Autism spectrum disorder

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Abstract | Autism spectrum disorder is a construct used to describe individuals with a specific combination of impairments in social communication and repetitive behaviours, highly restricted interests and/or sensory behaviours beginning early in life. The worldwide prevalence of autism is just under 1%, but estimates are higher in high-income countries. Although gross brain pathology is not characteristic of autism, subtle anatomical and functional differences have been observed in post-mortem, neuroimaging and electrophysiological studies. Initially, it was hoped that accurate measurement of behavioural phenotypes would lead to specific genetic subtypes, but genetic findings have mainly applied to heterogeneous groups that are not specific to autism. Psychosocial interventions in children can improve specific behaviours, such as joint attention, language and social engagement, that may affect further development and could reduce symptom severity. However, further research is necessary to identify the long-term needs of people with autism, and treatments and the mechanisms behind them that could result in improved independence and quality of life over time. Families are often the major source of support for people with autism throughout much of life and need to be considered, along with the perspectives of autistic individuals, in both research and practice.

Autism spectrum disorder (ASD), also known as autism, is a common, highly heritable and heterogeneous neurodevelopmental disorder that has underlying cognitive features and commonly co-occurs with other conditions. The behaviours, strengths and challenges of people with autism have attracted the attention of scientists and clinicians for at least 500 years (FIG. 1). Autism is a heterogeneous disorder and, reflecting this heterogeneity, the term autism has been used in various ways to describe both a broader presentation as well as a specific diagnosis following its consideration as a subgroup within the general diagnostic category of 'pervasive developmental disorders' (PDDs). PDDs are a group of disorders introduced in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) in 1980 to convey the idea of a broader spectrum of social communication deficits. Owing to a lack of clear borders between the PDDs and difficulties in reliably distinguishing them, the most recent diagnostic systems, the International Classification of Diseases 11th Revision (ICD-11) and DSM-5 use the umbrella term 'ASD', and differentiate individuals using additional clinical specifiers and modifiers. In this Primer, we use the term 'autism' to refer to ASD in general, both for brevity and out of respect for the preferences of self-advocates.

Manifestations of autism include impairments in social communication and interaction, sensory anomalies, repetitive behaviours and varying levels of intellectual disability (BOX 1). Together with these core symptoms, co-occurring psychiatric or neurological disorders are common in people with autism, of which hyperactivity and attention disorders (such as attention-deficit/hyperactivity disorder (ADHD)), anxiety, depression and epilepsy are fairly prevalent. A diagnosis of autism is reached after obtaining a detailed developmental history, often from the parents, and observation of the individual interacting with parents or other individuals[1,2]. Early intervention for children with autism is key owing to common difficulties in communication. The types of interventions used change throughout life and include parent-mediated interventions and/or therapist-delivered interventions in childhood, and school-based strategies and techniques to promote independence in adulthood. Pharmacological therapies can be used to treat some of the associated symptoms of autism, such as irritability, and comorbidities, such as anxiety.

This Primer discusses the epidemiology and mechanisms of autism, together with the diagnosis and treatment of people with this condition. Three themes are addressed: mechanisms of causality and change over

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time, heterogeneity within and between individuals with autism, and outcomes across the lifespan.

Epidemiology

Prevalence

Epidemiological administrative and community-based studies have suggested that autism is more common in males than in females, with reported ratios ranging from 2:1 to 5:1, with an estimate of 4:1 in the 2010 Global Burden of Disease study[3,4]. The sex ratio is slightly lower in studies that use population-wide testing to find community cases within a population than in the more common passive case-finding studies that review administrative data (for example, medical or special educational records), which may result in less plausible associations and may, therefore, artificially increase prevalence estimates[5]. Active case-finding that does not rely on administrative records has demonstrated an equivalent community rate of autism in men and women with moderate-to-profound intellectual disability[4]. Thus, even the most widely accepted tenet of our understanding of factors associated with autism is far from straightforward.

Estimates of the prevalence of autism in various populations and settings differ according to the method of ascertainment used in the study, including definition, sampling and the extent of independent population case assessment in contrast to administratively based sources. Of note, the Global Burden of Disease study uses all known data from administrative and community survey sources on a disease or disorder to model associations (particularly with time) to examine trends. In the 2010 Global Burden of Disease study, an estimated 52 million people had autism globally, equating to a prevalence of 1 in 132 individuals[6]. Worldwide, little interpretable variation in the prevalence of autism between regions, ethnicities or services and resource provision has been reported. Indeed, one systematic review did not find a strong effect of ethnic, cultural or socioeconomic factors on the prevalence of autism[7]. However, statistical power to detect any effects was limited in the available data sets, particularly in low-income countries. An increased prevalence of autism has been reported in migrant groups in some studies[8], with few clear factors that might contribute to a greater prevalence in an Afro-Caribbean population in higher-income countries[9–11] in the absence of any evidence of geographical variation[7]. However, a survey of adults in the general population has shown that rates of autism in black and minority ethnic groups may be lower than in the rest of the population[12]; data from indigenous and Aboriginal cultures are very limited.

Many individuals and groups presume that rates of autism are increasing over time, but this supposition is based on data from administrative records rather than community-based studies. Indeed, after accounting for methodological variations between studies, there was no clear evidence of a change in the prevalence of autism in the community between 1990 and 2010 (REF.[13]). In addition, general population and systematic case-finding community-based surveys (including testing of representative populations) have also confirmed the lack of significant change in prevalence rates in childhood[14] and adulthood[15] over time. No significant evidence is available supporting that autism is rarer in older people, which provides further evidence against the suggestion that autism is increasing in prevalence over time[4]. Even in high-income countries with strong autism public health policies, there is evidence that autism in adults goes largely unrecognized, whereas administratively recorded diagnoses in children increase year by year[16]. This finding highlights the importance of obtaining information on autism rates in settings where professionals may be able to improve its recognition. The prevalence of autism in mental health inpatient settings is estimated to be far higher than in the general population, ranging from 4% to 9.9%[17].

Environmental factors

One review of systematic reviews and meta-analyses of environmental risk factors for autism included a comprehensive coverage of the literature, a discussion of the limitations of research and the need for long-term prospective cohort-based studies to begin to address these limitations[18] (FIG. 2). This review and other studies identified environmental risk factors for autism as advanced parental age[19] and birth trauma, particularly if due to proxies of hypoxia[18]. Moreover, maternal obesity, a short interval between pregnancies, gestational diabetes mellitus and valproate use during pregnancy have all been associated with increased risk of autism (FIG. 2). However, it should be noted that these factors cannot be considered causal, but could be reactive, independent or contributory for autism. Studies evaluating risk factors for autism that have reported an absence of association are equally, if not more, important to note, including clear evidence that autism is not associated with vaccination[20]. Other negative associations include prolonged labour, delivery by caesarean section or assisted vaginal delivery, premature rupture of membranes and the use of assisted reproductive technologies, among other factors (FIG. 2). Environmental risk factors could trigger the risk of autism through several complex underlying mechanisms such as genetic and epigenetic effects (see Mechanisms/pathophysiology, below), inflammation and oxidative stress, or hypoxic and ischaemic damage[18].
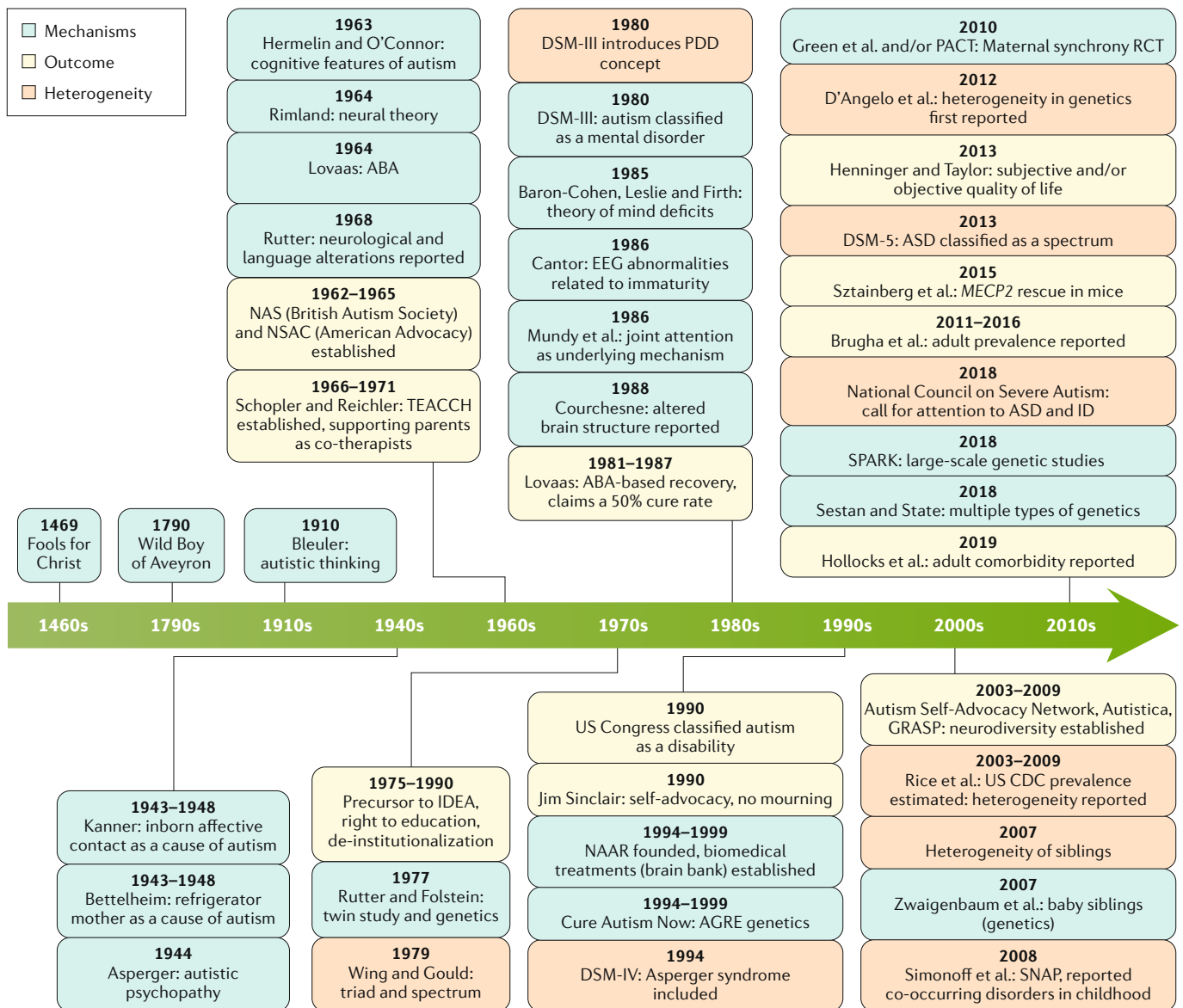
Fig. 1 | **Theories and findings regarding autism mechanisms, outcomes and heterogeneity.** Original descriptions of the cardinal features of autism were attributed to a range of causes, including being raised by wolves (the Wild Boy of Aveyron), inborn limitations in affective contact and unfeeling parenting (such as 'refrigerator mothers'), and holy people (such as Fools for Christ)[257]. Conceptualizations of autism as a common highly heritable neurodevelopmental disorder with underlying cognitive features began with the recognition of differences in brain function and cognition in the 1960s[258–261] and the first twin study in the 1970s[262]. Other proposed mechanisms include maturational lags in neurophysiology[94] and cognitive mechanisms such as joint engagement[176,263]. With the search for pathways to and sometimes out of autism on many levels, conceptualization of positive outcomes has been more recent but has also varied markedly. In the 1970s, autism societies and collaborative clinical programmes focused on community integration and de-institutionalization (such as National Autistic Society (NAS) and National Society for Autistic Children (NSAC))[264]. Priorities shifted in the 1980s and 1990s, with still unreplicated claims of 'recovery' in children who participated in intensive behavioural interventions[179], new advocacy groups focusing on biomedical discoveries to yield potential biological treatments and even 'cures' (such as National Alliance for Autism Research (NAAR) and Cure Autism Now)[257], and the neurodiversity movement[265], which rejected 'cures' and called for adaptation of environments to support autistic people, using terminology preferred by self-advocates and community participation. Recognition of the marked heterogeneity within autism began in the 1970s, with the triad of impairments in language, play and social interaction characterizing many children with intellectual disabilities (ID) or those with classical autism[266]. The first twin study demonstrated that monozygotic twin pairs, although concordant for difficulties associated with autism, differed in specific characteristics and co-occurring conditions, including ID[262]. More recently, phenotypic heterogeneity has been the rule in most, although not all, gene-first phenotypic studies[267]. Thus, developmental aspects of differences in strengths, difficulties and trajectories as well as biological factors require highly personalized conceptualizations of the needs of autistic individuals and their families. ABA, applied behaviour analysis; AGRE, Autism Genetic Resource Exchange; ASD, autism spectrum disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; GRASP, Global and Regional Asperger Syndrome Partnership; IDEA, Individuals with Disabilities Education Act; MECP2, the gene associated with Rett syndrome; PACT, Preschool Autism Communication Trial; PDD, pervasive developmental disorder; RCT, randomized controlled trial; SNAP, Special Needs and Autism Project; SPARK, Simons Foundation Powering Autism Research for Knowledge; TEACCH, Treatment and Education of Autistic and Related Communication-handicapped Children.

