Is Autism Inborn And Lifelong For Everyone?

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Abstract: Autism or autism spectrum disorder (ASD) is described as a lifelong condition with core behavioural symptoms appearing during infancy or early childhood. Genetic and other effects occurring during the earliest times of life are thought to play a significant contributory role to the presentation of autism, denoting that autism is typically seen as an innate or inborn condition. Such descriptions have, and continue to, define autism research and clinical practice. Inspection of the existing research literature, however, suggests that within the vast heterogeneity of autism, not everyone experiences autism in such a prescribed way. Various reports have observed the presentation of “acquired autism” following a period of typical development. Other findings have documented an abatement of clinically relevant autistic features and related comorbid pathology for some. Such reports offer important insights into the heterogeneity and complexity of autism.

Keywords: autism, regression, innate, lifelong, acquired, heterogeneity

Plain Language Summary
The label of autism is defined by the variable presence of core symptoms in areas of social communication and repetitive or restricted patterns of behaviour. The earliest clinical descriptions of autism emphasised how autism is innate and lifelong. Such descriptions have been key to the continued promulgation of the innate and lifelong narrative. Our analysis of the research literature reveals that not everyone experiences autism in such a prescribed way. We demonstrate that regression in previously acquired skills is becoming more readily recognised in research and clinical fields, alongside support for the idea of one or more acquired autism phenotypes. We also highlight research observing an abatement in clinically relevant autistic traits contrary to the lifelong description that traditionally follows a diagnosis of autism. Greater recognition of such issues provides important evidence for the pluralisation of the autism label. It also encompasses the idea that the heterogeneity of autism extends to onset and course of symptom presentation.

Introduction
Kanner1 is generally recognised as offering the first scientific description of autism. Including core diagnostic features in areas of social and communicative interactions alongside the presence of restricted and/or repetitive patterns of behaviour, his original case series was the template for the diagnosis of autism. Alongside his canny observations of the overt behaviour of the children being reported on, Kanner also remarked that he thought children with autism came into the world with an “innate inability” regarding their core features. His words, although considered old-fashioned by modern-day standards, similarly hinted that genetics and heritability were key features of autism following his observations of other family members within the context of his case series.
In his follow-up paper\textsuperscript{2} published some 30 years after the original cases were reported on, Kanner noted that although different life directions were taken by his cohort, to all intents and purposes, their core autistic characteristics persisted. Such views have been immensely important to our knowledge of autism today.

As a consequence of these and a multitude of other independent research findings, two primary principles outside of the description of autism or autism spectrum disorder (ASD) have endured the test of time: i) that autism and the processes pertinent to the development of autism typically begin in the earliest times of life akin to being innate and inborn, and ii) the characteristics of autism typically persist throughout the lifespan. These two themes have been widely disseminated.

Alongside these narratives, however, subtle hints have been noted in the scientific literature suggesting that within the extraordinary heterogeneity that autism entails, not everyone on the autism spectrum follows such inborn and lifelong rules in such a prescribed way. Some people diagnosed on the autism spectrum arrived at their diagnosis following a period of so-called typical development. Some people previously diagnosed on the autism spectrum no longer meet the clinically defined cut-off points for a diagnosis of autism. Autism may, therefore, not be inborn or lifelong for everyone.

Regression: Then And Now

Although there are several definitions of regression, in the context of this paper, we use the word to mean a relapse or reversion back to a less developed state. With behaviour and physiological functioning in mind, regression implies that there was a period of previously typical development and/or functioning that was either halted or halted and reversed to some degree. Such a description does not imply that regression is an absolute phenomenon nor that regression manifests in a uniform fashion in relation to autism.\textsuperscript{3} It merely acknowledges that some degree of skills were reversed or lost at some point and that loss was of varying degrees of severity across different individuals.

Regression is a term that has been increasingly used in the autism research literature following a long period where such an issue was not felt to be relevant to autism. The grouping of the condition known as Childhood Disintegrative Disorder (CDD) or Heller’s syndrome within the category called Pervasive Developmental Disorder (PDD) in previous diagnostic manuals\textsuperscript{4} points to the historical links between autism and regression.

CDD overlaps with autism as a consequence of the focus on issues with social communication skills and the production of restricted or repetitive behaviours that often accompanied regression in motor and toileting skills for CDD to be diagnosed. This overlap was however also accompanied by distinctions;\textsuperscript{5} not least the infrequency with which CDD presented compared with the growth in the number of people being diagnosed with autism. In the current incarnation of the diagnostic and statistical manual version 5 (DSM-5),\textsuperscript{6} CDD was, alongside various other diagnostic categories, subsumed into the larger autism spectrum disorder (ASD) description, thus cementing the relationship between regression and autism.

Prior to such revisions, regression applied to autism was rarely discussed in the peer-reviewed literature until the 1990s. A handful of papers appeared talking about “developmental regressions and unevenness across developmental domains,”\textsuperscript{7} but they were not numerous nor were the reports particularly detailed about the nature of the regression encountered. The publication of the Autism Diagnostic Interview (ADI) in 1994\textsuperscript{8} added to the interest in regression and autism. Diagnostic themes mentioning a loss of language and/or other skills perhaps followed the inclusion of CDD in the broader PDD category, but also served to reinforce the idea that regression can seemingly occur in relation to some cases of autism. Ever since, the research floodgates seemed to have opened to the idea of regression occurring in autism. Published papers talking about regression as being a “typical event in the natural course of autism”\textsuperscript{9} have followed.

