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Genesis, modelling and methodological remedies to autism heterogeneity

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ABSTRACT

Diagnostic criteria used in autism research have undergone a shift towards the inclusion of a larger population, paralleled by increasing, but variable, estimates of autism prevalence across clinical settings and continents. A categorical diagnosis of autism spectrum disorder is now consistent with large variations in language, intelligence, comorbidity, and severity, leading to a heterogeneous sample of individuals, increasingly distant from the initial prototypical descriptions. We review the history of autism diagnosis and subtyping, and the evidence of heterogeneity in autism at the cognitive, neurological, and genetic levels. We describe two strategies to address the problem of heterogeneity: clustering, and truncated-compartmentalized enrollment strategy based on prototype recognition. The advances made using clustering methods have been modest. We present an alternative, new strategy for dissecting autism heterogeneity, emphasizing incorporation of prototypical samples in research cohorts, comparison of subgroups defined by specific ranges of values for the clinical specifiers, and retesting the generality of neurobiological results considered to be acquired from the entire autism spectrum on prototypical cohorts defined by narrow specifiers values.

1. Background

There has been a surge in the reported prevalence of autism (from 1:150 in 2000–1:36 in 2020) (Maenner et al., 2023). This increase is attributed to a combination of the evolution of diagnostic criteria, case ascertainment issues, and socio-economic factors (Fombonne, 2018). There is little evidence to suggest that the increase is associated with environmental or genetic changes (Taylor et al., 2020). Recent meta-analytical work indicates that effect sizes have decreased by up to 80% in studies comparing neurocognitive variables between autism and neurotypical controls. Such a decline is evident for frequently used behavioral measures of emotional recognition, planning, and the capacity of cognitive perspective taking, together with brain size and EEG characteristics (Rodgaard et al., 2019). Furthermore, an autism diagnosis is given to individuals whose behavior is increasingly convergent with that of the non-autistic population (Arvidson et al., 2018). These findings suggest that the increase in autism prevalence may be partially caused by a broadening of the autism diagnosis. In parallel, a meta-analysis of the effect sizes of non-pharmacological early interventions has revealed a minimal or no overall effect in studies with a rigorous methodology (Sandbank et al., 2020), and authoritative practice guidelines (The NICE guideline, 2017) underscore how the benefit of such interventions varies between autistic individuals. Overall, there is not a single scientific statement that applies to all individuals composing the current spectrum.

This shift in diagnostic practices is generally seen as a step towards a better understanding of the autism entity, reflecting a spectrum of severity and various presentations. However, a more pessimistic interpretation is also possible: our capacity to distinguish between individuals with and without a diagnosis of autism may have decreased

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over time due to inclusion criteria that blur the signal of what autism actually is. Ultimately, autism is now typically construed as a spectrum of individuals whose phenotypic and adaptive characteristics vary significantly, which may hinder our capacity to build mechanistic models of the condition. Thus far, brain imaging has not significantly improved the diagnosis, prognosis, or staging of autistic individuals, despite substantial progress in methodologies and research concepts to characterize the autistic brain (Abraham et al., 2017; Bzdok et al., 2020). Similarly, although the genetic contribution to the risk of autism is high, genomic findings have not yet been translated into practical clinical applications, such as the identification of well delineated subgroups or pertinent behavioural dimensions, or into a refined molecular genetic architecture (Vorstman et al., 2017).

The conclusions derived from scientific studies on the nature of autism depend on the composition of the group under study, as different ways of constructing autism samples may over- and under-sample different parts of the autism population that may differ in the characteristics being studied, and results based on one sample may thus not generalize to other samples. The lack of reliability of the previous autism subcategories (Clarke et al., 2013; Regier et al., 2013) during the DSM-5 field trial gave way to a spectrum model that permitted the inclusion of heterogeneous samples in research. We have argued elsewhere (Mottron and Bzdok, 2020) how current diagnostic criteria can result in heterogeneity that assumes biological variability. Scientific studies carried out on this broader group may have resulted in inconsistent phenotypic and mechanistic findings, circularly confirming the heterogeneity of the autism spectrum (see (Mottron, 2021b) for further development and schema of such a self-amplifying circle).

The heterogeneity of autism and the reification issue evident in all mental health disorders was addressed by the multidimensional biobehavioral framework proposed by the Research Domain Criteria Initiative (RDoC), with great expectations (National Institute of Mental Health (NIMH), 2011). Twelve years after the RDoC matrix was launched, both the discovery potential of this strategy and the scientific justification behind each dimension and construct of the matrix remain open to discussion (Demetriou et al., 2019; Fusar-Poli et al., 2019; Ross and Margolis, 2019). Considerable research is still needed to test the power of discovery of its starting principle (Clark et al., 2017; Clarkson et al., 2019) and the exclusion of alternative models seems premature (Joober, 2013). There is a growing body of research based on DSM-5 spectrum diagnoses and using dimensional behavioral traits via instruments such as the Social Responsiveness Scale (SRS) (Constantino et al., 2003) and the Autism Quotient (Baron-Cohen et al., 2001). However, this line of research has not conclusively proven that the condition is essentially a continuum of autistic traits nor refuted it. We are interested in alternatives to the current dominant approaches being used to address the heterogeneity problem in autism research.

Here, we first review the history of autism diagnosis and subtyping, which evolved from the bottom-up recognition of a new prototypical condition towards a top-down diagnosis of an autism spectrum disorder given via the DSM-5 criteria. We argue that the implementation of DSM criteria in the standardized diagnostic instruments and their use for the selection of research cohorts have contributed to the observed heterogeneity of autism. We then review evidence of autism heterogeneity at the phenotypic, neuroimaging, and genetic levels. Finally, we propose two research strategies to address the current problems of heterogeneity: 1) stratifying the existing population into subgroups; and 2) taking an alternative path, turning away from very large and diverse databases in favour of prototype-based case ascertainment.

A disclaimer needs to be stated at this point. This article examines the strengths and weaknesses of a strategy that has dominated autism research for several decades and proposes a new heuristic strategy to address a specific research question. Although we may propose changes to inclusion criteria within *research* cohorts, we strongly advocate for a *care-based system* that should be available for everyone based on their individual and specific needs, independent of their research diagnosis.

2. From discovery of autism to research cohorts of autism spectrum

2.1. Reasoning in clinical science

Modern scientific studies of a psychopathological condition have generally followed a similar trajectory, transitioning from a prototype to a check-list description (Foucher and Greene, 2010; Vanheule, 2017). This section focuses on the balance between reliability and validity and maps the historical evolution from the prototype-based DSM-1 to the criteria-based DSM-5 for most psychiatric conditions.

