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on Early Childhood
Development

Autism

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Synthesis

How important is it?

Autism is a neurodevelopmental disorder characterised by difficulties in social relations and communication and by rigid patterns of behaviour in affected individuals. It also involves atypical processes of perception, attention and motor development. First defined narrowly as a disorder involving lack of affective contact, preservation of routine, fascination with objects and deficits in language communication, autism has now been recognized as a complex syndrome that varies enormously in its severity and its manifestations. This new awareness has led to a redefinition of autism as a spectrum of disorders. It is estimated that about 1 in 400 individuals exhibits the symptoms of the core syndrome of autism whereas 1 in 100 individuals falls into the autism spectrum.

Concern has been expressed in the mass media that the incidence of autism could be rising. There is however no conclusive evidence that autism is becoming more widespread for three main reasons: The definition of the disorder has changed, making it difficult to compare older and newer estimates of incidence; the methodology for estimating incidence has evolved; the increasing interest for autism could lead to the detection of more cases. A better understanding of the disorder will lead to more accurate estimates of its incidence.

Even if twin and family studies have shown that autism has a strong genetic component, so far no specific genes or other biological characteristics has convincingly been associated with the disorder, which is diagnosed on the basis of behavioural characteristics. The diagnosis is usually posed in the second year of life or later. The care of autistic children is highly demanding of parents and community resources, and even if many affected children will grow up to live fulfilling lives, many others will experience the lifelong negative impact of important medical, educational and social difficulties. Current research on autism seeks to understand the genetic and environmental underpinnings of the disorder, and to devise intervention programs that take into account the considerable differences between affected individuals as well as the changing manifestations of autism during development.

What do we know?

The way we understand autism has evolved considerably over the last decades. The perception of the disorder became more complex as scientists began to recognize heterogeneous conditions, varying in severity but still defined entirely by behavioural patterns and by social impairments. Today, the appellation “autism spectrum disorder” (ASD) is given to a set of conditions involving difficulties in social communication and restricted interests and behaviours. Moreover, recent research highlighted how many autistic individuals show atypical patterns of perception, attention and motor development. Autistics and ASD individuals do not show deficits in attention and information processing per se but, contrary to the general population, are biased toward non-social stimuli. For example, young autistic children are less likely to orient their bodies toward the voice of their caregivers but are able to detect rapidly and accurately non-social sounds. When looking at a face, they tend to focus less on eyes and more on other facial features. In fact, as long as non-social stimuli are the object, autistics tend to perceive and process visual and auditory patterns faster than average. They are also better at mentally manipulating two-dimensional objects. These findings are leading scientists to see autism in terms of qualitatively and quantitatively different patterns of processing information.

Little is known about the causes of autism and ASD. It is well established that this disorder has a genetic basis because the genetic relatives of an affected individual are more likely to be affected than people in the general population.

Whatever the causes of autism are, one defining characteristic is its early appearance. The diagnosis is usually made during the second year of life or a bit later, but retrospective studies of home videos of autistic children show atypical patterns of relating in infancy. These early symptoms cannot however be differentiated clearly enough from normal development to allow a diagnosis in the first year of life. In some children, the development of social skills seems to stop progressing or decline. Studies have found that social communication eventually improves over time in most autistic children even though keeping up with the growing complexity of their social world remains a challenge. Overall, autistic children vary enormously in their social communication outcomes, some reaching age appropriate language and others progressing little.

What can be done?

The growing public awareness of autism has resulted in a pressing demand for intervention programs, which has created in turn a need for research about autism intervention in order to devise evidence-based intervention programs, and sort out the different claims of intervention

success.

Autism is now recognized as a complex, multi-facetted condition, and interventions designed to improve the outcome of affected individuals must take into account this heterogeneity. Intervention studies are however limited because they are unlikely to address the full range of individual differences in the manifestations of autism and autism spectrum disorder (ASD). Another important challenge is to decide which symptoms of autism are to be assessed and which are likely to change in response to what type of intervention for which variant of autism. Moreover, as the prognosis for individuals with autism or ASD depends largely on their level of language and cognitive development, intervention studies must include both standard and autism-specific measures of achievement. For all these reasons, intervention studies in autism are difficult to conduct.

Two categories of intervention exist: those focusing on behaviour and those focusing on communication. The behavioural approaches are generally long term, intensive programs. An example of one such intervention is the Early Intensive Behavioural Intervention (EIBEI) which involves 30-40 hours/week of therapists working with the children and additional consulting time for parents. Less intensive interventions have also been tested but results are conflicting as to whether they are as effective as EIBEI. Behavioural approaches were shown to improve cognitive and language outcomes of autistic children but no improvement of autism-specific symptoms was obtained. Communication approaches to intervention are more centred on parents. This type of intervention has shown mixed results, but also improvement in parent-child interaction and communication although the improvement did not generalized to other contexts. To sum up, extensive intervention programs show that cognitive and communication outcomes of autistic children can be improved, but no intervention to date has resulted in decrease of autism severity.

The atypical perception and attention of autistic children should be taken into account when devising intervention programs and services. We could capitalize on our understanding of autistic children’s peculiar attentional characteristics, like their enhanced attention toward perceptual regularities of auditory and visual patterns, to help them understand the non-autistic world instead of asking them to fit the mould of typically developing children. Such an approach would require educating parents and caregivers about the current understanding of autism alongside offering support and services. Ultimately, a greater societal acceptance of the social differences of autistic children is needed.

Finally, more research is also needed to identify the biomarkers of autism. One challenge to the identification of biomarkers is the heterogeneity of the manifestations of autism at both behavioural and neurobiological levels. Another challenge is to take into account the environmental contexts affecting the biological processes.

Autism: Early Development

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Introduction

Autism is a neurodevelopmental condition characterised by social communication difficulties together with restricted and repetitive behaviours and sensory sensitivities.[1] Approximately 1 in 100 children are diagnosed with autism worldwide, and there is a higher prevalence in males compared to females with a ratio of 4:1.[2] Autism often co-occurs with intellectual disability, mental health difficulties and neurodevelopmental conditions such as attention deficit/hyperactivity disorder (ADHD).

Subject

Autism diagnosis is based on observable behavioural characteristics such as reduced eye contact, lack of to-and-fro conversation, restricted and/or unusual interests and sensory hypo- and hyper-sensitivities. It is therefore not typically diagnosed until toddlerhood at the earliest. Identifying early infant markers can elucidate the neurobiological mechanisms underlying autism, as well as offering the potential to augment current screening procedures and enable earlier intervention.

Problems

i. An over-reliance on the infant sibling design.

Twin studies have shown autism to be highly heritable.[3] In order to characterise the earliest signs of autism, longitudinal infant sibling studies follow infants who have an older brother or sister with a diagnosis. Approximately 10-20% of these infants go on to develop autism,[4] and researchers examine which factors in infancy are associated with a later diagnosis. Other study designs which enable the prospective study of autism include infants with genetic conditions (such as tuberous sclerosis complex) and pre-term infants. The aetiology of autism may be different in these populations. The majority of studies utilise an infant sibling design and findings may not be

generalisable to syndromic autism.

ii. The *specificity* of infant markers to autism is often unknown.

Autism co-occurs highly with mental health conditions such as anxiety, as well as other neurodevelopmental conditions (e.g., ADHD), which means that the *specificity* of early markers cannot easily be determined. In order to understand the developmental mechanisms underlying autism, it is necessary to measure other co-occurring conditions at outcome, yet only a handful of studies to-date have taken this approach.

iii. Small sample sizes may lead to low replicability.

The study of autism, and indeed the fields of psychology and psychiatry more broadly have struggled with a replication crisis, driven in part by studies with small sample sizes. The field has tried to tackle this problem through multi-site consortia with shared protocols. However, many of the experimental biomarker studies in the field still require replication with well-powered samples.

Research Context

The early autism field is moving towards large scale consortia, combining longitudinal data across multiple levels: genetic, neural, cognitive, behavioural, etc. The strength of this design is the ability to characterise the dynamic processes underlying the emergence of autism.

Key Research Questions

- Do infants who later develop autism show early cognitive differences?
- Are there differences in early brain development in autism?
- Does early intervention influence developmental outcomes?

Recent Research Results

Do infants who later develop autism show early cognitive differences?

Over the past decade, several cognitive markers have been associated with emerging symptoms of autism, helping to elucidate the underlying developmental mechanism.[5,6] While some studies have shown early differences in social processing (e.g., reduced attention to complex social stimuli[7]; less orienting to audio-visual synchrony displayed within biological motion[8]), others show

no difference compared to typically developing infants (e.g., orienting to a face in a static display[9]; reflexively following a gaze cue[10]). 'Social first' theories propose that an early reduction in infant social attention results in a developmental cascade leading to autism. Contrary to this, studies showing a declining trajectory of social engagement[11,12], suggest that difficulties emerge, rather than being present from immediately after birth. There is also evidence for broader attentional differences, including slower attention shifting[13], stronger pupillary light reflex[14] and enhanced visual search performance[15] being associated with autism outcome.

Are there differences in early brain development in autism?

Young children with autism tend to show a larger head circumference and greater brain volume. It has been suggested that hyper-expansion of the cortex in infancy may precede brain volume overgrowth.[16] An increase in intermediate neural progenitor cells has been proposed as the mechanisms linking cortical expansion with increased brain volume and disruptions in neural connectivity.[17] The evidence for connectivity differences, however, is less clear. There is a hypothesis that autism might be linked with long-range under-connectivity and local over-connectivity.[18] However, the pattern of findings for early connectivity differences in autism remains mixed, likely dependent in part on methodological factors.[19]

Does early intervention influence developmental outcomes?

