, not a new term. Like the term "neurodiversity," it is sometimes used in project proposals and the clinic as an alternative to "developmental disorder." Both terms, then, convey that autism and other developmental conditions (e.g., ADHD, Tourette, …) should not be seen as a "disorder" or a "disease" but rather as a human difference. The central premise of both terms is that diversity in development and functioning across humans is "a natural and valuable part of human variation" (31). However, it must be said that while developmental diversity and neurodiversity are complementary, they are not synonyms. It is essential to focus first on what *neurodiversity and neurodiversity-affirmative autism research* mean to understand what we put forward with the notion *of developmental diversity*.

Neurodiversity has its value as a political term referring to justice in the context of developmental disabilities. When we engage with the history of the neurodiversity movement, we notice that in the early 1990s, neurodiversity was primarily connected to identity politics. The notion emerged mainly in English-speaking online communities of autistic individuals and pointed out that autism is not something to be cured but is a natural part of diversity across humans. This acknowledgment does not imply that autism is not understood as a *disability*. Indeed, within the neurodiversity movement, autism is conceptualized using the social model of disability (32). This means that disability is conceptualized as resulting from a poor fit between a given individual's (physical, cognitive or emotional) characteristics and the characteristics of their social context. A disability is not simply a defect in the individual. It arises from the interaction between a person and an unaccommodating environment (23, 31). Even for those with the highest support needs, disability can often be minimized or avoided through environmental change and the provision of appropriate assistive tools. For instance, providing a non-speaking or minimal-verbal autistic person with an alternative method of communication may give them a voice (33), but, as den Houting states: "they will only truly stop being disabled when others listen" (23).

So, drawing on the social model of disability, neurodiversity was thus initially mainly deployed as a socio-political identity in line with other minority groups. According to this perspective, autistic people could (perhaps for the first time) be proud of their autism and claim political rights to promote social participation. But as with any social justice movement, this neurodiversity movement is not without its critiques (23). For instance, some stakeholders—mainly parents of autistic children with substantial intellectual, language and behavioral challenges—argue (d) that the neurodiversity movement (primarily consisting of verbal autistic adults without these challenges) does not represent their children's experience and that their children require interventions to achieve a reasonable quality of life (25, 31, 34). Although this is quite a challenging disagreement that needs more participatory action-research[3], it is essential to emphasize that the neurodiversity movement is not categorically opposed to support or intervention, as we will explain in more depth below.

Over the years, neurodiversity as a movement became supplemented by neurodiversity as a *standpoint*, indicating a critical attitude toward the frameworks on which our

3 In general more participatory action-research with adults and children with substantial intellectual, language and behavioral challenges is needed. As Tesfaye et al. and Van Goidsenhoven et al. rightly point out, this group is often neglected in research—also in more traditional autism research (35, 36). It can be argued that we need to be much more invested and creative in exploring the experiences of this group of people (and thus also collect data about their temporality and dynamics of experience). Research that does this, is mostly qualitative oriented and integrates arts-based research methods (33, 37, 38).

thinking and value systems are founded (24, 39, 40). Related, neurodiversity has also been conceptualized as a *new paradigm*, one that challenges the dominant paradigm that considers autism and other neurotypes as problems to be cured or solved (41). As a *standpoint*, neurodiversity deconstructs the neurotypical as a norm; it points out that also the dominant frames of thought and value systems are not self-evident or natural but have gained authority through particular contexts. This deconstruction and critical attitude is much needed because research and practice have been failing autistic people of all kinds for decades, promoting models that stigmatize more than they support (25). Moreover, all of this happened mainly without the input of any autistic people at all (42). So, taking a neurodiversity stance means a shift in focus from pathology toward neurodivergent wellbeing and lived experiences, as well as the inclusion and leadership of autistic people. A neurodivergent standpoint challenges the imaginary ideal of a cognitively "normal" subject and dominant notions of being human. It will also foreground complexity and ambiguity and multiple ways of being literate or social rather than working with clear structural barriers of normality that exclude people, as much is lost in reduction. As Erin Manning, a philosopher working on neurodiversity, argues: "Ambiguity is actually something to be embraced rather than to be avoided. It is an inevitable feature of human discourse" (43). It may be evident by this that a neurodiversity standpoint is not a synonym for an "autistic perspective," just as neurotypical does not simply stand for "non-autistic." Instead, the neurotypical standpoint stands for the dominant and, at the same time, invisible, so-called "neutral" stance that determines how we view concepts such as normality, knowledge, communication, a good life, etc. For example, a neurotypical view highly values rational learning, cognition, and independence. In this view, Intuition, dependence, and loving care are mostly not seen as full-fledged sources of knowledge (44). A neurodiversity standpoint instead raises critical questions about this. It deconstructs a society based on mental/neurological normality and autonomy and seeks to appreciate complex forms of dependency and otherness. It questions who determines what knowledge is and how it is valued—it stresses that science is never value-free (45).

Acknowledging the importance of including many different voices and appreciating different ways of being human does not mean that a neurodiversity stance opposes clinical support or intervention. Nor does it want to deprioritize medical research, block clinical care or neglect the difficulties an autistic person can experience.[4] Quite the contrary: neurodiversity stresses the equal value of every human being, promotes autistic rights (and these rights can include intervention and support whenever needed), de-stigmatizes autism and creates space for epistemic justice in conceptualizing health, disability and what it means to be human (46, 47).

The growth of the neurodiversity stance has brought about new ethical, theoretical, and political debates within autism theory, research and practice during the last 5 years. Some argue that autism research is structurally changing from "normal science" to participatory neurodiversity-affirmative autism science (31, 48, 49). Thus, autism research is gradually embracing the *neurodiversity paradigm*. It may be tempting to think that the shift from pathology to neurodivergent wellbeing and lived experiences mainly impacts autism research focused on adults.[5] However, more recently, there is increasingly more research into the implications of a neurodiversity-affirmative framework for early detection, interventions and therapy (31, 34, 50, 51). Of course, as Sue Fletcher-Watson points out, neurodiversity-affirmative early interventions research for children (with and without more profound intellectual, language and behavioral challenges) has several implications:

> *As researchers and practitioners, we need to be prepared to throw away the text book on what we think we know about early development. This includes radically re-thinking our language. I've used terms "intervention" and "outcome" here on purpose in order to highlight the contradictions, but increasingly I am learning to think about this topic in terms of support, growth and wellbeing. We must ask ourselves, what are the truly important outcomes and reasonable routes to those outcomes? And in doing so we need to incorporate diverse perspectives from the autism community (34).*

Leadbitter et al. reflect upon this in their study on neurodiversity-affirmative early intervention:

> *Whilst diversity brings fundamental collective advantages, within any one neurodivergent individual weaknesses are often the inextricable partner of strengths, and that individuals can want things to be different and still want to be themselves. It includes the understanding that some neurological differences are disadvantageous, either inherently or in interaction with the environment, and could benefit from correspondingly targeted intervention (31).*

4 For a clear introduction on how the neurodiversity movement is often misunderstood and how this paradigm is certainly welcoming (neurodiversity-affirmative) therapy, intervention, and support see: den Houting (23).

5 Examples of this impact are pointed out by Leadbitter et al. (31) and include: (a) debates over whether the social difficulties experienced by autistic people are best understood as being a problem within the individual, or a problem between two (mis-matched) individuals, and the resulting research into the Double Empathy Problem and diversity in social intelligence. (b) On improving mental health and quality of life in autistic individuals and an increase in research into effective, person-centered mental health interventions. (c) Research into community preferences over the language used to describe autism and autistic people.

In other words, when scientists challenge normative thinking about (early) development and when early interventions aim to provide opportunities for physical, sensory and emotional regulation, they can be compatible with the neurodiversity stance.

Important in the context of this article is also the connection of neurodiversity with biology. As the neurodiversity standpoint is not opposed to clinical intervention and support, it is not opposed to biological research about developmental conditions either. However, it does react against biological essentialism and the comparatively individualistic, fitness-based evolutionary model. Often neurodiversity scholars such as Robert Chapman assume an ecological model influenced by how ecologists talk about functioning (24). Chapman describes how ecologists are less interested in ranking individual fitness levels. They investigate how broader systems function as a whole, how functions emerge from relations between organisms, and how the dominance of some forms of organisms can be harmful to the functioning of others (24, 47, 52).[6]

Neurodiversity-affirmative autism research and clinical practice is the right way toward ethical and just research and practice. We argue that all autism research and intervention stakeholders must actively form partnerships with autistic people and engage with and understand neurodiversity as a concept, standpoint and movement. In so doing, we move away from both a deficit and individualist model and the idea that "normality" is what we should aim for. Such an approach implies reframing effectiveness, paying attention to environmental goodness-of-fit, developing tools to measure autistic prioritized outcomes, internal drivers and experiences, and focusing on autistic prioritized intervention targets (31). In this way, autistic developmental trajectories are taken seriously. Here neurodiversity connects with developmental diversity. Neurodiversity is *why* and *how* developmental diversity should be studied. Developmental diversity, as the object of neurodevelopmental research, embraces the neurodiversity idea *that developmental differences are always to be understood in relation to context and specific moments in time and beyond categorical boundaries*. To truly grasp a phenomenon such as autism, it is hence not only essential to explain it by referring to biological underpinnings. Such explaining can only ever be truthful if it is inspired by an understanding of what certain behaviors and experiences actually mean for a person. Before discussing how such research could be done, we will first try to understand what "development" means.

6 Drawing on both theoretical and empirical research, Chapman (24) argues hat the ecological model has greater utility for research and practice than the leading and dominant psychiatric functional analysis of mental functioning. The ecological model, however, is not used as a rival to evolutional models *per se*: Chapman's ecological model is focused on understanding human mental functioning only, and not for understanding biological functioning.

Dynamics and development: Systems biology and its conundrums

In the DSM-5, some explanation is given as to why conditions such as autism, ADHD and Tourette's are called *neurodevelopmental*. Unlike other diagnoses that are defined in the DSM, which often occur in or after adolescence, neurodevelopmental conditions are those conditions that start at an early point in life (5). It is deliberately left vague what this early period is and whether or when it ends, develops or changes. Moreover, not much is said about the causes of such developmental disorders. It is not because the first symptoms of autism occur during the first years of childhood that autism is caused by something that happened during those first years. The conceptualization of autism as a developmental disorder is also reflected in the diagnostic criteria of autism itself. Besides the wellknown behavioral criteria, the DSM-5 states that "Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life)" (5). Hence, people may be diagnosed later in life, but there must be proof that symptoms were already there in early childhood, although they may not have led to dysfunction. This requirement seeks to distinguish so-called "real autism" from, for example, conditions that may be associated with the same symptoms but that may result from trauma or other events that happened later in development (53, 54). Indeed, given the history of autism and the harmful "mother blaming" discourse of the second half of the twentieth century, much is at stake when we think about the origins of autism, and the suggestion that autism might be caused by psychosocial deprivation is contentious. For example, there seems to be a tendency to distinguish between "true autism" and "quasi-autism." The first one, "true autism," would then be the kind with which one is born as it is genetic (and so, for which no one is to blame). At the same time, "quasi-autism" refers to young children who show autistic-like patterns but where it is assumed that some adverse experience causes the behavior. Hence, the cause of their quasi-autism is supposedly genetic, but rather psychological deprivation as they, for instance, were reared in profoundly depriving institutions, such as some Romanian orphanages in the 1970 and 80s (53).

As stated above, "developmental," when referring to developmental disorders as defined in the DSM-5, refers to the manifestation of the behavior in the early years. It is assumed that autism is present from birth as a genetic variant that starts manifesting in the period of life where the behavior at stake becomes relevant. By equating development thus with the period of manifestation, a static concept of autism as an innate neuroatypicality is safeguarded. However, development also implies dynamics: an unfolding of form in reaction to internal genetic "programming," life events and environment. In what follows, we will first sketch a general discussion of development from a philosophy and history of science perspective. Secondly,

we will show that the tension between static, dynamic and developmental views on autism has existed from the beginning. Finally, we will state that this tension is also visible in the characteristics of current-day autism research, which often centers around genes, early detection and early intervention.

Development from a philosophy and history of science perspective

When diving into the discussions surrounding development from a philosophy and history of science perspective, we notice that the concept of "development" ties in with centuries-old discussions about the origins of forms (55). It is related to the debate on epigenesis vs. preformation. Epigenesis, in this sense, is a view of the development of organisms and is contrasted with preformation. A preformationist theory assumes that an organism's eventual form is already there from conception onwards. Think about the seventeenth-century idea of the homunculus. After discovering gametes, some researchers then assumed that the sperm cell would contain a "little man," which would merely become enlarged during development.