Mechanisms/pathophysiology

Many cognitive theories have been suggested to underlie the behavioural and developmental manifestations of autism, although the prominence and the consensus on the potential explanatory value of these theories have declined in the past decade. These theories range from 'social first' theories, such as the theory of mind (or mentalizing) and social motivational deficit theories, to global processing deficit theories, including attentional control, executive dysfunction and weak central coherence or enhanced perceptual processing theories[21,22]. Although many of these theories had a useful descriptive role and provide potential insights into differences in how autistic individuals might process and experience the world around them, the theories pertain to neurodevelopmental disorders in general and lack specificity for autism, they are largely non-developmental, applying only to a single point in time, and lack evidence as explanatory models. Nevertheless, they have been useful in clinical practice and underlie some recently proposed interventions, such as cognitive behavioural therapy (CBT)-oriented treatments for anxiety[23].

Following cohorts of infants from gestation or birth to 2 or 3 years of age (that is, to an age when a diagnosis of autism can be established) enables the study of the brain and behavioural manifestations of autism as they emerge[24]. Indeed, prospective studies of infants with a relative with autism have yielded several insights into the mechanisms of this disorder. For example, infants who develop autism later in childhood have substantially typical profiles of interest in faces[25] and eyes[26] at 6 months of age, which have cast doubt on social orienting theories in which autism originates from a primary deficit in innate patterns of subcortically mediated social orienting[27]. In addition, subtle but diffuse differences in electroencephalography (EEG) and other measures of brain function have been demonstrated in autistic people (see Findings from electrophysiological studies, below), which could represent alternative pathways to a common end-state phenotype or to whole-brain alterations in synaptic signalling pathways that have effects on development[28]. Such considerations highlight the limitations of deterministic models of autism, in which a genetic change leads to a synaptic change that relates to a canonical symptom[29]. Rather, there is probably a complex set of developmental interactions in which the child's emerging brain activity and behaviour have bidirectional relationships to synaptic signalling and gene expression[30].

Genetics

Twin and family studies consistently demonstrate that autism has a particularly large genetic contribution, with estimated heritability ranging from ~40% to 90%[31,32]. In addition, one analysis demonstrated that autism is among the most heritable common medical conditions[33]. More than 100 genes and genomic regions have now been confidently associated with autism[34,35], mostly based on the study of heterozygous, germline, de novo mutations. These genetic changes range in size from a single base (or nucleotide)[36–38] to submicroscopic segments of DNA of thousands to millions of bases (also known as copy number variations (CNVs))[39,40]. Whether these genetic changes lead to alterations in the sequence of DNA or in the structure of the chromosome, changes that have a functional effect on protein-coding regions of the genome have the strongest and most reliable association with autism risk. Collectively, these de novo heterozygous mutations are rare and confer relatively large risks of autism[41]. With genetic studies now including cohorts of up to tens of thousands of individuals and the associated increase in statistical power, common, transmitted alleles of modest effect size, mostly corresponding to the non-coding regions of the genome, have begun to be identified[42].

Studies of the genetics of autism contrast broadly with those of adult-onset psychiatric disorders in which most successful gene discovery has emerged from genome-wide association studies assessing common alleles of small effect size. Indeed, the earliest successes in autism presaged a more general finding that the contribution of rare, de novo mutations in coding regions of the genome is relatively greater among a range of early-onset disorders[43–45] than for typically later-onset common conditions such as schizophrenia and bipolar disorder, although there is also a surprising degree of overlap in genetic risk for overtly disparate neuropsychiatric phenotypes that remains to be further elucidated[31].

The extent to which rare, high effect size mutations account for autism risk raises some important definitional issues. Considering the overall population, the contribution of de novo mutations to autism risk is quite small (~3%)[32]. Indeed, most individuals who harbour a genetic risk for a common condition, particularly those with variants of small effect size, will never develop symptoms or need clinical attention. By contrast, there is a marked enrichment of individuals with rare and de novo mutations in the clinical autism population. Conservative estimates are that 10–20% of people with

autism harbour a de novo rare point mutation or CNV contributing to their presentation[34,46,47]. If the clinical population is constrained to those with autism who have a combination of factors, including being female, having

intellectual disability, multiple unaffected siblings, or seizures, ~20–30% have a rare de novo mutation; if an individual has several of these risk factors, the yield of de novo sequence and structural mutations would be expected to be even higher[34].

However, irrespective of the precise proportion of risk conveyed by these mutations, their most substantial contribution to the understanding of autism is likely to be in elaborating the mechanisms of this disorder[48,49]. In autism, a single de novo germline heterozygous loss-of-function point mutation can convey more risk than the cumulative effect of the top decile of polygenic risk for schizophrenia[47,50]. Unfortunately, although manifestly more tractable than modelling hundreds of alleles simultaneously, addressing a single autism mutation at a time is not synonymous with an easy avenue to clinical care of most people with autism.

Molecular pathophysiology. Over the past decade, there have been many studies using model systems to recapitulate so-called single gene (or monogenic) versions of autism, such as fragile X syndrome and tuberous sclerosis complex, which are cumulatively estimated to account for <10% of clinical cases of autism[51]. In addition, more recent studies have modelled the effects of rare and de novo mutations identified in idiopathic autism. This literature is too vast to review comprehensively here[52,53]. Although the study of autism risk genes in model systems has revealed a great deal about general biology, how these findings relate to the pathophysiology of autism is less clear[48,49]. In general, autism risk genes tend to have a role in multiple functions in many brain regions that unfold in a spatiotemporally defined manner across development. Consequently, although manipulation of a single risk gene in a model system may lead to interesting phenotypes, including social-behavioural phenotypes in evolutionarily distant organisms, it does not necessarily illuminate its contribution to human social disability. Moreover, although a single mutation can confer a several-fold increase in the risk of autism, these variants do not demonstrate the type of causal clarity that is associated with classic monogenic neurodevelopmental disorders such as fragile X syndrome, Angelman syndrome, Rett syndrome or tuberous sclerosis complex. In addition, the well-established sexual dimorphism of social disability adds yet another dimension to the expansive search space that exists between risk genes and human behaviour[48]. The challenges of disentangling the spatiotemporal dynamics of risk gene expression and protein function are made even more difficult by the reality that these may play out differently in males and females.

Owing to these challenges, multiple approaches have emerged focusing on convergence[38,40,54–57], that is, searching for points of commonality across different autism risk genes, with the reasoning that this approach could identify shared pathological mechanisms. In fact, the earliest successes in gene discovery quickly revealed important general properties that have held up well over time, including that, prima facie, most proteins encoded by autism risk genes are involved in either synaptic structure and function or chromatin
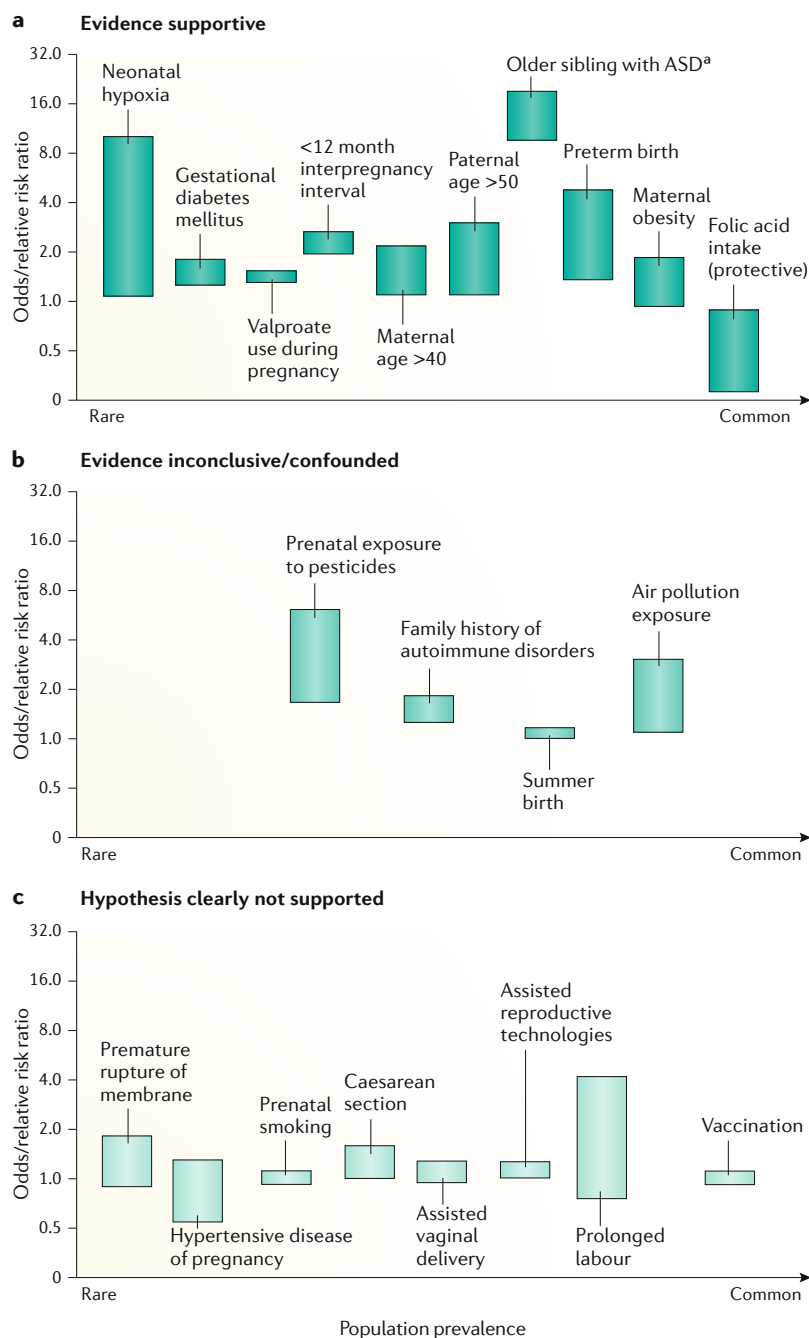

