Introduction

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The term 'Autism Spectrum' currently embraces a cluster of conditions known as Autism Spectrum Disorders or 'ASD', that are characterised by impairments in social functioning, verbal and non-verbal communication, together with repetitive and stereotypical patterns of behaviour and interests. Impairments within each of these 'core' clinical domains can range in severity from mild to profound, and intellectual disability may be present in more severe cases. The classification of ASD broadly includes classic autism (childhood autism; autistic disorder), Asperger syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) (Levy *et al.* 2009). Classic autism is frequently diagnosed around the age of 3 (and may be diagnosed as early as 2 years of age) (Baird *et al.* 2003; Landa, 2008). Asperger syndrome often presents with more subtle symptoms, and is usually diagnosed later on in childhood (frequently around 11 years of age), and occasionally in adults (Howlin and Asgharian 1999; Toth and King 2008).

While the precise causes of autism remain a mystery, prevalence estimates have risen almost exponentially within the last six decades, making autism a major global concern. Initially considered rare, current estimates suggest that as many as 1% of children under the age of 8 years may have an autism spectrum diagnosis (Baird *et al.* 2006), with boys being diagnosed up to four times more than girls. More than half a million people are thought to be living with autism in the UK alone (National Autistic Society, 2007), and in the US autism is considerably more common today than it was in the 1980s (Yeargin-Allsopp *et al.* 2003).

Terminology relating to the autism spectrum is markedly inconsistent between formal and informal contexts, and between different expert groups. The term 'autism' is often used colloquially as an umbrella term for the entire autism

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spectrum, as well as more specifically for the classic or prototypical form of autism spectrum disorder. Some researchers and autism advocates favour the term 'Autism Spectrum Conditions' (ASC), rather than Autism Spectrum Disorders or ASD, one rationale being that the first phrase avoids the connotation of autism as a disorder or disability, and is thus less discriminatory than the second. The terms 'high-functioning' and 'low-functioning' autism reflect a classification employed by many researchers, alongside the diagnostic distinctions, to distinguish those with normal or above normal intellectual abilities from those who are intellectually disabled. The question of whether high-functioning autism and Asperger syndrome denote the same, overlapping or different groups of individuals remains unresolved.

The two major classification systems, DSM-IV (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1993), also employ subtly different terms for the sub-groups within the spectrum. The forthcoming version of DSM (DSM-V due to be released in 2013) aims to reduce some of the complexity, and address unreliability in the diagnostic differentiation of sub-groups (American Psychiatric Association, 2010). The Neurodevelopmental Disorders Workgroup have publicised their intention to remove the diagnostic sub-types (autistic disorder, Asperger disorder and PDD-NOS) from the classification, replacing them with a single clinical entity 'Autism Spectrum Disorder', within which individual symptom patterns will be differentiated by a severity score (Swedo, 2008; 2009). Yet, despite its worthy aims, the proposal has stimulated considerable debate, underlining the wide range of views that still prevail in this area. Issues surrounding terminology, classification and diagnosis are discussed further in Chapter 1. In the remainder of this introduction, we will use the terms 'ASD' and 'autism' interchangeably to refer to the spectrum as a whole. In the remaining chapters of this volume we have left authors to adopt the terminology with which they feel most comfortable.

Autism: an evolving concept

Leo Kanner (1943) viewed autism as a syndrome, a specific developmental disorder with a characteristic set of symptoms, likely to have a single underlying cause. Evidence for a different and more nuanced interpretation existed in the contemporary work of Hans Asperger (1944), but it was 40 years before Asperger's work came to wider attention through the work of Lorna Wing (1981). Asperger's work, later translated into English and reprinted by Uta Frith (1991), provided the stimulus for Wing to make two radical proposals: firstly, the notion of autism as a spectrum, rather than a syndrome, and secondly, the idea of Asperger syndrome as a separable sub-type of autism.

The ramifications of these new ideas were profound, including revisions to the diagnostic criteria to include Asperger syndrome as a separate diagnostic

entity, diagnosis of many individuals who would not have been recognised as autistic by Kanner, recognition of the complex and possibly incidental relationship between intellectual disability and autism, increasing prevalence estimates and so on.

Three decades on from Wing's pioneering contributions, the concept of the autism spectrum is still evolving: further major changes are being considered with the growing appreciation that the autism spectrum may be best characterised as a continuum rather than as a cluster of sub-types (hence the radical proposals for DSM-V); the concept that autistic traits are graded from those individuals with full expression, to family members with 'shadow traits' constituting the Broader Autism Phenotype, to the existence of some autistic-like characteristics even in the 'neurotypical' population.