The emergence of a clinically recognisable pattern in an astute clinician's mind is followed by the *description of a prototype* by its discoverer. A prototype is a representation created from a subjective, implicit process of expert observers, accounting for the recognition of a concrete or abstract pattern (Smith, 2014). The creation of a prototype occurs by mentally averaging frequently encountered exemplars that possess an objective resemblance. In the case of a clinical prototype, this process can be made explicit and transmissible by a qualitative paragraph describing inter-related features in a complete and pure syndrome (Westen et al., 2012). It is therefore a bottom-up process (from observation to identification and labelling), averaging the characteristics shared by an emerging clinical pattern: there is no pre-existing relevant category before the seminal description of the new category. The clinical and scientific community then proposes a *standardized description* that conserves the essence of the initial one, without its subjective or anecdotal aspects. This allows the condition to be consistently rated by different clinicians, increasing reliability in the initial absence of a biomarker or diagnostic test. A later step consists of testing the *phenotypic and mechanistic homogeneity* of the resulting category. If growing heterogeneity is found while researching the pathophysiological mechanisms of the condition, the biological variability inherent in the category should be disentangled from the "epistemic" uncertainty that results from an incomplete understanding of the observed phenomenon. Autism research is undergoing a process such as that outlined above, which will be described in detail in the rest of this article.

2.2. Early recognition of clinical prototypes

The clinical pattern of autism symptoms emerged in the minds of several clinicians in the first half of the 20th century. Ssucharewa (Ssucharewa and Wolff, 1996) and Frankl and Weiss (Robison, 2017) detected it but did not influence future classifications. In contrast, Kanner's description of "autistic disturbance of affective contact" (1943) and Asperger's definition of "autistic psychopathy" (1944), with partially overlapping clinical patterns, had a major influence on the classification systems (Fig. 1, left). The first two clinical descriptions were relatively homogeneous, each emerging as a recognizable pattern independently of intellectual level.

Heterogeneity appears to have started to increase when the research community attempted to forge an explicit definition that encompassed several *recognizable* prototypes. This began with the suggestion by Wing and Gould (Wing, 1981; Wing and Gould, 1979) that Kanner's and Asperger's descriptions could be embedded in the same broad category of social abnormalities. Further, merging individual categories into such a meta-category had the effect that some individuals who were not included in either of the original categories were included in the new broader category. Hence, the combination of encountered psychopathological configurations increased heterogeneity, leading to the notion of a spectrum. The recent effort to leverage large multi-dimensional datasets to stratify the spectrum into subgroups may thus constitute a "back to the future" attempt to deconstruct the merging of several recognizable clinical patterns into an abstractly defined DSM category.

The balance between bottom-up recognition of a clinical symptom pattern and top-down, checklist-oriented, dimensional-battery measures evolved along with the versions of the DSM, up to and including a)

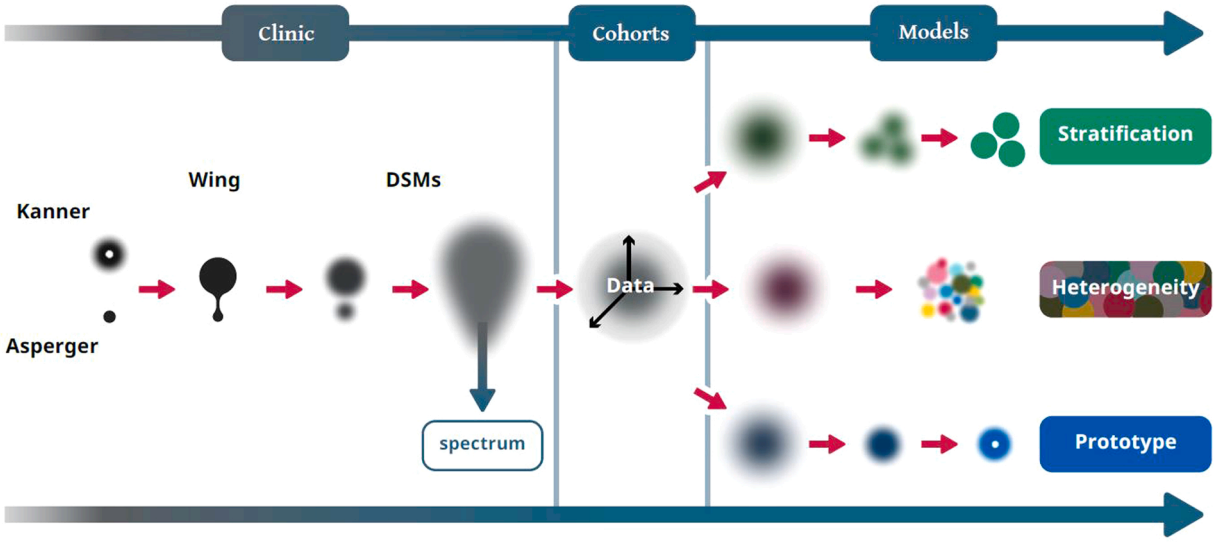

Fig. 1. Historical steps in the drift of autism from a prototype to a heterogeneous spectrum (left). The autism spectrum "filled the holes" between the original descriptions, previously individualized under the names of their discoverers, and thus reified the current continuous dimensional perspective. Addressing the ensuing heterogeneity issue may (from top right to bottom right) result in stratifying the initial category into homogeneous subgroups, dissolving it into an indefinite number of poorly related mechanisms, or reducing it to a narrower prototype.

abstractly described, b) unrelated, and c) dimensional elementary signs. This evolution is classically presented as a simple broadening of criteria, reflecting that the same condition has different degrees of penetrance, thus applicable to a steadily increasing number of individuals (Happe and Frith, 2020). Alternatively, an increasing mismatch between autism, as recognised by expert clinicians, and autism, as defined by a list of criteria, could have major consequences on autism research.

2.3. *The evolution of a DSM criteria-based standardised description*

Classifications mainly gather signs into recognizable syndromes and disorders and fulfill a technical and clinical need. Clinical diagnoses meet several criteria, including mechanisms and response to treatment (validity) and reliability (e.g. test-retest stability) (Jablensky, 2016). These constraints leave open the order in which they should be prioritized in the history of science. In psychiatry, in which the underlying mechanisms are largely unknown, later DSM versions opted for reliability as a first goal. Although some authors have argued that psychiatric diagnostic labels should fit scientific models (Foucher and Greene, 2010; Ghaemi, 2016), the DSM classification, while having a practical use and reasonable reliability, generally does not fit the validity criterion, and does not yet rely upon any mechanistic model or testable hypothesis (Bruckl et al., 2020). This limits its usefulness in a scientific context and in the worst case, may prevent scientific progress.

