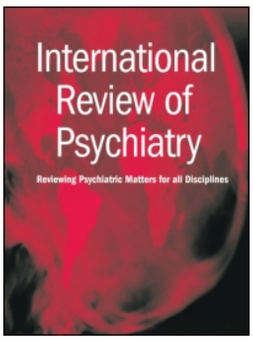

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ARTICLE

Leo Kanner and autism: a 75-year perspective

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ABSTRACT

In 1943, Leo Kanner published the first systematic description of early infantile autism. He concluded that this was a neurodevelopmental disorder and that 'these children have come into the world with an innate inability to form the usual, biologically provided contact with people'. Moreover, his astute descriptions of parental behavior in his first publications were prescient and underlie later recognition of the importance of genetics. Our understanding has grown over the ensuing years with revisions in diagnostic classification, recognition of the broader autism phenotype in families, appreciation of the importance of developmental models, advances in genetic methodology, better understanding of the relationship to intellectual deficits, recognition of syndromic autism in neurogenetic sydromes, advances in neuroimaging, and advances in animal models, both mutant mouse models and transgenic non human primate models. Kanner recognized diagnostic heterogeneity and opined that the children had not read those diagnostic manuals and did not easily fall into clear cut categories. Such heterogeneity continues to confound our diagnostic efforts. Always an advocate for children, when reviewing the DSM III criteria in 1980, Kanner emphasized that no matter how well developed our criteria each child must be treated as a unique person.

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Introduction

> Psychiatry is, and should be forever, a science dunked in the milk of human kindness (Kanner, 1942, p. 21).

Leo Kanner was the leading child psychiatrist of his generation, the academic father of child psychiatry, and a life-long advocate for children. He was the founding director of the child psychiatry programme at the Johns Hopkins University School of Medicine (1930–1959), and the author of the first textbook of child psychiatry, one that went through four editions over the ensuing 35 years (Eisenberg, 1981). He authored four other books (Kanner, 1941, 1957, 1964, 1973), was the founding editor of the *Journal of Autism and Childhood Schizophrenia*, now the *Journal of Autism and Developmental Disorders* (1971), and has written more than 250 scientific publications (van Krevelen, 1976). Today, Kanner is best known for his classic 1943 paper, Autistic Disturbance of Affective Contact,which was the first systematic description of this unique neurodevelopmental disorder (Kanner, 1943,1968). This year is the 75th anniversary of his initial description.

Kanner provided detailed case histories of 11 children with 'autistic disturbance of affective contact', based on his observations and detailed descriptions by parents about their children's behaviour. Kanner wrote that we must 'assume these children have come into the world with the innate inability to form the usual, biologically provided contact with people, just as other children come into the world with innate physical or intellectual handicaps'. Key features that he observed in these children included a lack of communicative use of language, preservation of sameness, restricted interest in activities, and stereotypical and repetitive patterns of behaviour, such as hand flapping and spinning, were subsequently replicated in new cohorts of children. Kanner emphasized autistic aloneness and an 'obsessive insistence on the preservation of sameness'.

Kanner's paper was included in a special section of the journal, *Nervous Child*, along with a paper by his colleague Georg Frankl, entitled, 'Language and Affective Contact' (Frankl, 1943). Frankl focused on affective contact in children who were deaf and others with language disorders. Among them, he described a boy with severe intellectually disability and tuberous sclerosis complex (TSC) with a communication disorder in social (pragmatic) language.

Frankl contrasted this patient to deaf/mute children who do not speak, but retain and use of non-verbal

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social gestures. This boy with a diagnosis of TSC showed no interest in people, and did not use words or gestures for the purpose of social communication. Frankl was familiar with the 'autistic disturbance of affective contact' cases Kanner reported, because he had collaborated with Kanner in evaluating them. Frankl did not find the other autistic features described by Kanner in the boy with TSC, such as anxiously obsessive preservation of sameness and repetitive stereotypies, thus distinguishing Frankl's subject from Kanner's autism. Thus, deficits in social (pragmatic) language communication were distinguished from idiopathic autism in these first publications. DSM-5 now recognizes this distinction by providing criteria for autism spectrum disorder and for social (pragmatic) communication disorder (APA, 2013).

Although Kanner's conclusion that infantile autism was an innate disorder eventually set the stage for modern genetic studies, at the time his paper was published, the focus in psychiatry, especially in psychoanalysis, was on the role of psychosocial factors as causative in the aetiology of psychiatric disorders. Moreover, at that time eugenic beliefs were current leading to people with intellectual disabilites being stigmatized. In Nazi Germany, legislation had been passed to enhance racial purity through sterilization of people with psychiatric disorders and intellectual disabilities (Strous, 2007). German and Austrian psychiatrists deemed children with severe intellectual disability and unproductive adults with mental illnesses as life unworthy of life. Many of these children were used as subjects for scientific experimentation before deliberately being killed (involuntary euthanasia) (Thomas, Beres, & Shevell, 2006).

In the US, the 1927 US Supreme Court case, Buck v Bell (*Buck v. Bell*, 274 US), legalized sterilization for people with intellectual disability, consistent with eugenic beliefs. Kanner addressed the issue of involuntary euthanasia for children with severe intellectual disability when he was invited by the *American Journal of Psychiatry* to debate this issue with Foster Kennedy, a prominent neurologist (Joseph, 2005; Kanner, 1942). If parents gave permission, Kennedy supported a 'mercy death' for children with severe intellectual disability (Kennedy, 1942). The editorial that accompanied the debate was titled 'Euthanasia', and spoke of the role for psychiatrists in helping parents resolve their 'morbid attachment' to their severely intellectually disabled children and potentially to give them up to a mercy death, an option proposed by Kennedy (Anonymous, 1942). Kanner vigorously challenged Kennedy's proposal, insisting that all lives matter, and that much is to be learned from people with intellectual disability. He wrote that 'Psychiatry is, and should be forever, a science dunked in the milk of human kindness', and concluded that we redeem ourselves when we redeem the lives of those with an intellectual disability (Kanner, 1942).