The implication of this still moving trajectory is that the characterisation and explanation of autism is far more complex than either Kanner or Asperger could have realised. Despite much progress in research, theory and clinical practice in this field over the last seven decades, autism remains a conundrum, a disorder, or group of disorders, which is compelling and yet elusive, and for which medical remediation (e.g. Coury, 2010) is as yet extremely limited. Moreover the status of autism as a 'disorder' rather than a difference has been contested: there is a substantial diversity of views on whether all forms of autism, and especially Asperger syndrome, require remediation.

What are the reasons for the persisting obscurity surrounding this spectrum or cluster of conditions?

Heterogeneity across the autism spectrum

There is consensus on the substantial variability of autism. The expression and severity of symptoms vary significantly from one affected individual to another, and furthermore, autism may present with or without: (i) full expression of the diagnostic triad of symptoms; (ii) intellectual disability; (iii) marked delay/impairment of language; and (iv) a range of different co-morbid conditions (most notably epilepsy). In addition, autism may affect a solitary member of a family, or occur in multiple family members. From this picture, and from a substantial body of scientific studies, it has become clear that the causal factors involved in autism are likely to be multiple, complex, and quite possibly variable from one individual case and one major symptom group to another, even if different influences can be said to converge towards a 'final common pathway' (Frith *et al.* 1991; Darby and Clark, 1992; Geschwind, 2008). Earlier notions that it might be possible to identify specific biological markers for autism, or even a single gene, as in cystic fibrosis for example, have foundered (see Happé *et al.* 2006; Geschwind, 2008).

Known single gene mutations account for less than 1% of all ASD cases, confirming the aetiological heterogeneity of autism (Geschwind, 2009).

Heterogeneity at both aetiological and behavioural levels has, in turn, led to methodological and interpretative difficulties in research. For instance, in psychological studies, there is limited consensus about the appropriate way of matching experimental and control participants (see for example the Journal of Autism and Developmental Disorders: Special Issue on Research Methodology-Matching, Jacob, 2004), and experimental groups may be heterogeneous in terms of sub-diagnosis and the presence or absence of co-morbid conditions. Experimental studies are also constrained by the difficulty of testing low-functioning individuals, with the result that insights tend to be confined to those at the high-functioning end of the spectrum. Neurobiological research is beset by related methodological difficulties. For instance, in neuropathological and neurochemical studies, samples may be small, clinically heterogeneous, often with co-existing/co-morbid conditions, and difficult to match with suitable controls (Palmen *et al.* 2004; Lam *et al.* 2006; Casanova, 2007). Brain tissue donors may also be at the low-functioning end of the spectrum. These limitations pose difficulties for cross-referencing and integrating psychological and neurobiological findings.

Blind alleys in autism research

As in many clinical fields where there is a pressing need for explanations leading to therapeutic interventions, some superficially appealing hypotheses have attracted undue interest, led nowhere and in the process, substantially undermined the progress of research and clinical practice. In the case of autism an early blind alley was Bruno Bettelheim's hypothesis that the causes of autism lay in emotional detachment and faulty parenting by mothers of those on the autism spectrum (Bettelheim, 1967). This erroneous interpretation of what may in some cases have been genetically mediated 'shadow traits' led to the stigmatisation of several generations of parents, and distress in children from whom they were separated for 'therapeutic' reasons. Bettelheim's theoretical and therapeutic approach to autism, now refuted, resonated strongly with psychoanalytical accounts of child development, which were extremely influential at the time (i.e. during the 1960s and 1970s).

An equally if not more damaging hypothesis put forward by Andrew Wakefield and his collaborators (Wakefield *et al.* 1998), subsequently retracted (Murch *et al.* 2004), identified the MMR vaccine as a possible cause of autism in children. Extensive research in this area, carried out over a number of subsequent years, has provided no evidence linking the MMR vaccine to autism. Such a link is unlikely to exist and cannot be considered a reason for the increase in incidence of autism

that has been seen in recent years (see Honda *et al.* 2005). Moreover, while the pattern of inheritance in autism strongly suggests that genetic factors interact with environmental influences to produce susceptibility (Pardo and Eberhart, 2007), the negative publicity that environmental hypotheses have attracted through the work of both Bettelheim and Wakefield has also engendered a greater apparent reluctance amongst researchers to identify significant environmental risk factors.