It has been suggested that the idea that what organisms will become is more or less fixed in the combination of genes acquired upon the fusion of the sperm and the genes can be characterized as somewhat preformationist. In the mid-twentieth century, Conrad Waddington introduced the idea of the epigenetic landscape (56). Waddington used the image of the landscape with valleys and hills to describe the development of a phenotype. Every cell has the same nuclear DNA, but they develop into specific types of cells depending on the place in the organism. Waddington describes two crucial concepts: plasticity and canalization. Plasticity is the ability of a given genotype to give rise to different types of cells in response to environmental circumstances, such as the place in the organism (56–59). Canalization is the adjustment of the developmental pathways to bring about a uniform developmental result despite genetic and environmental variations. For Waddington, it is not the genes that influence the landscape but a network of genes. Because of the canalization, a minor rearrangement will not significantly affect the cells' trajectories. However, if the landscape is wholly rearranged because of changes in the underlying network of genes or environmental changes, this will severely impact development. It is important to note that canalization and plasticity are not each other's opposites. They imply each other. Canalized development requires some plasticity to adapt to different circumstances (60).

Furthermore, adapting to different circumstances implies stability to withstand total annihilation. Indeed, stability requires dynamics to keep systems stable. Recently, Developmental Systems thinkers, inspired by Waddington and others, have challenged the predominance of the gene in thinking about organisms (61, 62). They do not want to deny the relative importance of genes in development, nor are they environmentalists in that they shift the balance toward the environment. Instead, they argue against a dualistic interpretation of causes as either genes or environment. Genes and many other factors play a role in life, and myriad interactions and interplays are ongoing throughout the life cycle. Hence, in this respect, development is not solely about what happens in the first few years. It occurs throughout a lifetime, interacting with what organisms encounter along the way. As such, understanding life means understanding the many different paths that life takes based on the obstacles and changes it faces. It is never solely about understanding the genetic code. In this article, we advocate this sense of development as the ongoing action and reaction of organisms during their life.

Static, dynamic, and developmental views with Kanner and Asperger

The concept of development and genes also play a role in autism's history—a history that is wellknown and amply documented (63, 64). Leo Kanner, a psychiatrist of Austrian descent, is the person most associated with establishing the concept of autism. He founded the department of child psychiatry at the John Hopkins Hospital in Baltimore in the 1930s. In 1943, he wrote the seminal text "Autistic Disturbances of Affective Contact" (65, 66). Readers of this paper are advised to read this original text if they have not done so already. It is often assumed that the children Kanner described all exhibited features of what we would now call "Kanner's" autism, unlike the children his German counterpart, Hans Asperger, described. Nevertheless, the text describes various children, all with their own challenges and personalities. In the text, Kanner suggests that autistic children, unlike children with childhood schizophrenia, do not withdraw from the world but are born with the condition (1). He also describes how the children gradually come out of their shelves toward the world: "our children gradually compromise by extending cautious feelers into a world in which they have been total strangers from the beginning" (1, 66). In later texts, he describes the adults some of the children have become: how many of them had gradually acquired social skills and how many had succeeded in finishing their education and establishing a place in society (67). So, these texts show that, although Kanner stressed that autism is innate, it is not a static, unchanging given. Kanner firmly describes autism as a developmental phenomenon: not solely because its symptoms become apparent in the first developmental years but also because its manifestation changes throughout the life course. This approach contrasts with de descriptions of Hans Asperger, the German pediatrician. He gave his name to the wellknown Asperger syndrome, which

was until recently considered a subtype of autism. It is often thought that Leo Kanner described more pronounced cases of autism, whereas Hans Asperger focused on autistic children without intellectual disability, what he called "little professors."[7] However, even in his seminal text "Die 'Autistische Psychopathen' im Kindesalter," not all children are intellectually gifted, and it contains descriptions of children with various behaviors (70). We believe the major differences between the two texts do not lie in the kind of behaviors children exhibit but rather in how the authors appreciate autism. As stated before, Kanner, a child psychiatrist, stressed the innateness of autism but also as developmental, dynamic, and adaptive to circumstances. After all, Leo Kanner wanted to jumpstart the field of child psychiatry in the United States. Such a description would probably serve better for that aim than a description that suggests autism is a static psychopathology. Asperger, however, saw autism as a personality disorder, a more static trait of one's personality that one is born with and with which one dies. We argue that the ideas that these archfathers of autism had about its nature reflect the different appreciations of autism today. On the one hand, autism is a developmental condition, of which the course is not fixed, and on the other hand autism is an innate neurological "difference" with strengths and weaknesses.

Static, dynamic, and developmental views today

The term developmental in developmental disorder can have different meanings. For instance, development in the context of *developmental disorder* can refer to the idea that the symptoms of a disorder are present early in life, in what is considered the developmental period. As such, the term developmental disorder is compatible with a view that sees autism as primarily static, genetic and innate. However, in biology and philosophy, development instead emphasizes dynamics (61, 62). For instance, a developmental theory of life stresses that what an organism is and how it functions is not only the result of genetic makeup or influences *in utero* or very early in life. From birth to death, organisms are in development: they maintain themselves and adapt in response to the specific contexts (physical, psychological, social, and cultural) they find themselves in. In this view, behavior is not solely the result of one's genetic programming but a meaningful response to what happens around us. This ties in with recent findings regarding systems biology and developmental systems thinking (58, 71). In thinking about organisms, genes have been losing their prime position as the final explanation of behavior and form. Such approaches also imply that looking at individual cases and situated experiences next to statistical tendencies in development is crucial. Systems biology seems to tell us that if we want to understand life, we need to understand both specific lives and life in general. We will come back to that later on.

Although systems biology approaches are gradually finding their way into autism research (3), and epigenetic effects and other omics studies become increasingly prevalent (72), most autism research can still be subdivided into two strands. A first strand of autism research is the already mentioned fundamental genetic, neurological and psychological research into the "causes" of autism. We have discussed the reasons and implications of the search for autism explanations above. The rationale of this kind of research mainly ties in with the view of autism as innate, fixed, and related to how our genes and brains work, although, as we also already stated, most researchers acknowledge that the reality of autism's biology is much more complex (20, 21). A second strand of autism research is research into early detection and intervention (73). This strand is not wholly separate from the search for causal explanations in the sense that there lingers hope that finding suitable biomarkers will aid the discovery of autism even before autistic behavior is present in young children (74). This is thought to have several benefits: parents will be more prepared to tackle specific challenges their child may face and understand their child better. It is also often claimed that early detection will enable early intervention. The idea that autism can be "prevented" through early intervention is heavily contested, as autistic people have asserted their rights to exist as autistic people (50, 75).

Hence, researchers into early intervention must balance a tight rope of advocating benefits for autistic people early on but not claiming that what they are targeting is autism traits. The assumption behind early intervention is that there is a critical developmental period in which brains are still flexible enough to be influenced, as neuronal plasticity is greatly enhanced in that period (76). We do not want to question the idea that brain plasticity is highest during the earliest developmental period, and we do not challenge the importance of proper care during this period. Nevertheless, we want to suggest a more encompassing view of "development." Indeed, current biological knowledge demonstrates that development is *ongoing throughout life* (77–79). This means that early childhood experiences, although relevant and crucial, do not necessarily set a person's further life course in stone. Speaking with the words of neuroscientist Francisco Varela, quoting a verse by the poet Antonio Machado, life is "laying down a path in walking" (80). The path does not stop after the first 3 years. Indeed, we believe that dynamic models of life and mind offer possibilities to look at neurodevelopmental conditions differently. Rather than seeing autistic people as people with fundamental flaws in their genes or software deficiencies in their brains that have to be explained in reductionist terms, autism appears as a phenomenon that

7 During the last two decades, several studies appeared with interesting analyses of how such metaphors as "little professors" in medical texts has influenced (and still influences) autism representations in popular culture and discourse (68, 69).

exists in interaction with the context, as a meaningful reaction to the environment. Taking a developmental diversity approach in research will give credit to this reality.

Whereto, autism research?

What does it mean to study developmental diversity rather than "autism"? What would taking a developmental diversity approach to research into childhood disability mean? We acknowledge that researchers already accept that studying such a diverse collection of experiences and biologies covered by the term "autism" is nearly impossible. It has been suggested that approaches such as the Research Domain Criteria may help look at autism and its causes more granularly (81). Moreover, the WHO's ICF framework has been used to develop core sets for autism that allow studying autism beyond the medical model in terms of functioning (82). A developmental diversity approach could integrate these approaches and take a step further by incorporating methods and insights from the humanities.

First, we argue that research, when taking a developmental approach, could take temporality into account, as it is crucial to incorporate dynamics and changes. The notion of "crip time" from Disability Studies can function as a way of thinking about such dynamics (83). Second, we highlight the importance of incorporating experience and understanding in studying developmental diversity. Therefore, such research is equally sensitive to general tendencies and quantitative measures of individual experiences and qualitative information. Third, we argue that a developmental diversity approach does not stop at disciplinary or diagnostic boundaries. It involves engaging with people from different neurotypes as co-creators of the research and encouraging fruitful collaboration between different disciplines, from genetics to psychology to the humanities and philosophy.

The role of longitudinal research and appreciating temporality

Appreciating development, as described above, as the lifelong dynamics of organisms interacting with the environment, has implications for autism research. For one, it may mean that research should put less emphasis on searching for explanations ("the hunt for genes") and more on investigating systemic biological and psychological processes and how they change or remain the same throughout a lifetime. With this, we do not want to suggest that research into genes is worthless. It could be the starting point for a more systemic approach that looks at organisms and people as the complex systems they are (84). Granted, many autism researchers we have spoken to already dream of such research and acknowledge the importance of longitudinal research to study the interaction between genes and environment and the factors that can help increase quality of life. At the same time, the way research practices are set up nowadays makes such longitudinal research almost impossible. In the timeframe of a typical 4-year research project, finding a genetic variant associated with a specific family may be possible, and this is a good outcome for a PhD. However, it is nearly impossible to investigate what this variant means at different stages in life and how it interacts with other factors if there is no guaranteed long-term funding. Moreover, many topical funding calls still use categorical diagnostic categories, forcing researchers to formulate their research plan in terms of these categories, as if they were fixed and stable entities to be grasped. Systemic and developmental approaches to autism research require systemic changes to research funding.

At the same time, we believe that when studying the diverse paths that development can take, an appreciation of diversity is also essential. It would be tempting to revert to research about "normal" vs. "abnormal" development. However, in our view, a developmental diversity approach challenges the concept of normal development. Researchers of developmental diversity could be inspired by the concept of "crip time," a term from disability studies. We will briefly elaborate on the concept as Alison Kafer and others conceived it (83).

Disability, as Alison Kafer demonstrates, is very often described in relation to time (i.e., prognosis, developmental disorder, chronic, childhood disability, medical history, etc.). These temporal framings are animated by a "curative imaginary," leading Kafer to the concept of "curative time." Curative time is a way to conceive disability in relation to normative temporalities (i.e., a linear understanding of a "future perfect," "a developmental correctness," and "the window of opportunity"). This curative imaginary is omnipresent in clinical programs in early childhood (83). Detecting early autism characteristics comes down to noticing whether the child develops the right skills at the right moment in time, compared to the "normal" temporal schedule of development. Early interventions are acclaimed to offer better odds of living well in the future when provided at the right time during the right window of opportunity. Most autism researchers know that the ambition to "cure" autism is long past its expiration date.

Nevertheless, it is still a challenge in the early intervention literature, if not impossible, to imagine a flourishing future for autistic children, at least not without deploying clinical interventions and without straightening the developmental path (50, 85). The idea is that an autism developmental path without interventions is a path no one wants. Kafer's aim is to challenge this, as the futures we envisage can reveal the biases of the present. Kafer, therefore, disrupts the linear, progressive, modernist, directional, getting better marking of time and development. For this purpose, Kafer conceptualized the idea of "crip futurities." Crip futures incorporate multiple, shifting, affective understandings of temporality that make space for, imagine and enact futures that include the bodyminds

left out of normative renderings of personhood and futurity (28). Research could, for instance, speculate with parents and healthcare professionals on an autistic child's future beyond curative imaginary (33).[8] It implies that studying developmental diversity is also studying neurodivergent flourishing and investigating which environment can enable that flourishing.

The role of experience

A developmental perspective on life implies that the study of said life should pay equal importance to general statistical and quantitative tendencies as to individual trajectories and experiences. General trends are not more scientific than research into specific cases. They both shed a different light on reality. However, until recently, quantitive and generalizable abstract data were considered far more scientific and even "real" than cases. However, given the partial open-endedness of development, from a developmental perspective, specific cases and life trajectories yield equally exciting and essential information. The study of such life trajectories should include the study of experiences (such as narratives and other creative forms of expressing experiences) in biological research and extend beyond genes-environment dichotomies. In our view, autistic behavior has substance; it is not the result of an infection or mutated genes but a *meaningful response to context and biology* (16). To understand this meaningful response, biological research needs to be complemented by how specific behavior is related to a particular experience of the world; explaining and understanding must go together (15, 50, 86).