Writing in the *Journal of Pediatrics* in 1944, and now reporting on 20 cases, Kanner introduced the diagnostic term, 'early infantile autism' to designate the innate disturbance of affective contact he described the previous year (Kanner, 1944). He also appreciated the marked heterogeneity associated with the disorder that was demonstrated in the outcomes of his original cases when seen in follow-up in 1971 (Kanner, 1971). He wrote in 1944:

> Among the individual patients there are great variations in the degree of the degree of the disturbance, in the manifestation of specific features, and in the step by step development in the course of time. Yet in spite of this seeming divergence they all present essential common characteristics to such an extent that they cannot but be considered as fundamentally alike from the point of view of psychopathology (Kanner, 1944, p. 211).

Over the ensuing years, the features Kanner described in the first report, lack of interest and lack of engagement in social contact, along with restricted and repetitive behaviours, continued to remain core features of the disorder.

Kanner excluded children with severe intellectual disability and known genetic syndromes in his diagnosis of autism. In his Keith Cameron lecture, he reflected on differential diagnosis (Kanner, 1969). He noted that:

> the children, unfamiliar with those books [Diagnostic Manuals] and articles simply do not have their symptoms arranged to indicate which are basic and dominant and which are incidental and derivative … It is up to us to go on studying these children as individuals with their own peculiarities patiently and pluralistically from every angle (Kanner, 1969, p. 349).

Kanner did not claim to be the first to use the term 'autism' diagnostically. He credited Eugen Bleuler with introducing the term 'autism' into the psychiatric classification, although in a somewhat different context. Although Kanner's initial description was replicated in the scientific literature, it was not until 1980, 37 years later, that his diagnostic term 'infantile autism' formally was entered into the American Psychiatric Association's *Diagnostic and Statistical Manual*, DSM III (APA, 1980).

This paper will review how our understanding of autism has grown over the years following Kanner's

original publication, emphasizing the following themes: (1) *Changes in diagnostic classification*—from infantile psychosis (schizophrenia) to autism spectrum disorder (ASD), a DSM-5 neurodevelopmental disorder, (2) *Parental involvement in pathogenesis*—from a focus on maternal neglect to recognition of the broader autism phenotype in families, (3) *Proposed Developmental Models*—from deficits in affective contact to social cognitive deficits (theory of mind) to intersubjective interpersonal dysfunction, (4) *Application of genetic methodology*—from examination of chromosomal abnormalities and copy number variations (CNV's) to whole exon sequencing, polygenic risk scores, and the impact of common variants on heterogeneity, (5) *Relation to neurogenetic syndromes*—from non-syndromal to syndromal autism, (6) *Relationship to intellectual deficits*—from exclusion of severe intellectual developmental disorders to inclusive use of syndromic neurogenetic syndromes as specifiers. (7) *Developmental neuroimaging findings*—from brain regions to brain circuits, (8) *Use of animal models*—from inbred knock out and knock in mutant mouse models to transgenic and targeted gene editing in non-human primates, especially in marmosets, and (9) Future directions.

Changes in diagnostic classification

Following the publication of Kanner's (1943) paper, there was considerable debate about how to classify the children he described. Some believed these children's presentation to be an early manifestation of schizophrenia, an early onset infantile psychosis. This lack of clarity led to autism being classified in DSM-II as an infantile psychosis under the diagnostic umbrella of childhood schizophrenia. In 1971, Kolvin published seminal research that clarified the distinction between autism and schizophrenia (Kolvin, 1971; Rutter, 1972, 1978). These findings were pertinent in defining the new DSM III category, early infantile autism, which was classified as a pervasive developmental disorder, distinct from schizophrenia and consistent with Kanner's initial description. Early infantile autism was defined as having an onset before 30 months of age, pervasive lack of responsiveness to others, deviant language development, unusual responses to the environment, and the absence of hallucinations and delusions as present in schizophrenia. Subsequently, in practice, the DSM-III criteria were deemed too restrictive because they were applied best to younger children who were more severely impaired. This led to the broadening of criteria when the DSM-III was revised in 1987 (DSM-III-R) (APA, 1987) and a change in name to autistic disorder. In addition, in the DSM-III-R, if diagnostic criteria for schizophrenia were met, both diagnoses could be given. Although the revised criteria were developmentally based, they substantially broadened the category, resulting in more false positive cases, thereby complicating both clinical practice and research use of the classification.

Influenced by research for the ICD-10 classification, the DSM-IV sub-grouped pervasive developmental disorder into four groups: autistic disorder, Rett Disorder, childhood disintegrative disorder, and Asperger Syndrome (Wing, 1981, DSM-IV APA, 1994). Each of these disorders are designated pervasive developmental disorders; they all involve disruption of more than one developmental line. The criteria in ICD-10 did not require social deficits for all pervasive developmental disorder diagnosis. For example, there is the diagnosis, overactive disorder associated with intellectual disabilities and stereotyped movements, that does not require social deficits. However, unlike ICD-10, DSM-IV did link all four of these categories to autistic features.