Fig. 2 | **Environmental risk factors for autism.** Data from studies aiming to identify risk factors for autism can be broadly split into three categories: those with evidence supporting an association (**a**), those with inconclusive evidence (**b**) and, importantly, those with no supporting evidence (**c**). Bars represent ranges. [a]Represents recurrence risk. Figure adapted from REF.[18] with added findings from select reviews and empirical papers: neonatal hypoxia estimate[268], childhood vaccines[20], valproate use during pregnancy[269], parent age estimates[270], preterm birth estimate[271,272], maternal obesity estimate[273], folic acid intake estimate[274], siblings estimate[275,276], interpregnancy interval estimate[277], assisted reproductive technologies estimate[278,279], pesticide and air pollution estimate[280], and caesarean section estimate[281]. Adapted from REF.[18], CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/).

modification and regulation of gene expression[38,46,47,58] (FIG. 3). More recently, there has been an additional focus on spatiotemporal convergence and several studies have supported a nexus in mid-fetal, glutamatergic neurons during cortical development, with modestly divergent findings regarding deep[56] versus superficial[54] cortical layers. With improvements in technology, additional regions, including the striatum, have also
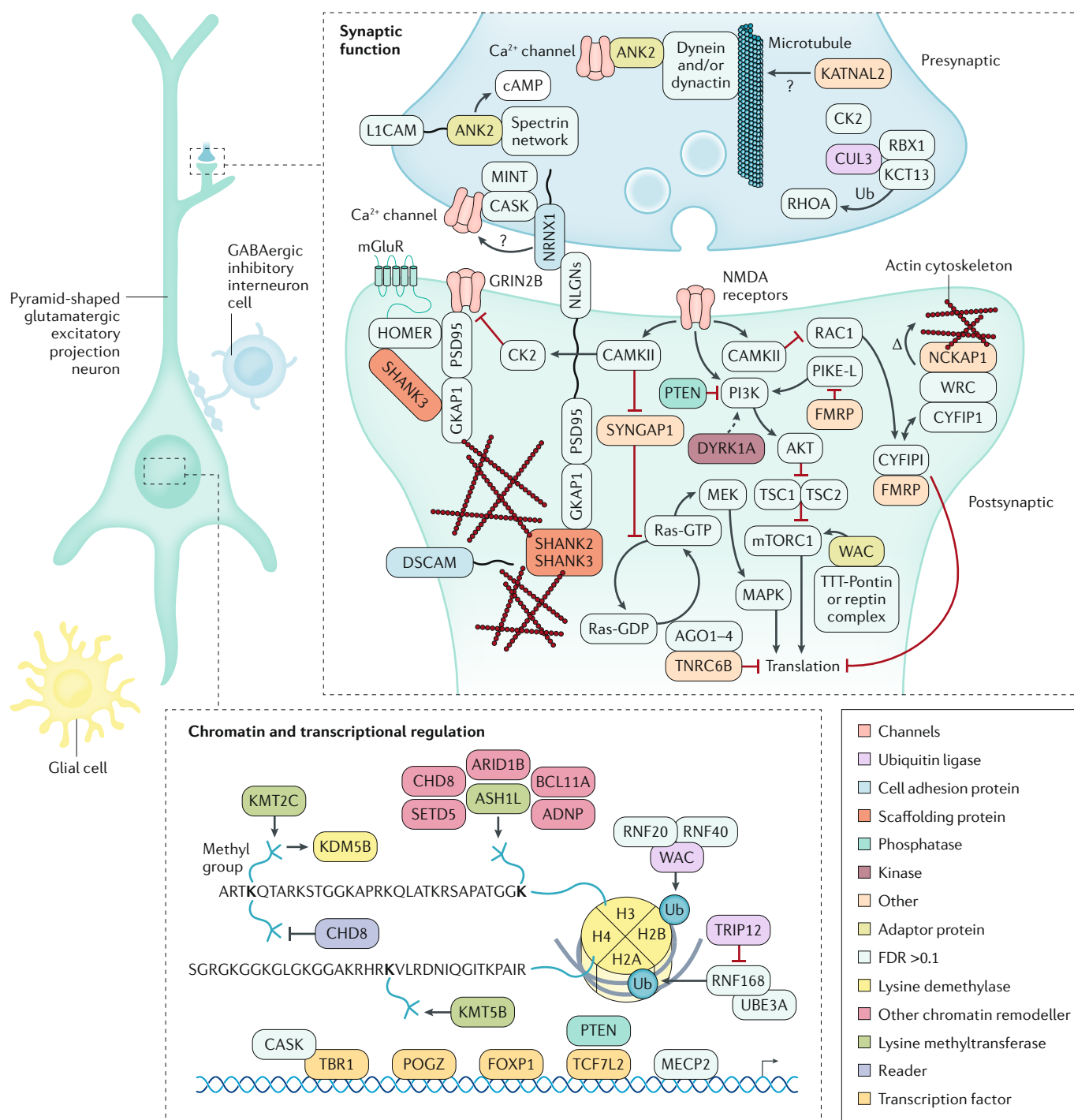

Fig. 3 | **Encoded proteins associated with autism risk.** Simplified schematic of the major cellular components of a neural circuit in the cerebral cortex, with a focus on pyramid-shaped glutamatergic excitatory projection neurons. Proteins encoded by selected high-confidence (false discovery rate <0.1) autism risk genes[34] and proteins encoded by selected syndromic autism genes have a role in these neurons during development. These proteins have a diverse intracellular distribution: those at the synapse have roles in cell adhesion, scaffolding and signalling. In addition, some of these proteins are localized to the nucleus and have been shown, broadly, to mediate chromatin modification and transcriptional control. Syndromic autism genes include *FMR1* (encoding fragile X mental retardation protein; fragile X syndrome), *UBE3A* (encoding ubiquitin-protein ligase E3A; Angelman syndrome), *TSC1* and *TSC2* (encoding hamartin and tuberin; tuberous sclerosis complex), *PTEN* (encoding phosphatase and tensin homologue) and *MECP2* (encoding methyl-CpG-binding protein 2; Rett syndrome). GABA, γ-aminobutyric acid; Ub; ubiquitin. Adapted with permission from REF.[48], Elsevier.

begun to emerge as points of potential risk convergence for autism[59].

The ability to constrain future experiments to examine mutations in specific risk-associated regional, cellular and developmental contexts should allow narrowing in on relevant mechanisms. Of note, one study used single-cell technologies to examine specific cell types and developmental stages using brain tissue from people with autism[60], and demonstrated changes in transcription in multiple cell types, including upper-layer cortical neurons. These types of post-mortem studies ask important but somewhat broader questions from the approaches described above regarding the underlying pathology and how the brain changes and responds to pathology over time. In these studies, similar to any cross-sectional study, it can be challenging to differentiate cause from effect. Consequently, the pursuit and intersection of studies that seek to define convergence early in development and those that examine subsequent molecular, cellular and circuit level changes will be critical to illuminating pathological mechanisms.

Indeed, given the success and US FDA approval of gene therapy for early-onset neurological disorders, particularly spinal muscular atrophy type 1 (REFS[61,62]), targeting single genes of large effect in both idiopathic and monogenic autism is being viewed as increasingly plausible. As rare syndromes such as fragile X syndrome, Angelman syndrome and Rett syndrome have offered some of the earliest insights into autism biology, these disorders are also likely to lead the way in illuminating the practical and important ethical challenges that will attend such efforts for idiopathic autism. Efforts aimed at the highest confidence risk genes identified in idiopathic autism, such as *SCN2A* and *CHD8* (REFS[34,35]), are almost certain to soon follow on attempts at gene therapy for monogenic neurodevelopmental disorders in light of the growing list of well-defined large-effect targets, the increasing options for addressing haploinsufficiency[63], the ability to manipulate gene products without leaving a DNA 'scar' (REFS[63,64]) and the increasing ability to readily detect mutations — and intervene — in utero and very early in postnatal development.

Neurobiology

Findings from MRI studies. MRI can facilitate understanding of how the brain structurally and functionally develops differently in people with autism, although, to date, MRI results in autism are not definitive. Although neuroimaging is typically more expensive than EEG and studies are limited by issues of replication (sometimes this is related to head motion occurring during the scan, which can erode signal[65]), structural studies including those using diffusion tensor imaging[66] and functional MRI (fMRI)[67] have accelerated our understanding of how altered neural circuits relate to clinical symptoms of autism[68,69]. Studying circuitry in childhood that is specifically associated with the social brain (a network of brain areas involved with processing social information), including visual areas, areas of the prefrontal cortex, subcortex and areas integrating information (such as temporal parietal function and superior temporal sulcus), could also offer insight into the neural mechanisms of autism[70].

In addition, MRI may facilitate understanding of the heterogeneity of autism, demonstrating subgroups of individuals with specific neurobiological alterations that could account for their symptomology. The summary of MRI studies in this section focuses on 0–2 years of age and addresses biomarkers for autism. Prospective study designs are largely covered as they represent a substantial portion of MRI research in autism.

The first MRI studies of autism focused on cerebral and cerebellar grey matter and white matter volumes in young children[71,72], although these studies were limited by studying toddlers and children aged ≥18 months, missing the opportunity to detect biomarkers of autism in the first year of life. More recently, longitudinal studies have obtained multiple brain MRIs of infants at high risk of developing autism (that is, those with a sibling with autism; known as baby sibling studies) during their first 2 years of life and assessed these children for autism at this age. In these studies, detectable differences in brain structure were observed at 6 months of age in the fractional anisotropy trajectories for 12 of 15 neural fibre tracts in the brain in children diagnosed with autism at 2 years of age compared with children not diagnosed[73]. Furthermore, abnormal growth in the cortical surface between 6 and 12 months of age and greater brain volume between 12 and 24 months of age were seen in children who were later diagnosed with autism, compared with those not diagnosed with autism[74] (FIG. 4). In addition, white matter integrity in the genu pathway at 6 months of age predicted the presence of restricted and repetitive behaviours at 2 years of age[75] and computational work demonstrated that whole-brain functional connectivity at 6 months of age predicted a diagnosis of autism at 2 years of age[76]. Collectively, these studies suggest the presence of disrupted neural pathways before the emergence of behavioural symptoms in children with autism and might provide clues about the underlying neural mechanisms of autism. Although data from MRI studies have revealed differences in neurobiology between young children diagnosed with autism and those without autism[77], given that replication has been particularly difficult in these studies, more work is required before MRI can be used as a reliable biomarker of autism[78].

