Annual Research Review

Looking back to look forward:

Changes in the concept of autism, and implications for future research

Accepted for publication 12 November 2019

Journal of Child Psychology and Psychiatry

Published January 2020

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Running head: Changes in the concept of autism

Abstract

The concept of autism is a significant contribution from child psychiatry that has entered wider culture and public consciousness, and has evolved significantly over the last four decades. Taking a rather personal retrospective, reflecting on our own time in autism research, this review explores changes in the concept of autism and the implications of these for future research. We focus on seven major changes in how autism is thought of, operationalized, and recognised: 1) from a narrow definition to wide diagnostic criteria; 2) from a rare to a relatively common condition, although probably still under-recognised in women; 3) from something affecting children, to a life-long condition; 4) from something discreet and distinct, to a dimensional view; 5) from one thing to many 'autisms', and a compound or 'fractionable' condition; 6) from a focus on 'pure' autism, to recognition that complexity and co-morbidity is the norm; and, finally, 7) from conceptualising autism purely as a 'developmental disorder', to recognising a neurodiversity perspective, operationalised in participatory research models. We conclude with some challenges for the field and suggestions for areas currently neglected in autism research.

Keywords

Autism spectrum disorders; Asperger disorder; neurodevelopmental disorders; social cognition

Introduction

Just over half a century after autism was first named and described, there has been a recent explosion of interest in the history of the diagnosis. This is manifest notably in books addressing a general audience, such as those by Grinker (2008), Feinstein (2010), Silberman (2016), Donvan and Zucker (2017), and Evans (2017). Given the ready availability of historical accounts covering a variety of social and clinical aspects, here we draw on our personal experience of the changing face of autism research over the last 30 years.

Without looking back, one might imagine that autism has always been conceptualised as it is today; a life-long neurodevelopmental condition with a spectrum of manifestations and high rates of co-occurring mental health difficulties. However, looking back over the past decades of autism research reveals dramatic re-conceptualisations with far-reaching implications, both theoretical and practical. We focus below on seven major changes in the conception of autism, and in each section attempt to draw out the implications for future research.

The changing concept of autism: 1. From narrow to wide

In the 1980s, when psychological research started to intensify, the concept of autism was far narrower than notions today. For example, the American Psychiatric Association's 3rd edition of the Diagnostic and Statistical Manual (DSM-III; APA, 1980), which included 'Infantile Autism' as a separate diagnosis for the first time, listed as one of six criteria, "Pervasive lack of responsiveness to other people". In contrast, the equivalent criterion for 'Autism Spectrum Disorder' (ASD) in the latest edition of DSM-5 (APA, 2013): 'Persistent deficits in social communication and social interaction across multiple contexts…", which can be met in a wide range of ways. Lorna Wing's suggested autistic social typology of 'aloof, passive, and active-

but-odd' can be seen as an early attempt to move from 'lack of responsiveness' to social difficulties that varied widely in manifestation (Wing & Gould, 1979). However, the perception remained in the 1980s that a child who was, for example, over-friendly, was not autistic.

Two more of DSM-III's six diagnostic criteria for Infantile Autism were "Gross deficits in language development" and "If speech is present, peculiar speech patterns such as immediate and delayed echolalia, metaphorical language, pronominal reversal". Note the focus on language rather than communication, and expectation that many autistic children would show no speech. Language disorder was seen as central to autism, and perhaps even explanatory for the difficulty in relating to people and objects in the usual way. Much attention continued to be paid to delayed and atypical speech in autism through the early 1980s such that, in 1989, Frith reflected that, "More has been written on the language of autistic children – the peculiar forms of their speech as well as their difficulties in comprehension – than any other of their psychological disabilities" (p.20).

Against this background, researchers and clinicians were surprised when some children acquired useful and even fluent language and yet remained autistic. Hans Asperger (1944) had described such cases, who were otherwise very similar to those described by Kanner (1943). Indeed, this is one of the main reasons why Asperger's Syndrome was eagerly taken up after Wing's 1981 paper and Frith's English translation of his work in 1991, first informally among clinicians, and then formally in ICD-10 (WHO 1990) and DSM-IV (APA, 1994). Added as a 'disorder of uncertain nosological validity', Asperger Syndrome in ICD-10 (and Asperger Disorder in DSM-IV) differed from autism only 'in the fact that there is no general delay or retardation in language or in cognitive development'. This new category gave rise to a dramatic change of research attention. Almost overnight, researchers were galvanised to find out more

about a group of autistic children who puzzlingly showed no language delay at all. Many did not come to clinical attention in early childhood, because they spoke well and did not have intellectual impairment. Up until this time, the majority of participants in autism research had intellectual disability/language impairments; through the 1990s this began to change, so that the vast majority of studies came to be carried out with verbal participants of average or above average IQ.

The focus primarily on autism without accompanying intellectual or language disability could be partly attributed to simply practical issues: research with this group is far easier than devising tasks accessible to minimally verbal individuals. However, we believe this focus must also be seen in the historical context of autism's relative recency as a diagnostic category, in addition to the more general move in psychiatry to a multiaxial classification system. In the last decades of the 20th century, there was still a need to show that studying autism as a developmental condition, distinct from intellectual disability, language disorder, and so forth, was valid. Showing that psychological differences could be demonstrated in individuals with 'pure' autism (i.e., without the confound of intellectual impairment and/or language disorder) was part of that effort. Where Hermelin and O'Connor (1970) had introduced the practice of comparing autistic groups with IQ or mental age matched comparison (non-autistic) groups (often intellectually disabled, but sometimes with, e.g., sensory disabilities), now researchers focused on so-called 'high-functioning' autism and Asperger Syndrome in order to understand what part of the behavioural and cognitive presentation of autism was distinct from intellectual and/or language disability.

While the behavioural diagnostic criteria widened, it should be noted perhaps that the psychological characterisation of autism became significantly more focused in the 1980s. The

'Theory of Mind' (ToM) deficit hypothesis proposed that failure in the ability to (meta)represent mental states in oneself and others is the cognitive cause of the characteristic autistic behavioural difficulties in social interaction and reciprocal communication (Frith, 1989). This theory – although much debated – has been so influential in the field that it is easy to forget that prior to this specific account, social difficulties in autism were generally rather amorphously characterised as a lack of sociability or interest in others. The precise ToM hypothesis allowed two important areas of progress in research; neuroimaging investigations of the neural underpinnings of key social processing differences in autism, and the delineation of intact social abilities in autism, including emotional empathy (see Happé, 2015 for a wider review of this topic).

From narrow to wide: Implications for future research

An unintended consequence of the focus on 'pure' autism, has been the neglect of intellectual disability and developmental language disorder in recent research. Russell et al. (2019), examining autism research papers published in 2016, covering 301 studies and more than 100,000 participants, estimated that 94% of all ASD participants had IQ in the average range, and 80% of studies showed selection bias against participants with intellectual disability. The authors contrast this with an estimated 50 -55% of the autistic population that have intellectual disability. This selection bias towards verbal and intellectually able autistic participants obviously threatens the generalizability of research findings, but will also undoubtedly have consequences for the direction of future theories, as well as shaping public understanding of autism.

Minimally verbal participants are rarely involved in research studies and this is particularly obvious in brain imaging studies (Jack & Pelphrey, 2017). Yet, arguably, we have never had more opportunity to assess and investigate the cognitive processes of these 'hard to reach' groups, thanks to rapid advances in technology. Wearable sensors and EEG allow monitoring of physiological and neural markers unobtrusively. Functional near-infrared spectroscopy (fNIRS) provides opportunities for measuring neural activity in naturalistic contexts (Pinti et al., 2018). Virtual Reality brings the outside world into the lab, for controllable, replicable yet realistic encounters. Eye-tracking technology gives a read-out of interest and attention without requiring verbal instruction or response. And the pervasive availability of tablets and smartphones, with touchscreen response and intuitive app development, means that most young people know how to interact with gamified tests, from their earliest years. As work by Laurie et al (2019) shows, autistic children and adults across the full IQ range, interact with technology for much the same purposes, and with much the same preferences, as their neurotypical counterparts. These new technologies should lead to a revolution in research, and herald the inclusion of intellectually impaired and minimally verbal children and adults in studies (e.g. Tager-Flusberg, et al., 2017).

The changing concept of autism: 2. From rare to common

The first autism prevalence estimate, by Lotter (1966), was approximately 4 in 10,000, and Wing, who introduced the notion of the 'autism spectrum', gave an estimate of 22 in 10,000 from her epidemiological study of children known to special educational needs services in Camberwell (Wing & Gould, 1979). Even in the 1980s, autism was considered to be a very rare condition. More recently, the median of prevalence estimates of ASD worldwide was given as

62/10 000 (Elsabbagh et al. 2012). A ballpark-figure of 1 in 100 is widely accepted today, with some estimates being even higher.