The term Asperger Syndrome was introduced in ICD-10 and DSM-IV to describe higher functioning people with social communication deficits. The term Asperger Syndrome did not exist until 1981, when it was introduced by Lorna Wing as a new term for autistic psychopathy (Asperger, 1991). In using this term, Hans Asperger's focus was on the personality dimension (Asperger, 1991), an autistic personality disorder. Asperger used the term autistic psychopathy throughout his paper. However, the English language translation of his paper also uses the term autism when translating autistic psychopathy; this has led to some confusion (Asperger, 1991).

Asperger originally described four children in 1944 whose intelligence was in the normal range, with good grammar and vocabulary. They were socially odd, had poor non-verbal communication, and limited and circumscribed interests (Asperger, 1991).

Asperger clearly distinguished his subjects from Kanner's early infantile autism, whom he viewed as a form of infantile psychosis. In discussion with Lorna Wing, Asperger did not accept the term autism spectrum disorder she proposed, but always maintained that his personality spectrum disorder was distinct (Donvan & Zucker, 2016).

In DSM-5, all four of the DSM-IV-TR sub-groups were eliminated, and a new term, autism spectrum disorder (ASD), was introduced. For example, patients with Rett syndrome were removed. Patients with Rett syndrome are profoundly intellectually disabled. Loss

of purposeful hand skills, loss of acquired spoken language, gait abnormalities, and stereotypic hand movements are the major criteria. Intense eye communication is a supportive criterion (Neul et al., 2010). Moreover, current revised diagnostic criteria for Rett syndrome do not list social deficits. Thus, Rett syndrome patients do not meet criteria for ASD. Childhood disintegrative disorder, unlike autism, involves severe continued cognitive decline and is no longer included in the classification. Because Asperger's syndrome is not sufficiently distinguishable from high functioning autism, it too was removed from the classification in DSM-5.

In addition, DSM-5 collapsed DSM-IV's three diagnostic criteria into two criteria; social communication deficits and repetitive patterns of behaviours and restricted activities or interests (Szatmari et al., 2006). When these two revised general criteria are compared to Kanner's original two key diagnostic features, autistic aloneness and preservation of sameness, the DSM-5 criteria are closer to Kanner than were the DSM-IV criteria. Kanner noted problems in sensory sensitivity and integration. DSM-5's inclusion of disordered sensory modulation, hypo- or hyper- reactivity to sensory input, is a new criterion in DSM-5. Ben-Sasson et al. (2009) provide a meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders.

For the clinician who considers the child's perspective, Kanner's focus on autistic aloneness and preservation of sameness may help the observer to empathize with the child's predicament. Considering them allows us to envision a socially perplexed child who does not socially engage and struggles to modulate sensory input from an ever-changing world.

In summary, advances in classification have resulted in refinements in diagnostic criteria that set the stage for identification of sub-types within the autism spectrum in the coming years

Parental involvement in pathogenesis

Bruno Bettelheim believed that autism was not innate, but resulted from maternal rejection. Under the prevailing psychoanalytic view at that time, if parents were to blame for their child's condition, rejecting parents could be treated psychoanalytically (Bettelheim, 1967). Contemporary research had shown that extreme deprivation could severely affect development. Kanner, unlike Bettelheim, did not blame parents for causing autism, nor did he agree that these children were psychosocially deprived. He found no evidence of parental abuse, and noted that the majority of these children lived in intact homes (Kanner & Eisenberg, 1956). He rejected psychological care rearing approaches that blamed mothers long before publishing his paper on autism. In his book, *In Defense of Mothers: How to Bring up Children in Spite of the Zealous Psychologists*, Kanner (1941) responded sympathetically to mothers who came to him despairing and overwhelmed with child rearing. He helped mothers regain self-confidence and trust their own feelings. In a 1965 paper, Kanner affirmed his position when he wrote that he did not agree with 'a tendency in this country to view [autism] as a developmental anomaly ascribed exclusively to maternal emotional determinants' (Kanner, 1965).

Kanner had described autistic traits in both parents and children in his 1943 and 1944 papers. Of the parents, Kanner wrote that 'For the most part the parents, grandparents, and collaterals are persons strongly preoccupied with abstractions of a scientific, literary, or artistic nature and are limited in genuine interest in people' (Kanner, 1944, p. 217). Yet, he remained convinced that autism is innate. In 1944, Kanner asked 'whether or to what extent the parents' personality contributed to the condition of the children?' He concluded that 'the children's aloneness from the beginning of life makes it difficult to attribute the whole picture exclusively to the type of the early parental relations with our patients' (Kanner, 1944, p. 217).

Twelve years later, in 1956, Kanner and his colleague, Leon Eisenberg, both viewed the disorder as a psychobiological one, which resulted from an interaction of an individual's genetic background and their social environment (Kanner & Eisenberg, 1956, p. 560–561, Wan et al., 2013). They wrote, 'If one considers the personalities of the parents who have been described as successfully autistic, the possibility suggests itself that they may represent milder manifestations and that the children show the full emergence of the latent structure'. They went on to point out that 'It is difficult to escape that the emotional configuration of the home plays a dynamic role' in the development of children with autism, noting that, if parents had difficulty recognizing their children's social cues, this would influence their child's development. Recognition of the impact of experience on development might lead to positive effects when parents were successful in social engagement with their children and negative effects when they were not (Hobson, Tarver, Beurkens, & Hobson, 2016). Kanner made clear that he entirely rejected Bettelheim's maternal rejection views at the first meeting of the National Society for Autistic Children in 1969, clarifying for the parents that:

> From the very first publication until the last, I spoke of this condition in no uncertain terms as 'innate' but because I described some of the characteristics of the parents as persons, I was misquoted often as having said that 'it is all the parents' fault' (Olmsted & Blaxill, 2010, p. 226).