Task-based fMRI studies investigate circuits that are responsible for core challenges in autism, such as language production and comprehension[79], and have demonstrated hyper-activation of the superior temporal gyrus and inferior frontal gyrus as well as hypoactivation of the bilateral middle temporal gyrus[76]. In addition, these studies have demonstrated challenges in processing emotions in faces and the 'social brain' (REF.[78]) and deficits in attention[79]. Studies have also demonstrated greater sensitivity to sensory information. Increased connectivity between the anterior insula and sensorimotor areas, and the anterior insula and amygdala, together was associated with greater sensitivity to slightly aversive sounds and tactile information[80]. Although this area of research has revealed similarities or differences in people with autism in relation to comparison groups, it has been limited by averaging data across many individuals, which can mask heterogeneity and differences across age groups. In addition, the
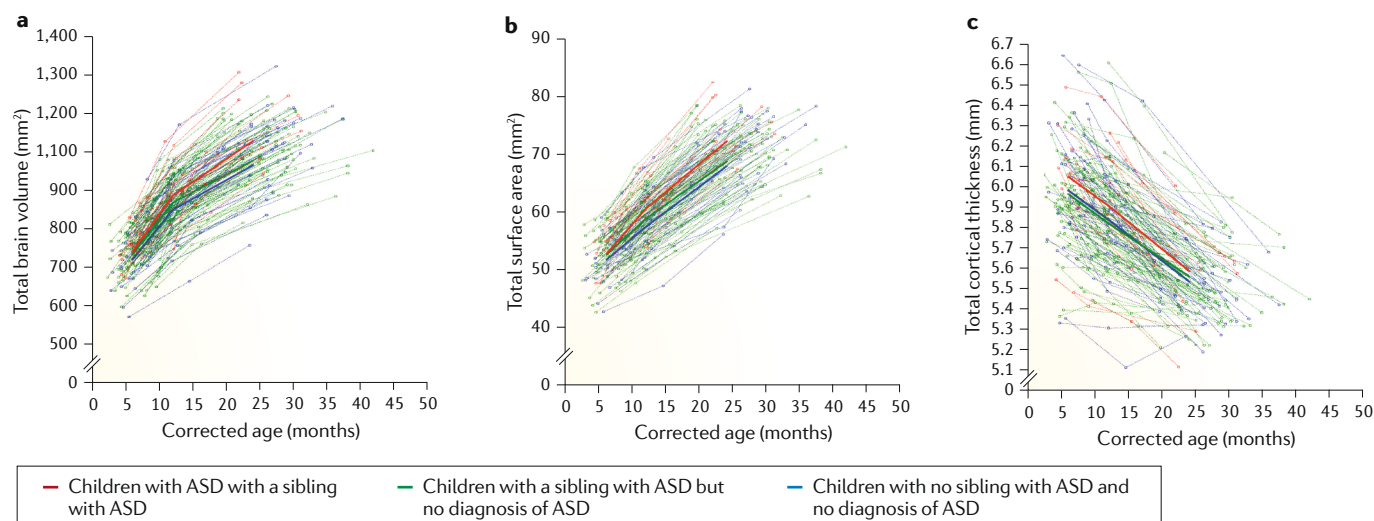
Fig. 4 | **Longitudinal trajectories of total brain volume, surface area and cortical thickness in autism.** Brain trajectories from 6 to 24 months of age for total brain volume (**a**), total surface area (**b**) and total cortical thickness (**c**). Toddlers diagnosed with autism spectrum disorder (ASD) had significantly greater surface area growth from 6 to 12 months than infants who were high risk for ASD but did not receive a diagnosis as well as than typically developing infants. Differences in surface area growth became more pronounced from 12 to 24 months of age for toddlers who received an ASD diagnosis. Corrected age refers to the age corrected by length (body size). Adapted from REF.[74], Springer Nature Limited.

work has been limited by small sample sizes and problems with replication probably caused by the many challenges with MRI data collection in people with autism, such as differences in data processing, inter-subject variability and data quality[80]. Longitudinal imaging[81] as well as associating neuroimaging data with longitudinal behavioural outcomes[82] can address some of these limitations characterizing differences within participants.

Resting state functional connectivity MRI studies that require participants to look at a blank screen with no task demands have been used to study intrinsic connections in the human brain. Large data sets, such as the Autism Brain Imaging Date Exchange (ABIDE)[83], have enabled researchers to pool data to allow more highly powered studies to address known limitations of small sample sizes, and many data sets have relied on resting state studies to study neural connectivity in autism. In these studies, evidence has emerged of both hyper-connectivity and hypo-connectivity in short-range and long-range connections throughout the brain[84,85]. Differences in results between studies could be due to the age of the participants[86], sex differences, heterogeneity, methodological concerns[87] or that both connectivity states exist in autism.

In future, MRI could be well suited to categorize subgroups of autism[88] as well as parsing out commonalities and distinctions among other developmental disorders[89]. Using MRI to better understand the differences between boys and girls on the spectrum[90], such as differences in whole-brain connectivity[90] or the social brain[91] — a field in its infancy — or as a marker of biological change due to treatment, has growing interest[92].

Findings from electrophysiological studies. EEG has historically been used for the diagnosis of comorbid epilepsy in people with autism[93], although it can also be used to study the mechanisms of autism. Compared with

MRI, EEG is more economical, easier to use and less invasive, which is particularly important for paediatric populations, while granting access to brain dynamics at millisecond timescales. Magnetoencephalography (MEG), although more expensive, provides higher spatial resolution than EEG.

Since the early recordings, the first focus of quantitative EEG was to study people with autism in task-free conditions. Pioneering studies have revealed alterations in oscillatory activity during resting state in people with autism, with more slow waves and less alpha waves as well as less intra-hemispheric and inter-hemispheric asymmetry than in people without autism[94]. More recent work has demonstrated the presence of developmental trajectories as revealed through increasingly sophisticated spatiospectral analyses, and has shown how differences in the trajectories of EEG power in high-risk infants may represent endophenotypes of autism[95,96].

In terms of mechanisms, other studies have started to focus on the task-based modulation of cognitive function such as low-level perceptual anomalies and action observation that relate to the autism phenotype. One theory proposing a specific failure in autism of the ability of the brain to 'mirror' observed actions of another person (thereby named the 'broken mirror' theory) was based on altered mu wave suppression in autism[97] but was later questioned both theoretically[98,99] and empirically[100,101], pointing towards a more complex picture of dysfunctional executive functions and visual attention[102]. Other studies, particularly those assessing event-related potentials, have demonstrated the modulation of sensory processing in people with autism, with observed changes in sensitivities and latency[103]. Differences in auditory and visual processing could have a role in the development of core features of autism, such as language delay and difficulty in emotion recognition, although this hypothesis requires further study. Although perceptual processes

appear different in people with autism, the electro-physiological underpinning is still far from clear regarding the main event-related potentials such as mismatch negativity[104] or the N170 (REF.[105]). Although data from meta-analyses have suggested smaller mismatch negativity amplitudes and delayed N170 latencies, on average, in people with autism compared with typically developing controls, additional studies are required that account for the large heterogeneity of this disorder by moving away from averaging the data to focus either on specific subgroups[106] or refined modelling strategies that can capture individual differences in developmental trajectories[95]. Although this avenue of research has not yet been fully explored, interactive tasks that encompass real-time social interaction could allow the study of brain activity in experimental contexts that are more relevant for core autism symptoms, rather than the more passive tasks that are used in most functional imaging studies[107]. Experiments focusing on human–human interaction[108] and human–machine interaction[109] have been undertaken but, so far, no study has ever made explicit use of such methods to study the electrophysiology of autism.

In a further search for mechanisms of autism, prospective baby sibling studies have suggested that the gradual emergence of behavioural symptoms of autism is preceded by earlier subtle alterations in the activity of regions and networks of the social brain[24]. For example, early work on a small group of 5–6-month-old infants who later developed autism observed faster but less prolonged neural activation and delayed sensitization responses to faces compared with infants who did not develop autism[110], and one report demonstrated that newborns with an increased familial likelihood of autism showed higher signal homogeneity within core social brain networks (the right fusiform and left parietal cortex[111]). By comparison, reduced frontal power, particularly in the high-alpha band, during quiet play at 3 months of age[112] and cortical hyperexcitability in the right tempo-parietal region during auditory repetition of pure tones at 9–10 months of age have been found in babies at familial risk for autism[113], suggesting that atypical patterns occur in brain regions other than those involved in social processing. Such alterations could have a cascading effect on social learning and contribute to the later emergence of behavioural symptoms of autism, although a causal link remains to be demonstrated. Replications across different research centres are needed because many of these studies had small sample sizes, different definitions of groups, and varied measures and time points.

Interestingly, results from MEG and EEG studies jointly point towards two physiological mechanisms of autism: excitation/inhibition imbalance and alteration of large-scale functional interactions of brain systems as quantified through connectivity analysis[114]. An excitation/inhibition imbalance is supported by results from computational modelling of how reductions in the amount of inhibition can account for the previously observed perceptual consequences of autism[115] and by transcranial magnetic stimulation studies demonstrating a neurophysiological deficit in γ-aminobutyric acid (GABA) receptor-mediated function in people with autism[116]. In parallel, decreased long-range functional connectivity has also crystalized as a consistent mechanism[117]. MEG studies have suggested a complex functional connectivity pattern in the somatosensory cortex with reductions in the feedback (top-down) direction but increased in the feedforward (bottom-up) direction[118]. Clarifying the extent to which this pattern is a methodological artefact that could result from the predominant average-brain approach, as suggested by fMRI studies, is critical[119].

Beyond use to understand the pathophysiology of autism, the scalability and accessibility of EEG suggest that this technique could be an ideal candidate for use as a brain-based biomarker. Measures from information theory have already provided promising case–control classification[120], but developing generalizable biomarkers may require a combination of multiple EEG measures supported by robust machine learning methods[121]. Against the background of the current reproducibility crisis that characterizes many studies[122] as well as the defining heterogeneity of autism, the next breakthrough will certainly demand large-scale collaboration between researchers and clinicians.

Diagnosis, screening and prevention

Diagnosis of autism is made on the basis of behavioural presentation. Although substantial heterogeneity exists between and within individuals across development, a set of core diagnostic features of autism (covering social interaction, communication, and restricted, repetitive or sensory behaviours) can be reliably identified by trained clinicians[123,124].