Such an approach allows us to build another bridge between the life sciences and the humanities. After all, there is already a pile of humanities research that argues in favor of looking at autism more ambiguously and incorporating experience stories (2, 18, 87–90). Autistic experiences change throughout one's life and what autism means has to be actively integrated into one's own multi-facet story repeatedly. In our research, we have experienced that a purely explanatory approach to autistic people does no justice to the experiences of these people in interaction with their environment.

A developmental diversity approach is neurodiversity-affirmative research and thus can also pay much more attention to the autistic experience by acknowledging the heterogeneity and indeterminacy inherent in developmental conditions such as autism. This indeterminacy, moreover, has two forms (2). On the one hand, there is interpersonal indeterminacy which means that there are fundamental differences among autistic people. On the other hand, there is intra-personal indeterminacy which means that even for the person facing a number of challenges at some point in their lives, it makes no sense to view these challenges as only the results of genes. Those challenges always depend on the specific context and previous experiences of the particular person (2). Consequently, autism may have different meanings depending on the life stage and context of the individual. Hence, understanding lived experiences is also indispensable.

For instance, in their phenomenological research on the experiences of adults who got their autism diagnosis later in life, Hens and Langenberg focused on how a formal clinical diagnosis changed autistic people's relationships with others and themselves. Some participants recognized themselves immediately in their diagnosis, while others needed more time to explore what the diagnosis could mean and do for them. For instance, Karel, 55 years and diagnosed when he was 40, said the following:

> *It offers an insight that can inspire, that can help you reorient yourself. But you still have to make it your own so that you can build it into your own actions. For example, now I can accept that I may sometimes go into too much detail. But that is again simplifying it. A diagnosis offers focal points, which you can research. How does this fit into my own pattern of actions? It is an extra critical factor that can be confronting or can offer peace of mind and a way to think about it. That was not explained to me when I received my diagnosis because the world of diagnoses is hyper flat (70).*

This and other conversations with and stories from autistic adults exemplify that (however much they have experienced problems and have felt different from others) their experiences cannot be easily be categorized or pinned down. Instead, we notice how a, perhaps neurological, vulnerability can lead to dysfunction at a certain point in life and, at the same time, how people have dealt with such vulnerability in their interactions with others throughout their lives. Probably, there is a certain predisposition—genetic or congenital—to atypical cognitive or social development that is not always "translated" into dysfunction. Moreover, it is particularly enlightening to notice how these people have dealt with their challenges before and after their diagnosis and how they learn from this. This suggests that an approach and research that focuses exclusively on problems, difficulties and causes in the individual (as embedded in the dominant autism discourse) is problematic and often beside the point. Research methodologically oriented toward lived experiences and how people interpret and narrate their own experiences allows for assessing the suitability of specific explanatory models. Moreover, we believe it is of utmost importance that research participants are not only enrolled as subjects whose experiences can be queried and investigated. Instead, people from different neurotypes should be actively engaged in co-creating relevant and meaningful research. Ensuring an ethical scientific and clinical practice entails including

8 Leni Van Goidsenhoven and Elisabeth De Schauwer did this kind of research in co-creation with a non-verbal young woman (33).

the viewpoints and explicitly paying attention to those who have held marginalized positions in healthcare. If we want to understand what health and pathology mean for different people, this means engaging honestly with those who have been ignored.

Crossing disciplinary and diagnostic boundaries

A substantial number of people diagnosed with autism have additional diagnoses such as ADHD, dyslexia, dyspraxia or intellectual disability. In some cases, autism is associated with a specific syndrome, such as Fragile X (91). Like the concept of development itself, the concept of comorbidity is equally hard to grasp. Does it mean that a specific neurodivergent person, who has a diagnosis of autism and ADHD, has two separate conditions that happen to occur in the same person? Is Fragile X the cause of autism? Or is the concurrence of, for example, autism and dyslexia a symptom of an underlying neurotype that can explain both, such as enhanced perceptual functioning? As present-day research often starts from diagnostic categories, it is unlikely to shed light on this matter (92). However, genetic research has indeed suggested that there is more overlap between the different categories than a categorical approach would suggest. An approach that would embrace the idea of developmental diversity could shed some valuable light on such comorbidities. We believe that such an approach could be most successful if development is studied as such, without starting from categories and including children and people who may not receive a diagnosis but may be diverse in their own ways.

Besides transcending diagnostic categories, research that wants to study life in all its diversity and that appreciates individual experiences as of utmost importance to understanding life presupposes an interdisciplinary approach. Such an approach includes vital input from social sciences, humanities and arts-based research and foregrounds complexity, ambiguity, and multiple socialities as the baseline of (autism) research. Indeed, we believe there is no need for a hierarchy between the exact sciences and the humanities regarding understanding development. Scholars in the humanities can join research consortia, not to serve exact scientists to write the informed consent forms for them but to provide a different kind of insight into studying the phenomenon at hand. It is equally important to include neurodivergent researchers in the research projects. In the words of Jorn Bettin:

> *"Neurodiversity friendly forms of collaboration hold the potential to transform pathologically competitive and toxic teams and cultures into highly collaborative teams and larger cultural units that work together more like an organism rather than like a group of fighters in an arena" (93).*

Finally, we also want to mention *neurodiversity studies* here, a new field of inquiry that aims to find new ways to support including neurodivergent perspectives in knowledge production. It questions the theoretical assumptions surrounding idea of the neurotypical (39). It analyses the role of neuronormativity in theory and science and aims to contribute to redefining what it means to be human (39, 94–97). We believe that any autism or developmental disability project should engage with fields such as neurodiversity studies or disability studies.

Some afterthoughts

In this paper, we have proposed developmental diversity as a concept that can function as a framework for neurodiversity sensitive approach. We have explored what a research practice that starts from developmental diversity could entail. We hypothesize that thinking with developmental diversity rather than categorical difference represents an opportunity for a more inclusive society and fundamentally can alter how we perform research. As such, it is in line with requests of neurodiversity and disability movements. Such an approach appreciates the temporalities and dynamics of experience and focuses on flourishing for all types of people. We did not give specific suggestions on how such an approach could be implemented in terms of methodological tools. As philosophers and humanities scholars, we do not have the expertise to suggest the variables sensitive to the dynamics of experience and temporality that should be included in the databases or what kind of statistics that could be used to include individual experiences. We hope people more knowledgeable in experimental psychology will take up the challenge. We also acknowledge that, at the moment, our proposed research may seem utopian. For one, although almost all autism researchers we speak with are sympathetic to such an approach and appreciate the need for longitudinal research into flourishing and away from diagnosis-based approaches, it remains the case that existing resources such as databases often are still based on such diagnostic categories. Moreover, funders often focus on specific categories as well, and particularly autism as a category is a phenomenon that seems to be of great interest to funding agencies.

Furthermore, it is often helpful for people to think about themselves in terms of autism, ADHD, or another neurodivergent identity. However, our suggestion is not to abandon these identities or to suggest that they are not real or mere constructs. They denote real experiences and are a valuable means of communication with those with similar experiences. At the same time, studying developmental diversity

and flourishing over a lifetime of many neurotypes may very well be an approach that is acceptable to the neurodivergent community. Whether that will be the case remains to be seen. Research practices and ideas about development may not change over time and will require a gradual shift in research discourse. With this paper, we hope to have contributed our drop in the ocean to enable such a shift.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Autism under the umbrella of ESSENCE

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This brief article gives a short overview of "comorbidity" in autism. The most common co-occurring disorders will be presented and discussed within the context of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations), a concept that provides a holistic perspective for neurodevelopmental disorders. The ESSENCE concept also considers the heterogeneous and changing clinical panorama of developmental disorders over time, and also the multifactorial etiologies, including so called behavioral phenotype syndromes. Aspects on behavioral interventions in autism are presented—interventions that need to be adapted and take into account all non-autism associated ESSENCE, including intellectual disability and Attention-Deficit/Hyperactivity Disorder (ADHD). The article also focuses on current research on pharmacological intervention based on the hypothesis of imbalance in excitatory/inhibitory transmitter systems in autism and some other ESSENCE.

KEYWORDS

autism spectrum disorder, comorbidity, early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE), attention-deficit/hyperactivity disorder, intellectual disability, etiology, intervention

Introduction

Neurodevelopmental disorders (NDDs) (1, 2) is a broad term encompassing several early onset disorders with origin in the central nervous system (CNS), usually with a chronic course, and with impairments generally lasting into adulthood.

NDDs can be classified according to the *main neurological/psychiatric/behavioral functions* affected, such as motor disorders [cerebral palsy, developmental coordination disorder (DCD)], cognitive, executive function, and communication disorders [intellectual disability (ID), autism spectrum disorder (ASD), henceforth referred to as "autism", attention-deficit/hyperactivity disorder (ADHD), and language disorder (LD)], and paroxysmal disorders (for example epilepsy).

They can also be grouped with regard to their *definite or assumed period of origin*, i.e., prenatal (before birth), perinatal (from birth to the completion of the first week or the 28th day of life) or postnatal (the period from birth up to the age of 1 year, or sometimes 2 years of age). Among the perinatally acquired disorders, two main groups encompass conditions in children born extremely preterm and in children born at term suffering hypoxic-ischaemic encephalopathy.

Yet another classification can be based on *specific identified etiologies*, including genetic/chromosomal abnormalities, a number of neurometabolic disorders, and acquired prenatal conditions, such as fetal alcohol spectrum disorder (FASD), and fetal valproate syndrome. Additional possible classifications include those based on *presumed affected brain areas,* and *types of neural networks/circuits/transmitter system aberrations in the CNS.*

Neurodevelopmental disorders

Although, the term "neurodevelopmental disorders" has a long history, it had not been included in previous editions of either the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) (3).

According to the ICD-11 (2), NDDs are grouped within the section: "Mental, behavioral and neurodevelopmental disorders". "Neurodevelopmental disorders" include (i) disorders of intellectual development, (ii) developmental speech or language disorders, (iii) autism, (iv) developmental learning disorders, (v) developmental motor coordination disorder, (vi) ADHD, (vii) stereotyped movement disorder, and (viii) a category labeled "other neurodevelopmental disorders".

NDDs according to the DSM-5 (1) include the main categories (i) Intellectual disabilities, (ii) Communication disorders, (iii) Autism spectrum disorder, (iv) Attention-deficit/hyperactivity disorder, (v) Specific learning disorder, (vi) Motor disorders and (vii) Other neurodevelopmental disorders; with defined subcategories.

ESSENCE

The term ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations, was coined by Gillberg (4). ESSENCE captures the early manifestations of NDDs that sometimes are unspecific, affecting motor, cognitive, communicative and social development, as well as sleep, feeding and temperament/behavioral regulation. The ESSENCE concept also emphasizes the very high rate of "comorbidities" and the changing presentations during early childhood and adolescence. The concept highlights signs of unspecific developmental deviations or delays, e.g., regarding speech and language and motor development. The importance of clinical follow-up to evaluate outcome and provide best-evidenced interventions is also underscored.

The ESSENCE concept includes the temporal and dynamic changes of developmental symptoms; early unspecific symptoms may become more evident and chiseled-out during the preschool and school years and later accord with a certain developmental diagnosis, a "named disorder". ESSENCE underscores that a first recognized symptom or identified disorder need to be followed over time in a holistic perspective, taking into account all possible developmental/behavioral problems, and not over-focusing on one specific disorder only. With an "ESSENCE perspective in mind" the risk of diagnostic overshadowing, i.e., overlooking co-occurring problems in a child with e.g., autism or ADHD is minimized.

The ESSENCE concept highlights the variety of etiologies and emphasizes e.g., that the so called behavioral phenotype syndromes (BPS), very often present with neurodevelopmental/ESSENCE symptoms rather than as a physical phenotype/known genetic/medical syndrome. A common clinical scenario is a child later presenting a clear clinical picture of autism, or intellectual disability or ADHD (or combinations of these) with a first symptom/diagnosis being speech- and language delay or LD.

The ESSENCE umbrella also covers the many neurodevelopmental/neuropsychiatric symptoms/disorders that accompany traditionally defined neurological diagnoses, including epilepsy and cerebral palsy (see below).

Language disorder, autism and ESSENCE

A common first symptom or problem in young children, later diagnosed with a specific disorder within ESSENCE, is speech and language delay. The prevalence of language delay at the Child Health Center (CHC) screening at 2.5 years is about 10% and the prevalence of a diagnosed LD in Sweden is around 6% (5).