Historically, psychiatric nosology aimed to fit reliability criteria after Spitzer and Fleiss (1974) criticized prototype-based diagnoses and advocated for a checklist-based process. Following such a trend, the DSM-III (1980) criteria included a category for "infantile autism" without a detailed description. Later onset or incomplete presentations were separated from the main category. The DSM-III-R (1987) criteria added extensive qualitative information, e.g. a rich description of autistic language signs, improving its reliability and utility (Rosen et al., 2021). The DSM-IV (1994) criteria expanded the pervasive developmental disorders (PDD) category to also include a category for Asperger Disorder. A gradient of prototypicality was preserved, with autism being more specifically described than Asperger Disorder, and Asperger Disorder more so than "PDD not otherwise-specified" (PDD-NOS). The DSM-IV criteria allowed the subgroups to be studied separately, but some results showed the inter-site reliability of PDD subgroups to be questionable, particularly the PDD-NOS category (Lord et al., 2012; Lord et al., 2012; Walker et al., 2004). It might have been beneficial to have conducted a rigorous scientific examination of PDD-NOS to demonstrate the common pathophysiological mechanisms with autism before merging it into a global autism spectrum category for scientific purposes (Mandy et al., 2011). Rett syndrome was included in PDD but still distinguished from other PDD diagnoses. Other equally "pervasive" neurogenetic conditions, with a phenotype partially overlapping that of autism (Angelman, William, Prader-Willi, Tuberous Sclerosis, Fragile X) were not explicitly included in PDD.

Planning for the upcoming DSM-5 revision, the contributors published a series of suggestions oriented to the research community to improve the scientific basis of the classification. In their research agenda, the authors noted that the "reification of DSM-IV entities, to the point that they are considered to be equivalent to diseases, is more likely to obscure than to elucidate research findings". These authors further noted that "research exclusively focused on refining the DSM defined syndromes may never be successful in uncovering their underlying aetiologies" (First et al., 2002). Despite warnings of the diminished reliability of spectrum diagnoses relative to core phenotypes and that broadened definitions would not necessarily enhance the findings (First et al., 2002), the DSM-5 replaced categorical DSM-IV subtypes by a single categorical diagnosis, Autism Spectrum Disorder. The DSM-5 preface states that the diagnosis must be made considering the clinical expertise of the acting healthcare professional and that the criteria cannot be applied as a check list. However, this precaution does not translate to guidelines on how to restrict the application of these criteria.

The DSM-5 criteria include three socio-communicative signs that are all required for diagnosis, which compared to the DSM-IV, in which two of four were required, was predicted to increase specificity (M. J. (Maenner et al., 2014). Contrary to this prediction, the reported prevalence kept increasing (Fig. 2). This increase was associated with large variations in autism prevalence estimates and detection methodologies among sites, revealing persistent case ascertainment issues (Chiarotti and Venerosi, 2020), as systematic community surveys did not confirm this increase (Disease et al., 2018). DSM-IV Autistic and Asperger syndrome individuals were also merged into a single category, as they were poorly discriminated. This decision increased the abstract nature of the category, with criteria that can encompass both of these clinical patterns. This was also the case for the PDD-NOS category, which was retrospectively included in the new spectrum.

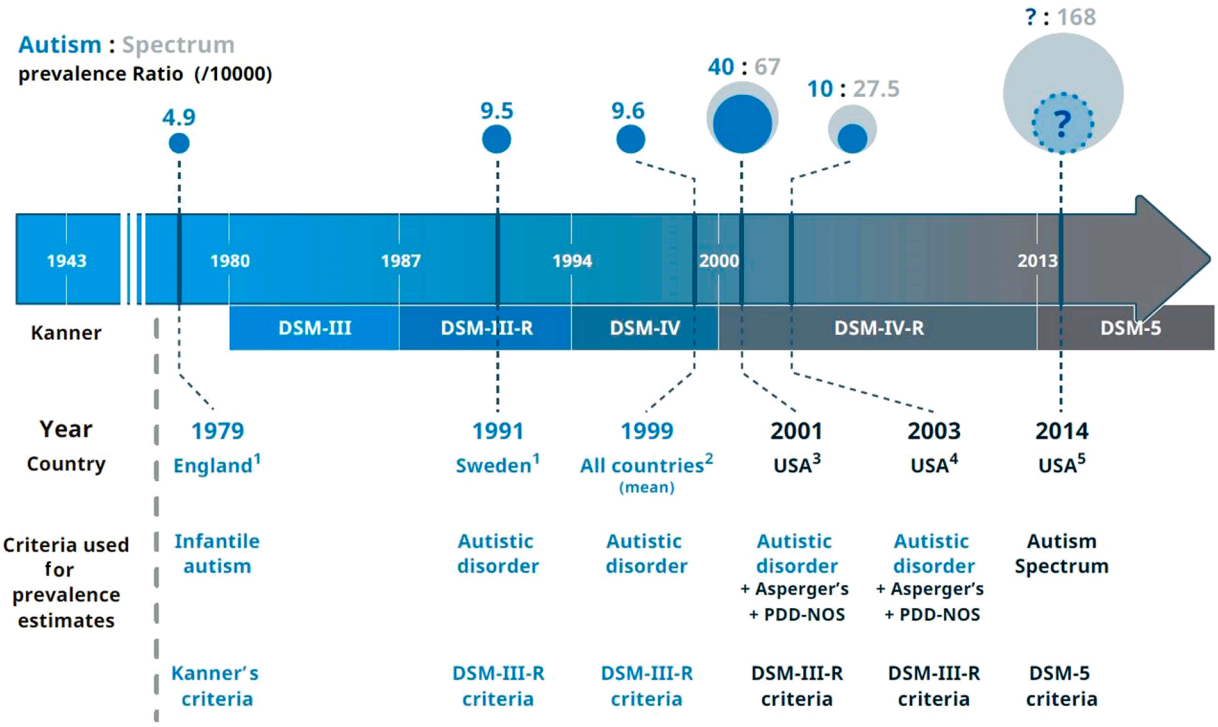

Fig. 2. Autism and Autism spectrum prevalence estimates through time and changing classification criteria. Methodologies may vary between studies. Relative proportions of autism (blue) and autism spectrum (grey) are colour coded. 1: (Yeargin-Allsopp, 2002); 2: (Gillberg and Wing, 1999); 3: (Bertrand et al., 2001); 4: (Tidmarsh and Volkmar, 2003), 5: (Baio et al., 2018).