Diagnostic criteria

The reformulation of the diagnostic criteria for ASD in DSM-5 (REF.[125]) (BOX 1), which is similar to the criteria in ICD-11 (REF.[126]), contains several changes from previous editions that were based on good empirical and clinical evidence[127]. First, the subclassification of 'Asperger's disorder' was subsumed under the unitary term ASD as the diagnosis was inconsistently applied even by expert groups[128]. This change is controversial, yet the evidence supporting the inclusion of Asperger's disorder as a separate condition is very weak[129]. The important issues are how to better consider the factors that characterize differences among autistic individuals and ensuring that these differences are measured and addressed using neurobiological and clinical research, rather than contained within very poorly defined categories of Asperger's and PDD not otherwise specified (NOS), as defined in DSM-IV[130]. In addition, some individuals with social communication problems but not restricted and repetitive behaviours who would previously have fallen into the now-removed subcategory of PDD-NOS now receive a different diagnosis of social communication disorder, which is not yet well validated. Although these changes have led to concerns that the DSM-5 ASD criteria are more restrictive than those in DSM-IV, many clinicians feel that the changes better reflect clinical consensus and practice. Second, the social and communication domains of the diagnostic criteria were unified to reflect the factor structure of symptomatology. Third, sensory anomalies

(hypersensory and hyposensory responsiveness and sensation-seeking) in DSM-5 were included under the 'restricted, repetitive behaviours and interests' domain to reflect their pervasiveness[131]. Fourth, the DSM-IV criteria required symptoms to be present in the first 3 years of life, but criteria in DSM-5 recognize symptom onset during the early developmental period with the caveat that symptoms might not fully manifest until social demands exceed limited capacities. This change recognizes the developmental nature of autism, wherein for some individuals, clear manifestation of autism might not be apparent until mid-childhood, adolescence or even adulthood. In addition, late diagnosis (that is, diagnosis beyond early childhood) can occur even in those who received intensive early monitoring[132]. The DSM-5 criteria support the use of specifiers that can denote those with dual diagnoses such as individuals with ASD and ADHD or other psychiatric disorders as well as with genetic conditions such as fragile X syndrome or Down syndrome. Beyond the clinic, these changes have implications for large-scale data pooling efforts, in considering domains of behaviour to be modelled, and in identifying shared and distinct developmental pathways to conditions such as autism and ADHD.

Diagnosis and screening in children

The two core elements of the diagnostic process of autism in children are a detailed developmental history that is usually obtained from parents, covering first concerns and early history to the present day, and an observation of the child's interactions with their parents and with unfamiliar adults during a combination of structured and unstructured assessments. Ideally, observations of the young person in peer-group settings such as school or nursery would also form part of the diagnostic process. Of note, in one population-based study in the UK, girls with similar levels of symptom expression to boys were less likely to receive a diagnosis of autism from clinical services[133]. This finding might

reflect sociocultural factors in the application of the diagnostic criteria, greater resilience or protective factors in girls that reduce the need for clinical services at a given symptom level, or the need for the revision of instruments used to identify symptoms to more fully cover female autistic traits[127].

A number of structured diagnostic interviews and observational assessments for autism exist, but only a limited number have been rigorously tested for diagnostic accuracy relative to the gold standard of expert clinician judgement. Although these interviews and assessments have reasonably robust sensitivity, specificity and reliability (see[134] for a review) and are widely used in some services in communities[135], there are also challenges to the widespread adoption of the best validated instruments: the Autism Diagnostic Interview-Revised (ADI-R)[136] and the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2)[123]. These challenges include the cost of the instruments and training, the time required to complete them and the need for substantial training to use them reliably[137]. Although expert clinical judgement was previously believed to be more reliable than reliance on instrument scores alone for the diagnosis of autism[138], more recent evidence suggests that this may not be true at least in toddlers and preschool children[139]. The need to take a global perspective on autism is driving attempts to develop more scalable tools but this work is currently in its infancy[140] (BOX 2).

The stability of a diagnosis of autism from the preschool years to mid-childhood is relatively high[1]. However, although diagnostic systems currently presuppose that autism is a lifelong condition, there is a growing recognition that autism has a heterogeneous developmental time course[141]. Indeed, subgroups of individuals with autism and improving or worsening symptoms over time can be identified[142,143]. Such developmental trajectories might be a more meaningful phenotype on which to map aetiological mechanisms than a static case–control dichotomy[74,144,145]. Some individuals diagnosed as children have no clinically meaningful (or even detectable) impairment later in life (so-called optimal outcome[146,147]); one critical question in identifying mechanisms is whether this profile is associated with the successful effects of early intervention or is an aetiologically distinct subtype of autism.

Screening and early identification. The potential for early testing to prospectively identify children with autism at a young age has considerable interest and several studies have evaluated the performance of parent-report instruments between 14 and 24 months of age such as the Modified Checklist for Autism in Toddlers (M-CHAT) and the Early Screening of Autistic Traits (ESAT)[134,148,149]. However, there are contrasting views on the strength of the evidence for universal population-wide testing, also known colloquially as screening[150,151]. Of note, research is lacking on the effectiveness of therapeutic interventions in those identified with autism through universal screening. In addition, although it is possible to identify some children with autism before parents or professionals have identified concerns, diagnosis is missed in many children[152], and most tested cohorts have not been

systematically followed up to identify later-onset autism in children who initially tested negatively[153]. Screening also often identifies children with broader developmental difficulties as well as those with autism[154]. In general, such instruments could be more useful for identifying possible signs and symptoms of autism in high-risk populations, for example, in young children with older siblings with autism[155] or in those referred for speech or other developmental concerns to community paediatric services[156]. In addition, population-wide testing may also have a role in improving awareness and recognition of the early signs and symptoms of autism of both professionals and the general public, which alongside ongoing developmental surveillance pathways in community services, could help to bring down the age of recognition and diagnosis. These principles also apply in low-income and middle-income countries in which testing for autism and other neurodevelopmental disabilities has only just begun to be implemented[154]. Very little research has been devoted to cultural and ethnic differences in either child early presentation and parents' understanding or the experience of autism, which may affect how screening instruments work and, therefore, affect parents and families as much as autistic individuals.

Early developmental profiles. Understanding of onset patterns of autism has dramatically expanded over the past 10 years through work on infants with a first-degree relative with autism who, due to the high heritability of the condition, have a 20% chance of developing autism themselves[25]. Symptoms of autism have a gradual developmental onset. Indeed, although the average age of autism diagnosis remains at ~4–5 years of age[157], parents typically report first concerns to health professionals at ~2 years of age[158]. In many individuals, symptoms emerge during the second and third year of life (although, as per the DSM-5 onset criteria above,

in others, onset might not be noticed until the child reaches school-age or later), whereas in others, symptoms become apparent after a seeming period of typical development, including a period of regression or stasis. To this end, conceptualization of what has been called 'regression' prior to 2 years of age has been reconsidered[159,160]. Over the first 2 years of life, a substantial proportion of infants who later receive autism diagnoses show gradually accumulating delays across social, communication and language domains, suggesting that 'regression' represents a spectrum ranging from frank loss of acquired skills, to a gradual erosion (or 'plateauing') of developmental potential to individuals in whom these skills never emerge[161].

Diagnosis and screening in adults

Information on diagnostic methods to identify autism in adulthood is in its infancy, with little methodologically acceptable evaluation of interview methods or screening questionnaires (including self-completion questionnaires). Clinical approaches rely heavily on extending methods developed for use in childhood to adulthood. These methods tend to rely on childhood developmental data, although validation research from adult general population-wide testing suggests good specificity and sensitivity for the observationally based ADOS Module 4 (REF.[162]). However, typically, much research has depended on the judgement of expert clinicians and on standardized data collection of early child development that is unlikely to be obtainable for many older adults. Given that (undiagnosed) autistic adults presenting for an autism assessment are also more likely to have co-occurring adult mental health disorders, any method of assessment must be capable of differentiating such abnormalities in symptoms and behaviour from abnormalities due to autism. This point has led to the suggestion that clinical examination methods to identify adult psychopathology could be extended to include autism in addition to depression, anxiety and psychosis, among other disorders[163]. Semi-structured adult psychopathology interviewing has been fruitful in the assessment of closely related neurodevelopmental disorders in adults, most notably ADHD[164]. Given that most people in the world who are autistic are adults, and as many of these individuals have not received a diagnosis of autism[4,15], the development and evaluation of such adult assessment approaches is an urgent research priority.

Co-occurring disorders

In addition to the core features of autism, co-occurring difficulties or disorders (FIG. 5) are much more widely recognized in research[165,166], although they are not necessarily adequately addressed in clinical practice[167]. For preschool children with autism, language delays, motor problems, epilepsy, difficulties with sleep and eating, and high levels of activity are most commonly observed[168,169]. By comparison, ADHD, anxiety, obsessive–compulsive disorder (OCD), intellectual disability, academic challenges, irritability and disruptive behaviours become more apparent in school-aged children[170]. The proportion of individuals with depressive symptoms becomes higher in adolescents and adults[171], whereas other issues
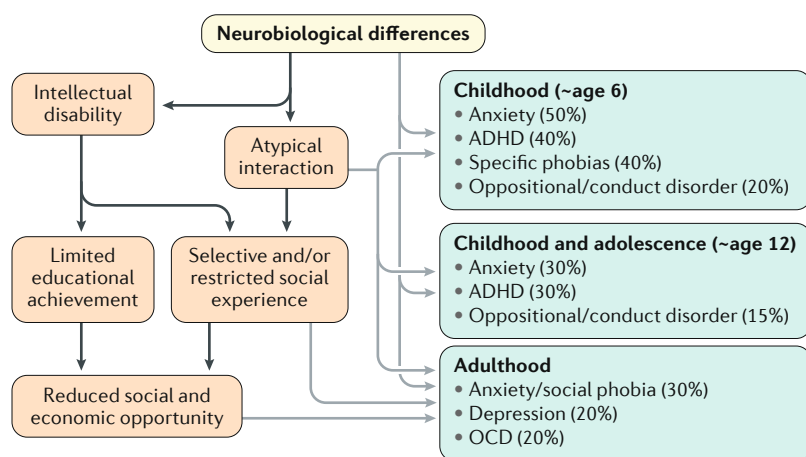
Fig. 5 | **Co-occurring disorders.** Primary and secondary disorders and disadvantage can accumulate through development in people with autism. These disorders can form additional targets for treatment and policy. Prevalence estimates are preliminary, derived from QUEST[282], SNAP[138,283] and EDX[147] cohorts, but are limited by the fact that many are based on clinical populations or data that are inherently biased (such as US Medicaid data, in which billing for treatment is contingent on having a non-autism diagnosis) and few well-designed population studies exist. ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive–compulsive disorder.

often remain. Moreover, growing evidence (although it is reliant on administrative case-finding data) suggests that people with autism have premature mortality[172,173] and increased risk of self-harm and possibly suicide, although the mechanisms involved have yet to be elucidated. Studies using electronic health records have demonstrated that adults with autism are more likely to be diagnosed with many physical health conditions, such as immune conditions, sleep disorders and obesity, than adults in the general population[167].

Collectively, these difficulties and disorders contribute to autism severity[174] as well as independence and well-being at each age[175]. However, it is important to note, in the context of heterogeneity, that the prevalence of each of these co-occurring conditions varies considerably with the context of the sample (such as from psychiatry referrals, neurological referrals or schools) and the methodology used (administrative, self-report or assessed) as well as with age, level of cognitive function and perhaps region[166]. As many of these conditions are treatable, they are very important as clinical considerations but are also more complex than sometimes conveyed.

Management
Early intervention
Early intervention is seen as a priority because many young children with autism struggle to communicate and interact with others, restricting their opportunities to learn and affecting their parents, who can find their child's behaviour perplexing and challenging to manage. Thus, outcomes of such interventions include changes in the individual's availability for learning and increased parent understanding. Intervention delivered in the preschool years at an age when there is increased brain plasticity might lead to additional benefit, although this theory has not yet been empirically supported.