In a study by Miniscalco et al. (6), children who had screened positive for speech and language problems at age 30 months at their CHC were followed up and examined at age 6 and 7 years. The study revealed that children in the general population who screen positive for speech and language problems before age 3 years are at very high risk of autism or ADHD, or both, at 7 years of age. Remaining language problems at age 6 years strongly predicted the presence of neuropsychiatric or neurodevelopmental disorders at age 7 years.

Over the past 20 years, there has been increasing awareness of speech and language delay as a marker of many other NDDs/ESSENCE, e.g., ID, ADHD and autism. In a multidisciplinary study, investigating children attending preschool units—specifically aimed for children with language impairments, without any other diagnosed developmental disorders before referral—revealed that about 90% had additional developmental disorders (7). A follow-up of these children 10 years later showed that a large number had persistent language problems and/or met criteria for other NDDs or had subthreshold diagnostic symptoms; mild intellectual disability, borderline intellectual functioning, autism or "autistic traits", ADHD or subthreshold ADHD and a large number had dyslexia (8).

In another follow-up study with the aim of analyzing the further development of children, 5 years after they had screened positive for LD and/or autism at 2.5 years, clinical registers covering all relevant outpatient clinics, were reviewed with regard to registered ICD-diagnoses. The study revealed that 40% of the cohort had remaining or other developmental problems at this follow-up. It was discussed that this rate most likely was a minimum frequency and that it was expected that more children would be referred for developmental problems later on (9).

Obviously, language delays/disorders in young children are often markers for other, later diagnosed NDDs, including ID, autism and ADHD; hence, teams responsible for assessments of children with language problems need to have a broad ESSENCE approach in order to provide best possible assessment and recommendation for interventions.

The ESSENCE panorama extends beyond early childhood. Children with LD will very likely experience difficulties in learning to read, and poor language may be a common risk factor for both reading disorder and mathematics disorder (10). Schoolchildren with autism may also exhibit comprehension difficulties and problems to

access and select meanings of ambiguous words which compromise their language comprehension (11).

Autism, ADHD, ID, other neurodevelopmental and psychiatric comorbidities and ESSENCE

Comorbidities are extremely common in children with autism at all levels of intellectual functioning and language delay and language disorder are common predecessors of autism with and without associated ID, and with and without other ESSENCE.

In a meta-analysis (12), psychiatric comorbidity in children and adolescents with autism was studied with regard to ID, ADHD, anxiety disorders, sleep disorder, disruptive behaviors, bipolar disorder, depression, obsessive compulsive disorder and psychosis. The highest prevalence estimates were found for ADHD 26.2%, ID, 22.9% and anxiety disorders 11.1%. Conclusions from the study were that the frequency of psychiatric comorbidity in children and adolescents with autism is considerable and that there is a need for better targeted diagnostic tools to detect psychiatric comorbidity in children, youth, as well as adults with autism. The authors emphasized that this represents a major gap comparted to the time and careful attention given to diagnostic accuracy of autism itself. Young children (under age 5 years) with autism almost invariably have major "other/non-ASD problems" (13).

Comorbid ESSENCE was analyzed in a population-based group of more than 200 children with diagnosed autism between the ages of 20–54 months, referred to an autism center for early intervention (14, 15). The children's developmental profiles were assessed at start of intervention and after 2 years. The children were assessed in great depth by a research clinical neurodevelopmental team consisting of physicians, psychologists and speech and language pathologists. Regarding motor development, "only" 66% of the children had started to walk unsupported before age 15 months, and 23 and 11%, respectively had started between 15 and 18 months or after 18 months of age. Children in the autism group demonstrated a marked delay in the development of expressive vocabulary. The general cognitive level was crucial in this respect. At the time of the first assessment, 13% of the children had no words at all, 33% had a few single words and 54% either had a few communicative sentences or had some phrase speech with or without echolalia. ADHD was not diagnosed at this early age but 42% of the children were classified by their parents—and confirmed by the examining physician—as definitely hyperactive, 8% had an activity that was alternating between hyper- and hypoactivity, 3% were reported to be hypoactive, and 47% had an activity level within the normal variation (14). At the 2-year follow-up at ages between 4 and 6.5 years, half the group had clear ID in addition to autism and about 25% had borderline intellectual functioning, and 25% average intellectual functioning, respectively (15).

Autism, DCD and other ESSENCE

Motor and language impairments are common and closely related in young children with autism (16). In a study of schoolchildren with autism, assessments with a motor performance test and parental reports of the child's motor and language skills revealed that 85% had motor and/or structural language deficits in addition to their social impairment. A conclusion from the study was that co-occurring motor and structural language deficits should be anticipated and assessed in the evaluation process of children with autism. Such assessment can provide a basis for specific interventions that will complement those targeting social skills deficits and other autism core symptoms (17). Children with ADHD and "comorbid" DCD often have autistic traits, whereas children with ADHD, without DCD, often have major oppositional defiant behavior/disorders (ODD) (16).

Autism, epilepsy and other ESSENCE

Epilepsy is a common comorbidity in autism, occurring at increasingly higher rates with increasing age and is strongly linked to the co-occurrence of ID (18, 19). In some children with autism and epilepsy, the first manifestation has been infantile spasms. This variant of early onset epilepsy has in some cases proved to be linked to specific syndromes, such as tuberous sclerosis, neurofibromatosis type 1 and Down syndrome, all now known to have a strong association with epilepsy (20). The co-occurrence of epilepsy and other ESSENCE has been extensively studied (21). Prevalence rates of autism, ADHD and behavior difficulties in young children with epilepsy and in children without epilepsy showed that of those with epilepsy, 18% had autism, 40% hade ADHD and about 75% had behavioral difficulties. Thus, young children with epilepsy had a very high level of parent reported behavioral difficulties and a high risk for ADHD and autism, highlighting the need for comprehensive multidisciplinary assessments. Behavioral concerns were not greater than for other children with non-epilepsy related neurodisabilities with the exceptions regarding attention and mood. Epilepsy-related factors were not associated with child behavior, suggesting that seizures *per se* do not confer a unique risk for behavioral difficulties. The importance of early recognition of social deficits in children with epilepsy is an important aspect of the comprehensive management of this patient group (18, 19).

Regressive autism and catatonia

Most children with autism have shown mild or marked developmental problems from early childhood (20). However, in a subgroup of about 20% there is a reported developmental regression after a typical or a marginally delayed development extending to about 18–24 (30) months of age (22–24). Children with a regressive developmental trajectory, with or without autism, always need a careful neuropediatric work-up to investigate possible neurological diseases that may lead to developmental regression, taking into account possible treatable conditions (23).

A marked functional decline or a late regression with symptoms according with catatonia can occur in adolescents with autism after a relatively stable childhood. Common symptoms are obsessive and compulsive rituals, speech regression, motor abnormalities including posturing, aggression and mood disturbance. Catatonia has been reported to be a common cause of late regression in individuals with autism (25). Although the etiology is unknown, disrupted gamma-aminobutyric acid has been proposed as the underlying pathophysiological mechanism. Key symptoms can be identified under 3 clinical domains: motor, speech, and behavior.

Benzodiazepines and electroconvulsive therapy are the only known effective treatments (26).

Autism, cerebral palsy and ESSENCE

A total population of school-age children with cerebral palsy were assessed with regard to the rates of autism and ADHD and the relationships between these disorders and motor function, ID, and other associated impairments. The study showed that 45% of the children met criteria for autism, ADHD, or both. ID was present in 51%. Two-thirds had autism, ADHD, and/or ID. It was concluded that autism and ADHD were common in this population of children with cerebral palsy and mainly independent of motor severity and cerebral palsy type. The strongest predictor of autism/ADHD was ID. Assessment for autism and ADHD is warranted as part of the evaluation in cerebral palsy in both term and preterm born children (27, 28).

Autism, ESSENCE and underlying etiologies, including behavioral phenotype syndromes

Every young person diagnosed with a neurodevelopmental disorder needs a medical evaluation. In children without specific complications indicating perinatal or postnatal adverse events, the etiology is most likely prenatal. Among the prenatal etiologies, there are chromosomal/genetic as well as acquired causes. A detailed history from parents, supplemented with data from records and an examination of the child will provide guidance for specific medical examinations. In children with autism, a specific medical/etiological diagnosis will be clinically established in about 20% of the cases and is more often identified when the child has concomitant ID (29).

There are several sex chromosome trisomies—XXX, XXY, and XYY—that are associated with autism (30). The most well-known syndrome due to an autosomal trisomy is Down syndrome, which is the most common, identified single cause of ID. Down syndrome, occurs in about 1/800 newborns. In 2001, Rasmussen et al. reported autistic disorders in Down syndrome (31). In a recent population-based study, 42% of children with DS also met criteria for autism. An important minority (34%) met criteria for ADHD (32).

There are many other behavioral phenotype syndromes with identified prenatal etiologies, mostly genetic but also prenatally acquired. Genetically defined behavioral phenotype syndromes include syndromes that have an identified genetic mutation; FragileX syndrome, Rett syndrome, Tuberous sclerosis and Neurofibromatosis type 1, to mention a few conditions for which the ESSENCE symptoms may precede the diagnosis of the genetic disorder (13).

Through extensive genetic research, a number of causes of neurodevelopmental disorders, including autism and other ESSENCE have been clarified and more than 1,500 genes associated with conditions such as ID and autism have been identified (33). These NDD genes are distributed over all chromosomes on autosomes, on the X chromosome, and a few on the Y chromosome and on the mitochondrial genome (33).

ESSENCE symptoms always need to be evaluated with regard to etiological and pathogenetic factors. Among these, genetic factors predominate. The heritability and genetic architecture of autism is complex and the genetic risk for autism is shaped by a combination of rare and common variants and thus the genetic susceptibility to autism can vary from one individual to another (34).

In a Swedish study, parents of all 9- and 12-year-old twin pairs born between 1992 and 2000 were interviewed regarding autism spectrum disorders and associated ESSENCE. Concordance rates and structural equation modeling were used for evaluating causes for familial aggregation and overlap across diagnostic conditions. A high comorbidity was found across the different ESSENCE neuropsychiatric disorders, and the data suggest that genetic effects are of major importance for this comorbidity (35).

Genetic disorders are variably expressive, in that the children with the same variant may show severe features while carrier parents show mild features. For example, in the assessment procedure of a boy with specific ESSENCE symptoms, including autism, an underlying condition may be an inherited Fragile X condition with a full mutation, while the mother has a premutation with no or a very mild cognitive/executive dysfunction (36).

By using chromosomal microarray analysis, a high resolution chromosomal technique to detect submicroscopic chromosomal rearrangements smaller than 100 kb, an increased prevalence of copy number variants (CNVs) and single nucleotide variants (SNVs), affecting genes, have been reported in patients with autism. Several recurrent CNVs have been associated with autism, reaching genome-wide significance, such as duplications at 15q11-13, deletions/duplications at 16p11.2 and 22q11.2 and 11q24.2-25 (37, 38).

There are several syndromes related to copy number variants, such as deletions and duplications. The 22q11 deletion syndrome occurs in about ¼,000 newborns and gives rise to many symptoms of varying severity. There is a high incidence of cardiac malformations, cleft palate, velopharyngeal insufficiency and immune deficiency due to hypoplasia or aplasia of the thymus. The syndrome can be inherited or occur as a new deletion. Cognitive symptoms within ESSENCE are common and mostly relatively mild; mainly autistic features, ADHD and mild intellectual disability (39).

Among the prenatally acquired syndromes, fetal alcohol spectrum is the most common and related to the fetus' alcohol exposure (40, 41). Common ESSENCE symptoms in these children are ADHD, mild intellectual disability and autism. Genetic aspects, e.g., ADHD-heredity, may also be involved.

An association between congenital hypothyroidism/hypothyreosis, i.e., thyroid hormone deficiency present at birth, and autism was reported 30 years ago (42). Newborn screening programs have led to earlier diagnosis and treatment, resulting in improved neurodevelopmental outcomes (43).

Another prenatal acquired syndrome that may cause autism and other ESSENCE is caused by a cytomegalovirus infection (CMV). The infection can be identified through analysis of the CMV DNA from the dried blood spots from the newborn metabolic screening. Congenital CMV is one of the many etiologies underlying autism and a rate of 3% of congenital CMV has been found in children with autism with intellectual disability (44).

Warrier et al. (45) have highlighted the considerable phenotypic heterogeneity in autism and emphasized that deeper phenotypic characterization will be critical in determining how the complex underlying genetics shape cognition, behavior and co-occurring conditions in autism.

Extremely preterm birth (i.e., birth occurring before a gestational age of 27–28 weeks) infers a much increased risk for ESSENCE. Follow-up studies conducted in the preschool years, school age and adolescence, and adulthood point to an increased risk for inattention, socio-communicative problems and emotional difficulties in individuals born extremely preterm (46).