Over the past decade, there have been a number parent-mediated interventions with infants who have an elevated likelihood for developing autism. The clinical aim of such interventions is often to support children's development or longer-term outcomes, but from a basic science perspective, randomised control trial methodology also enables the causal effect of changing the early environment to be measured. Based on the evidence to-date, a recent meta-analysis concluded that there were clear effects for parent behaviour change but no evidence for direct effects on child behaviours.[20] However, there may be more subtle effects on child outcomes. Yoder, Stone and Edmund[21] found that increased intervention fidelity mediated a trend towards improved child outcomes. Further, a different parent-mediated intervention, showed significant cumulative effects on child autism outcomes when children were followed-up later in development.[22]

Research Gaps

i. Robust biomarkers for autism are yet to be identified.

While many early markers have been associated with autism, they do not meet the criteria for 'biomarkers'.[23] Biomarkers must be objectively, reliably, and accurately measured, and linked to the underlying biological or pathogenic process. Before progress towards clinical utility can begin, there remains a key need for replication, establishing sensitivity and specificity as well as considering the 'value-added' over-and-above questionnaires or screening tools.[24] Given the heterogeneity of autism, one exciting future potential for biomarkers is in stratifying different subgroups within autism.[25]

ii. Mechanisms of resilience are not well understood.

Resilience, which refers to those achieving 'better than expected' outcomes, is not well understood in autism.[26] The field lacks a clear framework for characterising resilience processes.

Conclusions

Infant sibling studies have identified a range of neurocognitive markers associated with later autism outcome. Characterising the trajectories of these markers has been important in understanding developmental mechanisms in autism. Differences in social processing may emerge later in development, towards the end of the first year of life, with no evidence for an initial reduction in infant attention to faces and early gaze following behaviour. This is in contrast to 'social first' theories which propose that reduced infant social attention results in a developmental cascade leading to autism. While important from a basic science perspective, the lack of evidence regarding stability and robustness of these markers means that their clinical utility has been somewhat limited. Future large-scale consortia, which aim to to replicate effects, establish the specificity of early markers to autism, and test their potential utility in stratifying different subgroups of autistic children will be of key importance for the field.

Implications for Parents, Services and Policy

While a decade of infant sibling research has identified early markers related to autism, there remains a need for replication across large, representative samples. For successful translation to clinical practice, it is important not only to have robust markers, but also to consider the utility of such markers over-and-above existing screening procedures. The Research Domain Criteria framework[27] emphasises the importance of taking a dimensional approach, in which a child's profile can be more fully characterised; the use of biomarkers in stratification of profiles is a key aim for future research. The fields of psychology and psychiatry more broadly are moving towards

more personalised approaches. Precision medicine approaches offer the ability to test which individuals benefit most from particular intervention. In order to build towards more effective treatments, which improve outcomes for autistic children, there is a need to integrate robust trial methodology with an understanding of developmental mechanisms.

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5)*. 5th ed. American Psychiatric Association; 2013.
2. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, Yusuf A, Shih A, Elsabbagh M. Global prevalence of autism: A systematic review update. *Autism Research* 2022;15(5):778-790.
3. Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry* 2016;57(5):585-595.
4. Szatmari P, Chawarska K, Dawson G, Georgiades S, Landa R, Lord C, Messinger DS, Thurm A, Halladay A. Prospective longitudinal studies of infant siblings of children with autism: Lessons learned and future directions. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016;55(3):179-187.
5. Jones EJ, Gliga T, Bedford R, Charman T, Johnson MH. Developmental pathways to autism: a review of prospective studies of infants at risk. *Neuroscience & Biobehavioral Reviews* 2014;39:1-33.
6. Wolff JJ, Piven J. Predicting autism in infancy. *Journal of the American Academy of Child and Adolescent Psychiatry* 2021;60(8):958.
7. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. *Biological Psychiatry* 2013;74(3):195-203.
8. Falck-Ytter T, Nyström P, Gredebäck G, Gliga T, Bölte S; EASE team. Reduced orienting to audiovisual synchrony in infancy predicts autism diagnosis at 3 years of age. *Journal of Child Psychology and Psychiatry* 2018;59(8):872-880.
9. Elsabbagh M, Gliga T, Pickles A, Hudry K, Charman T, Johnson MH, BASIS team. The development of face orienting mechanisms in infants at-risk for autism. *Behavioural Brain*

Research 2013;251:147-154.

10. Bedford R, Elsabbagh M, Gliga T, Pickles A, Senju A, Charman T, Johnson MH; BASIS team. Precursors to social and communication difficulties in infants at-risk for autism: gaze following and attentional engagement. *Journal of Autism and Developmental Disorders* 2012;42(10):2208-2218.
11. Ozonoff S, Iosif AM, Baguio F, Cook IC, Hill MM, Hutman T, Rogers SJ, Rozga A, Sangha S, Sigman M, Steinfeld MB, Young GS. A prospective study of the emergence of early behavioral signs of autism. *Journal of the American Academy of Child & Adolescent Psychiatry* 2010;49(3):256-266.
12. Ganga DN, Boterberg S, Schwichtenberg AJ, Solis E, Young GS, Iosif AM, Ozonoff, S. Declining gaze to faces in infants developing autism spectrum disorder: Evidence from two independent cohorts. *Child Development* 2021;92(3):e285-e295.
13. Elsabbagh M, Fernandes J, Webb SJ, Dawson G, Charman T, Johnson MH, British Autism Study of Infant Siblings Team. Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. *Biological Psychiatry* 2013;74(3):189-194.
14. Nyström P, Gliga T, Nilsson Jobs E, Gredebäck G, Charman T, Johnson MH, Bölte S, Falck-Ytter T. Enhanced pupillary light reflex in infancy is associated with autism diagnosis in toddlerhood. *Nature Communications* 2018;9(1):1678.
15. Gliga T, Bedford R, Charman T, Johnson MH; BASIS Team. Enhanced visual search in infancy predicts emerging autism symptoms. *Current Biology* 2015;25(13):1727-1730.
16. Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, et al. Early brain development in infants at high risk for autism spectrum disorder. *Nature* 2017;542(7641):348-351.
17. Piven J, Elison JT, Zylka MJ. Toward a conceptual framework for early brain and behavior development in autism. *Molecular Psychiatry* 2017;22(10):1385-1394.
18. Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ. Autism and abnormal development of brain connectivity. *Journal of Neuroscience* 2004;24(42):9228-9231.
19. O'Reilly C, Lewis JD, Elsabbagh M. Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. *PloS One* 2017;12(5):e0175870.

20. Hampton LH, Rodriguez EM. Preemptive interventions for infants and toddlers with a high likelihood for autism: A systematic review and meta-analysis. *Autism* 2022;26(6):1364-1378.
21. Yoder PJ, Stone WL, Edmunds SR. Parent utilization of ImPACT intervention strategies is a mediator of proximal then distal social communication outcomes in younger siblings of children with ASD. *Autism* 2021;25(1):44-57.
22. Green J, Pickles A, Pasco G, Bedford R, Wan MW, Elsabbagh M, et al. Randomised trial of a parent-mediated intervention for infants at high risk for autism: Longitudinal outcomes to age 3 years. *Journal of Child Psychology and Psychiatry* 2017;58(12):1330-1340.
23. Parellada M, Andreu-Bernabeu Á, Burdeus M, San José Cáceres A, Urbiola E, Carpenter LL, et al. In search of biomarkers to guide interventions in autism spectrum disorder: a systematic review. *American Journal of Psychiatry* 2023;180(1):23-40.
24. Bedford R, Gliga T, Shephard E, Elsabbagh M, Pickles A, Charman T, Johnson MH. Neurocognitive and observational markers: prediction of autism spectrum disorder from infancy to mid-childhood. *Molecular Autism* 2017;8:1-10.
25. Loth E, Spooren W, Ham LM, Isaac MB, Auriche-Benichou C, Banaschewski T, et al. Identification and validation of biomarkers for autism spectrum disorders. *Nature Reviews Drug Discovery* 2016;15(1):70-73.
26. Elsabbagh M. Linking risk factors and outcomes in autism spectrum disorder: is there evidence for resilience? *BMJ* 2020;368:l6880.
27. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *American Journal of Psychiatry* 2014;171(4):395-397.

A Historical Perspective on Autism

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Introduction

The history of autism is plagued by misconceptions and distortions. This is due to the condition's heterogeneity and to the fact that a diagnosis of autism spectrum disorders (ASD) is based on descriptions and observations of behaviour. Although there is much evidence that autism is a neurodevelopmental disorder with a very strong genetic component, there is not yet a valid biomarker or biological test for autism.[1]

Research Context

Many of the symptoms first described by Leo Kanner in his seminal 1943 article providing clinical descriptions of autism[2] still apply to the way the term autism spectrum disorder is used now, although Kanner himself never accepted the broadening of what he saw as a narrowly-defined syndrome characterised by: a profound lack of affective contact with other people; an anxiously obsessive desire for the preservation of sameness in routines and environment; a fascination with objects; mutism or a kind of language that does not seem intended for inter-personal communication, and onset of the condition from birth or before 30 months.