Neglected topics in autism research

Just as some beguiling avenues of enquiry proved to yield little or no benefit, other potentially important but less seductive topics have been relatively neglected. One of these is the precise relationship of epilepsy to autism. In 1960 one of the first reports linking autism to epilepsy was published (Schain and Yannet, 1960). This was rapidly followed by others (e.g. Gubbay, 1970; Kolvin *et al.* 1971) which indicated that up to one-third of those with autism spectrum diagnoses may have epilepsy, while a review of studies published since 2000 has found that a much higher percentage (up to 60%) have atypical/epileptiform EEG activity (Hughes and Melyn, 2005; Spence and Schneider, 2009). Yet despite the steady accretion of evidence linking epilepsy and autism (see Hughes and Melyn, 2005; Levisohn, 2007; Spence and Schneider, 2009), and further work linking seizures to the sleep disturbances often reported in autism (Malow, 2004), the precise role that seizures play in the aetiology, developmental trajectory and long term outcomes of autism has been sparsely examined. This limitation has impacted further on our understanding of the differentiation of sub-groups within the spectrum. The disproportionate occurrence of epilepsy in those with autism and low IQ, and in females with autism (Amiet *et al.* 2008) highlights yet again the need for caution in generalising about this markedly heterogeneous condition.

There have been important omissions also at the psychological level of enquiry. The major foci of research on the psychology of autism, as well as the target areas for quite a number of interventions, have been the 'triad' of symptoms and characteristics included in the diagnostic criteria for autism. While the precise delineation of these three symptom groups has changed since separate criteria for autism were first included in the DSM-III diagnostic classification in 1980, they still centre upon three main areas of impaired functioning: communication, social interaction, and the rigid and repetitive quality of activities and interests (American Psychiatric Association, 2000; World Health Organisation, 1993). Both Kanner and Asperger documented other difficulties, notably sensory and perceptual problems, atypical memory, and special skills. Pioneering experimental research on memory, sensory and perceptual atypicalities was carried out by Hermelin and O'Connor in the 1960s (Hermelin and O'Connor, 1964; 1970), but due focus on

these topics in relatively recent. A recent review by Geschwind (2009) estimates that sensory atypicalities are observed in more than 90% of those with autism spectrum diagnoses. This resonates with the view of many parents and teachers of children on the autism spectrum, as well as individuals themselves, that sensory and perceptual difficulties are of paramount concern (Bogdashina, 2003). However, Rogers and Ozonoff (2005) argue that the evidence that such difficulties are more especially associated with autism than with other developmental disorders is unclear. Consequently, there is understandable reservation among experts about the explanatory status of sensory problems in relation to the autism spectrum, though at least one recent psychological account of autism has proposed atypical modulation of sensory and perceptual processes as a possible key to explanation (Mottron *et al.* 2006).

Other areas comparatively overlooked in research, but highlighted by Geschwind (2009) include the onset and development of motor signs, estimated to affect 60–80% of those on the spectrum, gastrointestinal problems (up to 50% of those on the spectrum) and co-morbid psychiatric diagnoses, in particular the presence of mood/conduct disorders, aggression and ADHD (between 25 and 70% of children on the spectrum). While it may be argued that the relationship of these symptoms to the autism spectrum is non-specific, and therefore their potential as 'core deficits' limited, their frequency of occurrence does emphasise the complex heterogeneity of the spectrum, which explanations need to encompass.

During much of three decades in which psychological theories have abounded, the major focus has been on explaining the deficits: it is only in more recent work that special skills have begun to attract more interest (see for instance Baron-Cohen *et al.* 2002; Happé, 1999). A constraint here has been a lack of clarity about what constitutes a special skill. Prodigious savant talents, as displayed, for instance, by the artist Stephen Wiltshire, are extremely rare, suggesting, once again, that this facet of autism should not be a central focus of explanation. However, according to recent estimates (Howlin *et al.* 2009) a much larger group of individuals on the spectrum (around 30%) have some measure of special skill. This then presents yet another phenomenon which, while not universal, characterises a major subpopulation of the spectrum, meriting consideration in what will be almost certainly (given the heterogeneity of the phenomena) a fractionated account of the whole field.

Finally, at both biological and psychological levels of enquiry, the developmental trajectory of autism, from infancy to adulthood, has been comparatively neglected. Many studies have characterised atypical functioning within a relatively narrow window of time, paying scant attention to the cumulative effects of early biological and psychological deficits in engendering these outcomes. A notable exception to this trend is theoretical work by Hobson (see for instance Hobson 1993; Hobson, 2002) seeking to explain how impaired capacity to engage

emotionally and socially with other humans from birth onwards, could fundamentally alter a child's developmental trajectory, resulting in both the cognitive and social deficits seen in autistic conditions. Baron-Cohen (1995) has also offered theoretical proposals for early developmental precursors of later theory of mind deficits. The value of the 'trajectory approach' to developmental disorders is elegantly demonstrated by Thomas *et al.* (2009), while recent studies of the developmental trajectory of behavioural symptoms (Richler *et al.* 2010) and neurobiology (Schumann *et al.* 2010) represent an encouraging shift of emphasis.