In a follow-up of children born before a gestational age of 24 weeks, 75% had neurodevelopmental disorders, including speech disorders (52%), ID (40%), ADHD (30%), autism (24%), visual impairment (22%), cerebral palsy (17%), epilepsy (10%) and hearing impairment (5%). The majority also had other specific medical diseases, such as asthma (63%) and failure to thrive/short stature (39%) (47).

Autism and behavioral intervention, the role of ESSENCE

In a systematic review by Howlin and her group of early behavioral interventions for children with autism, the authors formulated a conclusion that fits well with the concept of ESSENCE: "Assessing what treatments work for which children and identifying the individual characteristics that predict responsiveness to specific programs and approaches, are the challenges that lie ahead (48). The latest Cochrane systematic review of Early intensive behavioral intervention (EIBI) for young children with autism (49) emphasized that early intensive behavioral intervention (EIBI) is one of the more frequently used interventions, delivered for many years for autism, often at an intensity of 20–40 h per week, and based on the principles of applied behavior analysis (ABA). Conclusions from this Cochrane systematic review were that there is only weak evidence that EIBI may be an effective behavioral treatment for *some* children with autism and that additional studies using rigorous research designs are needed to make stronger conclusions about the effects of EIBI for children with autism. Among implications for research, the authors mentioned that individuals with autism are diverse in their symptom presentation and vary greatly in cognitive functioning level (for example, from severe intellectual disability to well-above average intelligence) and that comparative effectiveness studies are needed to determine if EIBI is more effective than other active treatments recommended for children with autism.

The conclusions from the Cochrane review were consistent with those by Frans et al. (50) discussing that while many early interventional approaches have an impact on child outcomes, study heterogeneity and quality had an impact on our ability to draw firm conclusions regarding which treatments are most effective.

In a study of clinical predictors for outcome of behavioral interventions in children with autism, the child's general intellectual level was the most important single predictor. Cognitive level at start of intervention (dichotomized into IQ<70 and IQ≥70) made a unique and statistically significant contribution to outcome prediction. The findings have significant clinical implications in terms of prognostic information given to parents at the time of clinical diagnosis and when planning intervention for preschool children with autism (51).

Early interventions in children with autism need an individual approach, focusing on improving the child's communicative abilities, social interaction and everyday functioning and measures have to consider the child's total clinical presentation, beyond autism and include also other problems/disorders under the ESSENCE umbrella. In a prospective, naturalistic study of more than 200 young children, half of whom with ID, effects on adaptive functioning of early intervention—intensive or non-intensive—were analyzed after 2 years. It was found that there was no significant difference between the intensive and non-intensive groups. The data did not support that children with autism generally benefit more from the most intensive ABA intervention programs than from less intensive interventions or targeted interventions based on ABA. Other ESSENCE, especially ID, need to be considered in the intervention planning approach (15).

Autism and pharmacological treatment

There is no Food and Drug Administration (FDA) approved pharmacological treatment for the core symptoms of ASD. Risperidone, a second-generation antipsychotic, was the first drug approved by the FDA to treat autism-related irritability and aggressiveness (52).

Research from both animal autism models and human subjects indicates that deficits in GABAergic signaling, may contribute to the symptoms found in patients with autism (53, 54). The mechanism is related to higher chloride levels in immature neurons, leading to paradoxical excitatory actions of GABA (55). Bumetanide a selective NKCC1 chloride importer antagonist, has been reported to alter synaptic excitation-inhibition (E-I) balance by potentiating the action of γ-aminobutyric acid (GABA), thereby attenuating the severity of autism symptoms in animal models (56). The first study with bumetanide in children with autism included five children and showed significant improvements on core autistic symptoms (55). Following randomized controlled trials, including larger patient groups have also reported improvements of core autism symptoms (56–58). However, the study by Sprengers et al. (59) did not show an effect on the primary outcome of broad autism symptomatology, but suggest efficacy of bumetanide on the secondary outcome measure, repetitive behaviors in a subset of patients. These findings highlight the complexity of autism heterogeneity in trial research and the necessity of inclusion of functional brain measures to understand treatment effect variability and to develop stratification markers (59).

ESSENCE in adulthood

Most disorders under the ESENCE umbrella persist into adulthood, but for some individuals full symptom criteria are no longer met in adult life. On the other hand, not all children with an ESSENCE disorder are diagnosed during childhood and individuals diagnosed with for example anxiety and depression as adults may have underlying ESSECE disorders, such as ADHD and/or autism. Thus, an underlying ESSENCE disorder is common among patients in adult psychiatry and should always be considered (13).

Summary and conclusion

NDDs/ESSENCE of different types are common (affecting at least one in ten of all children), occur mostly in combinations,

have different severities, numerous etiologies, and have effects on outcome during childhood and adolescence (and adulthood). Early symptoms in children with autism may be related to motor development, speech, language and communication and to regulatory problems, including sleep, feeding and emotional regulation. All levels of co-occurring ID have an impact on outcome in children with autism, receiving early intensive behavioral intervention. Some "comorbid" disorders/problems are not always evident before school age, but will become evident later during the school years. Identification, assessment in a multidisciplinary team, including a medical work-up, adapted interventions, parental psycho-educational support and follow-up through childhood and adolescence are key aspects for the child's overall development and health.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Does the current state of biomarker discovery in autism reflect the limits of reductionism in precision medicine? Suggestions for an integrative approach that considers dynamic mechanisms between brain, body, and the social environment

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Over the past decade, precision medicine has become one of the most influential approaches in biomedical research to improve early detection, diagnosis, and prognosis of clinical conditions and develop mechanism-based therapies tailored to individual characteristics using biomarkers. This perspective article first reviews the origins and concept of precision medicine approaches to autism and summarises recent findings from the first "generation" of biomarker studies. Multi-disciplinary research initiatives created substantially larger, comprehensively characterised cohorts, shifted the focus from group-comparisons to individual variability and subgroups, increased methodological rigour and advanced analytic innovations. However, although several candidate markers with probabilistic value have been identified, separate efforts to divide autism by molecular, brain structural/functional or cognitive markers have not identified a validated diagnostic subgroup. Conversely, studies of specific monogenic subgroups revealed substantial variability in biology and behaviour. The second part discusses both conceptual and methodological factors in these findings. It is argued that the predominant reductionist approach, which seeks to parse complex issues into simpler, more tractable units, let us to neglect the interactions between brain and body, and divorce individuals from their social environment. The third part draws on insights from systems biology, developmental psychology and neurodiversity approaches to outline an integrative approach that considers the dynamic interaction between biological (brain, body) and social mechanisms (stress, stigma) to understanding the origins of autistic features in particular conditions and contexts. This requires 1) closer collaboration with autistic people to increase face validity of concepts and methodologies; (2) development of measures/technologies that enable repeat assessment of social and biological factors in different (naturalistic) conditions and contexts, (3) new analytic methods to study (simulate) these interactions (including emergent properties), and

(4) cross-condition designs to understand which mechanisms are transdiagnostic or specific for particular autistic sub-populations. Tailored support may entail both creating more favourable conditions in the social environment and interventions for some autistic people to increase well-being.

KEYWORDS

autism, biomarker, precision medicine, neurodiversity, systems biology, reductionism, neurodevelopmental conditions

Introduction

Over the last 40 years, much of what (we thought) we knew about autism has changed or has been modified; ranging from the prevalence of autism to the conceptualisation and definition of autism, through to the research goals, priorities and conduct of research.

Autism was once considered a rare condition, with prevalence estimates of 3–4 in 10,000 individuals in the 1970s (1). It was also commonly considered a "severe disorder." The *qualitative* differences in the clinical presentation were highlighted, such that some authors argued it would be almost impossible for a non-autistic person to imagine what it is like to be autistic (2).

By contrast, currently 1–2% of the population or approximately 78 million people worldwide are estimated to be autistic—which represents a 20 to 30-fold increased prevalence (3, 4). One likely factor in this increase are various changes in the definition and diagnostic criteria over time. In the two major diagnostic manuals, the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD), autism has always been defined based on a set of behavioural features (or symptoms) rather than aetiology or biological characteristics [DSM-5 (5)]. However, across the latest revisions, the notion of *qualitative* differences in core domains has given way to the view of autism as a spectrum, with *quantitative* differences in autistic traits and a "broader autism phenotype" (6) shading into so-called "normality." Arguably, these changes have led to a decrease in specificity (7, 8) and an increase in the proportion of people diagnosed with autism without intellectual disability (ID) (from 31% in the 1980 to 61–83%) (4, 9). Moreover, from an ontological perspective, the neurodiversity paradigm, informed by first-person experiences, has criticised the ICD-DSM definitions of what is autism and instigated a fundamental shift from deficit models to emphasising differences in autistic perception, cognition and experiences (10–12). Also, while autism has originally been a male-dominant condition, recent studies indicate that differences in the behavioural presentation in females might mean that the actual sex ratio is less pronounced than originally thought (13, 14). Furthermore, co-occurrence of other neurodevelopmental, neuropsychiatric, and medical conditions has been noted. Whereas up until the DSM-5 (15) diagnosis of autism and ADHD was mutually exclusive, newer reports indicate that between 28 and 53% of autistic children meet criteria for ADHD and between 7 and 37% criteria for an oppositional defiant disorder or conduct disorder (16, 17). 42% of autistic adults—notably females diagnosed in adulthood (18)—have a lifetime prevalence of anxiety disorder and 37% of depressive disorder (19). Around 4–8% of autistic people have epilepsy, which increases to 20–40% in autistic people with Intellectual Disability (20). Autism also involves a markedly higher premature mortality rate compared to the general population owing to numerous mental health and medical conditions, notably a 9-fold increase in suicide rate and 40-times increased mortality rate from epilepsy (21). There is also increasing awareness that multiple systems of the body are affected, which include—alongside the neurological system—metabolic, gastrointestinal, immunological, and mitochondrial systems (22), and connective tissue (23), though it remains unclear to what extent they may play an etiological role.

This change in the autistic population has also affected changes in research priorities.

Although heterogeneity has been known for a long time (24), a dominant research goal was to develop a *unifying* theory that explains *all* symptoms in *all* autistic people (25). This has given way to a view that multiple cognitive or biological characteristics may underpin different clinical features (26). Indeed, no cognitive or biological characteristic has been identified that characterises all or most autistic people. We recently showed that across the most influential areas of autism research, small (d = 0.21) to large effect sizes (d = 1.1) in cognitive, EEG, and MRI studies translate to 45 to 63% of autistic people falling *within* 1 Standard Deviation of the typically developing control group; i.e., they do *not* have an atypicality in a statistical sense (27). Rødgaard et al. (28) showed that effect sizes in these areas decreased by up to 80% over the past 20 years, presumably owing at least in part to the increased heterogeneity of study participants.

As a consequence, many researchers have been sceptical that such a unifying biological characteristic or "final common pathway" exists among this diverse group. Some believe that it is important to understand this heterogeneity and shifted the goal to identifying biological "subgroups" to make more accurate clinical predictions (see below). Others take lacking evidence of a shared biological basis to argue for abandoning the categorical diagnosis of autism (29, 30) and indeed neurodevelopmental/neuropsychiatric conditions altogether (31), pointing to at times detrimental repercussions for clinical pathways and care. A third view is that the high prevalence rates reflect an inflation of autism diagnosis in people with broader atypicalities in the areas of social communication and repetitive interests. In particular, Mottron (7) proposed a research strategy that returns to a more narrow definition of autism, termed "prototypical autism," to identify the biological basis of people with a more homogeneous, qualitatively recognisable clinical presentation, notably in early development. However, shared among these different views is the recognition that the more diverse is a diagnostic group, the harder it is to make meaningful, clinically relevant predictions about an individual from the group information (32).

In this contribution to the special issue on the question "Is autism a biological entity?," I will first review the origins and concept of precision medicine approaches to autism, and summarise recent

findings from the first "generation" of biomarker studies to identify and characterise biological subgroups. The second part turns to discussing some methodological and conceptual challenges in this research agenda; in particular potential limitations of the reductionist approach in biomedical science, which tends to parse complex issues into simpler, more tractable units. The third part draws on insights and examples from systems biology, developmental psychology and neurodiversity to outline an integrative approach that considers the dynamic between biological and social mechanisms to understanding the origins of autistic features in particular conditions and contexts.