In fact, Hans Asperger was working in the field in Vienna[3] long before Kanner was in Baltimore.[4] Asperger said the condition was never recognised in infancy and usually not before the third year of life or later. A full command of grammar was sooner or later acquired, but there might be difficulty in using pronouns correctly. The content of speech was abnormal, tending to be pedantic and often consisting of lengthy disquisitions on favourite subjects. Perhaps the most obvious characteristic was impairment of two-way social interaction, due primarily to an inability to understand and use the unwritten, unstated rules governing social behaviour. Asperger, like Kanner, also reported certain skills, as well as impairments, such as excellent rote memories and intense interest in one or two subjects. Unlike Kanner, Asperger recognised wide variability in his syndrome.

For many years after Kanner's 1943 paper,[2] there was confusion between the terms "autism" and "childhood schizophrenia." It is generally considered that a distinction was clearly laid down in the 1970s.[5]

Thirty years ago, autism was considered to be a rare childhood disorder most often associated with severe intellectual disabilities, lack of social awareness and absence of meaningful expressive language.[6] Today, the spectrum of autistic disorders (or ASD) is recognised as a set of common developmental disorders. The causes of most cases of autism remain unknown. Once thought to be the product "*refrigerator mothers*", this notion has generally been discredited – although sadly not in some parts of France, Italy and a number of Latin American nations. There is common agreement today that ASD is a neurodevelopmental disorder that has a genetic basis (perhaps in interaction with the environment).

Recent Research Results

In the 1980s, less severe forms of autism were recognized as separate diagnostic categories within a broader class of what are now known as ASD denominated as "pervasive developmental disorders." Despite its earlier description, Asperger's disorder appeared in official nosographies only in the 1990s. The difference between high-functioning autism (affects individuals who exhibit autistic behaviours but are functional in a social context) and Asperger's syndrome remains a subject of debate. The validity of Asperger's disorder as a distinct syndrome from autism is unclear, partly because of the paucity of differentiating neurobiological evidence.

In the currently-used fourth edition of the Diagnostic and Statistical Manual (DSM-IV) published by the American Psychiatric Association,[7] Autistic disorder is defined by onset prior to three years of age and the presence of deficits or unusual behaviours within three domains: reciprocal social interaction, communication, and restricted, repetitive interests and behaviours. The DSM's broader category of PDD-NOS (pervasive developmental disorder not otherwise specified) encompasses a wider range of conditions sometimes referred to loosely as "atypical autism." In recent years, the definitions of autism have been further broadened, with an increasing reliance on a dimensionalisation of the autism phenotype.

For the new fifth edition of the DSM, the revised criteria include only two symptom domains (social-communication and fixated, repetitive interests), eliminate subtypes of ASD, and describe individual differences in severity of symptoms in the two domains, relative to developmental levels and chronological age. Thus, an individual with an ASD diagnosis would be described in

terms of dimensions of social-communication symptoms and severity of fixated or restricted behaviours or interests. This diagnosis could be associated with other known genetic or medical conditions (e.g., ASD and Rett's syndrome or ASD and Fragile X), language disorders, or other psychiatric conditions (e.g., ASD with ADHD, ASD with intellectual disability).

Research Gaps

Although the concept of ASD has become more familiar, important questions remain about its aetiology, the most accurate and efficient procedures for diagnosis, the apparent increase in prevalence of autism spectrum disorders, and the most effective treatments.

Despite ongoing attempts to "unpack" autism into separable components,[8] certain commonalities strongly define this group: significant and early-arising difficulties in basic aspects of social communication and restricted, repetitive behaviours or interests.

Some distortions and misconceptions about autism remain strong. For example, in terms of interventions, *spurious* pseudo-scientific claims of effective treatments have included *hyperbaric chambers*, chelation (the removal of heavy metals) and wrapping in cold wet sheets ("le packing" in France). Fortunately, there is also a tremendous amount of very solid scientific research now addressing questions about aetiology, epidemiology, diagnosis and treatment.

Conclusions

The research to date clearly indicates that ASD affects a diverse group of children and adults whose needs are varied across the lifespan, both in terms of assessment and intervention. Given the current variability in rates across states and the disparities in diagnosis across ethnic groups and parental education levels, it seems most likely that if disparities decrease, the numbers of children with ASD will rise even more.[9,10] Careful assessment is needed to determine the most appropriate services for different children, as well as for the same child at different points during the life course.

Implications for Parents, Services and Policy

Because the prognosis and treatment of individuals with ASD are strongly linked to cognitive and language levels, assessments must include standard developmental measures in addition to autism-specific measures. In terms of public policy, it is important to recognise that, as ASD has become a more heterogeneous category, one-size-fits-all approaches to diagnosis and assessment

are not appropriate.[11] The variability within rates of subtypes of ASD has significant policy implications. Because of the heterogeneity of the population, it is a difficult number for which to plan. A single program may not be appropriate for the majority of the children in a classroom because of the range in their ages and developmental levels. Even between birth and the age of three, the range of skills and needs of young children with ASD are variable.

References

1. Abrahams, B., & Geschwind, D. (2008). Advances in autism genetics: On the threshold of a new neurobiology. *Nature Reviews. Genetics*, 9(5), 341-355.
2. Kanner, L (1943). Autistic disturbances of affective contact. *Nervous Child*, 2, 217-250.
3. Asperger, H (1938). Das psychisch abnorme kind. *WienerKlinischen Wochenzeitschrift*, 51, 1314-1317.
4. Feinstein, A. (2010). *A History of Autism: Conversations with the Pioneers* London:Wiley-Blackwell.
5. Kolvin I, Ounsted C, Humphrey M & McNay A (1971). Studies in the childhood psychoses, *British Journal of Psychiatry*, 118: 381-419.
6. Lotter, V. (1966). Epidemiology of autistic conditions in young children. *Social Psychiatry and Psychiatric Epidemiology* , 1(3), 124-135.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed (text rev). (2000) Washington, DC: American Psychiatric Association.
8. Happé, F., & Ronald, A. (2008). The 'fractionable autism triad': A review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychology Review*, 18(4), 287-304.
9. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network. *MMWR Surveill Summ.*, 56(1):12-28.
10. Fombonne, E. (2005). Epidemiological studies of pervasive developmental disorders. In F. R. Volkmar, A. Klin, R. Paul and D. J. Cohen (Eds.), *Handbook of autism and pervasive developmental disorders*, Vol. 1 (3rd ed.) (pp.42-69). Hoboken, NJ: Wiley.
11. Gotham, K., Bishop, S. L., & Lord, C. (in press). Diagnosis of autism spectrum disorders. In Amaral, Geshwind, & Dawson (Eds.), *Autism Spectrum Disorders*. New York: Oxford University Press.

Epidemiology of Autism

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Introduction

Determining the prevalence of autism spectrum disorders (ASDs) and monitoring it over time is important to ensure the training of ASD diagnosticians, improve access to necessary interventions, and understand causal mechanisms of ASDs. We review the prevalence of ASDs and discuss the limitations and challenges in interpreting prevalence reports. We specifically consider factors contributing to variation in estimates and their change over time.

Problems

Because ASD is a behaviourally-defined disorder, determining its prevalence is more challenging than for a disorder where clear biological markers exist. The symptoms of ASD vary in severity and may present differently in children with a mixture of cognitive abilities.[1] Furthermore, how the data are gathered, analyzed and interpreted impacts the conclusions made regarding the prevalence of ASD.[2] Changes in societal awareness and the public health response also have an impact on prevalence estimates. As a result, there is controversy surrounding the prevalence of ASD, in particular whether the recent rise in reports of the disorder is due to a true increase in incidence or whether there are other factors that could be impacting estimates.

Key Research Results

ASDs and pervasive developmental disorders (PDDs) are often used interchangeably, and they are very similar in meaning. Based on current best estimates of the prevalence of ASD,[2,3,4,5] rates derived from studies published in English in the last decade show that the current prevalence of autistic disorder is approximately 20-30/10,000, while the prevalence rate for all ASDs is approximately 90-120/10,000. Males consistently outnumber females by approximately 5:1 for broader ASDs. While these estimates are predominantly based on studies in North America and Northern Europe, a recent systematic review that included a wider representation of global prevalence estimates yielded similar figures.[6] In all cases, prevalence figures as well as the

population characteristics from which they were derived are highly variable. Prevalence rates for specific DSM-IV categories including Asperger's syndrome (AS) and childhood disintegrative disorders (CDD) have been more difficult to estimate because of the rarity of those disorders, especially CDD, or the lack of clear differentiation of the clinical phenotype within the spectrum of ASDs, especially for AS.

Research Context

The recent Centre for Disease Control and Prevention (CDC) reports indicate a clear rise in prevalence of ASDs in recent years. News reports and some stakeholder groups have called this an "autism epidemic," with the recent CDC estimates suggesting that 1 in 110 children 8 years of age have an ASD.[7] When prevalence rates are considered against year of publication, there is indeed clear support for the claim for a rise in prevalence reported for autistic disorder over time.[8] This pattern has caused much controversy because it has generated confusion as to whether the rise in prevalence can be equated with a rise in incidence. Prevalence is the proportion of individuals in a population who suffer from a defined disorder at any point in time, while incidence is the number of new cases occurring in a population over a period of time. Incidence does not include individuals already diagnosed or treated for the condition, only the new cases occurring during a certain time period. Prevalence is useful for estimating needs and planning services. In the case of the ASD prevalence reports, one cannot imply incidence from prevalence data because they require different methodologies and analysis.