He emphasized that, in his early papers, he was describing parental behaviours he observed and reported in professional journals, not blaming them. At that first meeting of the society Kanner was applauded and awarded an official citation for his contributions to children with autism and their families (Olmsted & Blaxill, 2010).

In summary, there have been considerable advances in family participation in treatment and advocacy by parents in the years since Kanner's first description of early infantile autism.

Proposed developmental models

Kanner proposed that early infantile autism is an innate disorder of affective contact, just as there are other inborn developmental disorders, e.g. intellectual developmental disorder, cerebral palsy. When it was clearly agreed that maternal deprivation was not causative of 'emotional withdrawal' in autism, attention turned to Kanner's original focus on innate processes of interpersonal affective engagement as central vs an emerging interest in impairment in social-cognitive processes (Gaigg, 2012).

Following Kanner's original paper, several theoretical models were proposed to account for the primary deficits in autism. These are the emotional, meta-representational (cognitive), and intersubjective models (Harris, 1995; Rogers & Pennington, 1991). The emotional model refers to a lack of innate ability to interact emotionally with others, and the intersubjectivity model refers to impaired formation/coordination of self–other representations.

In recent years, among these models, greater attention in research has been given to cognitive than to emotional and intersubjective models in understanding autism. Cognitive models include the metarepresentational theory (i.e. theory of mind, mentalizing), weak central coherence model, and executive functioning models. Theory of mind is the ability to attribute mental states to oneself and others. Many individuals with ASD do not understand that other people have distinct plans, intentions, thoughts, feelings, and points of view different from their own. Central coherence refers to a limited ability to understand context or to 'see the big picture', and is a central disturbance in ASD. Executive functioning refers to cognitive processes used in the cognitive control of behaviour. These include focusing attention, cognitive inhibition, working memory, planning, and cognitive flexibility. These models reflect high-level cognitive functioning (Happé, 1999; Happé & Frith, 2006). It is hypothesized that abnormalities early in development may give rise to these atypical cognitive processes. A focus on earlier development brings renewed attention to the development of socioemotional processes that are critical to social engagement. This is consistent with Kanner's original focus.

Kanner's autistic disturbance of affective development formulation emphasizes several important developmental milestones in early social engagement and social reciprocity. These include affective attunement, social attachment, social engagement gestures, and social pragmatic interactions that include turn-taking in conversation, shaking the head no, and nodding yes. Other milestones are the emergence of self-conscious emotions (embarrassment, shame, guilt, and pride) and imaginative play as a means to integrate interpersonal experiences (Davidson, Vanegas, & Hilvert, 2017; Heerey, Keltner, & Capps, 2003). From a developmental perspective, Hobson's emotional theory (Hobson, 1991, 1993; Hobson & Lee, 1999), the polyvagal model of social engagement (Porges, 2001), and the importance of oxytocin and vasopressin in social development (Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008) build on Kanner's emphasis on the importance of affective contact as a core feature of ASD.

Hobson's emotional model has long emphasized the importance of a focus on the developing self in explaining autistic social engagement (Hobson & Meyer, 2005). Laboratory studies document that individuals with ASD have difficulty in recognizing and understanding the emotional expressions of others; naturalistic observations demonstrate that they use emotional expressions inappropriately, and rarely use them to regulate social exchanges with others (Gaigg, 2012). Hobson proposes, rather than 'simply interact', people engage interpersonally with others; they identify with and share the psychological orientations and attitudes (including emotional ones) with others (Hobson & Hobson, 2007; Hobson & Lee, 1999). Moreover, early in development, perception and actions are interlinked between mother and infant; this becomes apparent shortly after birth, when there is affective entrainment between infant and caregiver when the infant synchronizes their movements with the patterns, e.g. prosody of the mother's speech (Condon, 1979; Kato et al., 1983; Leclère et al., 2014). Such synchronized and emotionally patterned early social exchanges,

also known as biobehavioural synchrony, provide the basis for interpersonal engagement, whereby the infant discovers a connection between his behaviour and the behaviour of others and links behaviour to subjective experiences (Trevarthen, 1979; Trevarthen & Aitken, 2001). This allows the emergence of the infant's sense that other people are 'like me', and the beginning of a sense of we-ness in relationships, i.e. we are doing this together.

It is proposed that this capacity to identify with others does not adequately mature in individuals with ASD and gives rise to core ASD symptoms (Hobson & Hobson, 2007). As children with ASD grow older, their innate affective deficits are important impediments in symbolic play and language development (Hobson, Harris, García-Pérez, & Hobson, 2009; Hobson, Hobson, Malik, Bargiota, & Caló, 2013). Hobson proposes that flexible thinking may develop from early interpersonal affective engagement. If so, deficits in interpersonal relating during early development may play a role in the cognitive deficits detected in autism. Complex self-conscious emotions may too emerge from an infants' early interactive experiences as they become aware of being the object of the parent's attention. Development essentially proceeds with an ongoing intersubjectivity with attuned parental interpersonal engagement as the infant and child seek to make sense of relationships with other people and their surroundings. Such interactions lead to an understanding of the social emotions of embarrassment, pride, and shame. The lack of ongoing interactional coordination in ASD results in a lack of flexibility in thinking and in internalizing self-conscious emotions. Finally, symbolic play is linked to communicative engagement of emotion. Children with an ASD diagnosis show less joint engagement and less symbolic play (Hobson, Hobson, Cheung, & Caló, 2015).

Biobehavioural synchrony is being directly studied in ASD by examining covariation in psychophysiological arousal levels between interactive parent–child pairs (Baker et al., 2015). Social, affective, and behavioural difficulties in ASD can negatively impact the establishment of biobehavioural synchrony. Facilitating physiological attunement in children with ASD may promote emotional development. For example, many children with ASD like to spin. Picking the child up and spinning them around until the child makes eye contact is a way to utilize a preferred spinning behaviour to facilitate physiological attunement. The child then can be taught to raise his arms to be picked up to continue this game of social engagement.