Precision medicine approaches to autism

Precision medicine approaches to autism were motivated by the recognition that a categorical, symptom-based diagnosis of autism itself does not enable us to make accurate predictions about a particular autistic person, such as their likely natural development, treatment/support needs as well as efficacy of specific therapies, or the underlying cause of the condition (33–36). This approach, as much as the term *precision medicine* itself, follows a trend that first started in internal medicine and that was then imported to psychiatry; reminding us that heterogeneity is not only a phenomenon specific to autism but in fact prevalent across medical and psychiatric conditions. It aims to match new mechanism-based treatments with objective tests (predictive biomarker) to estimate which therapy is most beneficial for this particular person (37). Hence, a key tenet is that interventions/support will be more effective if they target underlying mechanisms rather than treating symptoms (i.e., symptomatic treatment) and that mechanisms—and thus treatment responses—may differ even between people with the same umbrella diagnosis (38). It also stresses that early identification and intervention closer to causal mechanisms likely have the strongest lasting benefits on cognitive, social, and emotional development because of substantial underlying brain growth and plasticity over the first months and years of life. This opens the possibility to shift the trajectory toward growth of strengths as opposed to amelioration of symptoms.

To enable this approach, a key pillar of precision medicine is identification of "biomarkers." The original definition by the Biomarker Working Group, (39) stressed a biomarker as a biological characteristic that can be *objectively* measured (as opposed to clinical judgement that is somewhat subjective). The Biomarker, EndpointS and other Tools (BEST) Resource of the FDA-NIH Biomarker Working Group (40) divided biomarker types by their specific clinical purpose ("contexts of use"). These include to aid in (1) the early detection of a condition, possible before behavioural features arise (likelihood biomarker), (2) more objective and reliable diagnosis (diagnostic biomarker), (3) predicting the "natural" developmental course without any intervention (prognostic biomarker), and (4) predicting treatment benefit as well as potential side effects (predictive biomarker), or for other purposes. A biomarker could be any measurable characteristic, from a gene to molecular marker, brain structural or functional read-out, cognitive or behavioural tests. Note that in homogeneous conditions, a biomarker should apply to all or most people with that condition—corresponding with the search for universal and specific characteristic(s) of autism discussed above. A biomarker may also apply to most/all individuals in a situation where different causes give rise to a "final common pathway" at one intermediate level but additional factors influence behavioural/clinical outcomes (41). By contrast, for heterogeneous conditions without a final common pathway, each of these biomarker types are variants of a *stratification biomarker* and only apply to a particular sub-group (see below for the interpretation of this term by the non-scientific autistic community). For example, it may help to objectively diagnose a specific subgroup of autistic people; such as those with increased likelihood for late onset epilepsy. A biomarker could be categorical (e.g., presence/absence of a gene), a quantitative measure that designates biomarker 'positivity' from a certain cut-off point, or it could be a panel comprising different measures.

If a diagnostic biomarker was found, it would redefine autism as a "biological entity." If it were found for a sub-population, it would make a subpopulation a "biological entity." This is effectively the case for several monogenic conditions that involve strong likelihood (penetrance) for autism. For example, approximately 0.5–1% of autistic people have Phelan McDermid Syndrome (PMS), and conversely 70–80% of people with PMS meet criteria for autism (42). Other genes are more pleiotropic, leading to a range of neurodevelopmental/psychiatric conditions (e.g., Fragile X Syndrome, 22q11.2). By contrast, a transdiagnostic biomarker is a biological characteristic or state indicative of a clinical feature that is shared across people with different conditions, such as neuroendocrine and neuroinflammatory markers of stress-related depression (43).

Thus, a biomarker is a biological characteristic or state *at a certain moment in time*. It does not necessarily have to be stable across development; i.e., it could be transient, and only detectable say in early development, and—as argued below- may vary across contexts or conditions. It is also not necessarily caused by a gene—but could result from environmental factors, for example early trauma, deprivation, or stress etc. In this regard, a biomarker is different to an *endophenotype*, which is thought to be relatively stable and must be inherited (44). Many biological processes in the brain, such as (increased) myelination, synaptic (over)production, synaptic pruning (which all play a part in cortical thickness) are *experience-dependent* biological processes, and therefore affected by exogenous as well as endogenous events.

Hence, it could be the individual child, the environment and/or the interaction between individual and environment (individual's life experience) that impacts biological developmental processes. It is this effort to identify biomarkers for autism that has substantially changed methodologies and the research culture over the past years.

Biomarker studies and subtyping approaches in EU-AIMS and AIMS-2-TRIALS

This approach is exemplified by EU-AIMS and AIMS-2-TRIALS, which are two linked consortia that were specifically set up to identify biomarkers in autism (45, 46). In EU-AIMS (2012-2019), the first generation of biomarker studies comprised two complementary approaches: (1) large-scale cohort studies to parse heterogeneity and (2) gene-first approaches to identify mechanisms in *a priori* genetically-defined subgroups.

First, to get the statistical power to recruit and assess larger cohorts needed to subdivide heterogeneous idiopathic autism groups,

we had to shift from small-scale studies (typically including 15–30 participants per group) to multi-centre studies. The *Longitudinal European Autism Project* [LEAP, (47, 48)] uses a case-control accelerated longitudinal design (N = 420 autistic, 350 non-autistic) to identify subgroups within the autism group. The categorical autism diagnosis is needed as a reference point. *Accelerated longitudinal* means that four cohorts of children, adolescents, adults without intellectual disability and adolescents/adults with mild intellectual disability were simultaneously recruited and then followed up on two time-points within 8 years. Deliberately there were few participant exclusion criteria. We allowed all co-occurring medical and mental health conditions (except psychosis) at a time where many studies excluded participants with co-occurring ADHD and included people with mild intellectual disability (ID) (around ∼18%) when most neuroimaging studies excluded people with ID. The sample was deliberately "enriched" for females (with a 1 female to 3 male ratio) to conduct sex-stratified analyses at a time when many studies focused on males only. The age range was chosen because brain imaging was a core assessment and we were not confident about viability of preschool MRI scanning at the time. Whereas most previous studies assessed participants on one or a few measures to test a specific hypothesis, each participant is comprehensively assessed across multiple domains and "levels" ("deep-phenotyped") to test/compare some of the most established hypotheses (theory of mind, executive functions, social motivation) and emerging hypotheses at the time (e.g., excitatory/inhibitory imbalance). More exploratorily, we aimed to link different assessments to map differences in genes to downstream molecular, brain systems level, cognitive and behavioural features. For the first time in autism research, we obtained qualification advice from the European Medicines Agency (EMA) to increase the chances that data generated by the study would be accepted for biomarker qualification for particular "contexts of use" (47).

Our analysis strategy comprised distinct steps. First, we conducted mean-group comparisons and dimensional analyses for each measure. Significant mean-group differences were found in functional connectivity [(49), as indexed by degree of centrality but not using Independent Component Analysis, (50)], social attention patterns, including temporal profiles (51), biomotion (52), theory of mind, emotion recognition (53) early-stage face processing [N170 latency, (54)] and functional activation during reward processing (55). No significant mean group differences were observed in functional activation in brain regions implicated in theory of mind (56), emotion recognition, EEG power spectrum or functional connectivity (57), and (largely) brain anatomy (58).

However, for biomarker discovery mean group differences should be treated as a starting point only. As stated above, the difference between a statistically significant and non-significant group comparison could be a matter of 45 vs 55% of autistic people performing below say 1 Standard Deviation (SD) of the "typical mean" (27); so it may be more indicative of the size of a potential subgroup. Therefore, we moved our focus from mean-group comparisons to identify individual profiles; and subgrouping approaches.

On the one hand, we defined subgroups *a priori* by sex/gender, age/developmental stage and other variables putatively affecting sub-populations and examined differences in neurobiology. This revealed similar effects of sex and diagnosis, as well as some sex-by-diagnosis interactions in intrinsic brain function (59). Also both autistic and non-autistic females showed on average stronger social attention than autistic and non-autistic males when watching static images, with subtle differences in dynamic looking patterns over time (51). We also carried out *sensitivity analyses* to examine potential differences between autistic participants who meet vs. do not meet ADOS/ADI cut-off scores. On the whole, sensitivity analyses increased somewhat but not drastically effect sizes, but in some instances crossed the significance level (p-value) divide (e.g., on some theory of mind tests). However, whereas these analyses predominantly reflect differences in the strengths of social-communicative features or repetitive behaviours, it remains to be tested whether commonalities in cognitive or biological characteristics may be more likely captured by clinical 'prototypicality' (7).

Secondly, we aimed to make individual predictions based on normed scores of cognitive or brain development using growth charts and then used data-driven approaches to identify subgroups. Reference scores or growth charts are routinely used in paediatrics to interpret a child's weight/height, or in IQ or educational assessments using standardised scores. More recently, such growth charts have also been created for brain development (60–62) and function (54) to assess individual variability relative to expectations based on a person's age, sex or other variables. We can then use these scores in clustering or other multi-variate analyses to identify subgroups at the clinical, cognitive level, neurobiological level, or a combination thererof.

This approach identified diverse atypicalities in brain anatomy in the autism group, which were not located in the same regions in all autistic participants and would have gone undetected in mean-group comparisons of *a priori* regions of interest (58, 63). For example, autistic participants showed highly individualised patterns of both extreme right- and leftward lateralisation, particularly in language, motor, and visuospatial regions. Language delay explained most variance in extreme rightward patterns whereas strengths of autism core features explained most variance in extreme leftward patterns (64). We also identified cognitive subgroups using robust clustering based on behavioural expression recognition performance across three tests. These subgroups were related both to clinical features (explaining more variance in social adaptive function than subgrouping by IQ) and functional activation in amygdala activation (53).

The question is then whether these subgroups can be used to inform prognosis or treatment choices. This approach is exemplified by the way speed of early-stage face processing (N170 latency, as measured by EEG) was investigated as prognostic biomarker (54, 63). Face processing has long been suggested as an early marker of atypical social information processing in autism (66). Here, we first replicated significant mean-group differences with medium effect size. Although slower N170 responses was only found in a subset of autistic participants, this subgroup showed on average poorer social prognosis as measured by adaptive socialisation skills over an 18-month follow-up period. In addition, N170 latency was associated with lower fMRI BOLD responses to faces in the fusiform gyrus during an fMRI task and polygenic scores for autism, triangulating links to social biology. Moreover, simulations showed that a distributional data-driven cut-off used to define "N170 latency biomarker positivity" as enrichment marker predicted improvements of power in simulated clinical trials targeting social functioning. From an ethical perspective, it is important to know what developmental trajectory likely entails what kind of difficulties for participants to weigh up likely costs/benefits in taking part in a clinical trial. For the first time in autism research, the N170 has now been included

in the biomarker work programme by the FDA [led by the ABC-CT consortium, (67)] and has been supported by the EMA as baseline covariate. The longitudinal character of LEAP (with the ongoing 3rd assessment wave) affords subgrouping performed based on clinical/functional development and to then examine markers that may relate to different developmental changes/trajectories (e.g., using social attention to predict if adaptive function stayed the same, improved, or decreased relative to age expectations).

In sum, biomarker approaches to autism, and the ambition of precision medicine to transform healthcare, has shifted the focus from mean-group comparisons to predictions about individuals. It led to larger-scale, comprehensively characterised cohorts, set new standards in methodological rigour, robustness, replicability and temporal stability (67, 68), and development and use of innovative advanced 'features' [(e.g., from ROIs to connectopics (69), from cortical thickness to cortical gyrification (70) areas of interest to temporal dynamics in eye-tracking (51)]. It also changed the research culture by instigating both multi-disciplinary and cross-consortia collaborations (46).

However, so far we have not found a clearly delineated biologically-defined autism subgroup. There remains considerable overlap between subgroups in terms of clinical features and separately assessed biological characteristics. Thus, the predictive value is probabilistic, in that biomarker positivity increases likelihood of a certain outcome. Although it is possible that the predictive value may be higher for smaller subgroups (say $< 10\%$), which could be highly clinically relevant, there is a danger of trying to slice autism into ever smaller sub-groups just to find a "biological entity."

Before discussing potential technological and conceptual factors in these findings, advances from the complementary approach that starts with a particular genetic "subgroup" are reviewed.

Gene-first approaches

Gene-first approaches focus on a particular neurogenetic or monogenic (sub-)group to identify mechanisms and markers linked to a specific gene or gene product in order to identify treatable molecular targets. Based on the premise that some genes may converge on common molecular pathways [e.g., affecting synapse development, (71)] the subsequent goal is then to explore whether any atypicality generalises to other 'types' of syndromic or even idiopathic autism. One example of this approach is biomarker research in Phelan McDermid Syndrome (PMS). PMS was originally defined as deletion of the distal long arm of chromosome 22 and is also called 22q13.3 deletion syndrome (72). Later it was identified that deletions or haploinsufficiency of SHANK3 cause many clinical features. However, the presentation and needs of autism in PMS substantially differ from that of many idiopathic autistic individuals, largely due to severe to profound ID in 75% of cases (42).