The variation in prevalence estimates may be driven by a wide range of factors including:

Case definition: Differences in the way various studies defined ASDs and identified them make it difficult to compare between studies and report on the changes in prevalence over time. Relative to early studies in the 1960s and 1970s which used a narrow definition of autism, autism has expanded into a broader class of ASDs. Unlike before, autism occurring without co-morbid mental retardation has also been recognized. The evolution of the case definition of autism into a spectrum disorder has created a challenge in examining prevalence rates between studies, especially over time.[3]

Diagnostic substitution and accretion: The modifications in the diagnostic criteria of autism to a spectrum disorder may be impacting more recent prevalence reports because it is possible that some of the cases which currently have an ASD diagnosis may not have received a diagnosis

previously using older diagnostic criteria. More specifically, diagnostic substitution – when a case receives one diagnosis at one point and then later receives a different diagnosis – may be playing a role.[9] For example, some cases may have received a diagnosis of mental retardation when they were younger, and then later received an ASD diagnosis because of the change in diagnostic criteria. It is also possible that some cases diagnosed with one disorder earlier in time may later acquire a co-morbid diagnosis that includes ASD, called diagnostic accretion. For example, other cases may have received a diagnosis of mental retardation when they were younger, and then later received a co-morbid diagnosis including autism.

Variability in study methods: Unique design features of different studies could have an impact on prevalence, making it particularly difficult to compare published rates over time. Some studies use pre-existing databases, such as service provider databases, special educational databases, or national registers to identify cases. Utilizing these databases to report prevalence excludes individuals who have the disorder but are not in contact with the agency maintaining the database. This results in an underestimation of the true prevalence. Another method used for case ascertainment includes a multi-stage approach, which involves a screening stage followed by a more in-depth diagnostic stage. The goal of the screening stage is to identify an exhaustive list of cases possibly affected with an ASD, leaving the comprehensive diagnostic assessment to the next stage. The number of data sources, the type of screening scale used, and the response rate influence the number of cases selected in the first stage, which then impacts the number of cases identified in the second stage. Even at the stage when participants are directly examined, assessments are conducted using various diagnostic instruments, ranging from a typical unstructured examination by a clinical expert to the use of a full battery of standardized measures.

Public health response, awareness and policy changes: Tracking prevalence has become a national priority in a few countries where such estimates are used in service planning and development. In the U.S., research funding for autism, as well as the number of autism research grants, has increased steadily over the past decade.[10] There is no doubt that increase in public awareness and access to services, and improved identification of autism in primary health care has contributed toward the increase in prevalence and may also account for regional variation within the U.S. Reports of the increasing prevalence of ASDs in research literature and in the media have helped to raise awareness in the general population, especially among parents of affected children. Parent groups have been discussing the rising rates of ASDs all over the U.S.,

Canada and many other nations. Government officials are taking notice of the public response, providing further impetus for awareness and identification efforts.

Conclusion and Implications

Current estimates for the prevalence of autistic disorder is 1/400 individuals,[2] and the prevalence of all ASDs combined is approximately 1/100 individuals. Additionally, comparisons of prevalence studies by year indicate a distinct trend of increasing rates of prevalence. However, whether this increase is the sign of a true ASD epidemic or not is subject to debate. Many factors can explain at least some of the reasons for increasing prevalence rates of ASD, such as changes in the diagnostic criteria for ASD included in the DSM and ICD over time, diagnostic substitution and accretion, and the variability in case ascertainment across studies. Affected families and advocacy groups have used the autism epidemic to improve the plight of individuals with ASD, which has led to the discussion of autism by governmental bodies, which regardless of the nature of the increase of ASD has been beneficial to those affected by it. In conclusion, it appears as though increasing rates of ASD can be explained by factors associated with the collection of data, and not necessarily by an actual increase in incidence although the latter possibility remains to be further investigated.

References

1. King, M., & Bearman, P. (2009). Diagnostic change and the increase in prevalence of autism. *International Journal of Epidemiology*, 38(5), 1224–1234.
2. Fombonne, E., Quirke, S., & Hagen, A. (2011). Epidemiology of pervasive developmental disorders. In D. G. Amaral, G. Dawson., & D. H. Geschwind (Eds.), *Autism spectrum disorders.* Oxford University Press.
3. Fombonne, E. (2003). The prevalence of autism. *Journal of the American Medical Association*, 289(1), 1–3.
4. Fombonne, E. (2005). Epidemiology of autistic disorder and other pervasive developmental disorders. *Journal of Clinical Psychiatry*, 66(Suppl 10), 3–8.
5. Williams, J. G., Brayne, C. E., & Higgins, J. P. (2006). Systematic review of prevalence studies of autism spectrum disorders. *Archives of Disease in Childhood*, 91, 8–15.
6. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, Montiel-Nava C, Patel V, Paula CS, Wang C, Yasamy MT, Fombonne E. Global Prevalence of Autism and Other Pervasive Developmental Disorders. *Autism Res*. 2012 Apr 11. doi:10.1002/aur.239. [Epub ahead of print] PubMed PMID: 22495912.
7. Center for Disease Control. (2009). Prevalence of autism spectrum disorders– autism and developmental disabilities monitoring network, United States, 2006. *Morbidity and Mortality Weekly Report Surveillance Summary*, 58, 1–14.
8. Campbell CA., Fombonne, E., Zakarian, R., Bennett, A., Meng, L., & McLean-Heywood, D. (2006). Pervasive developmental disorders in Montreal, Quebec, Canada: Prevalence and links with immunizations. *Pediatrics*, 118(1), 139–150.
9. Shattuck, P. T. (2006). The contribution of diagnostic substitution to the growing administrative prevalence of autism in US special education. *Pediatrics*, 117(4), 1028–1037.

10. Singh, J., Illes, J., Lazzeroni, L., & Hallmayer, J. (2009). Trends in US autism research funding.*Journal of Autism and Developmental Disorders*, 39, 788–795.

The Etiology of Autism

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Introduction

In recent years, there has been a major shift away from understanding autism as a narrowly defined, categorical disorder to understanding it as a spectrum of conditions that affect individuals differently.[1] As such, the impact of autism varies; some individuals can lead independent and fulfilling lives, but many develop substantial medical, educational and social difficulties that have a serious negative effect on their quality of life.[2] The heterogeneity of the condition has led some scientists to suggest that instead of one unique phenomenon, there are probably many "autisms" with different underlying biological processes and developmental pathways.

The current Diagnostic and Statistical Manual of Mental Disorders includes "autistic disorder," "Asperger's disorder" and "pervasive developmental disorder not otherwise specified" (PDD-NOS) as types of autism. Research has thus far failed to map these clinical subgroups onto a specific etiology or developmental pathway leading to each disorder. Today, there is increasing appreciation of the heterogeneity in the expression of the condition along numerous phenotypic dimensions, which overlap with those found in other conditions and in the general population.[4,5] As a result, the next edition of the Diagnostic and Statistical Manual of Mental Disorders will replace current categorical "subtypes" with a single category labelled "autism spectrum disorder."

Recent Research Results

Twin and family studies have demonstrated that both genetic and non-genetic factors contribute to an increased susceptibility to autism.[6] The involvement of some genetic factors is stronger than others and so far a heterogeneous mix of pathways, rather than a single causal pathway, has been indicated. There is, however, growing evidence for the involvement of genetic risk factors that interfere with synaptic development and plasticity. Risk factors include common and rare genetic risk variants, as well as non-genetic risk factors. Common genetic variants tend not to be associated with very high risk for autism relative to the general population, but replication and confirmation of the role of these variants is still awaited. Among the clearer associations with

autism are rare (defined as occurring in <1% of the general population)[6,7] *copy number variants*. Moreover, there is much overlap between some rare genetic syndromes and autism.

Currently, large-scale studies are ongoing to ascertain the extent to which each genetic risk factor is implicated in the etiology of the disorder. Hence, none of the genetic variants that have been identified so far can be considered clinically useful for the identification of autism in the general population.[8] Nevertheless, the testing for genetic variants of individuals diagnosed with a developmental disorder, including autism, aims to improve medical care by identifying variants that may give rise to co-morbid medical problems (e.g., the medical complications associated with tuberous sclerosis and micro-deletion and -duplication syndromes, such as epilepsy, and renal and gastrointestinal problems) and by establishing the risks of potential recurrence in future offspring of parents who already have a child with the condition. Non-genetic factors that increase the risk of autism are still poorly understood, and could include *epigenetic* and environmental factors.[9] Interactions between genetic and non-genetic factors can further contribute to autism risk in complex ways.[10]

The behaviours that are characteristic of autism first emerge and then evolve over the first few years of postnatal development. Nevertheless, recent evidence from studying infants at-risk for the condition suggests that alterations in brain development begin much earlier than the appearance of behavioural symptoms.[11] However, different infants exhibit variable early expression of autism both at the level of brain and behaviour that diverge into different developmental pathways over time.[10] As such, by adulthood, autism is associated with changes in a wide range of neurobiological systems. Many have suggested that autism is the consequence of an atypical process of specialization in various brain networks, and specifically in the social brain.[10]

Research Gaps

There is widespread hope that translation of the current body of evidence into valid biological markers for autism, a condition currently defined on the basis of behavioural criteria, will advance research and practice. The discovery of biomarkers could not only reveal causes of the conditions, but also be clinically useful in complementing or improving the behavioural diagnosis of autism and enabling earlier detection of the condition. Recently, molecular genetic techniques (e.g., chromosomal microarray, CMA) have been developed for detecting submicroscopic deletions and duplications. Several scientific-industry consensus reports have advocated the use of these more powerful techniques as a test for genomic abnormalities for individuals with a range of

developmental conditions, including autism. Studies using CMA to test very large samples of individuals who are already diagnosed with a developmental disorder have shown some form of genetic anomaly in 5–10% of individuals.[7] In addition to indicating co-morbid medical problems and recurrence risk, it is suggested that CMA testing may help families to understand the genetic contribution to the condition and thus provide insight into possible causes or factors leading to autism.