The work of Porges on the physiology of social communication and engagement (Porges & Lewis 2009; Porges et al., 2013, 2014) and others on deficits in interceptive integration (Garfinkel et al., 2016) are areas of interest. People with ASD have difficulties in identifying others' emotions and in regulating their own emotions. These affective deficits may result from abnormalities in interoceptive processing. Preliminary data suggest that individuals with ASD demonstrate an impaired ability to identify and objectively detect interoceptive bodily signals. These findings suggest that the emotion deficits and affective symptoms in ASD may originate at the interoceptive interface between body and mind (Garfinkel et al., 2016; Quattrocki & Friston, 2014).

The affective focus on intersubjectivity is also the subject of investigation with oxytocin and vasopressin hormones involved in social engagement (Carter et al., 2008; Feldman, 2012b; Feldman, Magori-Cohen, Galili, Singer, & Louzoun, 2011; Quattrocki & Friston, 2014). These neurophysiological and neuroendocrine approaches are in keeping with Kanner's emphasis on affective engagement. Oxytocin plays an essential role in birth, lactation, and parent–infant engagement. Throughout our lifetime, it continues to play a vital role in social sensitivity, interpersonal bonding, and establishing and maintaining of trust in relationships with others. Oxytocin release is very sensitive to emotional context and social context. Oxytocin involved in the regulation of emotion, of hypothalamic pituitary–adrenal axis activity, and of the autonomic nervous system responsiveness. Its effects on modulation of the autonomic nervous system is of particular importance. Oxytocin facilitates social sensitivity and reciprocal attunement in both the mother and child in the rearing an emotionally healthy human child. Intranasal oxytocin is being studied in treatment trials in ASD, and has been shown to have some short-term effects in affected children. It has been found to enhance intrinsic corticostriatal functional connectivity in women. (Bethlehem et al., 2017). Still long-term oxytocin use has proved less effective (Tachibana et al., 2013). Oxytocin use in clinical settings is complex, because its effects are context dependent (Harris & Carter, 2013).

Vasopressin is associated with parenting behaviour and social bonding; high levels of vasopressin are also associated with anxiety and aggression (Carson et al., 2015; Iovino et al., 2018). Moreover, vasopressin may play an important role in the integration of sensory input during complex social behaviour (Bester-Meredith, Fancher, & Mammarella, 2015). Finally,

vasopressin may amplify reactivity to stressors by increasing arousal to affect attention, verbal learning, and memory (Iovino et al., 2018). Vasopressin 1a receptor antagonists are currently in clinical trials aimed at improving social communication in autism (Umbricht et al., 2017).

Educationally, a focus on affective engagement and intersubjectivity is incorporated in developmentally-oriented autism treatment programmes. For example, the Early Start Denver Model (ESDM) is a comprehensive early intervention approach that provides a developmentally based curriculum intervention for children with autism aged 12–48 months of age (Dawson et al., 2010; Rogers & Dawson, 2009; Rogers, Dawson, & Vismara, 2012). The skills to be taught are defined and teaching procedures established to affect them (Rogers et al., 2012). ESDM is provided by therapy teams and/or by parents in group settings or individually, in either the clinic setting or carried out naturalistically integrated into the child's daily home life after school. The ESDM combines a developmentally focused intervention with well recognized applied behaviour analysis procedures. It focuses on shared interpersonal engagement with positive affect in the context of joint attention to facilitate an interpersonal sense of 'we-ness', based on attunement with parent or teacher. This approach seeks to facilitate social communication and language development.

In summary, psychosocial treatments are increasingly based on developmental models, and such treatments are tailored to the needs of individual children.

Genetic aetiology

In the years following Kanner's first publication, research has convincingly demonstrated the importance of genetics in understanding autism. Kanner's early recognition of parental personal traits, specifically over focus on details and limited interested in social interactions, set the stage for the later identification of the 'broader autism phenotype', which refers to the presence of mild ASD symptoms that do not meet diagnostic criteria for ASD. Subsequently, considerable research documents the presence of the broader autism phenotype in family members using behavioural measures that include questionnaires and semi-structured and blind interviews, neuropsychological tests, language testing, and, more recently, brain imaging (Harris & Piven, 2016; Landa et al., 1992; Losh et al., 2009; Sasson et al., 2013a; Sasson, Lam, Parlier, Daniels, & Piven, 2013b; Yucel et al., 2015). Kanner, together with Eisenberg, also reported that ~3% of siblings were affected (Kanner & Eisenberg, 1956); currently the proposed rate in siblings is nearer to 20% (Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Piven et al., 2013).

Genetic studies in identical twins initially confirmed the genetic basis of autism (Folstein & Rutter, 1977). In reviewing more than 13 twin studies since the original description, Huguet, Benabou, and Bourgeron (2016, p. 103) conclude 'the concordance for ASD is roughly 45% for MZ twins and 15% for DZ twins'. Subsequently, genetic studies have progressed from the study of chromosomal rearrangements in children with an autism diagnosis to identifying copy number variations and, more recently, to whole exome/genome studies (Huguet et al., 2016). Despite these advances, at least 90% of cases are non-syndromal and idiopathic. About 10%, primarily in people with intellectual disability, have inherited or *de novo* copy number variations (CNVs) or single nucleotide variants.