SHANK3 is a postsynaptic scaffolding protein at glutamatergic synapses involved in synapse development and function, and regulation of dendritic spine morphology. At the systems level, this predicts to result in perturbations of the Excitatory/Inhibitory balance, generating broad hypotheses of functional differences.

Biomarker studies using EEG found group-level atypicalities in brain functional integration and connectivity, which are likely also reflective of ID, and significantly increased alpha-gamma phase bias (73). However, findings of other 'proxy markers' of E-I imbalance such as reduced Mismatch Negativity, gamma band atypicalities, or 1/f are more mixed ((74), in press).

Also more variability among people with Phelan McDermid Syndrome at both the behavioural and molecular levels is now being reported than we first expected. In a recent collaboration with Mount Sinai we investigated differences in social (vs. non-social) orienting in 67 children with PMS, 45 autistic children and 28 TD children. Social orienting was previously hypothesised to be an early marker of social cognitive atypicalities in autism (75). While at the group level, children with PMS responded significantly less often to both stimulus types, some PMS children in fact did respond to both, others almost to none, and others selectively to either social or non-social stimuli ((76), in press). Likewise, molecular studies now show that people with specifically SHANK3 point mutation actually have variable expressions of SHANK levels that cannot solely be attributed to deletion size or location (77).

In sum, even when aetiology is known, it has turned out to be a long way to map the mechanistic pathophysiology from a particular gene to shared or variable biological, behavioural and clinical features. The next section discusses technological/methodological and conceptual factors that may have contributed to difficulties in finding markers and mechanisms that characterise autism subgroups.

Methodological and conceptual factors in biomarker discovery

Are our current methods and technologies not reliable enough to identify subgroups?

Evidently, the results we get depend on the technologies, methodologies and methods we use and the signal of each measure occurs in the context of noise and measurement error. Here, this illustrated using neuroimaging as an example as advances in neuroimaging have chiefly influenced neurodevelopmental research, but similar considerations may also apply to other technologies and methods. First, for a technology to be used as a clinical tool it is not trivial that acquisition rates and data quality can be very variable and are to some extent systematically related to participant characteristics (age, IQ, sensory sensitivities etc.). For example, MRI scanning is particularly difficult in preschoolers with neurodevelopmental conditions or people with ID. As a consequence, these sub-populations were often left out from neuroimaging studies. Hence, we need more tools to reliably acquire neuroimaging data in children, and people with complex needs (including silent sequences, motion correction procedures).

Some neuroimaging indices (e.g., voxels in Magnetic Resonance Spectroscopy) are still very coarse; and do not allow us to specify specific neuronal differences. This is exemplified by pre-clinical work showing low correspondence between atypicalities in particular neuronal signalling and neurotransmitter concentrations. Thus, it is likely that limited accuracy or granularity of some measurements contribute to moderate relationships between candidate biomarkers and clinical outcomes.

Recent studies also reported poor test-retest reliability of resting state functional connectivity, with average Intra Class Correlation (ICC) of.29 (78) and task activation with average ICC of.39 (79). These findings highlight a related issue in that test results may not only reflect limited measurement accuracy itself but the fact that the read-outs we obtain (e.g., functional connectivity in certain networks at "rest" or during task performance) are only a snapshot *at a*

particular moment in time and *in a particular context*. For example, regional activation (e.g., fusiform gyrus) can vary substantially across different conditions or tasks in the same individual within the same scan session. Unless we know that one condition is most clinically relevant, and why (amygdala activation to happy vs. fearful faces, or collapsed), it may be unclear which feature to carry forward as *candidate biomarker* and use to link to clinical features.

Likewise, many other candidate biomarkers are sensitive to condition and context effects. For instance, serotonin levels are known to vary across different times of the day (80), microbiome varies as a function of diet (81) that is influenced both by environmental factors and personal preferences. Research on double-empathy (12) shows that the ability or accuracy in understanding another person's perspective may depend on the relationship between self and other, such that even 'reliable' test scores on repeated experimental theory of mind tasks may still have poor face validity if they fail to capture the way someone interprets different real life social interactions. Hence, in contrast to the sometimes tacit assumption that candidate biomarkers measured in the laboratory at a certain moment in time should be representative for this individual's true state at a given *developmental stage*, potential variations across contexts or conditions are often unknown or untested. Although in biomarker research, these moderating factors should be established as part of "pre-analytic validation," the fact that they are often not considered may also reflect some implicit conceptual assumptions.

Are biomarker approaches too reductionistic?

Reductionism has been the predominant paradigm in biomedical science since Descartes. The fundamental approach of methodological reductionism is to understand complex issues, such as systems or processes, by dividing them into simpler and more tractable constituent units and their interactions. Methodological reductionism has been—often successfully- applied to the diagnosis, treatment and prevention of medical conditions, such as tumor type in predicting treatment and progression (37, 82). Ontological reductionism (not necessarily embraced by all precision medicine approaches) makes the stronger assertion that "higher" levels can be explained by "lower" levels (e.g., social sciences by psychology, psychology by biology, biology by chemistry, chemistry by physics). In autism research, we tend to separately investigate immune markers, metabolomics, brain structure or brain function as candidate marker for particular outcomes. However, the focus on specific "parts" of an individual neglects (1) that the interaction between them can produce a whole that is bigger than the sum of its parts—emergent properties, (2) the context or condition in which particular characteristics or processes operate, while (3) the focus on individuals neglects interactions between the person and their social environment. In brief, when approached through a "reductionist lens," personalised medicine may not only risk overlooking the person (83), but also divorces the person from their environment. Several separate traditions challenge the reductionist approach to precision medicine.

Systems biology: Integrating brain and body

Systems biology assumes that the whole cannot be understood by studying the individual constituent parts and explicitly appreciates holistic and dynamic characteristics of 'systems' during particular operations over time (84). One example used to support this argument is the human genome project, which shows that from a relatively small number of 20,000 to 25,000 genes, one individual carries on average 3 million genetic variants, which interact to encode for nearly 100 trillion cells in the human body. This rich information is not only derived from the genes themselves and the interaction between genes, but also interactions with their gene products. Critically, between each hierarchical level (DNA to RNA, RNA to proteins) modifications are made, such that thousands of molecules interact with one another to give rise to a complex regulatory network and particular phenotypic characteristics.

A systems biology approach to precision medicine aims to take into account and integrate information from multiple sources, including genes and the environment, and different 'parts' of brain and body, to make predictions about an individual. The question is then how properties *emerge* from the addition and/or interactions of multiple components in particular conditions, and over time [see also (85)]. This may help us to understand how even a rare variant (e.g., SHANK3 point mutation) can lead to different clinical or behavioural presentations in different people depending on their genomic background (86), environmental and/or stochastic factors, or why identical twins can be discordant for autism or differ in their presentation of autistic features (87).

Considering the *context* or *condition* in which particular functions operate and develop also gives rise to questions, such as how brain and cognitive development are affected by acute and persistent stress (experienced endogenously or exogenously, [see example in the next section], atypicalities in sleep, or compromised gastrointestinal or immune functions (88). For example, the gut is linked to brain development and function via the parasympathetic nervous system, the immune system, the gut endocrine system and neuroactive metabolites and neurotransmitters directly produced in the gut (89). Some of these effects are likely bi-directional and dynamic over time, and these mechanisms may be missed when studying markers of brain and other internal systems separately.

Placing the individual in their social context

The next step is to bring the autistic person back into their social environment. Most cognitive and neurobiological studies of autism (regardless of whether they explicitly aim to identify biomarkers) tend to examine autistic participants on their own, with relatively little consideration of environmental and social factors on behaviour and development. Speculatively, some factors in this may be the historic image of the "autistic aloneness," suggesting that autistic people were less influenced by their environment than non-autistic people, and recognition of high heritability, such that environmental factors were deemed less critical in searching for the causes of autism. Also rejection of the psychodynamic "refrigerator mother" hypothesis may have resulted in a tendency of the field to altogether shy away from social dynamics. In any event, the result has been that we often examine the autistic person in social isolation, which paradoxically includes studies of their *social* (cognitive) development. Insights from social psychology warn that a reductionist focus on an individual's (or group's) actions without acknowledging the dynamics of inter-actions and re-actions can readily lead one to pathologise the individual (90).

The importance of social mechanisms in development, behaviour and well-being has been the subject of several separate traditions in developmental psychology, social psychology, and psychiatry. With regards to autism, some of these arguments have been vividly

brought to the fore by neurodiversity proponents (10, 12, 91). Some proponents have put forward a two-component definition of neurodevelopmental conditions. "Impairment as objective scientific component" (which acknowledges the brain basis, as indeed implicit in the term *Neuro*-diversity) and a "normative, socially negotiated component." It is argued that a significant portion of distress and disablement—including anxiety, depression, suicidal ideation and suicide—is caused by social barriers and "ableist norms" created by a non-autistic sociality, rather than the cognitive traits associated with autism themselves (92). Thus, by locating the source of a great proportion of difficulties in the social environment (which includes the psychological and biomedical community itself) it suggests a so-called "downward causation" from the larger system to the individual.

Here, the hypothesised interplay between downward (social) and upward (biological) mechanisms is illustrated by stress reactions. It is well known that adverse social experiences (stress, abuse, trauma, neglect), notably during early development, substantially impact brain and social, cognitive and emotional development in *non-autistic people*, and significantly increase likelihood to develop mental health or behavioural issues (93, 94). While under normal conditions, acute stress responses, such as increased heart rate, surge in stress hormone levels, adrenalin rush etc, go back to baseline when the stressor is relieved, recurrent experiences of abuse or neglect result in constant activation of the stress system even at times when no apparent (physical) harm is present (95). A stress system that is permanently on high alert impacts the function of other developing systems. This generates predictions of the effect of stress on social and emotional development, and mental health, in autistic people. In fact, autistic people are more likely to experience social adversities, such as stigma or bullying than non-autistic people (96, 97). Moreover, it is likely that some core features of autism (sensitivity to sounds, difficulties adapting to unexpected changes) interact with environmental factors in creating more frequent and intense experiences of stress and trauma in (for neurotypicals) relatively mundane situations (e.g., eating lunch in a noisy kindergarten or canteen, going to the airport). Those intense stress reactions can drastically affect a person's functioning both at a certain moment in time and across prolonged periods. For instance, they may create further anxiety due to uncertainty about when and how the next sensory overwhelming experience may happen in an unpredictable environment. Consequently, the effect of sensory sensitivity on stress may be mediated both by changes in hypersensitivity as well as changes in environmental conditions, such that a child hypersensitive to sounds may function better in an environment where occurrences of loud unexpected noises are reduced. The example highlights two points: First, it illustrates that the Research Domain Criteria (RDoc) approach of studying different domains (social, arousal etc.) as well as behavioural/clinical features separately might risk missing critical interactions in the functioning and development of these domains. Second, we cannot make a prognosis about an (autistic) child or adult based on their biology alone. Instead, social mechanisms, alone and in interaction with biological mechanisms and random factors likely impact the prognosis and support/treatment needs of autistic people.

The next section discusses social and environmental factors in the *development* or early manifestation of autism. Throughout foetal life, brain development is largely determined by distinct temporal and spatial stages of gene expression and intrinsic neuronal activity. Although it is known that these processes are susceptible to environmental factors, such as malnutrition, alcohol, smoking and drug use, and maternal psychosocial stress, none of these have been specifically linked to autism. After birth, brain development becomes actively refined by interactions with the environment (98). For example, synaptogenesis and plasticity of fronto-parietal, fronto-temporal and fronto-striatal circuits—brain systems underlying higher level social-cognitive and language development—spike between 1 and 3 years (98), which roughly corresponds with the time when social and language-related atypicalities first become apparent in autism. As the newborn turns into an infant and toddler, some of their predispositions interact with increasing exposure to and requirements of the infant/child to engage with more complex and unpredictable environments. Interestingly, whereas genes implicated intellectual disability appear to be predominantly expressed *before* birth, genes linked to autism and neurodevelopmental conditions are often expressed *after* birth [(99), personal communication].

Several theorists have stressed infants' social visual engagement as early sign of autism. Of note, social visual engagement appears not to be atypical from birth but has been shown to change between 3 and 18 months (100). These early social precursors impact social experiences by altering aspects of the environment that the infant/child acts upon, as well as by modulating the responses from and the interactions with others (101). Recently, Mottron hypothesised that once engagement with non-social aspects in the environment becomes the preferred cognitive style, a bifurcation occurs to the clinically-recognisable "prototypical autism" (32). It suggests a discontinuous process within a specified time-window that results in a categorical outcome. Others regard autistic behaviours as a latent trait comprised of the aggregation of earlier-interacting predispositions (102). Some of these may be specific for autism, such as sensory sensitivities (103), and others domain-general or transdiagnostic (attention, motor coordination) (87, 104). Characteristic continuous autistic traits are thought to emerge as a homeostatic responses or adaptation to the infants' experiences (105, 106).