There are currently no scientific or industry guidelines for how CMA results should be reported to participants, but first steps towards such guidelines are underway.[7] Attempts to translate new genomic findings into clinical applications have resulted in mixed reactions from the scientific community and the public.[7,12] Difficulties often arise in cases where genetic variants are identified but their clinical significance remains unclear. The limited information regarding these variants means that accurate prediction of recurrence risk and developmental outcomes is not yet possible in most cases. In the future, a key scientific challenge will be to develop sufficiently large databases of genetic variants to ascertain their clinical utility in isolation or in combination with other genetic and non-genetic risk factors.

Other attempts to translate research on the neurobiological basis of autism into useful applications for identification and intervention have also met a number of key scientific challenges. First, experience in other areas of biomedical research highlights how challenging it can be to translate biomarker discovery into clinical applications, and very few clinically-useful biomarkers have as of yet been identified for neuropsychiatric conditions. Second, the identification of autism biomarkers has so far proved elusive, partly because definitions of the condition itself have changed considerably over time and are still developing. Researchers have primarily focused on mapping biomarkers onto clinically-defined categories, but such categories do not capture the current understanding of the increasingly multidimensional and complex clinical, cognitive and behavioural phenotype that is associated with autism and its overlap with other disorders. Third, developmentally invariant biomarkers for autism are particularly challenging because the phenotypic manifestations unfold as development progresses, especially during infancy and early childhood, reflecting dynamic developmental interactions among multiple risk factors.[10] Fourth, several proposed biomarkers were found not to be universal, and none has indexed the presence of autism in a majority of cases (poor sensitivity). Candidate biomarkers tend also to be associated with a range of other neurodevelopmental conditions and not only with autism (poor specificity). Finally, measuring some putative biomarkers is currently expensive,

laborious and reliant on a high degree of technical expertise, restricting the possibility of their application in most clinical settings.

Conclusions and Implications for Parents, Services and Policies

Despite major advances in the understanding of the genetic, neurobiological and developmental underpinnings of autism, many aspects of the condition are still poorly understood. Recent attempts to translate the current understanding of the neurobiology of autism into clinically-useful applications have been met with scientific and societal challenges. These challenges underscore the biological heterogeneity of the condition, which contributes to a complex picture of autism. Information received by the general public, however, rarely reflects this level of complexity.

The scientific community needs to continue building the understanding of autism as a complex condition that is probably determined by multiple, yet to be understood pathways that lead to heterogeneous outcomes. Ideally, biomarker discovery should lead to an increased understanding of the complex nature of the autistic spectrum, rather than to deterministic or reductive thinking about the condition.

Major challenges to be overcome include the current absence of systematic input from the community affected by autism and research about what determines the perspectives of various stakeholders. Failure to contextualize emerging evidence on neurobiology within the unique needs of diverse communities would only serve to undermine their potential value. Through adequately-supported processes of knowledge translation, more involvement of families and clinicians in the research process will improve the integration of evidence into practice. By contextualizing existing and new research knowledge within the real-life experiences of affected families, science communication regarding autism biomarkers can serve its primary purpose of informing the public and contributing to ethically-informed knowledge translation. In the future, parents' decisions and preparations can be better supported if they know which of the many forms of autism could develop in their child. In the meantime, families have the right to receive scientifically-grounded information about the causes and biological manifestations of autism alongside evidence-based services.

References

1. Wing, L. *The Autistic Spectrum: A Guide for Parents and Professionals*. London: Constable; 1996.
2. Farley, M. A. et al. Twenty-year outcome for individuals with autism and average or near-average cognitive abilities. *Autism Res*. 2009; 2: 109–118.

3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 4th edn American Psychiatric Association; 2000.
4. Georgiades, S. et al. Structure of the autism symptom phenotype: a proposed multidimensional model. *J. Am. Acad. Child. Adolesc. Psychiatry* 2007; 46: 188–196.
5. Volkmar, F. R., State, M. & Klin, A. Autism and autism spectrum disorders: diagnostic issues for the coming decade. *J. Child. Psychol. Psychiatry* 2009; 50: 108–115.
6. Abrahams, B. S. & Geschwind, D. H. Advances in ASD genetics: on the threshold of a new neurobiology. *Nature Rev. Genet.* 2008; 9: 341–355.
7. Scherer, S. & Dawson, G. Risk factors for autism: translating genomic discoveries into diagnostics. *Hum. Genomics* 2011; 130: 123–148.
8. Burke, W., Laberge, A. M. & Press, N. Debating clinical utility. *Public Health Genomics* 2010; 13: 215–223.
9. Currenti, S. A. Understanding and determining the etiology of autism. *Cell. Mol. Neurobiol.* 2009; 30:161–171.
10. Elsabbagh, M. & Johnson, M. H. Getting answers from babies about autism. *Trends Cogn. Sci.* 2010; 14: 81–87.
11. Elsabbagh, M. et al. Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Current biology.* 2012; 22,4: 338-342.
12. Pellicano, E. & Stears, M. Bridging autism, science and society: moving toward an ethically informed approach to autism research. *Autism Res.*2011; 4: 271–282.

The Emergence and Developmental Course of the Social Characteristics of Autism

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Introduction

Autism is a neurodevelopmental disorder that is the result of genetic and other organic etiological factors that affect brain development very early in life.[1] It is a behaviourally-defined disorder characterised by difficulties in social relating, social communication and rigid patterns of behaviour, and, for many individuals, sensory abnormalities.[2] Autism is now considered to be a "spectrum" of disorders; both in terms of etiology and in terms of the highly heterogeneous presentation amongst individuals meeting the diagnostic criteria and within individuals across development. It is now recognised that 1% of children meet the criteria for broadly defined autism spectrum disorder.[3,4]

Subject

Although autism is diagnosed on the basis of difficulties in a number of areas of development and behaviour, its core defining characteristics are difficulties in social relating and social communication. However, the social world and social behaviour of infants is very different to that of an individual in mid-childhood, adolescence or adulthood. The focus of the current entry is the nature of the early emergence of these social difficulties in infancy and the preschool years and their developmental trajectory into mid-childhood and beyond.

Problems

Despite the fact that, as initially recognized by Kanner,[5] in most cases autism has an onset in infancy, it is not often diagnosed until a child is two or three years of age, and in some cases considerably later.[6,7] In part this is because the full syndromic pattern of symptoms of impairments in social relating, communication and rigid and repetitive behaviours required for a diagnosis are not reliably identified before this age. As a consequence, until the last decade much of what we

knew about the early emergence of the social characteristics of autism had relied on retrospective parental report which is subject to a number of biases and influences.

Research Context

However, in the past two decades significant progress has been made towards earlier identification and diagnosis, motivated by the hope that early intervention may have a lasting positive impact for children and their families.[8] A number of research designs, including the retrospective analysis of home movies of children who later go on to receive a diagnosis and the study of infant siblings of an older child with a diagnosis, have allowed us to map the developmental trajectory of the core, defining social difficulties from their early emergence in infancy, through the school age years and into adolescence, and more recently into adulthood.

Key Research Questions

Following the emphasis on early identification and early intervention, one critical question has been: What are the earliest emerging signs of autism? Related to this, given the very wide variability in progress that different children with autism make in their social interaction and social communication outcomes, what are the internal and external factors associated with outcomes? What are the emerging early intervention approaches for which the best evidence-base exists?

Recent Research Results

From the retrospective study of infant home movies a wide range of early social-communicative differences are apparent, including reduced orienting to name; impoverished joint attention behaviours; some early motor abnormalities and reduced emotional expression.[9] These early symptoms were usually most clearly identified during the second year of life, although some studies identified differences around the child's first birthday.

Over the past decade a number of groups worldwide have initiated truly prospective observational studies by exploiting the relatively high recurrence rate of autism in families. This allows the possibility to recruit a cohort of younger siblings of an older child with an autism diagnosis and to follow their development over time to identify who will go on to develop autism.[10,11] To date, no clear behavioural differences have been identified in infants in the first year of life that predict later diagnostic outcome. Several groups have shown that from early in the second year of life some clear differences have emerged, including orienting to name, gestures and imitation, social

smiling, reactivity, social interest, and sensory-oriented behaviours. Recent studies have suggested that some social skills may plateau or decline for some of those children who go on to receive a diagnosis of autism, providing prospective evidence of the “regression” or loss of skill that has long been reported in the literature from retrospective parental report.[12]

Other studies have looked at the trajectory of social and communication symptoms from toddlerhood (two to three years) into mid-childhood. Charman et al.[13] found that social and communication symptoms decreased with development to age seven years. However, another significant challenge for many children with autism is the increasingly demanding social environment as children enter high school. Another study tracked language and communication abilities from two to nine years and found very wide variability in outcome despite many children having had delayed language milestones as toddlers.[14] At the later age some children had age appropriate language while others had made only very slow progress.