There was a widespread sense, in the 1980s, that autism was under-diagnosed, and more specialist diagnostic services were needed. Today, some authors have suggested that autism may be *over*-diagnosed. For example, Gillberg and colleagues reported no increase in levels of (parent-reported) autistic traits (at 9 or 12 years) in a Swedish population-based sample of children born from 1993 to 2003, but a significant increase in the rates of autism diagnosis over this 10-year period (Lundström et al, 2015). They also found a decrease in level of parent-reported autism (and related) symptoms and impairment for children receiving an autism diagnosis at age 7-13 years, over the period 2004 to 2014 (Arvidsson et al, 2018). The authors suggest the bar for diagnosis is now significantly lower – perhaps too low.

The huge rise in numbers of autism diagnoses has led some groups to speculate on possible environmental factors; the change was thought to be too rapid to reflect genetic factors (although secular changes, such as older parenthood, could in principle have some small impact; Wu et al, 2017). However, despite the US Centre for Disease Control (CDC) reporting a 78% increase in autism prevalence rate (in 8-year-olds, from record review) from 2004 to 2008, there is reason to doubt whether actual incidence of autism has increased. American state to state differences in prevalence and rise in numbers are striking, and highlight the wide range of factors impacting diagnosis rates (Sheldrick & Carter, 2018). Diagnostic substitution has been suggested; as autism diagnoses have increased, a parallel drop can be seen in diagnoses of Intellectual Disability, in some places. As discussed above, the widening of diagnostic criteria and introduction of Asperger's Disorder and 'Pervasive Developmental Disorder – Not Otherwise Specified' in the DSM-IV (in 1994) undoubtedly affected prevalence. Taylor et al.'s (2013) analysis of

information from the UK GP research database, found a fivefold increase in the annual incidence rates of autism during the 1990s in the UK, but that rates had held steady since. The many factors affecting prevalence estimates from different survey methodologies, and their likely impact on apparent rise in numbers have been eloquently discussed by Fombonne (2018).

In parallel with the rise in numbers of autism diagnoses, there has been a striking rise in research interest in autism over the last 30 years. In 1988, when the first author began her PhD, keeping abreast of published papers (hard copy only, of course) on autism was easy; 190 publications that year included 'autis*' in the title, and there were no more than 2,600 such publications in total across all previous years. A Web of Science search for the topic of 'autis*' in 2018, returned more than 6,000 publications, and the total corpus of autism papers at the time of writing exceeds 68,000. This publication explosion reflects, amongst other things, increases in research funding for autism. In the United States this was fuelled in part by influential parents lobbying for improved services and, in some cases, starting charities that specifically sought to bring into the field scientists who had previously had no interest in autism. In Europe, too, autism research has received some major funding awards in recent years, most notably EU-AIMS (Autism Innovative Medicine Studies), funded by the European Commission for c.£30 million, and the follow-on AIMS-2-TRIALS receiving c. £55 million from the European Union plus matched charity and industry contributions in kind; currently the largest single autism grant in the world (Loth et al, 2017).

No longer rare, but still under-diagnosed in females?

In the 1980's, the estimated male:female ratio in autism was 4:1, rising to perhaps 10:1 for those with Asperger Syndrome. The rule of thumb then was that females might be more rarely affected by autism but, when affected, were 'hit harder' (e.g., had autism plus intellectual disability). This pattern led to the hypothesis of a 'female protective effect'; some aspect of biology that meant that females required a higher etiological 'load' in order to manifest autism. Evidence in support of the female protective effect for autism has been reported; siblings (male or female) of autistic girls show higher rates of autistic traits/diagnosed autism than siblings of autistic boys (e.g., Robinson et al, 2013). Some molecular genetic studies find evidence of higher rates of relevant mutations (e.g., deleterious autosomal copy-number variants; CNVs) in autistic females versus males – even after adjusting for IQ differences (e.g. Jacquemont et al, 2014). The high male preponderance has also led to a number of specific etiological theories about autism, notably Baron-Cohen's 'extreme male brain' account, and his work on prenatal androgens and their putative association with social and non-social autism-related traits (e.g. Baron-Cohen et al. 2019; for debate see Ridley, 2019).

However, there is also the possibility that the lower numbers of females, and especially of females with good intellectual and language skills, might reflect poor recognition of autism in these groups. Older estimates of the male:female ratio were largely based on numbers from clinical or Special Educational Needs (SEN) registers. More recent studies, with epidemiological samples and using active ascertainment, find considerably lower male preponderance. A recent meta-analysis by Loomes et al (2017) estimated a male:female ratio of 3:1, and importantly found that this did not differ greatly by intellectual dis/ability. If current diagnostic methods and criteria are male-biased, this ratio may still be somewhat inflated.

The discrepancy between estimates from passive versus active ascertainment suggests that we have been missing or mis-diagnosing large numbers of autistic women and girls. Evidence is accumulating that females are diagnosed later than males, and require higher symptom expression for diagnosis (see Carpenter, Happé & Egerton, 2019 for a fuller treatment of this topic). Diagnostic overshadowing probably also plays a part in under-recognition of autism in women. For example, where eating disorders are the presenting problem, clinicians may not consider an autism diagnosis. Sedgewick et al. (2019) reported that at least 20% of women with anorexia passed cut-offs for an autism diagnosis, and elevated rates were still found in women who had recovered from anorexia (so were not merely due to very low weight).

Why might autism be overlooked in females? There are several reasons. First, research has often excluded female participants, and thus research evidence disproportionately reflects male autism. This research forms the basis for diagnostic criteria and tools and has historically shaped our notion of autism. Second, there is a general bias to think of autism as predominantly a male condition; thus parents, teachers and clinicians may not think of autism when they see a girl who is struggling socially. Third, autism may look different in females. There is as yet little robust research to tell us whether/how autism looks different in females, in part because of reliance on diagnosed samples who by definition meet current criteria (see discussion in Carpenter et al, 2019).

From rare to common: Implications for future research

In the 1980s, when autism was still considered rare, very small sample sizes were acceptable in research. Now, with much higher prevalence estimates, far larger scale studies are possible. This

coincides with increasing recognition of the importance of replication and large sample sizes. In the 1980s and even 90s, many researchers believed that our small sample sizes might prevent us from obtaining a statistically significant result, but that where we did find significant group differences, these were likely to be valid. A better understanding of the meaning of statistical significance has led to wider awareness, more recently, that small sample sizes are likely to give spurious false positive and as well as false negative findings.

An emphasis on increasing statistical power, and replication, means a move towards collaboration and consortia. While we would like to think that a single researcher, with little funding, can still make a conceptual breakthrough supported by small scale results from a cleverly designed and low tech experiment – this is clearly not the current trend. Consortia have proved vital for genetic research, to collect the hundreds of thousands of samples required. The AIMS-2-TRIALS network has collected cognitive data from hundreds of participants across several sites across Europe, alongside potential biomarkers (Loth & Evans, 2019). Consortia require agreed shared protocols and standardised tasks to pool psychological data. Currently, many of the measures routinely used in psychological research on autism lack good psychometric data/properties, and this must change.

Future research will also make use of 'big data' from registers and record linkage of routine data (e.g. electronic health and education records). These sorts of big data have typically been 'shallow', for example noting diagnoses, hospital admissions, or medications prescribed. However, technology for 'deep phenotyping' could allow detailed, personal data to be collected at scale (e.g. from mobile phones). Ethical concerns, and fears about privacy, have to be addressed and may require a shift in public attitudes. Attitudes within the research community

also need to change; there is the challenge of how to reward collaboration and data sharing, especially for early career researchers trying to make their names within very large consortia.

Regarding autistic females, researchers have begun to study how autistic women (not excluding men) modify their behaviour to fit in and pass as 'neurotypical' through camouflaging and compensation (Hull et al, 2019; Livingston & Happé, 2017). These concepts are operationalised as the discrepancy between 'external' levels of autistic traits (e.g. social behaviour as measured by the Autism Diagnostic Observation Schedule, ADOS; Lord et al, 1989) and 'internal' status (e.g. as self-rated on the Autism Spectrum Quotient, AQ, or as tapped by performance on ToM tests). The neural basis of camouflaging, and possible sex differences in this, are just beginning to be explored (Lai et al, 2018).

One clear implication of the past under-representation of females in research samples, is that future studies must include all genders. Empirical research is needed to identify if current diagnostic criteria and processes are gender-fair, or how to make them so. Until they are, it is important to avoid the circularity of including only volunteers with an existing diagnosis; population-based samples, actively ascertained are needed, e.g. to establish whether the female protective effect applies specifically to autism or across all neurodevelopmental conditions. Such research should also consider previously neglected topics of specific relevance to females, such as the autistic experience of adolescence, pregnancy, motherhood and menopause.

The changing concept of autism: 3. From childhood to lifespan

Why have we been so slow to realise that most autistic people are adults? Kanner and Asperger's first descriptions were, of course, of children – and as child psychiatrist and paediatrician,

respectively, the term ‘Infantile Autism’ reflected their disciplines. Autism continued to be the preserve of child psychiatry in both research and clinical practice for decades. It was not until 1971 that Kanner published his 30-year follow-up of his 11 original cases in adulthood. Even in the 1980s, autistic adults were largely invisible to research (with some notable exceptions, e.g. Schopler & Mesibov, 1983; Lund & Jensen, 1989). As described above, the majority of autistic people also had intellectual disability, and most adults would be in institutions or group homes.