The primary models of psychological intervention for preschool children with autism are developmental and behavioural. Although some consensus has been reached on the interventions that have more supporting evidence (termed naturalistic developmental behavioural interventions[176]), there is some uncertainty and disagreement about the strength of evidence for different approaches, with almost no direct comparisons of treatments or studies to assess which child should receive what treatment or the treatment intensity. Indeed, clinical trials in autism are limited by cost, time, placebo effects and limited outcome measures, and are far behind much other research. This gap leaves parents and practitioners with no options other than what is available and sometimes marketed in their region. Indeed, access to early intervention services is variable in most communities, including in high-income countries, and is mostly carried out by non-specialists supervised by specially trained professionals. In low-income and middle-income countries, most children and young people with autism — similar to those with intellectual and developmental disabilities — will not receive specialized services[177], although a number of groups have begun to test community delivery of early intervention in such settings[178].

Many current interventions build on the original applied behavioural analysis (ABA)[179] and have shifted to more natural, child-initiated developmentally appropriate strategies and tasks instead of dependence on repeated 'discrete trials' (known as discrete trial training (DTT)). In addition, considerable variation exists between different intervention models in terms of mode of delivery (for example, parent mediated versus therapist implemented), length (12-week versus 2-year programmes), intensity (from a few hours a week to ~15 hours per week) and the balance between the developmental or dyadic versus behavioural components.

Lower-intensity approaches include parent-mediated interventions whereby parents are coached to become more attuned to their child's communication signals and style (which are considered an intermediate child outcome) and to facilitate more joint engagement in play and everyday activities designed to increase social and communication skills in the child[180]. Some studies, such as the 12-week Joint Attention Symbolic Play Engagement and Regulation (JASPER) programme, both when delivered by parents in the home[181] and by teaching assistants in school[182], have demonstrated enhanced joint engagement and joint attention (which are considered important intermediate child outcomes) with these lower-intensity approaches in preschool children compared with a control group. However, other lower-intensity, time-limited parent-mediated interventions, such as focus playtime intervention (FPI)[183], have not improved child outcomes (such as social orienting and joint attention), although some interventions have increased parental responsiveness[184]. A longer programme (Preschool Autism Communication Trial (PACT)), which consists of fortnightly parent–therapist sessions for 6 months, then monthly sessions for another 6 months, demonstrated improvements in parent and child dyadic behaviours such as parental synchrony and child initiations when interacting with each other (those close to the intervention target) but not symptom reduction at immediate follow-up[185]. A subsequent 6-year follow-up to mid-childhood at age 7–11 years identified modest reductions in overall autism symptoms using the ADOS over the whole course of the study; these reductions were not detectable at the immediate end point, suggesting that a longer-term perspective is critical in considering outcomes[186].

A higher intensity, more comprehensive approach is the Early Start Denver Model (ESDM), which combines behavioural and developmental or dyadic approaches. The ESDM is delivered by therapists for ~15 hours per week, and as part of this programme, parents are trained to improve social communication and interaction with their child. A small-scale trial demonstrated improvements in child developmental and adaptive outcomes, primarily in the language and communication domains, following 2 years of ESDM compared with treatment as usual[187]. One larger multi-site trial found attenuated benefits with improvement in language outcomes at two of the three trial sites, but no differences between the treatment as usual and ESDM groups in overall developmental ability, adaptive behaviour or autism severity[188,189].

Many of these early intervention approaches are based on models of typical development. Increasingly, studies are using a combination of methods to define

treatment outcomes and to better understand the mechanisms and models of change of interventions. These methods include analysis of the degree to which changes in the direct target of the intervention (for example, parent behaviour) mediate later changes in child behaviour[186] and the use of experimental methods such as EEG to examine whether there are accompanying changes in relevant brain networks[190]. Many parents seek complementary medical approaches, which, to date, have not been supported and are sometimes dangerous[191]. A note of general caution is that, even in the context of significant treatment differences between groups, individual outcomes are very variable, and some children do not improve, although reliable predictors of response to treatment have not been demonstrated in rigorous, randomized controlled trials. As autism is a heterogeneous developmental condition, different interventions may be required at diverse stages throughout life and different individuals might benefit from different interventions. One area that many consider to hold much promise — neurobiologically or biomarker 'informed' psychological intervention — is on the horizon but such targeted therapies have not yet been developed.

School-age children and adolescents

Many children and young people with autism can also benefit from interventions at later ages. A number of programmes and approaches are available that focus on the core social communication difficulties of autism, for example, social skills training programmes, for which moderate evidence of benefit exists[192,193]. In addition, non-verbal young people with autism can benefit from the use of augmentative communication systems such as the Picture Exchange Communication System (PECS) and more-sophisticated speech generating devices that use picture symbols and behavioural training methods to allow children to request and make choices[194] or of other technology-based augmentative communication systems. Increasingly, more generic interventions that target co-occurring emotional and behavioural problems are being adapted for youths with autism, with initial studies suggesting moderate benefits[195]. These interventions include modified CBT for anxiety (modified, for example, to include parents, increase the duration of sessions, use more visual materials and specific work on understanding one's own emotional states)[196] and parent-mediated interventions for disruptive behaviour and ADHD[197]. More recently, there have been efforts to develop and test interventions that target aspects of parental wellbeing, such as parental stress and self-efficacy[198]. Increasingly, interventions for school-age children and young people with autism are being delivered within the school environment, rather than the clinic, which has natural advantages for programmes that consist of groups or peer-to-peer interactions with an emphasis on social skills. Indeed, it is hoped that this approach may facilitate generalization of the skills learned[199,200].

Adult services

As individuals with autism progress into and through adulthood, the focus of management shifts from treating the core symptoms of autism to addressing associated symptoms or behaviours and promoting independence. However, there are few intervention studies to guide treatment options in adulthood. Indeed, a 2012 systematic review identified only 32 studies published between 1980 and 2010 that evaluated treatment studies for adolescents and young adults with autism[201]. A more recent review identified 41 studies of interventions targeting social functioning in adults over a 37-year period[202].

Despite the low number of treatment studies, there is some evidence supporting treatment efficacy for a limited number of symptoms, behaviours and functional outcomes such as employment, social skills and anxiety; however, in general, the evidence base is weak[201,202]. For example, only three randomized controlled trials (all of which included small cohort sizes) that tested job interviewing skills curricula have been published. Social skills interventions have a somewhat more robust literature base (see[202] for review), but most of these studies had very small sample sizes and were not well controlled. In addition, it is unclear whether social skills interventions can be generalized to other social settings and situations, that is, whether skills learned in the treatment context are used by the participants in other settings such as with peers or at work. There is some evidence for the use of CBT for effectively treating anxiety in people with autism who have sufficient cognitive and language skills to participate in current programmes[203]. However, nearly all of the existing research has been conducted with children and adolescents rather than with adults[202], and individuals with substantial communication challenges are excluded from CBT studies. Furthermore, in contrast to the general population, CBT has not yet been shown to be effective for the treatment of depression in individuals with autism. Given this weak evidence base, it may be fruitful to explore therapies and treatments tested in other groups that may benefit those with autism.

Formal service systems and social care can help fill in the treatment gaps. Indeed, although many adults with autism do not receive adequate services and support[204], their receipt can improve outcomes across a number of domains[163]. For example, transportation services can allow adults with autism to engage in employment and access therapies and programmes in the community. In addition, comprehensive job support services can promote finding and maintaining employment, particularly for adults with more severe impairments[205]. Public health insurance can increase access to psychiatric care for those with co-occurring mental health problems and income support can reduce dependence on families.

Medications

All medications that have evidence of benefit for autism treat the associated symptoms or co-occurring diagnoses, rather than the symptoms of autism directly (including social communication or repetitive behaviours). As mentioned earlier, autism is an extremely heterogeneous disorder, and individuals with autism can have a number of common co-occurring disorders that can also vary in severity.

Risperidone and aripiprazole (both of which are often termed 'atypical antipsychotics') are approved in the USA to treat irritability and agitation, including

Table 1 | **Evidence-based medication in autism**

Medication	FDA or EMA, indication and age	Effect size (d)[286]	Common adverse effects
Typically used for ADHD symptoms			
Methylphenidate	FDA and EMA approval for ADHD (not specific for autism) in those ≥6 years of age	$d = 0.78$ (teacher rated)	Sleep disruption and decreased appetite
Atomoxetine	FDA and individual country approval for ADHD (not specific for autism) in those ≥6 years of age	$d = -0.68$ to 0.084	Decreased appetite, nausea and irritability
Guanfacine	FDA and EMA approval for ADHD (not specific for autism) in those 6–17 years of age	$d = 1.67$	Fatigue, sedation, and decreased pulse and blood pressure
Typically used to treat agitation and irritability			
Risperidone	FDA approval for irritability associated with autism and EMA approval only for other indications in those 5–17 years of age	$d = 0.94$	Increased appetite, sedation and weight gain
Aripiprazole	FDA approval for irritability associated with autism and EMA approval only for other indications in those 6–17 years of age	$d = 0.87$	Nausea and weight gain

ADHD, attention-deficit/hyperactivity disorder; EMA, European Medicines Agency.

aggression, self-injury and tantrums, in children and adolescents with autism[206–208]. However, both treatments are associated with adverse events, including sedation, risk of movement disorders and weight gain, which limit their use to people with severe irritability with agitation[208]. The anti-diabetic drug metformin has been shown to limit weight gain from these medications, possibly broadening their safe use[209].

As mentioned previously (see Co-occurring disorders, above), co-occurring mental health conditions are common in people with autism. Methylphenidate, atomoxetine and guanfacine are beneficial for ADHD symptoms in people with autism[210–212] (TABLE 1). Although serotonin reuptake inhibitors, such as fluoxetine and citalopram, are used for the treatment of depression, anxiety and OCD in the general population, their efficacy in people with autism is less well established. Indeed, although fluoxetine improves symptoms of OCD in adults with autism[213], citalopram has demonstrated poor tolerability and no benefit for repetitive behaviour in children with autism[214]. Medications for depression or anxiety have not been tested in people with autism.

Some excitement has accompanied the recent studies of medications targeting the neurohormonal oxytocin or vasopressin systems, both of which modulate social behaviour across species. Underpowered studies of intranasal oxytocin have demonstrated mixed results that are overall not supportive of a large effect size[215,216], with results from adequately powered studies (NCT01944046) still pending. In addition, a pilot study of intranasal vasopressin suggested possible benefit in people with autism, although this study was underpowered[217]. A large trial of balovaptan, a vasopressin AVPR1A antagonist, in adults with autism showed negative results on its primary outcome (a general rating of autism symptoms), with suggestive results on a key secondary parent report measure of adaptive behaviour, including social and communication behaviour[218]. A few studies have also focused on the hypothesis that, at the level of neural circuits, autism may result from excessive excitation or insufficient inhibition[219], with some promising but inconclusive results for medicines that target

the GABAergic system[220]. Medications targeting genetic syndromes that can cause autism have not yet yielded consistent improvement[221,222], but there is much hope for a precision medicine approach that links genetic subgroups with neurobiology-based treatments.

Quality of life
Objective and subjective measures

Several aspects of intervention research speak straight to the heart of current debates within the clinical field and broader autism community, including how a good outcome is defined for an individual with autism as well as who should decide what outcomes are used in intervention studies[223]. This point is aligned both with the debates about medical versus social models of disability but also with a more general shift in medicine away from focusing on symptom reduction to improving the wellbeing and quality of life (QOL) of patients. QOL research in adults with autism has focused on two aspects: objective and subjective QOL. Objective QOL encompasses social achievements such as employment, adequate living conditions, supportive relationships, and good physical and mental health[224], whereas subjective QOL focuses on individuals' perceptions and subjective assessments of their own lives[225]. Both subjective and objective QOL are often related but not synonymous, and both are important to take into account when considering outcomes for individuals with autism (TABLE 2).