After many decades when few randomised controlled trials were conducted in the autism field, the past ten years has seen an explosion in such studies.[15] Many have focused on enhancing early social-communication skills, either by working with children in kindergarten settings, working with parents or a combination of therapist-led and parent-training. Several studies have found improvements in interactive (“dyadic”) behaviour, both with parents and unfamiliar adults, and some have reported improvements in language. No studies to date have reported objective reductions in autism severity, although to date the length of interventions studied have only been over several months or at most one or two years. In combination with more general evidence that behavioural intervention approaches can benefit adaptive outcomes for children with autism, intervention approaches that focus on enhancing social communication abilities are now considered to have a good emerging evidence base.[16] Further trials of such programs rolled out to community services are required to establish their effectiveness.

Research Gaps

Despite the increase in the past decade in well-controlled intervention studies, further such trials are required to improve the evidence-base for established and newer interventions, in particular to identify the effective elements and moderators (“who benefits”) and mediators (“how does change occur”) of effectiveness. Only recently have longitudinal studies begun to examine the trajectories of social development beyond mid-childhood into adolescence and adulthood (for exceptions see reference 17). Mechanistic studies that employ experimental and neuroscientific

methodologies, where possible embedded within genetic and familial designs, are required to elucidate the neurodevelopmental processes that lead to the social difficulties in autism. Such studies will also help us to understand the associations between social difficulties and common comorbidities in adaptive function, sensory difficulties and mental health problems.

Conclusions

The common characteristics of atypical early social development in autism have now been well described. However, basic scientific questions about the underlying neurodevelopmental processes that lead to the autism phenotype, as well as associated common comorbidities, are less well understood. One common feature of the recent wave of longitudinal studies is the increasing heterogeneity in social and other outcomes over development. While there is an increasing evidence base for some early intervention approaches that improve outcomes at least in the short term, in particular those that combine aspects of behavioural and interactive social communication interventions, we know less about the effectiveness of interventions in mid-childhood and adolescence.

Implications for Parents, Services and Policy

The costs of autism to individuals, their families and society are considerable.[18] Once considered a rare condition, some form of autism is now understood to affect around 1/100 children and young people. Parents and professionals, in particular in early years community health and education settings, need to be educated about the earliest emerging signs of the disorder to help early identification and referral. Difficulties in social relating and social communication emerge as the core characteristic in many children soon after infancy, especially as children enter the more challenging social world of kindergarten and school. Social and communication abilities continue to develop into mid-childhood and beyond, although at different rates for different individuals. An evidence base is emerging for psychosocial interventions that target early social communication skills and behaviour. Internationally, as more children are recognised in the preschool period, demand for early intervention services will increase and require funding. A more general societal issue is the need for a greater acceptance of “social difference” alongside support for those affected, their families and those who care for them.

References

1. Levy SE, Mandell DS, Schultz RT. Autism. *Lancet* 2009;374:1627-1638.
2. American Psychiatric Association. DSM-5 Development. Available at: http://www.dsm5.org. Accessed May 25, 2012.

3. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet* 2006;368:210-215.
4. Center for Disease Control. Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. *MMWR Surveillance* 2009;18:1-20.
5. Kanner L. Autistic disturbance of affective contact. *Nervous Child* 1943;2:217-250.
6. Charman T, Baird G. Practitioner Review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children. J Child Psychol Psychiatry 2002;43:289-305.
7. Mandell DS, Novak MM. Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. Pediatrics 2005;116:1480-1486.
8. Charman T. Developmental approaches to understanding and treating autism. *Folia Phon Logopaed* 2010;2:166-177.
9. Yirmiya N, Charman T. The prodrome of autism: early behavioral and biological signs, regression, peri- and post-natal development and genetics. *J Child Psychol Psychiatry* 2010;51:432-458.
10. Rogers SJ. What are Infant Siblings Teaching Us About Autism in Infancy? *Autism Res* 2009;2:125-137.
11. Elsabbagh M, Johnson MH. Getting answers from babies about autism. *Trends Cogn Sci* 2010; 14:81-87.
12. Ozonoff S, Iosif AM, Baguio F, Cook IC, Hill MM, Hutman T, et al. A prospective study of the emergence of early behavioral signs of autism. *J Am Acad Child Adolesc Psychiatry* 2010; 49:256-266.
13. Charman T, Taylor E, Drew A, Cockerill H, Brown JA, Baird G. Outcome at 7 years of children diagnosed with autism at age 2: predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. *J Child Psychol Psychiatry* 2005;46:500-513.
14. Anderson DK, Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Welch K, Pickles A. Patterns of growth in verbal abilities among children with autism spectrum disorder. *J Consult Clin Psychol*2007;75:594-604.
15. Charman T. Glass half full or half empty? Testing social communication interventions for young children with autism. *Journal of J Child Psychol Psychiatry* 2011;52:22-23.
16. Rogers RJ, Vismara LA. Evidence-based comprehensive treatments for early autism. *J Clin Child Psychol* 2008;37:8-38.
17. Szatmari P, Bryson S, Duku E, Vaccarella L, Zwaigenbaum L, Bennett T, Boyle MH. Similar developmental trajectories in autism and Asperger syndrome: from early childhood to adolescence. *J Child Psychol Psychiatry* 2009;50:1459-67.
18. Knapp M, Romeo R, Beecham J. Economic cost of autism in the UK. *Autism* 2009;13:317-36.

Sensory, Motor and Attention Characteristics of Autistic Children

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Introduction

In contrast to the common notion of autism as simply a disorder of social development with one or more specific impairments related to understanding and participating in reciprocal social interactions, more current conceptualizations are based on the notion of a condition that involves complex patterns of atypical processes, especially in the areas of perception, attention and motor development.[1] Associated in some cases with relative strengths and in others with weaknesses, the processing and production of information and action across these systems are altered among persons in such general ways that it suggests “hard-wired” neurological differences.

Subject

Autism is increasingly conceptualized and even diagnosed in relation to attention, sensory and motor characteristics. For example, in the realm of attention, fewer than typical instances of spontaneous initiations of *overt joint attention* and unusual overt responses, such as reduced instances of alternating gaze, in joint attending opportunities in naturalistic settings have become essential features of diagnostic instruments that are based on direct observations of preschoolers. In the realm of perception, perceptual atypicalities are now highlighted in the diagnosis of autism by the inclusion of “sensory issues” in the working drafts of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, which will soon be adopted as the standard for classification and diagnosis in North America. The centrality of manifestations of atypical motor development, such as the occurrence of repetitive movements, to the autism phenotype has long been acknowledged in virtually all diagnostic systems.

Problems

The earliest and most striking aspects of autism include significantly diminished overt and spontaneous attention to voices and faces that are associated with increased attention to non-

social, as opposed to social, aspects of the world. These types of behaviours, which involve many of the “negative symptoms’’ – behaviours that are never or rarely seen in this population although they are common in the general population – are central to social models of autism or to more general models of atypical attention and perceptual processes, such as those related to atypicalities in the selection of attention target and the processes of the voluntarily planning of this selection. This could also indicate that the series of process by which humans detect, recognize, store and mentally manipulate representations of socially relevant patterns are uniquely and intrinsically different from the norm in autism.

Research Context

Atypical attention in autism was initially, in the 1960s and 1970s, discussed in terms of “overselectivity,” an excessive focus on certain features of a stimulus or the environment, or in terms of problems in “arousal” modulation, with both over-arousal and under-arousal suggested as the source of attention and other basic atypicalities in autism. By the 1980s, models of autism were based on evidence of deficits on parameters of attention (e.g., switching of attention from one focus to another), “joint attention’’ and competition between social and non-social targets in the triggering of attention behaviours. Perception is studied in the context of “sensory hypersensitivity” – the search for specific auditory and visual patterns, perceptual peaks, impaired face perception, and generally enhanced low-level perceptual encoding. The study of motor cognition is still in its infancy.

Key Research Questions

The study of attention in autism is largely focused on disentangling the potential sources of impairments – do they emanate from a problem in one or more attention mechanisms per se (e.g., control, switching and filtering), in their relation with goal-related executive mechanisms, or as secondary effects of atypical processes in other domains such as perception?

The study of perception includes considerable emphasis on enhanced perceptual processing – at which level of processing does it occur (i.e., early encoding, pattern formation and manipulation or both)? Is it more evident in *basic (bottom up) or higher-order (top down) systems of processing*? And, is it an example of a category-specific perceptual abnormality, such as social stimuli for example?

The study of motor development is focused on individual differences among the subgroups of autism spectrum disorders. Why do some autistics display some kind of *motor apraxia* while most others are proficient at this level? Do the sub-groups of autism spectrum disorders differ (autism versus Asperger's) in motor development? And to what extent are differences found across subdomains of functioning (gross versus fine motor skills; speech versus other motor abilities)?