As the diagnosis widened in the 1990s to include Asperger Syndrome, so awareness of adults rapidly increased. Digby Tantam was one of the few adult psychiatrists interested in autistic adults (and, specifically, similarities or differences versus ‘schizotypal’ adults; Tantam, 1988), and provided case studies that likely encouraged interest from other adult psychiatrists. Descriptions of highly intelligent ‘Asperger’ adults led to a new phenomenon; parents of recently diagnosed autistic children would recognise themselves when reading around the topic. At the same time, in research labs, the advent of neuroimaging was a driver to identify and recruit intellectually able autistic adults for research studies, using first PET and then (f)MRI. For the very first neuroimaging study of ToM in autism, in the early 1990s, such adults were still so hard to find that we collaborated internationally and even flew volunteers over to the UK specially to take part (Happé et al, 1996)!

The Office of National Statistics household survey (Brugha et al, 2011) showed that the prevalence of autism in adults was the same as in children, and suggested that most autistic adults at that time were undiagnosed. It is still the case that many adults are coming for first ASD diagnosis late in life, and the DSM-5 criteria explicitly allow for late recognition of characteristics that have been present since early development but ‘may not become fully manifest until social demands exceed limited capacities’.

Although ‘Infantile Autism’ has become ‘Autism Spectrum Disorder’, there is still a paucity of research with adults and particularly with older adults (Roestorf et al, 2019). There is still little awareness of autism amongst most adult services, especially old age psychiatry. Raising awareness is vital, both to understand the life course in autism, and also because of indications that autistic adults suffer high rates of mental and physical problems (Croen et al., 2015). Using population-wide data from the 2011 Scottish census, for example, Rydzewska et al (2018) found that 47% of autistic adults (identified as 0.2% of the total population) had poor general health, about twice the rate in the general population, and that older adults and women had especially elevated rates of ill health.

From childhood to lifespan: Implications for future research

So little research exists addressing ageing in autism, that the implication for future research is rather simple; the developmental trajectory of later life must be studied in autism with the same rigour applied to child, and recently prospective infant, studies. Does the characteristic cognitive profile (e.g., strength in detail-focused tasks, impairment in specific socio-cognitive tasks) change with age in autism? Preliminary findings of preserved skills in some areas, relative to neurotypical ageing, are intriguing, but require further study (Lever & Geurts, 2016; Zivrali-Yarar, 2017).

The variability in life trajectories for autistic adults is huge. The traditional markers of ‘good outcome’ (living independently, having a job and friends) are increasingly questioned, with greater recognition that quality of life needs to be defined in broader terms through consultation with autistic people and their families (e.g., McConachie, et al., 2019).

We need to know if rates of age-related mental/physical illness are elevated in autism and, if so, why. Possible reasons include shared genetic predisposition, or 'phenotypic' links mediated by, for example, stress, isolation, reduced help-seeking, and social disadvantage. Establishing the causes of any elevation in age-related ill-health is the first step towards preventing this health inequality for older adults on the autism spectrum.

To accomplish this research, epidemiological approaches are needed. It is not currently clear where to find the presumably 1% of the aging population meeting criteria for autism. Establishing retrospective diagnosis in, for example, dementia clinics, with little hope of gathering developmental history, will be challenging. Longitudinal studies following adults from midlife into old age are necessary, with account taken of changes in diagnostic criteria that create differences between those adults diagnosed in childhood (in the 60's) and those receiving first diagnosis by the current broader criteria.

Although challenging, research into aging in autism is important, not only for practical reasons (planning services, preventing poor health), but potentially also for theoretical and fundamental scientific insights. Studies of infant brain trajectories in autism, suggesting 'overgrowth' in the first 4 years of life in a subset of children, have given rise to theoretical accounts of the neurobiology of autism (e.g., failure of typical synaptic pruning). Brain changes in later life may also give important clues to the biology of autism, or indeed of other conditions, just as the study of early-onset dementia in Down Syndrome contributed to neurobiological understanding of Alzheimer's.

The changing concept of autism: 4. From discrete to dimensional

The original conception of autism was as a distinct entity, distinct from typical development and from other conditions. Indeed, in the opening sentence of Kanner's famous 1943 paper, he remarks, 'there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits…a detailed consideration of its fascinating peculiarities' (p.217). Early research focused, for example, on identifying the unique ('pathognomonic') features distinguishing autism from other disorders, in order to help clinicians make a categorical judgement of 'autism' or 'not autism'. Interestingly, Wing's work as early as 1969 compared parental report of social, 'executive' and other features in autistic children and children with sensory (e.g. visual) impairment, language disorder, or Down Syndrome, and concluded that although aspects of 'autistic' behaviour could be found in 2- to 5-year-olds in these other groups, autism could be 'clearly differentiated…by consideration of the complete clinical picture' (Wing, 1969). In the same paper, however, Wing discusses whether inclusion of less clear or borderline cases of autism would have altered these results. Indeed, Wing is widely credited with introducing the notion of the 'autism spectrum', with a parallel intended with the spectrum of coloured light, which is heterogeneous but also continuous.

Measuring autistic traits or symptoms quantitatively was necessary to measure differences within the spectrum, as well as to track developmental change or treatment effects. Perhaps the first detailed interview schedule specifically designed for autism was Wing and Gould's 'Children's Handicaps, Behavior and Skills' (HBS) schedule, which was used in the original Camberwell study (Wing & Gould, 1978). This can be seen as the predecessor to the development in the late 1980s of widely adopted diagnostic scales, such as the Autism

Diagnostic Interview (ADI; LeCouteur et al, 1989) and ADOS (Lord et al, 1989), which have been important in the attempt to establish comparability of research samples across studies.

The notion that autism behavioural dimensions might extend beyond autism is a relatively recent idea, albeit one mirrored in many other diagnoses (e.g., ADHD). Interest in the characteristics of first-degree relatives of autism probands grew in the wake of twin studies, which showed high concordance for autism and also for a wider set of cognitive and language difficulties. Sula Wolff was possibly the first researcher to report empirical data on social differences in parents of autistic children (Wolff, Narayan & Moyes, 1988), although both Kanner and Asperger noted unusual social manner in some parents of the children they diagnosed. However, it was not until the end of the 20th century that these subclinical autistic traits, the 'broad(er) autism phenotype', were systematically measured (Piven et al. 1997; Pickles et al, 2000; for review, see Rubenstein & Chawla, 2018).

A further extension of the broad autism phenotype beyond those with a genetic connection and into the general population, began with instruments such as the AQ (Baron-Cohen, 2001) and Social Responsiveness Scale (SRS; Constantino et al, 2000). These questionnaires began as 'screeners' to identify individuals who might warrant diagnostic assessment, but quickly gained popularity as measures of individual differences. In the last ten years there has been a sharp increase in studies 'of autism' that have included no diagnosed individuals at all, rather examining correlates of high autism trait scores in neurotypical groups. One limitation of most of this research has been the sole use of self-report measures. It is interesting, however, that some studies of self-rated subclinical autistic traits have found a relationship with objective markers highlighted in studies of diagnosed autism; for example, higher (subclinical) AQ scores predicted

more accurate pitch and temporal processing (Stewart et al. 2018), and lower performance on tests of social cognition and executive function (Gökçen, Frederickson & Petrides,.2016).

Autistic trait measures such as the AQ show a smooth continuum between diagnosed autism and subclinical individual differences; there is a normal distribution of traits, rather than a bimodal distribution (although see Abu-Akel et al, 2019 for a different modelling approach with large scale self-report data that supports both dimensional and categorical conceptions). While it should be born in mind that the same behaviour can have different underpinnings, it does appear that, at the behavioural level at least, one can be 'a bit autistic'.

At the genetic level, too, it appears that the genetic influences on subclinical autistic traits largely overlap with those on diagnosed autism, based on both behavioural genetic (Colvert et al, 2016; Robinson et al, 2011) and molecular genetic approaches (Massrali al, 2018). Indeed, for the majority, the genetics of autism is just like the genetics of height; their autism is the result of many common genetic variants, each of miniscule effect. We all carry many of these variants, and so a dimensional characterisation of autism is also plausible genetically. Only in a minority of autistic people are rare genetic mutations of high penetrance, relevant to their autism – and even in these cases, genetic 'background' in terms of those common variants, remains relevant. Polygenetic scores, which add up the weighted effects of those hundreds or thousands of common variants, are found to be elevated even in families whose autistic child shows a de novo genetic mutation associated with autism (Weiner et al, 2017).

Those conducting early studies of brain structure in autism, initially post-mortem, then using increasingly sophisticated neuroimaging in vivo, expected to find striking and specific neural differences underlying the often dramatically different behavioural phenotype identified as autism in the late 20th century. However, recent large meta-analyses and studies pooling MRI

scans across hundreds of autistic participants, diagnosed in terms of the current wider criteria, reveal little by way of qualitative differences from neurotypical samples (e.g., Pua, Bowden & Seal, 2017). However, there are multiple quantitative differences in structural findings, as reviewed by, for example, van Rooij et al. (2018).