Objective QOL. Adults with autism tend to have poor objective QOL. Unemployment is high in this population, and even among those employed, individuals are often working below their skills and abilities[226,227]. Moreover, independent living can be a challenge, and adults often lack meaningful relationships with peers[228]. When aggregating across these domains of life, many adults with autism have 'poor' or 'very poor' outcomes[229,230].

Autism is a highly heterogeneous condition and several factors have been associated with higher versus lower objective QOL. Most of the studied factors associated with higher objective QOL have been characteristics of the individuals (versus families, service system or

Table 2 | **Factors that affect QOL**

Type of QOL	Factor	Description
Objective QOL	Early language	Follow-up studies of adults with autism who were diagnosed as children have examined the amount of spoken language during early childhood. Individuals with autism who had fluent speech are more likely to have higher levels of objective QOL in adulthood than those with phrase speech or those with no speech or who spoke in single words
	Indicators of intelligence	Studies examining IQ scores using standardized IQ tests administered in both early childhood and adulthood find that individuals with autism and higher IQ scores have higher levels of objective QOL than those with lower IQ scores. Other, less-standardized measures of intelligence (such as those used in large cohort studies) have similar findings
	Adaptive behaviour	Higher levels of adaptive behaviour — and particularly more activities of daily living — are associated with better objective QOL in people with autism. Adaptive behaviour is a challenge for many individuals with autism, who have scores below what would be expected based on IQ[287]. Adaptive behaviour is changeable, making it a promising avenue for interventions to improve objective QOL
	Autism symptom severity	Individuals with more severe autism symptoms tend to have lower objective QOL in adulthood
	Challenging behaviours	Higher levels of challenging behaviours in people with autism, which can include both internalizing problems and externalizing problems, are related to lower objective QOL
	Sex or gender	Sex or gender associations with objective QOL have been demonstrated in terms of employment or post-secondary education; indeed, women with autism obtain employment and post-secondary educational positions at the same rate as men with autism but have a more difficult time maintaining those positions over time
Subjective QOL	Perceived stress	Many adults with autism perceive high levels of stress in their own lives; these perceptions are related to lower subjective QOL
	Supports	Several different types of supports have been related to subjective QOL, including formal services, support from family members (most often parents) and more general social support from others

QOL, quality of life.

communities), and consistent predictors of higher objective QOL include better early language development, higher IQ and adaptive behaviour scores, less severe autism symptoms and fewer challenging behaviours[231]. In addition, more recent research suggests that women with autism may have a more difficult time maintaining employment positions[232], and are more likely to 'camouflage' their autism symptoms than men, which can lead to mental health challenges[233].

Subjective QOL. Meta-analyses have suggested that, across the lifespan, subjective QOL tends to be lower among individuals with autism than among typically developing peers[234] but is often more positive than indicators of objective QOL[229,235]. Predictors of subjective QOL tend to be inconsistent across studies, except for perceived stress and support, the latter of which encompasses services, family and social support[236–238].

Self-advocate perspective

It is clear that autism has heterogeneous outcomes and biological underpinnings; what is less clearcut are the differing and nuanced views of autistic people regarding how autism should be approached and researched (BOX 3, Autistica[239], see also Ontario Brain Institute[240]). Indeed, some people with a diagnosis see autism as being a fundamental part of their identity, whereas other people do not. In addition, many people feel that social change is required[241], whereas others want therapies to meet a range of their needs[242]. The key is respect for a variety of views and ultimately respect for autistic people. Researchers can demonstrate respect by considering how autism as a topic is distinct from, for example, cancer. To this end, terms such as 'disease' are inappropriate and are scientifically inaccurate when referring to autism. Ultimately, active participation in the design, implementation and interpretation of research studies, clear consideration of research ethics, and the consequences of research involvement and broad consultation of autistic people in research is key to authentically addressing the substantial inequalities that autistic people face as a group and ensuring that they live long, healthy and happy lives.

Box 3 | **Top questions for autism research from autistic people, families and professionals[a]**

1. Which interventions improve mental health or reduce mental health problems in people with autism? How should mental health interventions be adapted for the needs of people with autism?
2. Which interventions are effective in the development of communication and language skills in autism?
3. What are the most effective ways to support or provide social care for autistic adults?
4. Which interventions reduce anxiety in autistic people?
5. Which environment supports are most appropriate in terms of achieving the best education, life and social skills outcomes in autistic people?
6. How can parents and family members be supported and/or educated to care for and better understand an autistic relative?
7. How can autism diagnostic criteria be made more relevant for the adult population? And how do we ensure that autistic adults are appropriately assessed and diagnosed?
8. How can we encourage employers to apply person-centred interventions and support to help autistic people maximize their potential and performance in the workplace?
9. How can sensory processing in autism be better understood?
10. How should service delivery for autistic people be improved and adapted in order to meet their needs?
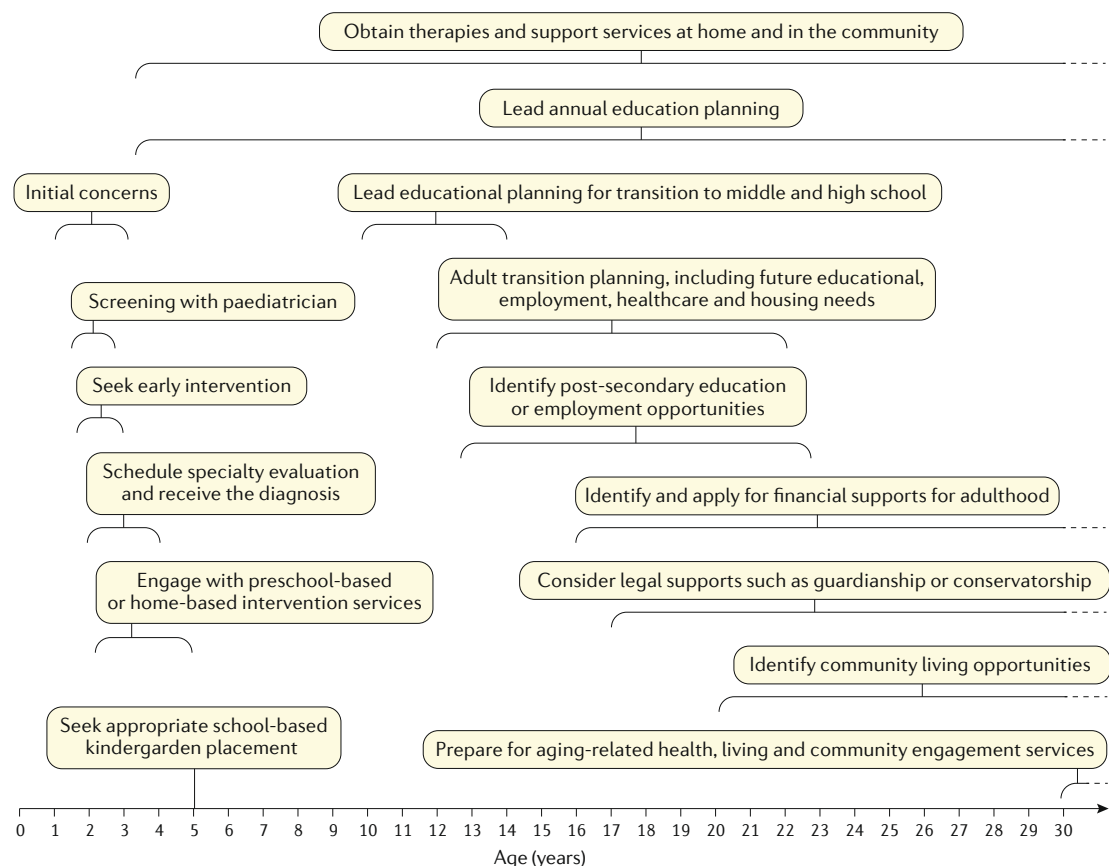
[a]Based on REF.[239].

Fig. 6 | **Major parental milestones in advocating and supporting their child with autism.** Families of children and adults with autism have many decisions and expectations across the lifespan of their children, from seeking initial diagnostic evaluation and intervention to preparing for ageing-related services. These decisions vary across different cultures, regions and countries, and depend on many factors, including the resources and services available. However, several decisions are common across all regions, including low-income and middle-income countries, such as choices about who will care for their child if the parents are temporarily unable, the amount of time parents and other family members can spend with the child with autism versus meeting other needs, ways to modify their home environment to ensure the safety and independence of the individual with autism and the kinds of behavioural expectations that are most helpful for their child or adult. Of note, for many families, these choices and responsibilities are lifelong and are relevant for children, adolescents, adults and elders with autism.

Family perspectives

Families of people with autism are also heterogeneous, yet, as a group, they experience lower QOL than families with a member with other neurodevelopmental conditions, even before receiving the formal diagnosis[243]. Thus, it is essential that parents, other family members, clinicians, educators and the entire external support system coalesce around common goals for outcomes while accessing and maximizing resources for the betterment of the child and family. Parents are typically at the centre of this support network and carry much of the responsibility of direct care, coordination and advocacy, over and above typical parental responsibilities[244,245]. The exact parental roles are dependent on the child's strengths and challenges, and frequently shift over time (FIG. 6). During this process, it is important that parents maintain motivation by setting realistic goals and tracking progress to experience the many achievements that their loved one with autism can attain.

Effective parents often work closely with experienced providers who can track the development of the child with autism and can provide guidance on next actions[246]. Early in childhood, this role includes identifying and engaging with early and school-based interventions. It is never too early for parents to begin planning for the adult transition process, including (dependent on the capacity of the person with autism) promoting self-advocacy, preparation for life after secondary education, vocational training and employment support, living needs, community participation and long-term financial considerations. During adulthood, for cognitively able adults, parental roles might shift to more traditional relationships[247], whereas for those with cognitive disability, parental caregiving often continues and culminates in planning for late life needs[248]. Although the journey can be challenging, for many parents, it can be incredibly rewarding and a source of life meaning.

Many parents recognize the need to give back to the community through research. Accordingly, it is crucial that researchers foster this desire carefully, communicating with parents to ensure that any potential immediate or future risks or benefits are clear. Even if the

study period is brief, in many cases, the goal should be to develop a positive longer-term relationship, as this can lead to parents and people with autism continually re-engaging in and developing positive feelings about the research process.

Outlook

Autism research has substantially expanded in the past 50 years, and particularly in the past 20 years, as reflected in the websites listed in BOX 4. Although it seems unlikely that the incidence of autism is truly rising at the rate suggested in administrative prevalence studies, these data have increased the awareness and the numbers of diagnosed children in schools and clinics, although adult services and recognition run far behind. The lives of people with autism diagnoses have improved at least in some high-income countries, with a greater proportion of children using some language[249], more adults with educational qualifications and less institutionalization[249], although the changing nature of diagnoses has to be considered when interpreting historical trends. Some risk

factors for autism have been identified, which has implications at least for more careful follow-up. In addition, the genetics of autism has yielded surprising discoveries, with substantial implications for heritable neurodevelopmental disorders such as ADHD, language delay and named syndromes associated with profound intellectual disability. The perceived value of routine genetic screening for autism diagnosis is disputed, with American medical academies strongly in favour, whereas those in other countries are much more selective. Studies of brain structure and function have added similarly intriguing findings that are just beginning to be integrated into both developmental and more mechanistic models of behaviour with possible targets or markers for change. Despite the intellectual contribution of these studies to research, at this point, neither EEG nor imaging are recommended as part of standard practice for the diagnosis of autism but can be used for other neurological indicators (such as if there are concerns beyond autism symptoms that merit an EEG or imaging). In this field, replication of findings across sites and even within individuals as well as larger samples through collaboration are the promise of the future.