Positive trends in biology, psychology and practice

Findings gathered over the last four to five decades have resulted in a substantial contemporary framework of understanding about the causes and key phenomena of autism. From initial sources such as the influential monograph by Bernard Rimland (1964) and the pioneering concordance study by Folstein and Rutter (1977; see also Folstein and Rutter, 1978) came persuasive evidence for biological and genetic factors in the causation of autism. The 1970s and 1980s brought a steady stream of further findings concerning biological aspects of autism. This field has taken significant leaps forward since the 1990s, thanks to revolutionary advances in the fields of brain imaging (Minshew and Keller, 2010; Verhoeven *et al.* 2010) and molecular genetics (Abrahams and Geschwind, 2008; Geschwind, 2008; Weiss, 2009). In relation to the neurobiology of autism there is now little doubt that there are subtle atypicalities in the structure and functioning of the brain and neural pathways in people on the autism spectrum (Amaral *et al.* 2006; DiCicco-Bloom *et al.* 2006; Pardo and Eberhart, 2007). Current opinion views autism as a disorder of functional 'connectivity' between cortical networks (Minshew and Williams, 2007), in which key brain areas involved in verbal and non-verbal communication, social interaction, planning and flexibility, as well as networks that govern emotional responses (including fear and anxiety), facial recognition, and the ability to conceptualise mental states in self and others (theory of mind) are affected to varying degrees. Although a unifying pathology has not been identified, and is perhaps even unlikely to be identified for autism, given the heterogeneity in clinical and behavioural presentation of the spectrum, changes that affect early brain development (evidenced by early brain overgrowth during the post-natal period) are indicated in a significant proportion of children with autism (Courchesne *et al.* 2007). Developmental involvement of the frontal and temporal lobes and the amygdala are strongly implicated (see Geschwind, 2009).

Neurochemical investigations have focused on several transmitter systems in autism, including serotonin, dopamine, noradrenaline, acetylcholine, glutamate, gamma-aminobutyric acid (GABA) and oxytocin (McDougle *et al.* 2005; Lam *et al.* 2006). Overall it has been difficult to draw firm conclusions from these studies

mainly due to the limitations highlighted earlier (i.e. heterogeneity of the spectrum, co-morbidities, sample sizes and matching to controls). Although a central role for altered serotonergic function in autism has gained the most empirical evidence, this still requires further investigation and validation. Promising new areas of research include the possibility that oxytocin (the so-called 'social hormone') signalling is perturbed in autism.

Concerning genetic factors, the heritability of autism is now well established. The main focus of interest is in identifying candidate genes and their mode of action on the developmental trajectory in autism (Abrahams and Geschwind, 2008; Geschwind, 2008; Weiss, 2009).

Psychological findings have also played an important role in theory and research on autism from an early stage. Besides offering detailed descriptions of the phenomena of autism, psychological approaches have offered a number of theoretical models seeking to identify the core psychological processes underlying the observed phenomena. A significant breakthrough in the field of theoretical models came with the work of Baron-Cohen, Frith and Leslie (Baron-Cohen *et al.* 1985) initiating two and a half decades of important research on theory of mind deficits in people with autism. An additional impact of this model has been to stimulate the development of a number of rival models, each originally presented as an account of the single 'core deficit' which could explain the full range of symptoms and characteristics in autism. Recently this era of model building has entered a new phase with the realisation that underlying processes proposed within mutually exclusive accounts may in fact constitute parallel factors which operate together to produce the observed pattern of symptoms in autism.

Progress in the field of interventions for autism has been somewhat slower. Some of the most widely used psychological interventions for autism remain those such as the TEACCH framework (Treatment and Education of Autistic and related Communication-handicapped Children) and the behavioural approach pioneered by Ivar Lovaas (Pasco and Roth, 2010). Both originated several decades ago and though reasonably effective in ameliorating certain symptoms of autism, and promoting scope for education, cannot be considered as treatments. Progress in the development of effective pharmacological interventions remains extremely limited. However, some encouraging trends are evident in recent work. For instance, a growing number of interventions seek to address core psychological problems in autism, such as theory of mind or mind-reading deficits (see for example, Golan *et al.* 2010). Moreover, advances in the design and implementation of critical evaluations have greatly enhanced the evidence base for a whole range of treatments, thus limiting the scope for practitioners to make unfounded claims about 'cures' (Pasco and Roth, 2010).