A century of evolution has considerably broadened how we understand autism and by extension (Malpas and Davidson, 2012), the group of individuals that is given the diagnosis. This historical trend can be represented as a move toward a higher level in the hierarchical taxonomy. In the DSM-IV, autism was, together with Asperger syndrome and PDD-NOS, under the PDD category, and at the same level as myriads of neurodevelopmental conditions. The transition to a spectrum moved autism to a higher level in the taxonomy, encompassing all PDD categories. Finally, the inclusion of neurogenetic conditions under the comorbidity specifier introduced the syndromic fraction into the spectrum. This models the apparent gain in reliability between "autism spectrum" and the DSM-IV subgroups, the apparent increase in the prevalence of the autism spectrum according to DSM-5, and the finding of autistic traits in an indefinite number of non-autistic conditions (Mottron and Bzdok, 2020). However, it may also model the loss of specific information documenting the lower level of the hierarchy, including prototypical autism. We have highlighted some of these questions, with further details in Table 1.

Table 1
Dominant versus alternative cohorts and analyses addressing major autism research questions.

Research question	Dominant practices and beliefs	Instruments and Methods	Existing cohorts	Alternative hypotheses	Instruments and Methods	Suitable cohorts
Are there homogeneous subgroups in the Autism spectrum?	Autism spectrum heterogeneity reflects an indefinite variety of mechanisms	*Semi-quantitative or quantitative instruments * Unsupervised **Subgroup-last** clustering	Large, untruncated "spectrum" cohorts	Prototypical autism is homogeneous, reflecting a specific mechanism distinct from its risk factor	*semi-supervised **Subgroup-first** strategy *case-control, maximizing differences	Truncated-compartmentalized cohorts, crossing prototype judgment and check-list diagnosis
Are there autism-specific symptoms?	Independent autistic traits are normally distributed in the non-clinical population and over-represented in the non-autistic clinical population	Quantitative-trait studies in the general population and non-autistic conditions	idem	Constellations of signs form a recognizable prototype distinct from "autistic traits"	Qualitative sign studies refining their autistic nature	idem
Are there distinct neurobiological mechanisms for syndromic and non-syndromic autism?	Non-syndromic and syndromic autism both result from large series of distinct genetic mechanisms	* Quantitative instruments (SRS, AQ) * Genetic studies on large cohorts merging clinical and non-clinical populations * Animal models built from identified genetic syndromes	"Mutated" cohorts	Non-syndromic autism has a distinct aetiology, phenotype and trajectory, different from that of syndromic autism	*Qualitative instruments *mutated/non mutated comparisons *Del vs. Dup comparisons	Independent "mutated" and "non-mutated" cohorts Independent "prototypical" and "traits" cohort

We will now examine how the uncertainties in the delineation of the autism category translate into research methodologies through the use of standardized diagnostic instruments and broad inclusion criteria.

2.4. Implementing DSM criteria: inclusion of participants in autism research

2.4.1. Diagnostic instruments for autism diagnosis used to include participants in research cohorts

In the absence of a biological gold standard for the diagnosis of autism, the validity of diagnostic instruments is measured by comparing the diagnostic threshold of the instruments with that of clinical experts. When these experts use the DSM-5 criteria for their decision, validity is, at best, the correspondence between the two sets of criteria. As one set of criteria is constructed to map the other, any decision concerning validity is plagued by circularity.

The gold standard for the inclusion of autistic individuals in research studies is an above-cut-off score for the retrospective Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000; Lord et al., 2012) standardized instruments. These instruments were created approximately 30 years ago to provide a reliable method to score DSM-III-R and later DSM-IV diagnoses for research purposes. ADI-R and ADOS-G provide semi-standardized contexts, allowing scoring of the presence or absence of an autism sign. The sum of scores for a selected series of signs, each with an equivalent weight, is compared to two diagnostic thresholds, a higher one for autism and a lower one for autism spectrum in the ADOS-G. Similar to studies using quantitative instruments focussed on social signs (Constantino, 2011), these instruments provide a continuous distribution of autism and autism spectrum signs (Lord et al., 2000). The diagnostic "threshold" of the *severity* score can be reached as a result of either "lots of 1 s" or, alternatively, "a few 2 s". In other words, several signs, each low and unreliable by themselves, can be combined to give the same autism classification as that given to an individual with few clear prototypical signs.

Although ADOS inter-rater reliability is excellent (Lord et al., 2000), its test-retest stability varies from high (Lord et al., 2000) to very low throughout development (Bachmann et al., 2018). The specificity of ADOS is approximately 80% at preschool age (de Bildt et al., 2009; Kamp-Becker et al., 2013; Randall et al., 2018), but may be substantially lower in some age groups and settings. Specificity has been shown to decrease after preschool age. When ADOS is used in a clinical environment (Fombonne, 2018; Molloy et al., 2011) and by less specialized clinicians (Kamp-Becker et al., 2018), the specificity also decreases in the presence of emotional and behavioral issues (Havdahl et al., 2016), intellectual disability (Pedersen et al., 2017; Sappok et al., 2013), and complex psychiatric conditions in adults (Maddox et al., 2017). These limitations are even more evident for the subthreshold "autism spectrum" ADOS cut-off (Kamp-Becker et al., 2013), with approximately 30% of participants misclassified relative to the clinical judgment. Despite these limitations, the ADOS scores and DSM criteria are currently universally used as the gold standard for inclusion in studies and research databases, as we will discuss in the following section.

2.4.2. Inclusion criteria in autism research

The databases on which a growing part of autism research is carried out no longer distinguish between the potentially different clinical forms represented within the autism population. Although the DSM-5 recommends modulating the application of diagnostic criteria by clinical experience, no guidelines are provided for such a process. To the best of our knowledge, prototypicality has never been used as an inclusion criterion in the major existing autism research cohorts, such as the Simons Simplex Collection (SSC), LEAP, ABIDE I and II, the Australian Autism Biobank, and Pathways, nor in ad-hoc construed worldwide cohorts obtained by merging more limited local samples. The set of DSM-IV and DSM-5 criteria and specifiers allows significant variability concerning the prototypicality of autism, which is transferred to the enrolment process of participants in research databases.

Examination of the inclusion criteria of the autism databases mentioned above shows the three main subgroups defined by the DSM-IV (e.g. autistic disorder, PDD-NOS, and Asperger syndrome) to be included in the SSC, Pathways, and ABIDE I. The entire autism spectrum is included when using the DSM-5 criteria, which is used in ABIDE II. Several other databases are recruiting participants on the basis of a diagnosis using either DSM-IV or DSM-5 criteria, such as the Australian Autism Biobank and the LEAP cohort. It must be noted that some of these databases are being created on a longitudinal timeframe (SSC, LEAP), which might add complexity to the recruitment criteria (accepting DSM-IV or DSM-5 or ICD-10 criteria, for example) and that the inclusion into the databases is sometimes executed retrospectively to the phenotypic and imaging characterisation of the participants (ABIDE I and II). These retrospective methods of recruitment in ABIDE I and II are justified in the research community by the need for large databases and the difficulty of developing prospective experimental neuroimaging studies (Di Martino et al., 2014).