Transactional models highlight the role of the dynamics between child and caregivers (and significant others) in the emergence of autism (85). Parents of infants with higher familial likelihood for autism have been shown to adjust to their child in various ways, by offering less social input, or by using more directive or enriched styles to scaffold their child (107). These findings have opened the possibility that changes in the response of the parent could therapeutically influence early developmental processes. In support of this notion, a recent "pre-emptive" intervention trial with infants between the ages of 9–15 months (who had shown early behavioural signs of autism during enrolment) found that video-based parental social-communication training statistically reduced autistic behaviours 24 months afterward (108). These approaches require careful discussion with autistic people as to what outcomes are considered to be positive or desirable, and affirmative of neurodiversity (109).

In sum, these examples highlight that the way the infant/child engages with other people and the world, at each moment, every day, and across development, interacts with critical brain maturation processes. These processes cannot be captured by a reductionist approach that attempts to explain "higher level" phenomena by "lower level" processes in a linear fashion.

Way forward: Integrating brain, body and the social environment

The precision medicine approach to autism is a framework that was devised by the biomedical community to increase our understanding of the mechanisms underpinning (the development of) autistic subgroups and particular clinical features so to offer tailored support and targeted therapies for core and/or associated features. The ultimate goal is to positively impact the lives of autistic people and their families. Within the ten years I have been working on this approach, empirical findings from our and other studies, insights and criticisms from neurodiversity approaches, and particularly the input of autistic people with lived experience from our AIMS-2-TRIALS "Autism Representatives" have prompted me to revisit some of the assumptions and directions. While this research approach started off with a focus on the individual and search for biological subgroups, the argument made here is that we need to incorporate *both* biological and social mechanisms to better understand the origins of particular autistic features in particular contexts so to make more accurate predictions about a particular person. It broadens the concept of '*bio*-markers' to 'markers', defined as an objectively measurable state or characteristic of either a person, environmental condition, or their relationship, in a particular condition or context. This change in focus may lead us to change the term *precision medicine* itself to *precision support* to reflect this broader remit.

Within this framework, it is proposed that new studies require (1) an epistemiological change in how we conduct research, including closer collaboration with autistic people and families to increase the face validity of concepts and methods (110, 111), and explicit acknowledgement of the perspective one adopts; (2) the development of measures that enable repeat (or continuous) assessments of social and biological factors in different conditions and contexts, (3) new models and analytic methods to study (simulate) these interactions, and (4) cross-condition designs to understand which mechanisms are shared (i.e., transdiagnostic) with other neurodevelopmental/neurotypical populations or specific for particular autistic sub-populations. As a consequence, support may entail both interventions for some autistic people or particular features that impact the person's well-being *and* changes in the environment to create more favourable conditions (including family, school, society at large).

Is autism a biological entity? When does it matter? For whom?

Even if we are currently still removed from having markers with the strong predictive value needed for clinical utility, it is now the time to work with autistic people and their families to understand what markers are desired and needed, and for what purpose.

Many verbal autistic people emphasise that they recognise each other as being of the same kind—in the absence of a known shared biology. Critically, this recognition and shared identity spans across levels of abilities and support needs, and it is particularly evident in families where family members can substantially differ in their presentation of clinical features. Therefore, it is important to communicate to the autistic community for what purposes subgrouping approaches are expected to be useful in clinical or educational settings, so to avoid potential mis-interpretations and to meaningfully explore acceptance. There are instances where biological characteristics of the individual clearly matter to understand if a given treatment or intervention is likely going to be effective for this person, or to estimate level of side effects. Anecdotally, it appears that for many autistic people efficacy of anti-depressants is lower and side effects can be stronger than for many non-autistic people.

While many researchers have used the term stratification biomarker in a medical context synonymous with sub-division for a particular purpose, in a recent AIMS-2-TRIALS panel discussion (Lisbon, 4th Annual General Meeting, 22 September 2022) it became apparent that some autistic people interpreted it as implying a hierarchy, a better or worse of some subgroups as denoted by social or economic stratification. This would entail unwanted and unintended segregation between autistic people. It is important to understand whether reservations and concerns are to do with such rectifiable miscommunications (by using a different term) or are rooted in more fundamental concerns and disagreements.

Another example of the benefits vs. danger of potential exclusion due to biological subgrouping recently occurred in the wake of scientific advances in Phelan McDermid Syndrome. As said earlier, PMS was originally defined based on chromosomal abnormalities in the 22q1.3 region, and it was later specified that most but not all PMS people have deletion or mutation in SHANK3. Studying specifically participants with SHANK3 haploinsufficiency is important for investigations on the effect of this gene on molecular and cellular processes, but it should not lead to exclusion of people that are part of a community with similar characteristics and needs, and that provides support for each other. To overcome this, a new inclusive classification system was proposed that differentiates between PMS-SHANK3 related and PMS-SHANK3 unrelated (112). Thus, we need to understand how subgroups (including genetically or clinically defined subgroups, such as in the "prototypical autism" proposal) relate to autism and neurodivergence as a whole.

In the AIMS-2-TRIALS biomarker working group with Autism representatives we are currently systematically looking at the acceptability, benefit, ethical and practical concerns of different types of biomarkers for different purposes ("context of use"). It is likely that acceptability and concerns substantially differ between, for example, the use of EEG in predicting epilepsy, (preventative) treatment of hypermobility/pain, cognitive profiles to inform education support, or genetic markers intended for prenatal screening. In fact, in the autistic community, considerable concerns, anxiety and uncertainty related to ethical ramifications of specifically prenatal genetic screening (not pursued in AIMS-2-TRIALS) may have dominated discussions and perceptions of all other types of biomarker research.

Thus, we also need to involve bioethicists and policy makers in these discussions to be aware of and address the ethical and legal ramification for when such markers may become available. This includes fundamental questions, such as legislation around termination and for what purpose, who can take decisions for children and those unable to consent for themselves, or who can access potentially expensive personalised interventions where they are desired.

New technologies, methodologies and methods: The conceptual emphasis on the condition and context in which characteristics are measured requires more frequent sampling and in different naturalistic contexts (rather than one-off shot in the experimental lab). Rapid developments of wearables (e.g., actigraphy) and portable, mobile technologies (EEG, fNIRS) promise new ways to assess participants in more naturalistic environments (home, nursery, school), which is expected to increase ecological validity (113). These

methodologies likely improve reliability relative to a single snapshot (e.g., MRI scan at one time-point within a longitudinal study) as well as our understanding of context effects and dynamic stability over time (e.g., whether a child consistently shows consistently sustained attention, or varies in different conditions). In our new UKRI funded network, RESPECT4Neurodevelopment, we involve autistic people from the start in the development of the next generation neurotechnologies for infants and children with neurodevelopmental diversity. We also need validated and standardised measures that are comparable across age and ability levels, including children with Intellectual disability, who are often excluded from research (114).

Next, we need new analytic tools to integrate information on biological and social processes. A first step is to create a comprehensive profile or "report card" for each person across different measures acquired. We can then use both data-driven multivariate approaches (such as clustering) to identify subgroups and theory-driven modelling/simulation approaches to identify additive and interactive mechanisms. Arguably, even data-driven clustering does require some theoretical input (linked to non-trivial variable selection and possible weighting). Different clustering approaches not only face the challenge of robustness but also of finding the subdivisions that are most clinically relevant. Another pivotal problem with Artificial Intelligence algorithms is their focus on classification at the expense of 'explaining' their predictions. This has raised the need to get to augment AI with explainable/interpretable AI (XAI) to understand what is inside the black box, and to trace the most predictive factors and mechanisms (115).We also need theory-driven models to study or simulate the dynamics of processes.

Study designs: Finally, in order to determine whether any markers and mechanisms are specific to autism (subgroups) or cross diagnostic boundaries, we need cross-condition designs to directly compare autistic participants with participants with other primary neurodevelopmental conditions, such as ADHD and Intellectual disability (116). In our current AIMS-2-TRIALS[1] and CANDY[2] biomarker studies, we adopt a life-span approach, with linked studies from infants to adults and characterise each participant in terms of the same transdiagnostic domains, including social, emotional, cognitive, reward, sensory and predictability processing. This includes infant sibling studies (STAARS) where one family member (parent or sibling) is either autistic or has ADHD, which increases likelihood of the infant to develop either neurodevelopmental condition as well as sub-threshold traits, and cross-condition studies, such as the Preschool Brain Imaging and Behaviour Project (PIP), which follows 500 children diagnosed with autism, developmental delay, and/or epilepsy from 3 years of age (and ADHD from 4 years) through to 6 years, multiplex family studies, and experimental medicine studies). We use different study designs as each design has advantages, disadvantages, and systematically affects some participant characteristics (46). For example, PIP children who have received a clinical diagnosis of autism at 3–4 years are likely to have both stronger clinical features and care needs, to comprise a higher rate of co-occurring ID and to come more often from simplex families than autistic or ADHD children identified through infant-sibling designs (which are by definition multiplex). They may also include a higher percentage of Mottron's "prototypical autism" than LEAP, which includes participants who were diagnosed in adolescence or adulthood. Here, we adopt a more inclusive approach to participant selection (even if rarely truly autism-population representative), which has the advantage that we can directly compare mechanisms and markers between autistic participants that are *a priori* divided by particular characteristics (e.g., the developmental trajectory of "prototypical" vs less prototypical autistic children (7, 32). Hence, the study design needs to be taken into consideration when interpreting results of "subgroups" and replication attempts between study cohorts.

Conclusion

Over the past decade, biomarker studies aimed at informing precision medicine for autism have substantially influenced the research culture by impacting the design, sample size, quality, method development and methodological rigour. They necessitated and enabled multi-disciplinary collaborations of researchers across different areas of expertise, which more recently includes participatory research with autistic people and families. To date, the majority of studies has focused on identifying biomarkers based on single characteristics (or within the reductionist framework, individual "parts"). This was an important and (certainly from a practical perspective) necessary first step. Findings suggest that while some markers have probabilistic value of clinical utility, so far no characteristic has been identified that can demarcate diagnostic subgroups—as would be required to define autism as a biological entity. In this perspectice article I discussed both conceptual and methodological factors in these findings.

Conceptually, we need to explicitly acknowledge the context/condition in which 'parts' are measured, and consider their interactions. This includes the dynamic processes of brain and body over time (with the individuals as a "system") and dynamic processes of the individual interacting with others in their social environment (as broader social system).

I argued that as a field we are now in a position to develop such an approach. We have set up the infrastructure to conduct multi-disciplinary studies with sample sizes necessary to examine interactions. We have (and are developing) new technologies that allow us to examine participants over time at home, in school, nurseries. And we have changed the research culture to include autistic people and families with lived experience as equal partners in our research to ensure face validity and acceptance of models and methods aimed at increasing autistic well-being.

Ethics statement

The studies involving human participants were reviewed and approved by local/national ethics committees at each site. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

1 https://www.aims-2-trials.eu/

2 https://www.candy-project.eu/autism/

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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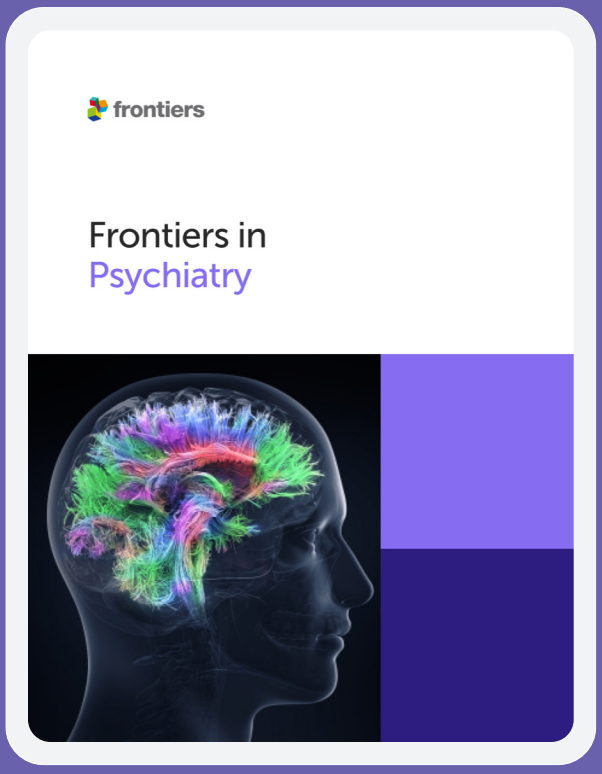

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