Genetic susceptibility differs from one individual to another, due to low risk alleles (common variants that make up the genetic background) in combination with rare deleterious variant mutations. The major genetic contribution may be from common variants, with a smaller contribution from rare variants (Huguet et al., 2016). In some instances, the genetic background may compensate for a rare variant, but in other instances it does not. Thus, the interaction of rare variants and genetic background leads to diversity in the phenotype, with a 50% contribution from each (Huguet et al., 2016). Rare *de novo* mutations are genetic causes, but they 'do not contribute to heritability, since they are only present in the patient' (Huguet et al., 2016).

Studies of multiplex families indicate that a relevant mutation may differ among siblings from one affected sibling to another in a single family. The hope is that, despite there being many ASD-risk genes, those involved may converge and affect a very limited number of biological pathways and are enriched in proteins with identifiable functions. Many of the genes found linked to autism are involved in neuronal development, synaptic plasticity, and chromatin remodeling (Zoghbi & Bear, 2012). Still this is not unique to autism. In intellectual disability (intellectual developmental disorder), epilepsy, schizophrenia, and attention deficit disorder involvement of DNA structure within neurons and maintenance of synaptic integrity are recognized as important.

In summary, advances in genetics are providing promising leads into our understanding of the underlying neurobiology of autism spectrum disorder and are providing the means to identify sub-types.

Relation to neurogenetic syndromes

More than 100 genetic syndromes have been linked to ASD (Betancur, 2011). The number of genetic syndromes associated with ASD reflects its clinical heterogeneity (de la Torre-Ubieta, Won, Stein, & Geschwind, 2016). Overall genetic findings, diagnostic methodology, clinical differences, within-syndrome comparisons, distinctiveness of behavioural phenotypes, and individual developmental trajectories must be considered. Similarities and differences among syndromes and non-syndromic autism must be carefully evaluated by detailed fine grained analysis of the full behavioural phenotype of each syndrome. For those with genetic syndromes and social deficits, the new DSM-5 diagnosis of social (pragmatic) communication disorder might be more appropriate.

Therefore, care is needed in interpreting the significance of what may be superficial similarities between ASD and the behavioural phenotypes of certain genetic syndromes. The full behavioural phenotype should be considered in individuals with genetic syndromes to ensure they receive appropriate behavioural management and the correct educational placement.

Whether monogenetic syndromic disorders are sufficient human models for idiopathic autism is a subject of an ongoing debate. Typically, syndromal autism is distinguished from idiopathic autism in having a different natural history or developmental trajectory of its features (Harris, 2010). The nature of the social communication deficit and types of stereotypies in these syndromes are variable. For example, there are significant differences in the profile of social and communicative symptomatology in FXS when compared with individuals diagnosed with idiopathic autism (Dalton, Holsen, Abbeduto, & Davidson, 2008; Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010; Harris, 2011b). There are differences in chronological age of onset, non-verbal cognitive ability, and expressive vocabulary (Thurman, McDuffie, Kover, Hagerman, & Abbeduto, 2015). Moreover, in genetic syndromes such as fragile X syndrome and Tuberous Sclerosis complex, which are associated with ASD, the majority of individuals with either of these disorders do not have the ASD diagnosis. The more pertinent question in research with these and other syndromes is within syndrome comparisons to find genes involved in social deficits in those with the syndrome who have ASD (Harris, 2011a).

In research protocols, the Autism Diagnostic Interview, revised (ADI-R) is typically used in assessment in both idiopathic and syndromic ASD cases. However, ADI-R items were standardized from cases with idiopathic autism. In the standardization, genetic syndromes were excluded in sample selection. Thus, because the ADI-R was not designed or standardized including children with neurogenetic syndromes, diagnoses using ADI-R may not hold up under detailed inquiry that may find subtle qualitative differences in symptom presentation (Harris, 2016). ADI-R diagnostic algorithms for ASD might be met in syndromic disorders because of excessive social anxiety in some individuals with Fragile X syndrome (FXS), from severe social pragmatic language disorder in Tuberous Sclerosis Complex, social withdrawal behaviour during the encephalopathic phase in Rett syndrome, and severe receptive and expressive language disorders in Cornelia de Lange syndrome. Caution is required when assessing ASD symptomatology in genetic syndromes where there is a severe intellectual disability. Still the degree of ID cannot fully account for the heightened prevalence of ASD characteristics in some genetic syndromes (Harris, 2016; Moss & Howlin, 2009; Moss et al., 2013).

In summary, additional research with fine-grained investigation of behavioural phenomenology within individual syndrome groups is essential. Increasingly such detailed examination in genetic disorders and in children with severe intellectual disability supports Kanner's caution in making the diagnosis of autism in these individuals.

Relationship to intellectual deficits

The best predictors of social outcome in children with an ASD diagnosis are cognitive skills and language skills. Both were recognized by Kanner as important to outcome, and are currently listed as specifiers for ASD in DSM-5. Because verbal and non-verbal IQ scores can be widely discrepant in ASD, non-verbal IQ is frequently used in outcome studies; those with non-verbal IQ in the normal range have the best outcomes. If non-verbal IQ is less than 50 when measured in the pre-school years, the child is much less likely to acquire useful spoken language, and the risk of poor social functioning is increased in adolescence and adulthood (van Engeland & Buitelar, 2008). However, higher IQ and better language skills alone are not sufficient to guarantee good social outcomes because of the severity of social deficits. Targeted special psychoeducation classes beginning early in life are essential. Particular consideration must be given to facilitate educational transitions from primary to secondary school with planning for adult life. Even higher functioning people with ASD may find employment and independent living quite challenging,

and the support of the family and social agencies may be needed to maintain life in the community (Howlin & Magiati, 2017).

In summary, we now have a better understanding of the importance of cognitive and language skills to long-term outcome. This understanding is being applied to facilitate transition into adulthood and adjustment in later life.