Despite assessing participants through the ADOS and/or ADI-R tools, meeting the autism threshold is not always mandatory in some databases, such as the SSC (for which meeting the "autism spectrum" subthreshold of ADOS-G is sufficient) and ABIDE I and II (for which the final inclusion decision is dependent upon the best clinical judgment and/or prior medical record documenting the ASD diagnosis, whether the "autism" threshold with the ADOS/ADI-R is attained or not). These various methodological decisions suggest that current research using autism databases is largely based on the idea of a spectrum, consistent with the DSM-5. In the following section, we will describe how cognitive, imaging, and genetic studies are hampered by the resulting heterogeneity of the populations they study.

3. Testing the phenotypic and mechanistic homogeneity of the autism category

3.1. Autism heterogeneity in cognitive models

The studies of cognitive markers of autism experienced a golden age at the end of the 20th century. Several cognitive models centered on the deficit or the over-functioning of a cognitive function were proposed to account for autistic behavioral symptoms: theory of mind (ToM), weak central coherence, and enhanced perceptual functioning (EPF). Each model produced its share of explanations of social and non-social signs and followed the same historical evolution: starting by trying to explain common signs in a majority of autistic people, then limiting themselves to certain signs in a subgroup of the spectrum. This was the case, for example, with ToM cognitive models (Frith and Frith, 2005). A deficit of ToM was first proposed as a unifying basis underpinning the collection of autistic socio-communicative abnormalities. A second generation of studies demonstrated older, more intelligent, and more highly verbal autistic people could often pass in ToM (Bowler, 1992) tasks. This is also the case for EPF in the visual modality. This type of research showed large differences between prototypical autism and neurotypical controls (Caron et al., 2006). These cognitive differences, consistent with atypical functioning in the perceptual expertise regions in brain imaging (Hong et al., 2019; Sapey-Triomphe et al., 2019), were only modestly reflected in meta-analyses (Van der Hallen et al., 2015). A similar trajectory for EPF occurred in the auditory modality. Superior perception of pitch in prototypical autistic individuals (Bonnel et al., 2003; Heaton, 2003; O'Connor, 2012), became blurred when measured in an autistic population with fewer prototypical presentations (Bonnel et al., 2010; Eigsti and Fein, 2013; Jones et al., 2009). Such a trend, which is independent of sample size, has occurred for many markers of constructs relevant to autism (Rodgaard et al., 2019).

3.2. Autism heterogeneity in neuroimaging

By opening a non-invasive window into the structure, function, and connectivity in the living brain, at the millimetric and increasingly sub-millimetric scale, neuroimaging techniques, such as magnetic resonance imaging (MRI), represent a natural choice to identify the biological substrates of autism. These measurements also promise to bridge molecular mechanisms with behavioral symptoms (Bernhardt et al., 2017; Lariviere et al., 2019). Furthermore, recent open-access initiatives, such as ABIDE (Di Martino et al., 2017; Di Martino et al., 2014), have aggregated the neuroimaging data of hundreds of individuals with an autism diagnosis (DSM-IV as well as DSM-5, generally idiopathic autism) and incorporated matched neurotypical controls across multiple sites. In parallel, meta- and mega-analytical efforts, such as the ENIGMA initiatives (van Rooij et al., 2018), have provided a solid complementary platform to pool large, multi-centric cohorts of individuals with autism alongside neurotypical controls. More recently, the advent of trans-diagnostic samples, such as the healthy-brain network (HBN) (Alexander et al., 2017), offers the analysis of individuals with an autism diagnosis vis-à-vis typical non-autistic individuals and those with other neurodevelopmental conditions. Furthermore, the EU-Aims initiative provides unmatched longitudinal data from individuals with autistic and typically developing people (Loth et al., 2017).

Autism neuroimaging research has traditionally followed conventional case-control designs that compare individuals with a broad autism diagnosis to controls (Lombardo et al., 2019; Ecker, 2017; Bernhardt et al., 2017 for reviews). At the level of structural brain imaging, these studies have generally converged on patterns of cortical thickening in individuals with autism relative to controls, affecting largely frontal and temporal lobe regions (Bedford et al., 2020; Valk et al., 2015; van Rooij et al., 2018). Effect sizes have been small to moderate and the strength of the effect is somewhat heterogeneous across sites (Abraham et al., 2017). Other work has shown cortical thinning or null findings (Haar et al., 2016). In addition to the variability in case-control differences, a further challenge has been the difficulty to identify structural markers that correlate with the severity of the condition when an entire ASD population is analyzed (Hong et al., 2018; Valk et al., 2015). Heterogeneity in the findings has been recognized and certain studies furthermore emphasized that aspects of preprocessing, confounding factors, and sample characteristics may influence findings and conclusions (King et al., 2019; Mueller et al., 2012).

At the level of functional connectivity, numerous studies based on resting-state acquisition have indicated that autistic individuals often present with a mosaic pattern of reduced connectivity between distributed cortical regions relative to controls (Di Martino et al., 2014; Hong et al., 2019; Mueller et al., 2012), often in both higher-order association cortices and lower-order sensory and motor regions. These reductions in connectivity in cortical regions sometimes co-occur with patches of increased connectivity, for example between cortical and subcortical nodes (Cerliani et al., 2015).

A few studies have explicitly tackled heterogeneity in broadly defined autism cohorts, based on both dimensional as well as categorical decompositions of structural as well as functional imaging markers. These studies overall support the notion that neural substrates are indeed heterogenous, and that such efforts could potentially help to identify more clinically meaningful subgroups within the larger autism 'spectrum'(Buch et al., 2023; Hong et al., 2018, 2020).

3.3. What genetics has taught us about the heterogeneity and mechanistic architecture of autism

Autism is a highly heritable psychiatric condition (64–91%) (Tick et al., 2016). In the early years of DSM-IV, the community of autism researchers was divided between those who believed autism to be explained by only a few mutations, each forming a homogeneous subgroup (Rutter, 1999), and those for whom autism was a phenotype of multiple conditions, most being genetically determined by a large number of inherited mutations (Gillberg and Coleman, 1996). Consistent with this latter model, many well defined and rare developmental disorders include autistic features in their presentation. Genetic studies have since identified a steadily increasing number of rare and common variants associated with a diagnosis of ASD.

In contrast to neurological conditions, for which there is often a correspondence between a clinical diagnosis and a genetic variant (e.g. Spinal Muscular Atrophy) (Melki et al., 1990), the genetic architecture of autism, and psychiatric conditions in general, has proven to be highly complex. Current data have shown that a) most of the heritability is driven by common variants (Gaugler et al., 2014), b) common and rare variants associated with autism are often associated with other psychiatric conditions (Brainstorm et al., 2018), c) rare large effect-size variants are all associated with a decrease in cognitive abilities (Myers et al., 2020) and like common variants, most are associated with more than one condition and a range of cognitive and behavioral symptoms, d) the clinical presentation of syndromic autistic individuals associated with rare variants substantially diverges from prototypical autism in most (Bishop et al., 2017; Moss and Howlin, 2009), but not all cases, e) the contribution to a large proportion of autism risk and severity remains unaccounted for (Pohl et al., 2019), and f) the overall risk for autism and other conditions (i.e. schizophrenia) appears to be highly redundant and distributed across the genome (Boyle et al., 2017; Douard et al., 2021).