Recent Research Results

Attention

The notion of a primary deficit of general attention functioning is incompatible with recent evidence of faster than average detection of non-social patterns,[2] including multimodal ones, and superior detection of targets that are peripheral to faces.[3] With regard to selective attending to social information, the relevant mechanisms of attention appear to be intact, although without the typical category-specific bias to faces. Similarly, the abilities to switch attention from one target to another and to disengage attention from one target in order to attend to another are intact, although initial suggestions were that they were impaired due to high levels of rigidity. In contrast, autistics show an atypical interaction between perception and attention in the form of a "local bias'' or attentional orientation toward parts over wholes, that contrasts with the typical bias in favour of global targets.[4]

The interaction of atypical mechanisms of attention and perception in autism are also manifested in characteristically "random" face-scanning strategies, in which the focus on eyes is diminished considerably – despite all the possible information that can be extracted from the eyes. However, this is not just a case of "gaze avoidance'' as the focus on eyes tends to be replaced by efforts to scan other face parts. Similarly, the long-held notion of the lack of any gaze following gives way to more fine-tuned understanding as autistics are able to follow other peoples' gaze, especially when gaze orientation reliably predicts the presence of an object.

In the auditory modality, the diminished overt attention and body orientation to caregivers' voices is an essential aspect of the autistic phenotype in toddlerhood. Whereas brain indices of attention toward speech-like stimuli are diminished, those involved in the detection of non-social auditory targets are fast and accurate.

Perception

Perception includes the selection, organization, interpretation and the construction of the representations of external stimuli within the sensory system. Perceptual processes range from low-level perception, such as the extraction of elementary features from within a figure, to higher level perception, such as the identification of representations of an object representation. The perception of social information becomes increasingly distinguished from non-social information as the development of the mechanisms for social information entails increasing specialization that is distinct from that of other types of information.

Some perception-related behaviours among persons, such as atypical visual, random exploratory behaviours and lateral glance when exposed to periodic motion are relatively specific to autism. In addition, children with autism appear to fixate from an early age on audio-visual synchrony, as in the case of non-arbitrary coincidence between a visual and auditory event, and recurrent geometric patterns.[5] Examples of superior visual and auditory low-level perceptual processing are common, including pattern detection, construction, manipulation, and the discrimination of luminance, pitch[6] and symmetry. Although the integration of mechanisms appears intact under some experimental conditions, the typical spontaneous bias in favor of global aspect of information is diminished in autism. In contrast, the frequent suggestion that the perception of motion is impaired is not well supported by the scientific evidence.

Autistics are better on tasks requiring detection of embedded targets as early as three years of age. The finding of an enhanced manipulation of two-dimensional (block design) objects is one of the most replicated cognitive finding in autism, and extends even to three-dimensional (mental rotation) objects. However, this strength is partly, but not entirely, a methodological artifact that arises from the use of verbal tests that underestimate the intelligence of autistics and therefore leads to matching procedures with less intelligent non-autistic comparison participants.[7]

Despite the early notions of a face processing deficit, the evidence is now more nuanced. Autistics show typical levels of performance on face perception tasks that involve facial images, although their scanning, sampling and later processing of faces are atypical.[8] In the auditory modality, the enhanced processing of the physical aspect of speech may be associated with speech delay, a characteristic that is unique to autistics. All aspects of perception in autism appear to be less influenced by verbal, emotional, and generally by non-perceptual aspects of cognition. Rather, perception appears to play a prominent, if not always beneficial, role across a range of areas of functioning including language and problem-solving and reasoning.[9] This is supported in the visual modality by compelling evidence from a functional imaging meta-analysis of all tasks of visual

stimuli in which autistics were found to consistently display superior activity across brain regions involved in visual perception and expertise.

Motor abilities

Motor atypicalities include difficulties in basic motor control, coordination, posture, speed of execution and gait, movement planning and anticipation of motor responses. Several aspects of atypical motor development are found in subgroups of ASD, and not across the entire population. Whereas oral apraxia is not common to all autistics, the limitations of motor impairment to speech in some children raises questions. Atypicalities in visuo-motor coordination or “clumsiness,” are more often associated to Asperger syndrome, who do not present with visuo-spatial and auditory peaks, than to autism per se. Conversely, among autistics per se, those with histories of speech delay, but not those without speech delay, display profound peaks of visuo-spatial processing.

Research Gaps

One promising line of research is to bridge the well-established evidence of enhanced attention orientation toward perceptual regularities like auditory and visual patterns to initiatives in early intervention, in order to favour speech, literacy and improved understanding of the non-autistic world. At a fundamental level, we need to fill the gap between our understanding of behavioural and electrophysiological indices of attention and perception and the relation to cellular and genetic contributors. The role of the social and non-social aspects of the stimuli in perceptual skill and expertise needs to be better understood.

Conclusions

The visual and auditory systems of autistics provide the rest of the brain with qualitatively and quantitatively different information than typical persons, yet that does not necessarily imply deficit.[10] For example, attention is not biased to prioritizing social information, but socially-relevant material may still be processed effectively. Perception is more autonomous with regard to emotions, expectations and language-mediated processes. It is also more truthful and less distorted by top-down influences among autistics than among typical individuals. Although autism is characterized by a distributed, multilevel alteration of neuro-cognitive mechanisms, it is especially unique with regard to specifics of attention, perception processing and motor cognition.

Implications for Parents, Services and Policy

Parents' understanding of atypical attention, perception and related behaviours, particularly in relation to the development of speech, should be addressed psycho-educationally. For example, aversive reactions due to auditory hypersensitivity, and positive emotions related to visual contemplations, may be a major element of daily interactions with an autistic toddler. In developing services and policy for early intervention, parents and professionals should consider that it might be more ethical and effective to present young children with autism information within a format that triggers their attention instead of forcing them to follow programs based on typical development and painful conditioning procedures.[11]

References

1. Müller RA. (2007) The study of autism as a distributed disorder. *Ment Retard Dev Disabil Res Rev*.;13(1):85-95. Review. Erratum in: *Ment Retard Dev Disabil Res Rev*. 2007;13(2):195. 11.
2. Kaldy Z, Kraper C, Carter AS, Blaser E. (2011) Toddlers with Autism Spectrum Disorder are more successful at visual search than typically developing toddlers. Dev Sci. Sep;14(5):980-8. doi: 10.1111/j.1467-7687.2011.01053.x. Epub 2011 Apr 25.
3. Pierce K, Conant D, Hazin R, Stoner R, Desmond J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Arch Gen Psychiatry*. Jan;68(1):101-9. Epub 2010 Sep 6.
4. Wang, L., Mottron, L., Peng, D., Berthiaume, C., Dawson, M., (2007) Local bias and local-to-global interference without global deficit: A robust finding in autism under various conditions of attention, exposure time and visual angle, *Cognitive Neuropsychology*, Jul;24(5):550-74.
5. Klin A, Lin DJ, Gorrindo P, Ramsay G, Jones W. (2009) Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature*. May 14;459(7244):257-61.
6. Bonnel, A., McAdams S., Smith B., Berthiaume, C., Bertone, A., Ciocca, V., Burack, JA., Mottron, L., (2010) Enhanced pure-tone pitch discrimination among persons with autism but not Asperger syndrome, *Neuropsychologia*, Jul;48(9):2465-75. Epub 2010 Apr 28.
7. Dawson, M., Soulières, I., Gernsbacher, M.A., Mottron, L., (2007) The Level and Nature of Autistic Intelligence, *Psychological Science*, Aug;18(8):657-62.
8. Chawarska K, Volkmar F, Klin A. (2010) Limited attentional bias for faces in toddlers with autism spectrum disorders. *Arch Gen Psychiatry*. Feb;67(2):178-85.
9. Samson, F., Mottron, L., Soulières*, I., Zeffiro, T.A., (2011) Enhanced visual functioning in autism: an ALE meta-analysis, *Human brain mapping*, Apr 4. doi: 10.1002/hbm.21307. [Epub ahead of print].
10. Mottron, L., Dawson, M., Soulières, I., Hubert*, B., Burack, JA., (2006) Enhanced perceptual functioning in autism: an updated model and eight principle of autistic perception. *Journal of Autism and Developmental Disorders*, special issue: perception in autism, 36(1): 27-43.
11. Dawson, M., Mottron, L., Gernsbacher, MA., (2008) Learning in autism. In : J. H. Byrne (Series Ed.) & H. Roediger (Vol. Ed.), Learning and memory: A comprehensive reference: *Cognitive Psychology*, pp 759-772, New York: Elsevier.

Early Intervention in Autism

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Introduction

Many interventions for autism have been promoted within and outside mainstream health systems, often making startling claims of effect. Pressure from families, service providers and policy makers for new intervention programs is understandable, and these are reinforced in some areas by statutory imperatives. In such a context the need for rigorous evaluation is clear but has often been lacking. Fortunately there is now increasing resource devoted to sophisticated intervention testing, and substantive progress beginning. This review focuses on early intervention programs in the pre-school period that have been subjected to rigorous evaluation.

Subject

Autism is a severe, highly heritable[1] neurodevelopmental disability, with an estimated prevalence of 0.4% for the core disorder and about 1% for the broad autism spectrum.[2] Impairments in social reciprocity, communication, and behaviour have a profound effect on children's social development into adulthood[3] and result in a high economic cost for families and the community.[4] Diagnosis by three to four years of age is now common in developed health systems[5,6] and the importance of early intervention has been advocated in reviews.[7,8]

Problems

There are relatively few well-conducted published trials in autism at any age.[8-11] Many (highly quoted) early trials of interventions were of poor qualityand there are indeed many challenges in designing such studies and in detecting relevant change; "the heterogeneity in this disorder, both behaviourally and etiologically, works against even the most well-designed trials."[9]

Research Context

Autism is multi-dimensional and heterogeneous; no single intervention is likely to address all aspects. A central challenge is the identification of what it is appropriate and susceptible to

change. Linked to this is important debate about choice of outcome measures. Autism is a chronic disorder and interventions also need to be seen within the context of chronic health care within medical, social care and educational systems.