Moving forward – contemporary issues in autism, from diagnosis to development and education

As we have outlined, progress in understanding the autism spectrum combines encouraging progress in some areas with a history of conceptual and methodological difficulties, false trails and puzzling omissions. One important goal of this volume is to redress this uneven and patchy coverage. The selected topics combine contemporary developments in areas widely accepted as fundamental for understanding autism, with new work representing some less widely researched themes and approaches. A recurring theme throughout the volume is the need to develop a suitably nuanced account of autism, fully informed by the heterogeneity and complexity of the phenomena which it presents. All chapters in this compendium are by leading contributors at the forefront in the field of autism theory, research and practice. Their wide-ranging contributions embrace classification and diagnosis, genetics, neurology and biochemistry through to socio-cognitive, developmental and educational perspectives, reflecting the multilevel emphasis of current thinking. This volume aims to promote a broader, more balanced and contemporary understanding of the autism spectrum.

The first section of the book examines classification and diagnosis. In the opening chapter on 'Early assessment and diagnosis of children', Professor Ann Le Couteur from the Institute of Health and Society at Newcastle University first addresses the challenge of dissecting and clarifying the difficult terminology of the autism spectrum, offering an invaluable framework for the volume as a whole. The remainder of this chapter focuses on key aspects of assessment and current diagnostic procedures, including the use of the best estimate clinical diagnosis for clinical and research practice. Difficulties and challenges surrounding diagnosis of childhood autism and ASD are explained and discussed in depth. These are placed in context for the reader with reference to landmark and ongoing studies.

The next section (Chapters 2–6) deals with genetics, neurology and biochemistry. In Chapter 2, 'Unravelling the genetics of autism spectrum disorders', a team of investigators from the Wellcome Trust Centre for Human Genetics at Oxford University led by Professor Anthony Monaco, an integral part of the International Molecular Genetic Study of Autism Consortium (IMGSAC), provide an exceptional insight into this crucial topic. They review and evaluate the extensive body of evidence from linkage and association studies (including genome-wide association), focusing on candidate genes, single gene mutations, epigenetics and copy number variations. They emphasise that the complex aetiology of ASD, which is likely to involve multiple interacting genes and pathways, calls for several different strategies of enquiry, and show how this field of research may move forward, with

larger-scale sequencing efforts required to unravel the causal variants involved in ASD.

Dr Michael Spencer at the Cambridge Autism Research Centre and colleagues from the Centre for Clinical Brain Sciences, Royal Edinburgh Hospital Department of Psychiatry consider 'Brain imaging and the neuroanatomical correlates of autism' in Chapter 3. They provide a detailed overview of structural alterations within neural circuits and brain areas involved with social functions, and restricted and repetitive behaviours in autism. Importantly, they discuss key factors that impact on the interpretation of brain imaging studies which, besides the established heterogeneity of the spectrum, include the gender and intellectual ability of individuals, the developmental trajectory of autism, as well as differences in analytical and technical approaches. They conclude that longitudinal studies exploring the developmental trajectory in ASD, and interdisciplinary efforts to combine neuroimaging with genomic techniques, relating these to neuropathological findings, represent a productive route to further important insights into the neurobiology of autism.

In the chapter which follows, 'Magnetoencephalography (MEG) as a tool to investigate the neurophysiology of autism' (Chapter 4), Dr Sven Braeutigam from the Oxford Centre for Human Brain Activity (OHBA) and colleagues introduce this modern functional neuroimaging method, describing its application to investigating dynamic brain activity and neural processing in autism. The technical and analytical approaches are outlined before the authors move on to the 'functional systems', focusing on key aspects of neural processing which may be affected in autism–auditory processing, semantic processing, face processing and theory of mind-associated with activity within the so-called 'mirror neuron' network. An important feature of MEG highlighted in this chapter is the scope it offers to define and further characterise subclinical epilepsy and epileptiform activity (seizures) that may remain otherwise undetected in a significant proportion of individuals on the spectrum. The authors emphasise that while MEG is a relatively new tool, the few studies conducted to date broadly support the notion that autism involves altered cognitive strategies as opposed to cognitive impairments or 'deficits' *per se*. The technique is presented as holding significant promise for advancing understanding of the neural basis of autism.

In the next chapter 'Autism and epilepsy' (Chapter 5), this critically important and often understated relationship is the focus of discussion by Professors Gillberg and Neville, from the University College London Institute of Child Health and the University of Gothenburg in Sweden. They discuss prevalence, gender and differential diagnostic aspects, before examining autistic regression and epilepsy and taking a closer look at the various types of seizures that may be associated/coexist with autism, as well as early-onset epilepsy syndromes. The authors consider