The existence of "subclinical" forms, juxtaposed with the gradient of prototypicality found within so-called clinical subgroup presentations, is a major argument favoring the concept of an autism *spectrum*. The notion of a broader autistic phenotype (Boddaert et al., 2001), which emerged towards the end of the 20th century but suspected by Kanner and Asperger, represents a range of social, behavioral, emotional, cognitive, and personality atypicality found in the first-degree relatives of an autistic individual (See Bailey et al., 1998; Parr and Le Couteur, 2013) for historical reviews). Beyond the broad autism phenotype (BAP), a range of psychiatric diagnoses have been established in siblings of individuals with autism. A Finnish prenatal registry (Jokiranta-Olkoniemi et al., 2016) showed that 37% of siblings presented a psychiatric diagnosis (RR = 2.5). Autism represented the highest risk, but the diagnoses covered a broad range of adult and childhood onset conditions, including ADHD, tics, conduct disorders, and psychosis, consistent with the genetic correlation observed between these conditions and discussed above. BAP is, along with the increased familial risk of recurrence and twin concordance studies, one of the three pillars demonstrating the role of genetics in autism (Tick et al., 2016).

Common variants have been estimated to account for a major part of ASD risk, but robust results have only been published recently due to the difficulties of assembling large cohorts (Gaugler et al., 2014; Grove et al., 2019). Several genome-wide association studies (GWAS) have established the positive genetic correlation between autism, high IQ (Rao et al., 2022), and high education attainment (Clarke et al., 2016), as well as major depression, schizophrenia, and ADHD. Although these correlations are weaker than those between more closely related conditions, such as bipolar disorder and schizophrenia ($r = 0.8$), such commonalities imply that genetic risk factors are shared between ASD and other clinical conditions or non-clinical traits (Grove et al., 2019).

De novo large effect-size copy-number variants (CNVs) and gene-disrupting single nucleotide variants (SNV) have been identified in 10–20% of individuals with autism, as currently defined (Jiang et al., 2013; Monteiro et al., 2019; Napoli et al., 2018; Sanders et al., 2015; Tammimies et al., 2015). They collectively explain less than 5% of the overall heritability. The largest autism case-control association studies to date formally associated rare variants in 102 genes and 16 CNVs at 13 genomic loci with autism (Sanders et al., 2019). Many more genomic loci are likely to be involved, as suggested by the overall increase in CNV burden associated with autism (Abrahams et al., 2013; Krumm et al., 2015; Marshall et al., 2017; Moreno-De-Luca et al., 2013; Sanders et al., 2019). Rare variants that affect gene dosage (CNVs and loss-of-function

SNVs) invariably decrease IQ and gross motor skills but they nevertheless remain associated with autism –as currently defined– even after adjusting for their effects on cognitive ability (Douard et al., 2021). That is, individuals with autism and an IQ > 85 have more mutations that decrease IQ than IQ-matched controls.

Although there are reasons to be optimistic about the role of genetics in autism research and its future role in the understanding of autism heterogeneity, several big challenges loom ahead. We have certainly gathered sufficiently large cohorts and designed the proper tools, but currently, genomic variants only account for a small fraction of autism risk. Gene-first studies aiming to understand the effect of genomic variants are lagging behind genomic association studies. Our ability to understand the impact of variants on psychiatric symptomatology and domains and neurocognitive ability is limited in several ways: the effect sizes of common variants are too small to be studied individually and the effect on cognitive and behavioral traits remains poorly understood. Most studies of large effect-size variants were performed through neurodevelopmental and autism cohorts, which presumably represent a significant bias related to the clinical inclusion criteria of these groups. Only a few studies have been conducted in unselected populations presenting these variants (Huguet et al., 2018). Large-scale genetic-first studies combining a variety of ascertainments, including prototypical autism, other psychiatric conditions, and general population cohorts, is recommended to avoid this potentially circular process. We will now present two different approaches that could reduce the heterogeneity in autism research.

4. Redefining the population of interest

4.1. Top-down stratification of the autism spectrum

The current level of heterogeneity suggests that the umbrella term of the autism spectrum may encompass a collection of several subgroups. If this is true, traditional case-control analyses of the entire autism spectrum may blur or misinterpret the composite signal originating from the subgroups (Easson et al., 2019; Khundrakpam et al., 2017). It is possible that such subgroups could be identified from patterns that exist in only a part of the autism population. The existing literature contains several cases of such patterns. For example, grouping individuals with autism based on the presence or absence of speech onset delay results in group-level differences for multiple variables, which could be explained by speech onset delay being an indicator for separate autism subgroups (Mottron and Bzdok, 2020). Similarly, genetic data has provided suggestions for possible autism subgroups. The largest autism GWAS to date showed that genetic correlations between autism, IQ, educational attainment, and other psychiatric diagnoses varied across four autism subgroups: childhood autism, Asperger's, atypical autism, and other PDDs (Grove et al., 2019). Although schizophrenia and major depression showed similar genetic correlations with all four subgroups, only higher IQ and higher educational attainment showed correlations with autism and Asperger's. On the other hand, neuroticism showed higher correlations with PDD and atypical autism. Approaches comparing genetic findings across the autism spectrum have also shown that heritability is higher in autism without ID than in autism with ID (Grove et al., 2019), which may be due to higher levels of *de novo* mutations in autistic individuals with ID. Autism associated with large effect-size rare variants and polygenic autism may represent separate subgroups of which the reciprocal informative value may therefore be more limited than currently accepted, due to their phenotypic and genetic dissimilarities.

In addition to suggesting autism subtypes based on group-level differences in phenotype or observed mechanisms, the current autism spectrum could be subdivided using data-driven approaches, such as cluster analysis. Cluster analysis is a set of analytical methods that aim to divide datasets into smaller subsets or clusters to identify subgroups that are more homogenous than the sample as a whole (Tan et al., 2005). Methods such as hierarchical clustering (Hong et al., 2018), k-means clustering (Easson et al., 2019), normative modelling (Zabihi et al., 2019), and hybrid latent factor modelling techniques (Kernbach et al., 2018) have been used in autism research on cognitive, behavioural, and symptom severity data, some of them since the 1990s (Eaves et al., 1994; Sevin et al., 1995) to better understand the nature of autism heterogeneity. Cluster analyses in autism research have mainly included phenotypic variables, such as IQ scores (Bitsika et al., 2008), ADI-R data (Hu and Steinberg, 2009), and sensory processing data (Lane et al., 2010). Recent years have furthermore seen novel attempts to identify subgroups based on structural and functional neuroimaging features (Easson et al., 2019) (for reviews on this topic, see (Hong et al., 2020; Lombardo et al., 2019)). Agelink van Rentergem et al. (2021) have recently reviewed methodologies used in autism subtyping studies, and discuss different approaches to validating the clustering results, including replication in independent sample and external validation.