Behaviourally, genetically and neuroanatomically, then, a dimensional characterisation of autism appears warranted. What about the cognitive level? Cognitively autism may present a qualitative difference in some respects and not in others. The original ToM deficit account posited a qualitative difference: autistic children do not meta-represent others' propositional attitudes, while neurotypical children do (Frith, Morton & Leslie, 1991). More recent versions distinguish implicit from explicit ToM, and place emphasis on lack of spontaneous, automatic, (and perhaps effortless) tracking of mental states in autism (e.g. Schuwerk et al. 2016). There is scope, then, for either a qualitative or quantitative distinction to be drawn. Individuals on the autism spectrum also differ from one another in their ToM task performance, and this can change with age; whether these differences should be interpreted as reflecting differences in core socio-cognitive characteristics or 'compensation' is an interesting question addressed elsewhere (Livingston & Happé, 2017).

Other cognitive characteristics of autism may more easily fit a dimensional approach. Executive dysfunction is described in autism, and many other groups, as quantitatively different from typically developing samples. The 'weak central coherence' account described quantitative differences in detail-focused cognitive style with an explicitly dimensional approach in which both extremes (configural bias and featural bias) may have advantages for different tasks (Happé & Frith, 2006). This account also addressed sensory differences in autism (e.g., failure to

habituate to stimuli; Frith, 1989), which have only recently been recognized in the diagnostic system despite their significant impact on autistic people's everyday lives.

The more recent Bayesian explanations of sensory and perceptual atypicalities in autism stem in part from an intensified interest in sensory issues. These accounts also lend themselves to quantitative interpretations; for example, Pellicano and Burr (2012) suggest that cognitive and sensory differences in autism result from attenuated Bayesian priors, while Lawson, Rees and Friston (2014) posit an imbalance of the precision ascribed to sensory evidence relative to prior beliefs.

Discrete to dimensional: Implications for future research

The failure, to date, to find qualitatively distinct 'diagnostic' biomarkers distinguishing autism from non-autism, has led to a shift to search instead for stratification biomarkers; markers that might predict differences in e.g., prognosis or treatment response, within groups of autistic individuals (Loth & Evans, 2019). It will be interesting to see whether huge studies such as AIMS-2-Trials will reveal distinct biological subtypes. In principle, qualitatively different causes can underlie a smooth continuum of quantitative differences in behaviour.

As sample sizes in autism genetic consortia rise, polygenic scores for autism may begin to explain a meaningful proportion of variance in autistic traits. It is important to note that such scores will not be useful for individual prediction of autism diagnosis; the probabilistic nature, the relatively weak signal, and the low base rate of autism in the population mean that any attempt to screen for autism would not only be ethically problematic but also practically doomed to failure. Polygenic scores for autism are likely, however, to have a profound effect on autism

research. While established in discovery samples of hundreds of thousands, polygenic scores can be applied in studies of hundreds of participants, and will be feasible to include in psychological as well as biological research. Genomic structural equation modelling, for example, allows the interrogation of the genetic structure (overlap, independence) of different traits or conditions. Already, Warrier et al (2017) have been able to collect phenotypic and genetic information on more than 50,000 people via commercial genotyping service 23&Me. Using Baron-Cohen's Systemizing Quotient and Empathizing Quotient self-report questionnaires, their work supports the distinction between social and non-social aspects of autism, behaviourally and genetically (Happé, Ronald & Plomin, 2006; see below).

A challenge for the future is that the huge volumes of data collected, and the astonishing advances in genetic and analytic methods, will only produce information as good as the measures employed. There is a need for new methods to collect deep phenotyping at scale, and to supplement current reliance on self-report questionnaires. For example, exploring sensory sensitivities with physiological measures, and establishing agreement with subjective self-report will be important (Kuiper et al, 2019). Sensitive assays that can distinguish between social difficulties with different causes (e.g. autism versus social anxiety), and that target distinct and separable aspects of social processing (e.g. ToM versus emotional empathy versus social motivation) are needed; to be optimally useful in the new era of big data and polygenic scores, these need to be user friendly, remotely administered, and automatically coded.

The changing concept of autism: 5. From one to many

Although autism was historically conceptualised as a discrete, categorical diagnosis based on a coherent syndrome of co-occurring symptoms, current conceptions question the unity of autism

in two key senses: first, a growing realisation that autism in different individuals likely has different causes or aetiologies; and second, that even in a single individual, different core symptoms may have different origins.

From one to many: The 'autisms'

The original conception of autism was as a single entity, and scientists searched for a single cause. There was from the start, however, a clear recognition of the behavioural heterogeneity; even the cases Kanner described showed a wide range of levels of adaptive and intellectual functioning. Rutter, in his 1968 review, describes the variation in intellectual and language ability, as well as in developmental trajectories, and the relevance of this for various possible accounts of the 'primary defect' in autism.

Over the years there has been a concerted effort to parse the huge behavioural heterogeneity of the autism spectrum into meaningful subgroups (e.g., Zheng et al, 2019). This in part reflects a concern that relative lack of progress in understanding the neurobiology of autism, might be due to biological heterogeneity in study samples. Identifying distinct (and more homogeneous) behavioural subgroups was expected to advance our understanding – in much the same way as the current trend for studying genetically homogeneous subgroups (see below). However, while there have been huge efforts of subtyping, both by behaviour (e.g. regression) and biology (e.g. macrocephaly, serotonin levels), they have had rather little success to date.

The inclusion of 'Asperger's Disorder' as a separate diagnostic category from Autistic Disorder in DSM-IV (see above), was one such attempt, to make sense of heterogeneity in early language and cognitive development in the autism spectrum. Despite more than 100 papers

comparing those diagnosed with Asperger's Disorder versus 'high functioning autism', the results were largely negative (no group differences) or circular (differences on variables included in the diagnostic process, such as clumsiness). Indeed, an influential study by Lord et al (2012) showed that even comparing specialist clinics in the States, the best predictor of what diagnosis an individual received (Asperger, Autism, PDD-NOS) was not any characteristic of the person, but rather which clinic they attended. These considerations led to the absorption of Asperger's Disorder into ASD in DSM-5 (Happé, 2011).

Despite increasingly large samples and sophisticated statistical methods, studies have largely failed to 'cut nature at the joints' with any greater intricacy than dividing autism with versus without intellectual disability (in the past unhelpfully referred to as 'high' or 'low-functioning'), and autism with versus without language disorder (Gillespie-Lynch et al., 2012). Both of these aspects, which are additional and in some respects orthogonal to the core features of autism, have profound impact on prognosis and degree of support needs.

Despite this failure to find behavioural subtypes, current consensus is that there are many different biological routes to autism; many different etiologies, represented by the use of the term the 'autisms' (Coleman & Gillberg, 2012).

From one to many: Unitary to 'fractionable'

The second sense in which autism has changed conceptually from one to many, concerns the suggestion that the symptoms that define autism may have separable causes even in a single individual. The 'fractionated triad' hypothesis suggests that the social, communicative and rigid/repetitive aspects of autism have separable underpinnings at the genetic, neural and

cognitive levels (Happé, Ronald & Plomin, 2006). The idea that autism is a 'compound condition' is not new; Wing and Wing (1971) suggested that autism is best understood as "a combination… of impairments…", based on the observation that "isolated fragments of the full clinical picture frequently occur…'. However, relevant evidence from population-based samples was not collected until Ronald and colleagues began to examine the behavioural and genetic association between autistic traits, measured in the Twins Early Development Study (TEDS). They found that parent-reported social and nonsocial autism traits correlated only modestly in children in the general population, and even in subgroups with high traits and/or autism spectrum diagnoses (see Happé & Ronald, 2008 for review, and e.g., Kim et al, 2018 for replication). While social, communication and rigid/repetitive difficulties did co-occur somewhat above chance, many children showed pronounced difficulties in only one of the 'triad' of autistic traits. Using twin modelling, Ronald and colleagues were also able to show distinct genetic influences on different autism symptom domains, in the general population and amongst high trait/diagnosed autism samples (reviewed in Happé & Ronald, 2008). As mentioned above, recent studies using polygenic scores in huge samples of adults, support this conclusion, finding distinct genetic signals for the social versus non-social dimensions of autism (Warrier et al, 2017).

At the cognitive level, too, it has been suggested that autism may be characterised by a compound of deficits/differences (e.g., impaired ToM, executive dysfunction, detail-focused processing bias), and that attempts to find a unitary psychological explanation for social and non-social behavioural features have largely failed (Happé & Ronald, 2008; Brunsdon et al, 2015). The particular pattern of cognitive strengths and weaknesses should, in principle, be reflected in everyday skills, and perhaps help explain behavioural heterogeneity (Brunsdon et al, 2015).

Although tracing such links is complex, some examples exist; Jones, Simonoff, Baird et al, (2018) found direct links between ToM (but not executive function) task performance and parent-rated symptoms in autistic adolescents.