Developmental neuroimaging

Leo Kanner described an abnormally increased head circumference in autism. We now know that head circumference is normal at birth, but, in a minority of children true brain overgrowth occurs, leading to an abnormally large brain. The abnormally rapid rate of brain growth in these children, when it occurs, is noted in the first 18 months of life (Lainhart, 2015). Evidence suggests that abnormal brain enlargement may occur primarily in boys with behavioural regression, but not in girls (Nordahl et al., 2011). Research examining the growth curve of whole brain volume over time in ASD demonstrates increased brain volumes in young children with autism, followed by decreased volumes during adolescence. Moreover, the volume of many brain structures continues its atypical decline into adulthood. These finding indicate that ASD is a dynamic disorder, and that complex changes take place in whole brain and in regional brain volumes over the years from childhood into adulthood.

ASD is a heterogeneous disorder with multiple behavioural features that are being examined at the neurobiological level. For example. a systematic review of over 40 behavioural, seven eye tracking, and 22 brain imaging and electrophysiological studies concludes that autistic individuals extract motion from faces differently than comparison groups (Harms, Martin, & Wallace, 2010). Clinically, deficits in visual motion processing in individuals with ASD may be recognized in the first year of life, and may be linked to specific dysfunction in primary visual areas where motion is initially detected.

Longitudinal neuroimaging studies of dynamic brain development from infancy to young adulthood is ongoing to establish the neurobiological trajectory of ASD. Neural network dysfunction and dysconnectivity has been observed. It is proposed that abnormal integration of information in distributed brain networks may be a source for many core clinical features of ASD; however, there is also evidence that neural dysfunction in primary sensory and motor cortical areas and in the thalamus may underlie these features long before the stage of higher-order integration (Uddin, Supekar, & Menon, 2013). Children with ASD have reduced long range connectivity between default mode network nodes and increased local connectivity within Default Mode Network nodes and the visual and motor resting-state networks and salience networks. If the failure of long-distance connections to develop during adolescence is confirmed such findings will provide further support for the 'developmental disconnection model' of ASD (Washington et al., 2014). Resting state connectivity studies have been used to distinguish autism and schizophrenia (Mastrovito, Hanson, & Hanson, 2018).

A promising approach to understanding brain development focuses on prospective monitoring of infants with a sibling with an ASD, placing them at increased risk. The Infant Brain Imaging Study (IBIS) Network is engaged in studying brain and behavioural trajectories in infants at risk. To date these infants have been evaluated at 6, 12, and 24 months of age using detailed behavioural assessments and high-resolution brain magnetic resonance imaging (MRI). Some of the findings from this work indicate abnormal cortical surface area expansion in high risk compared to low risk infants, and these abnormalities appear to be related to the severity of social deficits (Hazlett et al., 2017). These findings suggest that early brain changes are apparent during the period of time when autistic behaviours are emerging and first becoming apparent (Hazlett et al., 2017).

The Autism Brain Imaging Data Exchange (ABIDE) is a major resource in the study of brain connectomics in ASD. The ABIDE II database builds on ABIDE I, and their combination provides investigators with 2156 unique cross-sectional data-sets for sample selection. This large sample size will facilitate the identification of neurobiological sub-groups, including an examination of sex differences in ASD. Moreover, ABIDE II includes psychiatric variables to enhance our understanding of the neural correlates of co-occurring psychopathologies. There are 284 diffusion imaging data-sets. It is anticipated that the breadth of information available will contribute to greater understanding of heterogeneity in ASD (Di Martino et al., 2017).

In summary, advances in brain imaging are leading to earlier identification of children at risk for autism spectrum disorder through examination of brain connectomics identifying sub-groups.

Animal studies

Mutant mouse models in inbred strains are historically and typically used to study rare genetic or

environmental risk factors for ASD, and these account for the majority of this research as models of ASD (Ornoy, Weinstein-Fudim, & Ergaz, 2016). None of the mutant mouse studies model the full human condition, although they may model features of the disorder. Because genetic alterations may underlie the behavioural features of ASD, animal models are being targeted to advance our understanding of disease mechanisms and to facilitate the development of treatments.

Mutant mouse models of neurogenetic syndromes have shown symptoms of these disorders can be reversed, suggesting that information gleaned from studying these rare syndromic disorders may be pertinent to the idiopathic ASD (Harris, 2016; Sztainberg & Zoghbi, 2016). However, despite success in adult mutant mouse models, so far human trials based on these models have not been successful. For example, in Fragile X syndrome the clinical trial of the mGluR5 antagonist mavoglurant (AFQ056), based on such models, resulted in negative findings in large international clinical trials involving both adult and adolescent subjects (Berry-Kravis et al., 2016).

In addition to animal models of monogenic syndromes, such as Fragile X syndrome, another approach is to develop models of single nucleotide variants involved in synaptic functioning. Among these are ASD SHANK3 models involved in synapse formation (Mei et al., 2016; Monteiro & Feng, 2017) and CHD8 (Barnard, Pomaville, & O'Roak, 2015), that is involved in chromatin remodeling. It must be kept in mind that mouse brains differ in major ways to those of humans. During the more than 83 million years in evolutionary distance between mouse and humans brain circuits, cognitive and emotional capacity, and adaptive behavioural changes have evolved into two functional domains in the human brain. The first of these is the functional domain for reward, emotion, and memory that is conserved in all mammals. The second functional domain is one that has uniquely evolved in primates. That domain involves an increase in the growth of the cerebral cortex. It has led to new cognitive capacities, language, tool use, and self-awareness. These new motor, perceptual, and cognitive capacities involve the frontoparietal attention network, imitation, tactile use of the hands to grasp, social systems, and social hierarchies.