The number of reported clusters varies widely between previously published cluster analyses in autism research (Syriopoulou-Delli and Papaefstathiou, 2019) and many studies have not replicated the reported clusters in an independent sample (Wolfers et al., 2019). Only a few studies have attempted to externally validate the clusters, e.g. by comparing them on variables at a different level (e.g. genetic, structural and functional neuroimaging, or cognition and behavior) than those used to create the clusters (Wolfers et al., 2019). Almost no studies found the autism population to not consist of multiple clusters (Agelink van Rentergem et al., 2021), which may in part be explained by the fact that commonly used clustering methods do not compare the identified clusters to the null hypothesis that there is only a single large cluster (Wolfers et al., 2019). Multi-cluster solutions may thus be incorrectly favored because clustering algorithms can mistakenly identify random variations in the data as evidence of distinct subgroups (a false positive). Such methodological challenges may have contributed to the previous results not being consistent.

Even if the above methodological problems are addressed, it is still uncertain whether future cluster analyses will identify reliable and biologically valid subgroups. The ability to identify such subgroups is challenged by the *curse of dimensionality*. This term describes the phenomenon that the sample size required for accurately estimating a multivariate distribution grows exponentially when the number of variables increases (Feczko et al., 2019). If a cluster analysis includes many variables that are unrelated to the subgroups, the sample size necessary to detect the subgroups becomes prohibitively large. Therefore, cluster analysis algorithms should be performed using variables that are selected based on their biological relevance to autism subgroups or their correlation with such biologically relevant variables (Feczko et al., 2019). This constraint makes it unlikely that new categorical autism subgroups can be identified by blindly analysing a vast number of diverse variables using cluster analysis. By contrast, decades of autism research and clinical work have highlighted phenotypic domains in which potential subgroups might differ, including speech onset history (Mottron et al., 2014), and the cognitive profiles (Chiang et al., 2014).

Such knowledge of clinical indicators may allow researchers to select variables that reflect subgroup differences (Lai et al., 2013) and thereby constrain the analysis to a manageable number of variables. However, subgroup differences may exist only during certain developmental periods (Hatch et al., 2020) or under certain conditions (Jackson et al., 2018). In this case, and as long as these conditions are unknown, this will drastically increase the number of variables that must be considered and increase the sample sizes required. Whether cluster analysis can successfully identify potential categorical autism subgroups will likely depend on whether the subgroups differ for variables that can be easily measured and how consistent these differences are throughout development and across situational contexts. It is also possible that the ASD spectrum, as currently defined, has become so heterogeneous that it contains a large number of essentially different groups that cannot be disentangled through a cluster-analysis approach. In that case, ASD may be best described not by subgroups, but at the individual level (Wolfers

et al., 2019). Such diversity might be reduced through careful case selection based on features such as age, sex, IQ, age when autism was diagnosed, or behavioural traits (Bedford et al., 2020), or it may require a bottom-up redefinition of the phenotype.

4.2. Bottom-up redefinition of autism

In addition to the top-down stratification of the autism spectrum, we suggest that the current issues concerning heterogeneity could be addressed through a bottom-up redefinition of autism. This strategy consists of creating a prototypicality measurement based on the expert judgment on the *frequency* at which a similar presentation has been previously encountered and considered to be autistic, the *speed* at which autism has been clinically identified, and the *exemplarity* of the encountered individuals for teaching purposes. Whereas diagnostic checklists verify the presence or absence of relevant independent behaviors, prototypicality rating consists of holistically grading how a clinical case matches a prototype (Westen, 2012). Although prototype diagnosis has been demonstrated to be equally reliable to criteria-based diagnosis for personality disorders (Westen et al., 2010; Zimmerman, 2011), mood disorders (DeFife et al., 2013), anxiety (Huprich et al., 2019; Nagar et al., 2018), and eating disorders (Ortigo et al., 2010), only limited empirical investigations have been conducted in autism. (de Marchena and Miller, 2017) Our proposition for a research program allowing to redesign a prototype of autism comprises three stages: weighting of a grid of qualitatively defined signs, construction of an instrument with weighted signs, and study of the distribution of these signs in a sample of autistic children and a pediatric control sample. In the first stage, a list of qualitatively defined social and behavioral signs (e.g. lateral/obstructed glances (Miller et al., 2021; Mottron et al., 2007)) will be submitted to experts through a DELPHI methodology. This step will result in a list of signs that will be weighted depending on their respective contribution to autism diagnostic certainty. In the second stage, a clinical algorithm tool whose sum-variable is prototypicality, and not severity, will be created from the weighted signs. In the third stage, this prototypicality measurement tool will be tested in different clinical and non-clinical populations. The tool could then be used in the building of research cohorts.

Limiting the possible divergence from prototypicality in research-oriented cohorts represents an alternative, unexplored approach to delineate a phenotypic gold standard (Mottron, 2021a). A prototypical autism cohort would gather individuals with a high sum-score at the prototypicality measurement and who are maximally similar in terms of specifier values: *language* (being non or minimally verbal at least during the preschool years), *intelligence* (average or above average non-verbal intelligence), and *comorbidity* (accepting only comorbid diagnoses that are suspected to overlap with a prototypical clinical presentation, such as ADHD and speech disorder), *sex* (same number of males and females for each subtype), and *age* (duplicating each subtype with a preschooler and an adult cohort) (Fig. 3). The inclusion of a group without speech onset delay (or without speech atypicality, such as delayed echolalia) in the definition of autism is likely to be a contributor to the current autism spectrum heterogeneity (Hinzen et al., 2019). This type of autism might require to be recognized on its own, thus is to be studied separately from