From one to many: Implications for future research

With regard to parsing the 'autisms', the search for 'stratification biomarkers' to discover autism subgroups for 'personalised' interventions is already underway (Loth & Evans, 2019). There is also considerable research effort focused on understanding the biological path to autism in genetically homogenous subgroups (e.g. Chromosome 22q13 deletion). Clinical groups defined by etiology, such as Fragile X, have been viewed as a tractable target and a step towards finding a putative 'final common pathway' relevant also to 'idiopathic' autism. However, it remains unclear whether 'autistic' symptomatology seen in these groups is qualitatively the same as that in autism; early studies of FraX mistook eye-gaze avoidance for social impairment, and recent neuropsychological studies of children with 22q13 deletion have suggested social difficulties may be less important than language difficulties (Laura et al, 2018). Some have argued that the study of specific etiological groups in which autism is common has established the final common pathway as perturbation in synaptic functioning and excitatory/inhibitory imbalance (e.g., Oliveira et al, 2018). However, it may be that these fundamental and complex neural processes can be disrupted in so many different ways, that this 'final common pathway' is so broad as to represent, in effect, a plethora of distinct 'roads'.

Regarding the 'fractionated triad' notion, does this imply that autism, per se, does not exist? We would suggest not; the particular mixture or compound of causes (genetic, neural,

cognitive) may be qualitatively more than the sum of its parts. Thus, although autism may share genetic or cognitive (e.g. executive dysfunction) aspects with other clinical groups (e.g. ADHD), these may interact with the other aspects of autism to create a unique and distinct condition. The fractionated triad hypothesis would, however, suggest that transdiagnostic studies, comparing different neurodevelopmental groups, will be worthwhile. It will also be important, in future work, to consider how to distinguish core cognitive characteristics of autism from aspects that relate to compensation or lack of it, such as lower intelligence or perhaps poor executive function. In addition, if a sizeable percentage of children do indeed show autism-like symptoms in only one of the traditional triad domains, it would be important to know whether these are qualitatively different from the (e.g. social) difficulties seen in autism, and what if any clinical needs such 'single deficit' individuals have. Lastly, the behavioural genetic work suggesting largely non-overlapping genetic influences on social and non-social aspects of autism, would argue for polygenic scores to be created not for autism as a whole, but for individual differences in social skills/deficits, and separately for rigid/repetitive traits.

The changing concept of autism: 6. From pure to complex

In medical tradition, some diagnoses 'trump' or over-write others. In the 1980s there was debate as to whether a diagnosis of autism was trumped by an etiological medical diagnosis; if a brain lesion was discovered or Tuberous Sclerosis diagnosed, argued some, the autism diagnosis should be removed. 'Idiopathic' autism was considered by some as 'real' autism, as distinct from autism that was secondary to a known neural or genetic basis. This view was part of the historical search for a single biological characterisation of autism, discussed above – and stands in sharp contrast to today's conception in which autism is quintessentially a behavioural

diagnosis that can accompany a wide range of biological conditions. There is still, however, some diagnostic overshadowing, and some clinicians may be slower to diagnose autism in children with a known genetic syndrome (e.g. Down Syndrome; Wester Oxelgren et al, 2019) than those without.

Despite some early voices flagging the high rates of co-occurring physical and psychiatric conditions accompanying autism, most notably Gillberg (reviewed in Gillberg & Billstedt, 2000), only recently has there been widespread awareness that autism rarely occurs alone. Historically, an autism diagnosis trumped a wide range of psychiatric diagnoses, including anxiety, ADHD and, problematically, Asperger's Disorder (in DSM-IV). Only in DSM-5 (APA, 2013) were multiple diagnoses allowed in combination with ASD for the first time. It is now clear that additional difficulties are common in autism, and although clinic samples are naturally enriched for complex and comorbid cases, population-based studies also show elevated rates of many physical and mental health problems. A recent meta-analysis by Lai, Kassee, Besney et al (2019) of 83 studies produced the following estimated rates of co-occurring psychiatric conditions in autism: ADHD 33%, anxiety disorders 23%, sleep-wake disorders 13%, depressive disorders 12%, obsessive-compulsive disorder 10%, disruptive/impulse-control/conduct disorders 10%, schizophrenia spectrum disorders 5%, and bipolar disorders 5%. The seriousness of mental health problems in autism is becoming clear; population-based data on suicide (from >27,000 adults) suggested an odds ratio >7 for autistic adults, with suicide risk being especially high for autistic women and those without intellectual disability (Hirvikoski et al, 2016).

Alexithymia (difficulty identifying and talking about your own feelings) is an important co-occurring trait that appears to affect about half of autistic adults (see Kinnaird et al 2019 for a meta-analysis). First studied by Hill et al (2004), later work by Bird and colleagues established

links between high alexithymia and difficulty recognising others' emotions and responding empathically to them. Bird's work, comparing autistic and non-autistic groups high and low in alexithymia, suggests that it is co-occurring alexithymia and not autism itself that is associated with reduced recognition of and empathic response to others' emotions (Bird & Cook, 2013). Alexithymia is also common in many other clinical conditions, including depression, substance abuse, psychosis and eating disorders. Interestingly, historically Råstam et al (1997) noted high levels of alexithymia in women with anorexia who also showed 'empathy disorders', a wider term that for Gillberg included autism.

From pure to complex: Implications for future research

A James Lind Alliance survey in 2018 by research charity Autistica, and a similar large survey of stakeholders in North America (Frazier et al, 2018), found that mental health was a top priority research area identified by autistic adults. Why is autism so often accompanied by mental health, difficulties? A number of possibilities exist, which are by no means mutually exclusive (and which might be marked with more nuanced terminology; see, Rubenstein and Bishop-Fitzpatrick, 2019). First, apparent 'comorbidity' can be due to selection bias, and additional problems may raise the likelihood of an individual requiring clinical services. One analysis of twin data (Tick et al, 2016) suggested a phenotypic link from raised hyperactivity to autism, interpreted by the authors as hyperactive behaviour making diagnosis of autism more likely (when another child with the same level of autistic traits might not be diagnosed if quiet and not disruptive). Second, real phenotypic causal associations may exist between autism and co-occurring conditions; for example social exclusion or bullying may lead to anxiety, depression and even PTSD. Communication difficulties central to autism may reduce help-

seeking, with negative effects on health. Unusual eating patterns, restricted diets and sensory sensitivities may have adverse gastro-intestinal effects. Associations may be due to a third factor affecting both autism (manifestation/diagnosis) and the co-occurring condition. Examples might include reduced resources for compensation, due to socio-economic disadvantage or executive dysfunction. Fourth, there may be shared aetiology, environmental, genetic, or both (Tick et al, 2016). Knowing which of these different possibilities underlies high rates of co-occurring conditions in autism matters because it may inform intervention; for many autistic people, it is not the autism but the co-occurring anxiety, depression, epilepsy, or sleep problems that most impair quality of life. Much more research is needed to understand these, and less well recognised co-occurring problems such as catatonia (motor 'freezing', temporary muteness, difficulty initiating movement; Shah, 2019). Establishing the reasons for high rates of co-occurring problems in autism is an important aim for research. Longitudinal studies are often suggested as the best way to establish causality, but while they can (sometimes) establish order of emergence of conditions or traits, moving beyond association is complex (Happé, 2001), and may require, for example, intervention designs.

It is now clear that studies of autism will not be representative if researchers exclude participants with common mental health problems such as anxiety, in search of 'pure' autism. Perhaps less clear in the field is that this, debatably, means we must also stop screening out common mental health conditions in our comparison 'typically developing/ed' control groups. Considering co-occurring conditions, and their possible confounding effects, in autism vs. comparison group differences is essential. Does low self-esteem/depression inflate correlations between self-report measures (including autism trait self-ratings) that focus on deficits and difficulties? The presence of co-occurring alexithymia may be particularly important to note in

research studies, where it may help explain heterogeneity in (emotional) task performance, and in clinical work, where it may affect treatment engagement and response.

Given the high rates of additional difficulties, the surprising subgroup becomes those autistic children and adults without mental health problems. Population-based studies may be needed to find these (perhaps undiagnosed) individuals, who may give us insight into resilience factors (individual or environmental) that are important for living a happy autistic life.

The changing concept of autism: 7. From 'developmental disorder' to neurodivergence

Over the last 30 years, and rapidly in the last decade, concepts of autism in many places have shifted from a purely medical model to a more social model of disability (Shakespeare, 2017; see also discussion in Fletcher-Watson & Happé, 2019). The traditional notion that autism is a disorder defined purely by deficits inherent to the person, has been challenged. Instead, autism may be considered a difference ('neurodivergence') that constitutes a disability in the context of the demands of the neurotypical world. This change to a neurodiversity perspective has been driven by autistic voices; for a full history of autistic self-advocacy and the neurodiversity movement, the reader is referred to the edited volume by Kapp (2019). It is notable that the first - and highly influential – autistic autobiography, by Temple Grandin, was published in 1986, and that today there are hundreds of first-person accounts.