Another important difference between primates and mice is that mice do not have a fovea in their retina that allows them to focus visual attention. Primates do have a fovea. It provides them the ability to move their eyes to align and attend to a specific visual target. The high resolution fovea that not only enhances visual acuity, but it fundamentally changes how the world is seen as a three-dimensional representation of the visual world (Belmonte et al., 2015).

Overall, the development and structure of the central nervous systems in non-human primates (NHPs) makes them better models than other mammals in modeling human brain diseases. Moreover, non-human primates with germline transmission are increasingly available to study human diseases (Jennings et al., 2016; Sasaki et al., 2009). In the marmoset, neuroimaging studies of developmental patterns of various brain structures are underway for comparison with humans. For example, one study used magnetic resonance imaging to measure the development of the orbitofrontal cortex, cingulate cortex, amygdala, and hippocampus in the common marmoset (Callithrix jacchus) (Uematsu et al., 2017). A Rett syndrome knock out model of MECP2 is published that combined primate-unique eye tracking tests and brain imaging via MRI to demonstrate physiological, behavioural, and structural abnormalities resembling some clinical features (Chen et al., 2017). Moreover, a SHANK3 mutations in cynomolgus monkeys using the CRISPR/Cas9 genome editing method illustrates the importance of using non-human primates to model *SHANK3* in a model of autism spectrum disorder. The *SHANK3*-deficient foetus showed a significant loss of neuronal cells, that has not been found in any line of *Shank3*-knockout mice, consistent with a unique and critical role of *SHANK3* in early brain development in primates for ASD modelling (Zhao et al., 2017).

In summary, mutant mouse models, and potentially transgenic non-human primate models, are being used to identify convergent biochemical pathways or brain circuits pertinent to autistic behaviours.

Future directions

The DSM-5 classification of ASD is best considered a transitional classification, in which ASD is on a spectrum, not a continuum of severity. There is a long-standing debate over where to set its diagnostic boundaries, because ASD is a highly heterogeneous and complex disorder. Refinements are needed in classification with continued efforts at sub-typing, in establishing developmental models, and clarifying age of onset. Longitudinal follow-up studies that take into account developmental trajectories to validate subgroups are needed, as is continued study of ASD's complicated genetics, consideration of new non-human primate animal models, examination of

neurobiology and neuropathology, and continued efforts to identify biomarkers.

The following recommendations build on current developments in neurobiology to address heterogeneity.

a. *Refinements in case identification*: ASD criteria are comprehensive, but have been interpreted broadly and widely applied, resulting in an increase in prevalence since Leo Kanner first described the disorder. It is a heterogeneous diagnosis, and there is considerable interest in identifying sub-types. Those sub-types should take into account the natural history or developmental trajectory of currently diagnosed non-syndromal autism. A suggested approach is to facilitate subtyping by adding additional specifiers that will allow greater discrimination among cases (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013).
b. *Developmental models*: In keeping with Kanner's focus on autistic disturbance of affective contact, greater emphasis on affective models is needed, with consideration given to social developmental milestones, self-conscious emotions (pride, embarrassment, shame), the examination of bio-behavioural synchrony, interoception, the polyvagal model of social engagement, and the roles of oxytocin and vasopressin in social behaviour.
c. *Age of onset and recognition*: Developmental age of onset or recognition is an important consideration. Continuing studies in high-risk populations, such as younger siblings of affected children or survivors of extreme premature birth with low birth weight are needed. Studies of high risk infant siblings in families that already have a child with autism are important in understanding onset in families with a particular genetic background, and may be extended to understand onset to larger populations.
d. *Longitudinal studies that combine behaviour and MRI studies with large cohorts*: Developmentally focused, prospective studies are essential. Neuroimaging studies will continue to be needed to examine relationships between brain connectivity and circuits and patterns of behaviour and development over time. The IBIS Network and The Autism Brain Imaging Data Exchange (ABIDE) are major resources.
e. *Neuropathology*: Neuropathological studies are expected to increase in number with more brains becoming available for study with the establishment of the post-mortem brain Autism Brain Network sponsored by Autism Speaks and the Simons Foundation, in collaboration with their institutional partners. This will allow studies to use new technologies with larger samples. It is essential to include younger subjects free of comorbidities, such as severe intellectual disability and epilepsy, in the sample.
f. *Complex genetics*: ASD genetics are complex. Common variants are important, as are rare variants. Progress in schizophrenia using genome-wide association study (GWAS) in detection of common risk variants suggest that larger sample sizes of autistic spectrum disorder cases will be needed to identify common variants in ASD. Next generation sequencing technology, which focuses on the whole exome, may be used to identify risk variants that underlie linkage peaks identified in families with multiple family members affected. There is an ongoing need for sub-grouping with identified biomarkers or a well-defined clinical profile to address heterogeneity.
g. *Treatment*: Randomized and large-scale studies are important to understand and determine the intensity of individualized treatment needed, and to identify those specific symptom domains that can be expected to improve. Studies in targeted sub-populations will follow the identification of genetic findings or biomarkers, and support potential new avenues for treatment. Continuing study is needed for medication treatment of social defects and new approaches for the treatment of co-occurring conditions.

In conclusion, considerable advances have been made in diagnosis and classification, developmental models, family support, genetics, neuroimaging, animal models, hypothesis-based research, and evidence-based treatments in the past 75 years. Leo Kanner always emphasized that professional advocacy is an obligation of us all. Both professional and family advocacy over these years has resulted in better case identification, more supports, and better care for children and adolescents with autism spectrum disorder diagnoses.

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