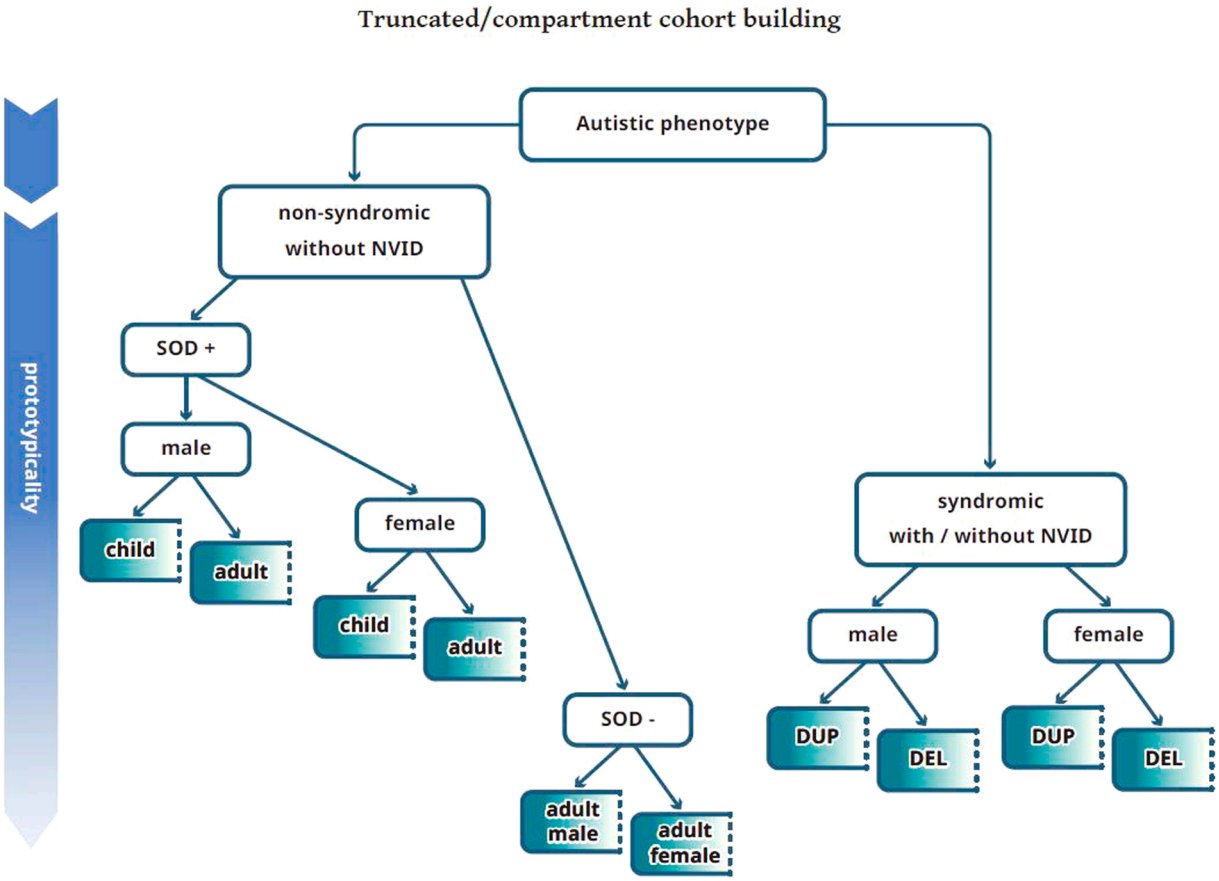

Fig. 3. Compartment allocation and truncating strategy; separated compartments categorized by clinical subgroups. A compartmentalized strategy comprising a cohort enrolled according to the decreasing prototypicality of the participants, truncated at a sufficient sample size. Each participant is enrolled according to a decreasing level of similarity to an autistic phenotype. Each compartment represents a plausible subtype defined by a narrow range of specifiers (age, non-verbal intelligence, language, comorbidity). SOD+ : presence of speech onset delay; SOD-: absence of speech onset delay; NVID: non-verbal intellectual disability; DUP: duplication; DEL: deletion.

the other groups. We propose dedicating a cohort compartment to autistic individuals without speech onset delay or abnormalities, as adolescents or adults, with an equivalent sex ratio. Similarly, a cohort of individuals with potentially relevant mutations should be constructed. Given the recent demonstration that pleiotropic effects of gene dosage largely influence the prototypicality of autistic presentation, individuals with deletions and duplications would be separately enrolled by decreasing prototypicality and in equal numbers (Douard et al., 2021). Finally, the compartment strategy implies inflating the subtypes poorly represented in usual recruitment settings to reach sufficient sample sizes within each compartment of the cohort.

In emphasizing the possible existence of a discretely delimited prototype, we do not presume that the external (between autism and non-autism) and internal (between autism subgroups) boundaries of autism are necessarily discrete. Neither do we presume monocausal theories (Kendler, 2019). Maintaining a trend of research on clinically-defined prototypical autism and comparing it to other clinically-defined subgroups will make it possible to test whether the distribution of weighted signs is linear or non-linear. It should also make it possible to reconnect with studies on qualitatively distinct signs and groups of signs: “the issue is not the inclusion of similar symptoms in different diagnoses, but the paucity of research on the differential characteristics of those symptoms in different disorders” (Angold et al., 1999).

4.3. Limitations of the prototype approach

The prototype-oriented strategy comes with several limitations. First, this research strategy is supported by less empirical work. Moreover, the bottom-up design has opposite strengths and weaknesses relative to the top-down design. Namely, although its specificity is expected to be better, its inter-judge agreement remains to be established. Furthermore, the notion of expertise, defined by exposure to a large number of individuals corresponding to a certain prototype, may be modulated by "clinical-site biases" linked to differences in the reference process. As each expert center has its own target population (i.e. children with autism, adults with autism, individuals with autism without intellectual disability, complex neurodevelopmental disorders, etc.), expertise is mainly based on repeated exposition to this specific population. Experts may therefore develop divergent prototypes for each specific type of neurodevelopmental presentation. The potential benefit of this proposed line of research for the large number of individuals within the autism spectrum that do not match one of the prototypes may be assessed only after the question of generalizability is answered.

5. Conclusion

There has been progress in autism research despite existing uncertainties in the delineation and subtyping of the autism category. However, comparisons of behavior, psychiatric comorbidity, brain organization, and genetic factors between autistic participants and neurotypical controls strongly depend on inclusion criteria in research cohorts, which appear to have broadened over time. Several lines of evidence suggest that current inclusion criteria result in pervasive heterogeneity, which may hinder further discoveries. Attempts to resolve the observed heterogeneity by stratifying the autism population into more homogeneous subgroups have been published since the 1990’s but have thus far not yielded consistent results. We have described a number of methodological issues that should be addressed in future stratification studies. In parallel to these efforts, an alternative strategy could be pursued. We suggest that autism research could benefit from establishing a line of investigation of clinically defined cohorts based on prototypicality. Although prototypicality does not necessarily reflect the biological boundaries of autism, we propose that rigorously defined cohorts emphasising specificity over sensitivity may help reduce the problem of heterogeneity in autism research. Although we suggest a more central role of prototypicality in research, access to health and social services should be guided by individual needs and not be influenced by prototypicality.

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