Under this new conception, the old talk of 'curing' autism is no longer applicable or acceptable. There is however, a tension, however, between autistic adults promoting autism as a part of neurodiversity, and parents of those individuals who are severely disabled by intellectual

impairment/language disorder/epilepsy. The research priorities that grow from these different experiences of autism, are naturally different. Of course, nobody disagrees that many of the co-occurring conditions common in autism are valid treatment targets. No one wants to keep their depression, crippling anxiety, sleep problems or gastrointestinal conditions. Similarly, interventions for intellectual disability and language disorder would be welcomed and do not stigmatise autism, or threaten its characterisation as a different, not deficient, way of being.

As discussed above, the dimensional conception of autism has no natural cut-off point where high autism traits become 'autism'. In DSM-5, an ASD diagnosis requires that the autistic traits 'cause clinically significant impairment in social, occupational, or other important areas of current functioning'. If 'impairment' is a function of the interaction between the person's characteristics and the demands of the environment/context, this means that an autism diagnosis based on current behavioural assessments could potentially come and go. That is, the same person may live happily with their autistic traits in one context or at one age when they find their niche, but be impaired by them in another context that is less accommodating. Are we ready to consider autism as something that comes and goes? Do we need a term for autism/high autistic traits that are not impairing; not a diagnosis, then, but a cognitive style or personality type, perhaps? If so, this might be the most dramatic re-conceptualisation of autism yet.

From 'developmental disorder' to neurodivergence: Implications for future research

Traditionally the autism research agenda has been scientist- or funder-led, with some notable (autism) parent-scientists making a major contribution historically (e.g. Wing, Rimland)

and currently. In the States in particular, parent-led charities raised funds and influenced the direction of research by attracting to the field scientists not previously interested in autism. More recently, research charities such as Autistica have embraced the new era of stakeholder- and self-advocate led research (Fletcher-Watson et al, 2018). New participatory research models challenge non-autistic researchers to collaborate with autistic people at every stage of research, from identifying key questions, designing methods, recruiting participants, interpreting findings, to dissemination and public engagement. Such ways of working open new research avenues; sensory issues would have been a major scientific focus much sooner if researchers had been working more closely with autistic people. Although sensory differences had been addressed in the psychological experiments of Hermelin and O'Connor (1970), it took the direct input from autistic individuals to give them the prominence they now have, and their inclusion in DSM-5.

The challenge for the future will be how to ensure that *all* the diverse voices within the autism spectrum, with as well as without intellectual and/or language disability, are heard. There is also the need, as in all science, to allow 'blue skies' and theoretical work alongside research with obvious and direct practical 'impact', recognising that concrete benefits often emerge unplanned from unexpected lines of research.

Conclusions: Challenges and Opportunities

The concept and diagnosis of autism has seen gradual as well as dramatic changes in the last few decades and it continues to evolve. We have drawn on personal recollection to trace some of the major changes in the last 30 years or so and captured these changes under seven headings, considering the implications for future research. Our review has identified a number of future challenges for researchers. We believe that the change from narrow to wide, can account for the

increased prevalence of autism spectrum disorders. The change from rare to common is still ongoing, with questions about the under-representation of females. The change from childhood to lifespan highlights the need for research on ageing. The change from discrete to dimensional poses new questions regarding non-impairing traits. The change from one to many requires that we consider the fractionation of autism. The change from pure to complex acknowledges that additional mental health problems are common and may be confounds in research. Finally, the change from 'developmental disorder' to neurodiversity requires collaborative approaches to research with the very diverse autism community.

In the course of looking back to look forward, some neglected topics emerged. There is little research on intellectual impairment, evidence-based educational approaches and technological aides for the many autistic people with ID. Language, once such a focus for autism research, is now relatively little studied but many important questions remain; for example, how are some autistic children able to acquire language apparently without delay or atypicality, given the apparently vital role of social processing (e.g. recognition of speaker's intentions) in word learning? What is the role of motor impairment, or some as yet unquantified deficit in volitional action, in the language impairment of 'minimally verbal' autistic people?

By contrast with these neglected areas, some areas of autism research are flourishing around the world. These include the groundbreaking infant-sibling studies, which track from birth children at elevated genetic probability of autism; early intervention programmes are increasingly being held to the same standards of evidence as traditional medical trials; and genetic consortia with open-access data are reaching critical mass for major discoveries. The full impact of these will be felt in the coming decades.

Autism research has typically focused on white males in high income countries, and it is only very recently that researchers are recognising that most autistic people live in low and middle income countries. How culture, ethnicity, and socio-economic status affect not only pathway to diagnosis, but the manifestation of autism and developmental adaptation, has yet to be properly explored.

While autism so far remains a purely behavioural diagnosis, important questions arise about how we recognise it in women, in the elderly, and how far we would allow their phenotypes to stray from our textbook cases and still be called 'autism'. Will newly developed cognitive tests, or polygenic scores help by taking us beyond behaviour; could they ever aid diagnostic decision-making? Could cognitive assays assist recognition of autism that looks different, perhaps uncovering layers of compensation or camouflage?

Future research is likely to be increasingly dominated by big data, but it would be a serious mistake for researchers to lose sight of individuals. Students and early career researchers exploring autism in secondary analysis of huge data-sets, need also to work directly with autistic people, to really understand their experience and concerns. Furthermore, the power of sharing information between researchers and community members, as well as making joint decisions about research priorities, is invaluable. Participatory research models and co-design with autistic people and the wider autism community, can ensure that autism never becomes just a variable in a spreadsheet.

For those just setting out on their own journey in autism research, this is an exciting time; our understanding of autism has changed so much over the last few decades, it is almost impossible to imagine what our concept of autism will be in 2060.

Key points

- Originally, and even as late as the 1980s, autism was conceptualised as a rare and overwhelmingly male disorder of childhood, categorically distinct from typical

Acknowledgements

FH is part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Thanks go to Isabel Sinha for kind help with references, and to Chris Frith for useful discussion.

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References

Abu-Akel, A., Allison, C., Baron-Cohen, S. & Heinke, D. (2019). The distribution of autistic traits across the autism spectrum: evidence for discontinuous dimensional subpopulations underlying the autism continuum. *Molecular Autism, 10*(1), 24.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders: DSM-III.* (1994); *DSM-IV*. (2013); *(DSM-5®)*. American Psychiatric Pub.

Arvidsson, O., Gillberg, C., Lichtenstein, P. & Lundström, S. (2018). Secular changes in the symptom level of clinically diagnosed autism. Journal of Child Psychology and Psychiatry, 59(7), 744-751.

Asperger, H. (1944). Die „Autistischen Psychopathen" im Kindesalter. *European Archives of Psychiatry and Clinical Neuroscience, 117*(1), 76-136. English translation by U. Frith (1991), Asperger, H. (1991). 'Autistic psychopathy' in childhood. In U. Frith (Ed.), *Autism and Asperger syndrome* (pp. 37-92).

Baron-Cohen, S., Tsompanidis, A., Auyeung, B., Nørgaard-Pedersen, B., Hougaard, D.M., Abdallah, M., Cohen, A. and Pohl, A., 2019. Foetal oestrogens and autism. *Molecular psychiatry*, pp.1-9.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J. & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31, 5–17.

Bird, G., & Cook, R. (2013). Mixed emotions: the contribution of alexithymia to the emotional symptoms of autism. *Translational Psychiatry*, *3*(7), e285.

Brugha, T. S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., et al. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of General Psychiatry, 68*(5), 459-465.

Brunsdon, V.E.A., Colvert, E., Ames, C., Garnett, T., Gillan, N., Hallett, V., Lietz, S., Woodhouse, E., Bolton, P. & Happé, F. (2015) Exploring the cognitive features in children with autism spectrum disorders, their co-twins, and typically-developing children within a population-based sample. *Journal of Child Psychology and Psychiatry,* 56, 893-902.

Carpenter, B., Happé, F. & Egerton, J. (Eds) (2019) *Autism and Girls*. London: Taylor & Francis/Routledge.

Coleman, M. & Gillberg, C. (2012). *The Autisms. (4th Edition).* Oxford University Press USA.

Colvert, E., Tick, B., McEwen, F., Ames, C., Curran, S., Woodhouse, E., Gillan, N., Hallett, V., Lietz, S., Garnett, T., Ronald, A., Plomin, R., Rijsdijk, F., Happé, F., & Bolton, P. (2015). Heritability of Autism and Autism Spectrum Disorder in a UK twin sample. *JAMA Psychiatry, 72, 415-423.*

Constantino, J. N., Przybeck, T., Friesen, D., & Todd, R. D. (2000). Reciprocal social behavior in children with and without pervasive developmental disorders. *Journal of Developmental and Behavioral Pediatrics, 21,* 2-11.

Donvan, J. J., & Zucker, C. B. (2017). *In a different key: The story of autism*. Broadway Books.

Elsabbagh, M., Divan, G., Koh, Y. J., Kim, Y. S., Kauchali, S., Marcín C., et al. (2012). Global Prevalence of Autism and Other Pervasive Developmental Disorders. *Autism Research, 5,* 160-179.

Evans, B. (2017). *The Metamorphosis of Autism. A history of Child Development in Britain*. Manchester: Manchester University Press.