Key Research Questions

Which is the best theoretical model to approach autism intervention? Systematic enquiry aims to differentiate *specious* claims from valid paths.

What outcome measures? An obvious focus is on the defining symptoms of the disorder itself; but arguments can also be made for addressing quality of life for child or family, school performance, emotional adjustment or modification of co-occurring behavioural difficulties.

Who should rate outcome? Family or user ratings are highly relevant but prone to biases from hope and expectation; “objective” measures blinded to treatment received are taken more seriously as evidence of actual treatment effect but often less sensitive.

What works for whom? Trials need to be designed to address the heterogeneity in the disorder.

Recent Research Results

Behaviour-learning approaches

Interventions based on psychological learning theory were some of the earliest to be widely adopted in autism – typical would be Early Intensive Behavioural Intervention (EIBI, previously known as ABA). EIBI involves multiple therapists working with the child for 30-40 hours/week, plus additional consultation time for parents, typically over a duration of 2 to 4 years.[12] Two small *RCTs (randomized controlled trials)* recently tested EIBI against less intensive parent training. Children treated ranged greatly in severity; outcomes were general development rather than autism-specific. The first study (n=28)[13] suggested superiority for EIBI, mainly in the less severely autistic children in the sample, on general cognitive ratings but not in adaptive functioning or behaviour. The second study (n=23)[14] showed no comparative advantage for EIBI, with about half of both groups showing relatively good progress at follow-up after four years. The Early Start Denver Model (ESDM) expands the behavioural approach to include developmental elements and work with parents on shared engagement and responsivity.[15] A recent medium sized RCT (n=58),[16] compared ESDM with mean 15 hours/week therapist input and 16 hours/week parent work at home over a two-year period with less intensive general community-intervention. ESDM showed

relative improvements in language, language aspects of IQ and adaptive behaviour, but no treatment effect on other autism-specific symptoms.

Communication approaches

These approaches focus on developmental aspects of parent-child social interaction and communication; they tend to be less intensive and involve parents more centrally. A recent moderate sized RCT (n=62) tested Hanen's "More than Words" (HMTW) – a group parent-training[17] provided over 3.5 months –against "*usual care*" and illustrates treatment effect heterogeneity:[18] children with less developed object interest at baseline showed positive effects with HMTW on communication, children with better object interest did worse than usual care. A more individualized approach tested a targeted six-month program to improve *interpersonal synchrony* in toddlers with autism spectrum disorder[19] and found a related specific outcome – socially engaged imitation improved, but not initiation of joint attention or shared positive emotion. A larger recent RCT (n=152) compared "Preschool Autism Communication Therapy" (PACT), a parent-mediated intervention over a year using video with biweekly to monthly therapist input and daily parental homework,[20] to usual care in children with core autism. It measured specific autism outcomes as well as detailed measures of the process of intervention.[21] PACT showed a strong effect on parental communicative behaviour and improvement in child communication with parent, but greatly attenuated effects when more generalized language and autism symptom outcomes in other settings were looked at using objective tests (parents reported strong intervention effects on communication and adaptation in everyday life).

Overall, recent autism trials have reported many positive results, largely in "proximal" outcomes of intervention, such as dyadic interaction, joint attention, and child imitation. Less treatment effect has been found on more general child functioning; two studies report improvements on standardised measures of child language and communication[16, 22] but three do not.[18,19,21] The two studies to use a standard autism diagnostic symptom measure as outcome[16,21] found no significant intervention effect on this.

Research Gaps

A common set of measures for comparison across studies needs to be debated and developed. Given the complexity of autism, trial designs need to become more sophisticated, with a focus on layers of measurement and understanding the process of intervention effect.

Intervention trial work needs to link more with developmental neurobiological research to identify biomarkers for differential treatment effects – this will then help address the heterogeneity issue. Much larger sample sizes will be needed to understand heterogeneity better.

Trial designs need to address autism as a long-term developmental disorder, with a greater focus on service delivery and use of approaches developed in relation to other chronic illnesses.

An ideal would be a sequence of trials on common cohorts extending from the earliest infancy interventions onwards – to test long-term outcomes and the added value of using sequentially-phased and developmentally-adapted interventions over time.

Conclusions

Many approaches to autism intervention are passionately advocated but a systematic evidence base on effectiveness is only recently emerging. Findings from recent studies are convergent; well targeted interventions of various kinds can indeed improve developmentally important immediate outcomes such as parent-child communication and joint attention, but generalising such change “downstream” to core autism symptoms and adaptation in real world contexts is much more challenging. Since we know that children with autism find generalising new learning across contexts very difficult, this is not a surprising result – even if it is sobering. There has been little testing of how well sustained any early treatment effects will be in the longer term. Nevertheless, as the evidence grows, we are getting a much better insight into the process of change in autism and the methods we can use to measure it. We are beginning to understand which children may benefit from which type of intervention at what time – the goal of personalised healthcare across medicine. Accelerating basic science work is bound to suggest previously unanticipated forms of intervention in the future. We are increasingly in a position to debate best treatments on the basis of shared evidence from better quality studies. That’s where real progress lies – even if it takes time.

Implications for Parents, Services and Policy

Faced with the difficulties and perplexities of autism, parents are understandably desperate for guidance and hope, and policy makers for models to use. In the end, cumulative effectiveness research is going to be the best guide – even though this can seem slow when definite help is needed immediately. The pace of research into treatments is quickening but in comparison with many other areas of health is at an early stage. We have models of stunning intervention success

against what were initially thought intractable disorders (such a childhood cancer or HIV-AIDS), growing out of a well funded, cumulative collaborative international effort involving iterations of systematic trials and basic science work. We can see the beginning of this in autism – but the key will be now to sustain this effort for enough time to get the progress we want.

References

1. Bailey A, Le Couteur A, Gottesman I, et al. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med*. 1995;25:63-77.
2. Baird G, Simonoff E, Pickles A, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet*. 2006;368:210-15.
3. Howlin P, Goode S, Hutton J, Rutter M. Adult outcome for children with autism. *J Child Psychol Psychiatry*. 2004;45:212-29.
4. Knapp M, Romeo R, Beecham J. Economic cost of autism in the UK. *Autism*. 2009;13: 317-36.
5. Le Couteur A, Baird G, Mills R, et al. *The National Autism Plan for Children (NAPC)*. London: National Autistic Society; 2003;2.
6. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. *JAMA*. 2001;285:3141-42.
7. Lord C, Wagner A, Rogers S, et al. Challenges of evaluating psychosocial interventions for autistic spectrum disorders. *J Autism Dev Disord.* 2005;35:695-708.
8. Rogers SJ, Vismara LA. Evidence-based comprehensive treatments for early autism. *J Clin Child Psychol.* 2008;37:8-38.
9. Spence SJ and Thurm A. Testing autism interventions: trials and tribulations. *Lancet*. 2010;375:2124-2125
10. Spreckley M, Boyd R. Efficacy of applied behavioral intervention in preschool children with autism for improving cognitive, language, and adaptive behavior: a systematic review and meta-analysis. *J Pediatr*. 2009;154:338-44.
11. Levy SE, Mandell DS, Schultz RT. Autism. *Lancet*. 2009;374:1627-38.
12. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. *J consult clinical psychol*. 1987;55:3-9.
13. Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. *Am J Ment Retard*. 2000;105: 269-285.
14. McEachin JJ, Smith T, Lovaas OI. Long-Term Outcome for Children With Autism Who Received Early Intensive Behavioral Treatment. *Ment Retard.* 1993;97:359-372.
15. Vismara, L. A., & Rogers, S. J. The Early Start Denver Model. *J Early Interv.* 2008;31,91-108.
16. Dawson G, Rogers S, Munson J, Smith M, Winter J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver *Model. Pediatr*. 2010;125:e17-e23.
17. Sussman F. *More than words: The Hanen program for parents of children with autism spectrum disorder*. Toronto, Ontario, Canada: Hanen Centre; 1999.
18. Carter AS, Messinger DS, Stone WL, Celimli S, Nahmias AS, et al. A randomized controlled trial of Hanen's 'More Than Words' in toddlers with early autism symptoms. *J Child Psychol Psychiatry*. 2011;52(7):741-752.
19. Landa RJ, Holman KC, O fNeill AH, Stuart EA. Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: a randomized controlled trial. *J Child Psychol Psychiatry*. 2011;52(4):13-21.

20. Aldred C, Green J, Adams C. A new social communication intervention for children with autism: pilot randomised controlled treatment study suggesting effectiveness. *J Child Psychol Psychiatry*. 2004;45:1420-1430.

21. Green J, Charman T, McConachie H, Aldred C, Slonims V, et al. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. *Lancet*. 2010; 375:2152-2160.

22. Kasari C, Paparella T, Freeman S, Jahromi LB. Language outcome in autism: randomized comparison of joint attention and play interventions. *J Consult Clinical Psychol*. 2008;76(1):125-37.