One way of bringing the three themes of mechanisms, heterogeneity and outcomes of autism together is to consider the trajectories of this disorder over time (FIG. 7), how knowledge of these trajectories can contribute to investigations of the biological and cognitive underpinnings of autism, and how treatments and supports could make the lives of children and adults with autism more positive.

In terms of mechanisms, despite earlier hopes for simple genetic explanations of autism, we have instead identified many single-gene, germline loss-of-function point mutations yielding some initial models of disruption in very basic molecular patterns as well as common genes with small effects that are just beginning to emerge[29]. Attempts to study genes first have shown heterogeneity even within highly specific CNVs, with a few exceptions. In addition, hope exists that genetically based interventions for autism may be possible, although this will probably involve much further research. Data from genetic approaches that might yield targeted genetic interventions may be most relevant to rare and severe neurodevelopmental difficulties in general rather than autism as a specific entity. With more information about the differing developmental trajectories of autism, more continuous measures of symptoms and measures of language and intellectual function, behavioural phenotypes and changes over time can be quantified across different neurobiologically defined subgroups. This approach could potentially identify different 'routes' to different outcomes, whether autism or not, and could have a practical benefit in terms of selecting and monitoring appropriate treatments. In addition, with the heterogeneity of autism, our growing understanding of mechanisms, be they causal or mechanisms for change, needs to be linked to trajectories in development and not considered as static[250]. Researchers modelling autism in other species might find the incorporation of early developmental manifestations, such as regressions or motor delays, more tractable than the

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Box 4 | Examples of autism websites

Sites for health-care professionals or research scientists

- American Academy of Paediatrics: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/autism-initiatives.aspx
- International Society for Autism Research: https://www.autism-insar.org
- National Autistic Society: https://www.autism.org.uk
- Royal College of General Practitioners: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/asd-toolkit.aspx

Information about treatment, research and advocacy for people with autism and their families

- Autism Canada: https://autismcanada.org
- Research Autism: http://www.researchautism.net/
- Autism Europe: https://www.autismeurope.org/
- Autism India: http://www.autism-india.org
- WHO: https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders
- Autism Spain: http://www.autismo.org.es
- Autism Speaks: www.autismspeaks.org
- Autismus Deutschland: https://www.autismus.de
- Autistica: https://www.autistica.org.uk

Information about research funding and up-to-date information for people with autism and families

- Simons Foundation: https://www.sfari.org
- US NIH: https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml
- Autism Science Foundation: https://autismsciencefoundation.org

Epidemiological and surveillance information

- US CDC: https://www.cdc.gov/ncbddd/autism/index.html
- Adult Population Autism Surveys, England: https://digital.nhs.uk/data-and-information/publications/statistical/adult-psychiatric-morbidity-survey/adult-psychiatric-morbidity-survey-survey-of-mental-health-and-wellbeing-england-2014
- Mental Health of Children and Young People (including autism) in England, 2017: https://digital.nhs.uk/data-and-information/publications/statistical/mental-health-of-children-and-young-people-in-england/2017/2017
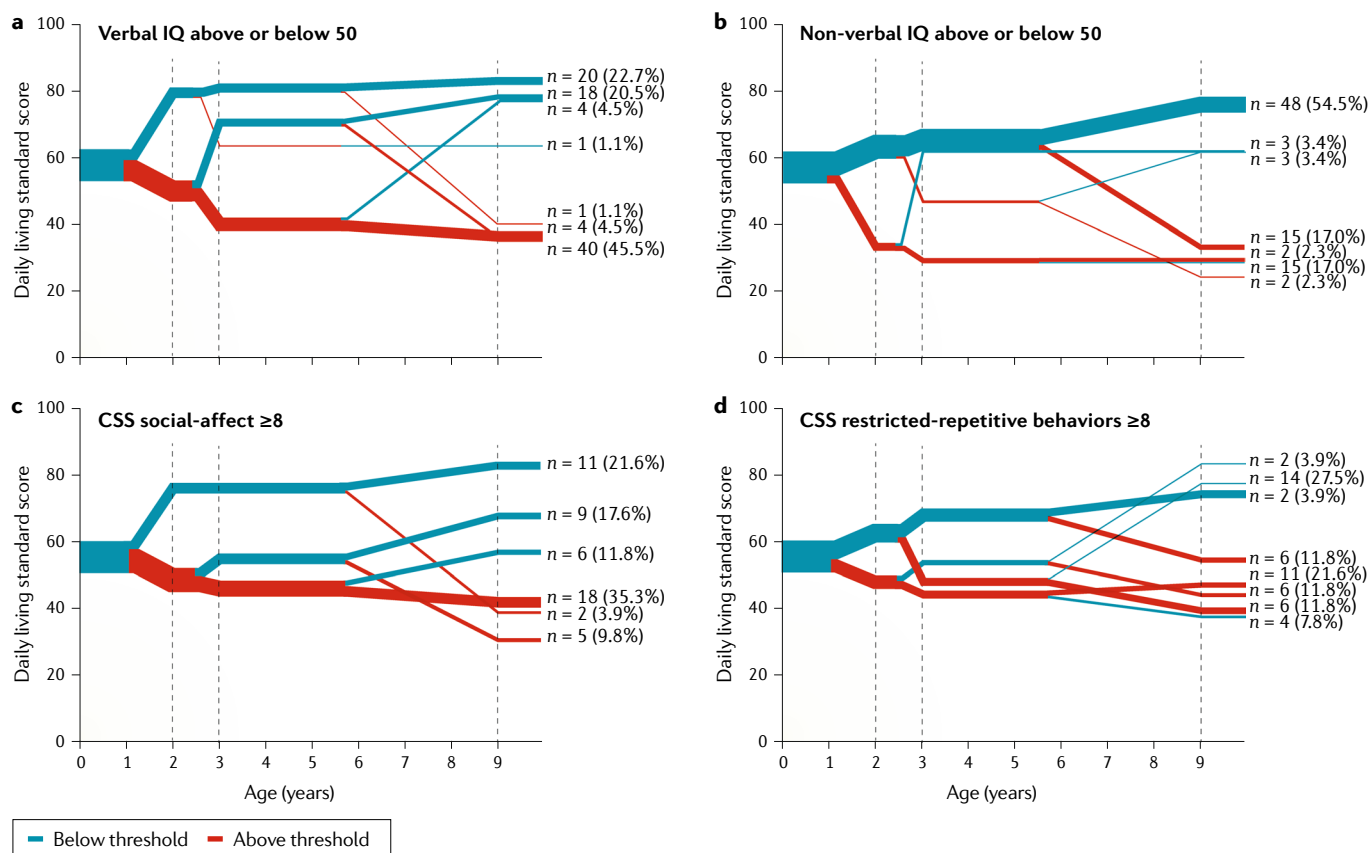- The University of Queensland, Queensland Centre for Mental Health Research: Global Burden of Disease Programme (autism): https://www.uq.edu.au/news/article/2014/08/autism-rates-steady-two-decades

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Fig. 7 | **Changes in daily living scores as predicted by IQ scores and autistic symptoms.** Changes in independent daily living skills can be observed in people with autism over time. This sample consists of ~100 young adults with autism with a mean age of 26 years, who were evaluated at 2, 3 and 9 years of age and followed up to 26 years of age. Daily living scores are very diverse, ranging from age-appropriate levels of independence at adulthood (represented by a daily living score of 100, assessed using Vineland II[284]) to very limited skills (represented by a score of <30). Increasing divergence shows where measurement after 2 years of age is additionally predictive, with the line thickness indicating the proportion of early referred children that followed each trajectory. Heterogeneity in intellectual functioning and severity of autistic symptoms (social communication and restricted, repetitive, sensory behaviours) can be observed. In addition, improvements and worsening of autistic symptoms and intellectual functioning can occur over time. **a,b** | Referred children had verbal IQs predominantly <50 (over 3 standard deviations below average) but could show improvement in daily living standard scores from 2 to 3 years of age that were indicative of eventual greater independence in adulthood. Relatively less early change in non-verbal IQ is seen but, like verbal IQ, by adulthood the association with eventual adult daily living skills is strong. **c,d** | Variation in autism symptom severity in social communication (CSS refers to the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) comparison scores) showed a stronger association with adult independence than restricted, repetitive behaviours and continued to change over the lifespan following more divergent pathways than intellectual functioning. Data from the EDX cohort compiled from REFS[1,147,285].

current focus on autism-related social communication symptoms seen in humans. With collaborations and studies of sufficient sample sizes, investigators have begun to focus on findings within different developmental periods that could provide insight into trajectories and targets for intervention. Thus, more study of the development of autism, both in studies of human behaviours and in animal models, might influence the identification and treatment of autism as a neurodevelopmental disorder. Prospective studies, including epidemiological and direct behavioural work across developmental periods, moving beyond very young children to later childhood, adolescence and adulthood are needed.

Similarly, limited findings about adult development and patterns that lead into autism (FIGS 5,7) call for measurement of different outcomes that respect individual differences in autistic people and in families (BOX 3). By young adulthood, available supports for places to live, employment and mental health services are needed for individuals who have a range of skill levels, with supports not always well matched to the needs of individuals; however, comparisons of treatments or treatment intensities have not historically been made, even though they are continually called for. The types and specific goals of treatments differ greatly for autistic people who are verbally fluent versus those who have difficulty speaking for themselves, such that alternative systems need to be in place that consider co-occurring conditions, strengths, preferences and challenges. More studies of well-defined, more homogeneous subgroups of autistic children and adults over time would provide different and more useful information about real-life issues (TABLE 2) than large-scale surveys of very heterogeneous samples[251].

Progress in the biology of more generally defined neurodevelopmental disorders may have the greatest yield for children with autism in their early years. Clinical

trials that compare known treatments (both psychosocial and biological) with new ones and treatment-as-usual would allow us to build on previous findings in a more meaningful way and begin to address the priorities listed in BOX 3, which, strikingly, are seldom priorities in autism research. To move from science to practice, including evaluation and treatment, autism researchers need to find a way to select and fund studies of more mundane, but critical evidence gaps in understanding heterogeneity, mechanisms of change and outcomes that affect practice in any circumstance, not just internationally, within academic systems that reward creativity and novelty. Unique methodologies, including the baby

sibling studies, accumulation of large data sets (such as ABIDE and the Simons Simplex Collection (SSC)), prospective epidemiological studies and mechanistic studies of intermediate biomarkers may begin to bring together information from molecular to pathophysiological to cognitive and behavioural levels. However, for now, as for other neurodevelopmental and psychiatric disorders including schizophrenia[252], the distance between science and practice remains great, and the amount of research that attempts to address solvable problems for autistic people alive today and their families remains modest.

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Author Contributions

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