Feinstein, A. (2011). *A history of autism: Conversations with the pioneers*. John Wiley & Sons.

Fletcher-Watson, S., Adams, J., Brook, K., Charman, T., Crane, L., Cusack, J., et al. (2018). Making the future together: Shaping autism research through meaningful participation. *Autism 23*(4), 943-953.

Fletcher-Watson, S. & Happé, F. (2019) *Autism: A new introduction to psychological theory and current debate*. London: Routledge.

Fombonne, E. (2018). The rising prevalence of autism. *Journal of Child Psychology and Psychiatry, 59*(7), 717-720.

Frazier, T.W., Dawson, G., Murray, D., Shih, A., Sachs, J.S., & Geiger, A., 2018. Brief Report: A survey of autism research priorities across a diverse community of stakeholders. *Journal of autism and developmental disorders, 48,* 3965-3971.

Frith, U. (1989). *Autism: Explaining the enigma.* Oxford: Blackwells.

Frith, U., Morton, J. & Leslie, A. M. (1991). The cognitive basis of a biological disorder: autism. *Trends in Neurosciences, 14*(10), 433-438.

Gillberg, C. & Billstedt, E. (2000). Autism and Asperger syndrome: coexistence with other clinical disorders. *Acta Psychiatrica Scandinavica, 102*(5), 321-330.

Gillespie-Lynch, K., Sepeta, L., Wang, Y., Marshall, S., Gomez, L., Sigman, M., & Hutman, T. (2012). Early childhood predictors of the social competence of adults with autism. *Journal of Autism and Developmental Disorders, 42*(2), 161–174.

Gökçen, E., Frederickson, N., & Petrides, K. V. (2016). Theory of Mind and executive control deficits in typically developing adults and adolescents with high levels of Autism traits, *Journal of Autism and Developmental Disorders,46,* 2072–2087.

Grandin, T. (1986). *Emergence, Labeled Autistic.* Academic Therapy Publications.

Grinker, R.R., 2008. *Unstrange minds: Remapping the world of autism*. Basic Books.

Happé, F. (2001) Social and Non-social development in Autism: Where are the links? In J. A. Burack, T. Charman, N. Yirmiya & P. R. Zelazo (Eds.) *Perspectives on Development in Autism* (pp. 237-253). New Jersey: Lawrence Erlbaum Associates.

Happé, F. (2011). Criteria, categories, and continua: autism and related disorders in DSM-5. *Journal of the American Academy of Child & Adolescent Psychiatry, 50*, 540-542.

Happé, F. (2015). Autism as a neurodevelopmental disorder of mind-reading. *Journal of the British Academy*, *3*, 197-209.

Happé, F., Ehlers, S., Fletcher, P., Frith, U., Johansson, M., Gillberg, C., et al. (1996) 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. *NeuroReport, 8*, 197-201.

Happé, F. & Frith, U. (2006) The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 36, 5-25.

Happé, F. & Ronald, A. (2008) 'Fractionable Autism Triad': A review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychology Review, 18*, 287-304.

Happé, F., Ronald, A. & Plomin, R. (2006) Time to give up on a single explanation for autism. *Nature Neuroscience.* 9, 1218-20.

Hill, E., Berthoz, S. & Frith, U. (2004). Brief report: Cognitive processing of own emotions in individuals with autistic spectrum disorder and in their relatives. *Journal of Autism and Developmental Disorders*, *34*(2), 229-235.

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. *British Journal of Psychiatry, 208*, 232–238

Hull, L., Mandy, W., Lai, M. C., Baron-Cohen, S., Allison, C., Smith, P. et al. (2019). Development and validation of the camouflaging autistic traits questionnaire (CAT-Q). *Journal of Autism and Developmental Disorders, 49*(3), 819-833.

Jack, A., & Pelphrey, K. A. (2017). Annual Research Review: Understudied populations within the autism spectrum – current trends and future directions in neuroimaging research. *Journal of Child Psychology and Psychiatry, 58,* 411–435.

Jacquemont, S., Coe, B. P., Hersch, M., Duyzend, M. H., Krumm, N., Bergmann, S., et al. (2014). A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. *American Journal of Human Genetics, 94*(3), 415-425.

Jones, C. R., Simonoff, E., Baird, G., Pickles, A., Marsden, A. J., Tregay, J., et al. (2018). The association between theory of mind, executive function, and the symptoms of autism spectrum disorder. *Autism Research,11*(1), 95-109.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous child*, *2*(3), 217-250.

Kanner, L. (1971). Follow-up study of eleven autistic children originally reported in 1943. *Journal of Autism and Childhood Schizophrenia*, *1*(2), 119-145.

Kapp, S. (Ed.) (2020). *Autistic Community and the Neurodiversity Movement: Stories from the Frontline.* Palgrave MacMillan.

Kim, H., Keifer, C.M., Rodriguez-Seijas, C., Eaton, N.R., Lerner, M.D. and Gadow, K.D., 2018. Structural hierarchy of autism spectrum disorder symptoms: an integrative framework. *Journal of Child Psychology and Psychiatry*, *59*(1), 30-38.

Kinnaird, E., Stewart, C., & Tchanturia, K. (2019). Investigating alexithymia in autism: a systematic review and meta-analysis. *European Psychiatry, 55*, 80-89.

Kuiper, M.W., Verhoeven, E.W. & Geurts, H.M. (2019.) Stop Making Noise! Auditory Sensitivity in Adults with an Autism Spectrum Disorder Diagnosis: Physiological Habituation and Subjective Detection Thresholds. *Journal of autism and developmental disorders*, *49*(5), 2116-2128.

Lai, M. C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., et al. (in press). Prevalence of Co-Occurring Mental Health Diagnoses in the Autism Population: A Systematic Review and Meta-Analysis. *Lancet*.

Lai, M. C., Lombardo, M. V., Chakrabarti, B., Ruigrok, A. N., Bullmore, E. T., Suckling, J., et al. (2018). Neural self-representation in autistic women and association with 'compensatory camouflaging'. *Autism*, 1362361318807159.

Laurie, M. H., Warreyn, P., Uriarte, B. V., Boonen, C., & Fletcher-Watson, S. (2019). An international survey of parental attitudes to technology use by their autistic children at home. *Journal of autism and developmental disorders*, 49(4), 1517-1530.

Lawson, T.P., Rees, G. & Friston, K.J. (2014). An aberrant precision account of autism. *Frontiers in Human Neuroscience*, 8, 302.

LeCouteur, A., Rutter, M., Lord, C., Rios, P., Robertson, S., Holdgrafer, M., et al. (1989). Autism diagnostic interview: a standardized investigator-based instrument. *Journal of autism and developmental disorders*, *19*(3), 363-387.

Lever, A.G. and Geurts, H.M. (2016). Age-related differences in cognition across the adult lifespan in autism spectrum disorder. *Autism Research*, *9*(6), 666-676.

Livingston, L. & Happé, F. (2017). Conceptualising compensation in Neurodevelopmental Disorders: Reflections from Autism Spectrum Disorder. *Neuroscience & Biobehavioral Reviews*, 80, 729-742.

Loomes, R., Hull, L. and Mandy, W. P. L. (2017). What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(6), 466-474.

Lord, C., Petkova, E., Hus, V., Gan, W., Lu, F., Martin, D. M., et al. (2012). A multisite study of the clinical diagnosis of different autism spectrum disorders. *Archives of General Psychiatry*, *69*(3), 306-313.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L. et al. (1989). Autism diagnostic observation schedule: A standardized observation of communicative and social behavior. *Journal of autism and developmental disorders*, *19*(2), 185-212.

Loth, E., Charman, T., Mason, L., Tillmann, J., Jones, E.J., Wooldridge, C., Ahmad, J., Auyeung, B., Brogna, C., Ambrosino, S. and Banaschewski, T., 2017. The EU-AIMS Longitudinal European Autism Project (LEAP): design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. *Molecular Autism*, *8*, 24.

Loth, E. & Evans, D. W. (2019). Converting tests of fundamental social, cognitive, and affective processes into clinically useful bio-behavioral markers for neurodevelopmental conditions. *Wiley Interdisciplinary Reviews: Cognitive Science*.

Lotter, V. (1966). Epidemiology of autistic conditions in young children: I. Prevalence. *Social Psychiatry*, *1*, 124-137.

Lund, J. & Jensen, J. (1989.) Dimensional approach to infantile autism in mentally retarded adults. *Acta Psychiatrica Scandinavica*, *80*(4), 389-394.

Lundström, S., Reichenberg, A., Anckarsäter, H., Lichtenstein, P. & Gillberg, C. (2015). Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples. *British Medical Journal*, *350*, h1961.

Massrali, A., Brunel, H., Hannon, E., Wong, C., Baron-Cohen, S. and Warrier, V. (2018). Integrated genetic and methylomic analyses identify shared biology between autism and autistic traits. *bioRxiv*, p.493601.

McConachie, H., Wilson, C., Mason, D., Garland, D., Parr, J.R., Rattazzi, A., Rodgers, J., Skevington, S., Uljarevic, M. and Magiati, I. (2019). What Is Important in Measuring Quality of Life? Reflections by Autistic Adults in Four Countries. *Autism in Adulthood*.

Oliveira, B., Mitjans, M., Nitsche, M.A., Kuo, M.F. & Ehrenreich, H. (2018). Excitation-inhibition dysbalance as predictor of autistic phenotypes. *Journal of Psychiatric Research, 104*, 96-99.

Pellicano, E. & Burr, D. (2012). When the world becomes 'too real': a Bayesian explanation of autistic perception. *Trends in Cognitive Sciences, 16* (10), 504-510.

Pickles, A., Starr, P., Kazak, S., Bolton, P., Papanikolaou, K., Bailey, A., et al. (2000). Variable expression of the Autism Broader Phenotype: Findings from extended pedigrees. *Journal of Child Psychiatry & Psychology, 41*(4), 491-502.

Pinti, P., Tachtsidis, I., Hamilton, A., Hirsch, Aichelburg, J. C., Gilbert, S. et al. (2018). The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. *Annals of the New York Academy of Sciences.*

Piven, J., Palmer, P., Jacobi, D., Childress, D. & Arndt, S. (1997). Broader autism phenotype: Evidence from a family history study of multiple-incidence autism families. *American Journal of Psychiatry, 154*, 185-190.

Pua, E. P. K., Bowden, S. C. and Seal, M. L. (2017). Autism spectrum disorders: Neuroimaging findings from systematic reviews. *Research in Autism Spectrum Disorders*, *34*, 28-33.

Råstam, M., Gillberg, C., Gillberg, I. C. & Johansson, M. (1997). Alexithymia in anorexia nervosa: a controlled study using the 20-item Toronto Alexithymia Scale. *Acta Psychiatrica Scandinavica*, *95*(5), 385-388.

Ridley, R. (2019). Some difficulties behind the concept of the 'Extreme male brain' in autism research. A theoretical review. *Research in Autism Spectrum Disorders, 57,* 19-27

Robinson, E. B., Koenen, K. C., McCormick, M. C., Munir, K., Hallett, V., Happé, F., et al. (2011). Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes (5%, 2.5%, and 1%). *Archives of General Psychiatry, 68*(11), 1113–21.

Robinson, E. B., Lichtenstein, P., Anckarsäter, H., Happé, F. & Ronald, A. (2013). Examining and interpreting the female protective effect against autistic behavior. *Proceedings of the National Academy of Sciences, 110*(13), 5258-5262.

Roestorf, A., D. M. Bowler, M. K. Deserno, P. Howlin, L. Klinger, H. McConachie, J. R. Parr, P. Powell, B. F. C. Van Heijst, and H. M. Geurts (2019). "Older Adults with ASD: The Consequences of Aging." Insights from a series of special interest group meetings held at the International Society for Autism Research 2016–2017. *Research in Autism Spectrum Disorders*, 63, 3-12.

Rubenstein, E. & Bishop-Fitzpatrick L. (2019). A matter of time: The necessity of temporal language in research on health conditions that present with autism spectrum disorder. *Autism Research*, 12(1):20-25. doi: 10.1002/aur.2010. Epub 2018 Sep 5.

Rubenstein, E. & Chawla, D. (2018). Broader autism phenotype in parents of children with autism: a systematic review of percentage estimates. *Journal of Child and Family Studies*, *27*(6):1705-1720.

Russell, G., Mandy, W., Elliott, D., White, R., Pittwood, T., & Ford, T. (2019). Selection bias on intellectual ability in autism research: a cross-sectional review and meta-analysis. *Molecular Autism,10*(9).

Rutter, M. (1968). Concepts of autism: A review of research. *Journal of Child Psychiatry & Psychology, 9 (1)*, 1-25.

Rydzewska, E., Hughes-McCormack, L.A., Gillberg, C., Henderson, A., MacIntyre, C., Rintoul, J. & Cooper, S.A. (2018). Prevalence of long-term health conditions in adults with autism: observational study of a whole country population. *BMJ open*, *8*(8), .e023945.

Schopler, E. & Mesibov, G. B. (1983). *Autism in Adolescent and Adults.* New York: Plenum Press.

Schuwerk, T., Jarvers, I., Vuori, M. & Sodian, B. (2016). Implicit Mentalizing Persists beyond Early Childhood and Is Profoundly Impaired in Children with Autism Spectrum Condition. *Frontiers in Psychology*, *7*, 1696.

Sedgewick, F., Kerr-Gaffney, J., Leppanen, J. and Tchanturia, K. (2019). Anorexia Nervosa, Autism, and the ADOS: How appropriate is the new algorithm in identifying cases? *Front. Psychiatry, 10*, 507. Published online 2019 Jul 18. doi: 10.3389/fpsyt.2019.00507

Shah, A. (2019). *Catatonia, Shutdown and Breakdown in Autism. A Psycho-Ecological Approach.* London: Jessica Kingsley.

Shakespeare, T., 2006. The social model of disability. *The disability studies reader*, *2*, pp.197-204.

Sheldrick, R. C. & Carter, A. S. (2018). State-level trends in the prevalence of Autism Spectrum Disorder (ASD) from 2000 to 2012: A reanalysis of findings from the autism and developmental disabilities network. *Journal of Autism and Developmental Disorders, 48*(9), 3086-3092.

Silberman, S. (2015). *Neurotribes: the legacy of autism and how to think smarter about people who think differently.* Sydney: Allen & Unwin,

Stewart, M. E., Griffiths, T. D. & Grube, M. (2018). Autistic traits and enhanced perceptual representation of pitch and time. *Journal of Autism and Developmental Disorders, 48*(4), 1350-1358

Tager-Flusberg, H., Plesa Skwerer, D., Joseph, R. M., Brukilacchio, B., Decker, J., Eggleston, B., et al. (2017). Conducting research with minimally verbal participants with autism spectrum disorder. *Autism, 21*(7), 852-861

Tantam, D. (1988). Annotation: Asperger's syndrome. *Journal of Child Psychiatry & Psychology, 29,* 836-840.

Taylor, B., Jick, H. & MacLaughlin, D. (2013). Prevalence and incidence rates of autism in the UK: time trend from 2004–2010 in children aged 8 years. *BMJ open*, *3*(10), p.e003219.

Tick, B., Colvert, E., McEwen, F., Stewart, C., Woodhouse, E., Gillan, N., et al. (2016). Autism Spectrum Disorders and other mental health problems: exploring etiological overlaps and phenotypic causal associations. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(2), 106-113.

van Rooij, D., Anagnostou, E., Arango, C., Auzias, G., Behrmann, M., Busatto, G. F., et al. (2017). Cortical and Subcortical Brain Morphometry Differences Between Patients with Autism Spectrum Disorder and Healthy Individuals Across the Lifespan: Results from the ENIGMA ASD Working Group. *American Journal of Psychiatry,175*(4),359-369.

Warrier, V., Toro, R., Chakrabarti, B., Borglum, A., Grove, J., Hinds, D., Bourgeron, T., Baron-Cohen, S. & 23andMe Research Team (2017). Systemizing is genetically correlated with autism and is genetically distinct from social autistic traits. *bioRxiv*, p.228254.

Weiner, D.J., Wigdor, E.M., Ripke, S., Walters, R.K., Kosmicki, J.A., Grove, J., Samocha, K.E., Goldstein, J.I., Okbay, A., Bybjerg-Grauholm, J. & Werge, T. (2017). Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. *Nature Genetics*, *49*(7), 978.

Wester Oxelgren, U., Åberg, M., Myrelid, Å., Annerén, G., Westerlund, J., Gustafsson, J., et al. (2019). Autism needs to be considered in children with Down syndrome. *Acta Paediatrica*.

Wing, L (1969). The handicaps of autistic children—A comparative study. *Journal of Child Psychology and Psychiatry*, *10*(1), 1-40.

Wing, L. (1981). Asperger's Syndrome: A clinical account. *Psychological Medicine*, *11*, 115-119.

Wing, L., & Gould, J. (1978). Systematic recording of behaviors and skills of retarded and psychotic children. *Journal of Autism and Childhood Schizophrenia*, *8*(1), 79-97.

Wing, L. & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *Journal of Autism and Developmental Disorders*, *9*(1), 11–29.

Wing, L. & Wing, J.K. (1971). Multiple impairments in early childhood autism. *Journal of Autism and Childhood Schizophrenia*, *1*(3), 256-266.

Wolff, S., Narayan, S. & Moyes, B. (1988.) Personality characteristics of parents of autistic children: a controlled study. *Journal of Child Psychology and Psychiatry*, *29*(2), 143-153.

Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J. & Zhang, Z. (2017). Advanced parental age and autism risk in children: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *135*(1), 29-41.

Zheng, L., Grove, R. & Eapen, V. (2019). Spectrum or subtypes? A latent profile analysis of restricted and repetitive behaviours in autism. *Research in Autism Spectrum Disorders, 57*, 46-54.

Zivrali-Yarar, E. (2017) *Ageing and Autism Spectrum Disorder*. Unpublished PhD thesis, King's College London.