Having already mentioned that social communication skills as being an important part of regression in autism research literature, it is unsurprising that these form the backbone of reports of regression.\textsuperscript{10} They offer the most evident manifestations of regression, where communicative speech, in particular, is closely monitored by parents and other organisations during infancy and early childhood. Any reduction or loss of speech is going to be noticed and noticed quite promptly.

Communicative speech, however, represents only one part of the regression profile discussed with autism in mind. Other aspects of social interaction such as play and motor skills have also been noted to regress in similarly varying degrees to that seen in relation to speech and language. Regression in play skills, for example, is much harder to quantify and pinpoint a precise time of change. This is perhaps an important reason why such an issue has been overshadowed by more immediate observable differences in behaviour.
Accepting that there is significant heterogeneity in the presentation of autism, attention has turned to whether there may be some important differences in the behavioural expression of autism as a function of regression or not. Gadow and colleagues reported that based on parental report, those with regression mentioned in their clinical profile experienced more severe communication difficulties and showed elevated rates of intellectual (learning) disability than non-regressive comparators. They also observed an increased frequency of schizophrenia spectrum symptoms in their regressive cohort. Other findings have similarly observed differences in those who regressed compared with those who did not, emphasising, in particular, the increased severity of certain core autistic features in those who were reported to have regressed.

Insofar as the question of how often does regression occur in relation to autism, various estimates have been detailed. The question of regression prevalence rates is clotted by factors such as what criteria for regression are used, who reported on the regression and important issues such as recall ability and telescoping effects potentially affecting reports. With such factors in mind, the rates vary from 30% of children with autism experiencing some sort of regression to over 50% detailed in some studies. Some authors have gone as far as suggesting that regression in autism is the rule, not the exception such is the distribution of reports.

Various factors have at one time or another been suggested to be linked to the regressive onset of autism. Some have proved contentious and have not survived further inspection despite some lingering concerns in some quarters. Other factors continue to gain momentum as potential drivers of regression. Epilepsy and/or seizure disorder have been examined in the context of regression and autism. The emergence of autism-related behaviours temporally linked to the appearance of epilepsy sits well with the central involvement of the brain to autism. It also offers some testable hypotheses about possible mechanisms. Other research, on the other hand, has not observed any differences in the rates of epilepsy between regressive and non-regressive autism types accepting that there are a number of different presentations of epilepsy outside of the classical signs of seizure. Despite this, Thompson et al concluded that those displaying the regressive autism phenotype required a “careful neuropediatric work-up to investigate possible neurological disorders” that may be causative of such regression.

Another area related to the aetiology of regressive autism is a possible correlation with mitochondrial dysfunction comorbid to the presentation of autism. The case report published by Poling and colleagues detailed a connection between oxidative phosphorylation disorder and the presentation of regressive autism. Further research has added to the idea that mitochondrial issues may correlate with at least some cases of regressive autism. Indeed, as part of a wider research base talking about mitochondrial disease manifesting alongside cognitive deterioration, further investigations are implied.

A role for infection or issues with the biological response to infection in relation to some cases of regressive autism has also been suggested. Jyonouchi et al reported that issues with the innate immune response could be a contributor to the biological profile of regressive autism. This follows a whole slew of research findings talking about atypical immune functioning being present alongside various “parts” of the autism spectrum. Febrile illness, where fever presents, has been discussed in the context of regressive autism. Scott et al observed that the rates of febrile illness up to 6 months prior to parental concerns about autism were 30% in their regressive group compared with 0% in the non-regressive control group. They coupled this finding with a greater frequency of familial autoimmune disease in their regressive cohort suggesting that inflammatory and autoimmune pathways may be important drivers of regression in relation to autism.

Specific infectious agents have also been discussed in the context of regressive autism. Autism already has some well-known associations with diseases such as rubella (german measles) and cytomegalovirus (CMV), particularly in the context of prenatal exposures and their effect on the developing foetus. Other exposures outside of the critical window of conception through to birth have been described in the scientific literature.

Enterovirus, a causative factor of various types of meningitis and encephalitis, has been discussed in the context of regressive autism. Case reports talk about a “massive regression” as being a feature of such cases, also occurring across age ranges well outside of the timeframe when autism usually manifests. Various case reports describing autistic regression following contraction of specific types of encephalitis can also be found. A specific focus on the behavioural effects of anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis has been noted on several research occasions. Anti-NMDA receptor encephalitis is potentially an important connection on the basis of the manifestation of antibodies targeting of N-methyl-d-aspartate receptors and more general links to autism.
The question of whether targeted interventions may be useful in cases of regressive autism arises. This, on the basis that if one is able to identify a specific “trigger” temporally or otherwise related to a particular instance of autistic regression, one may be able to plan accordingly. Duffy and colleagues\(^{33}\) reported preliminary findings following the use of corticosteroids with a small cohort of regressive cases. Improvements in behavioural and language domains were noted. Other groups have similarly discussed the use of immunotherapies such as intravenous immunoglobulin (IVIG) in relation to cases of a possible autoimmune encephalopathy manifesting as regressive autism,\(^ {34}\) albeit with limited success and more detailed focus on the testing regimes being required\(^ {35}\).

Although a nebulous term requiring much more detailed investigation, there is little doubt that regression of previously acquired skills is an important part of various manifestations of autism. For nearly 30 years now, autism research and practice has acknowledged that autism, for some people, is not characterised by the expression of autistic traits or features from the earliest days. Rather, for some, periods of typical development have been recorded, followed by a regression of skills representative of autism. The notion of acquired autism, therefore, gains plausibility. Such acquired autism gains further ground as a consequence of other science talking about animal models of autism, for example, and the various ways and means that typically developing animals may be induced to present autistic signs and features; albeit with caveats.\(^ {36}\)

Alongside the rise in the acceptance of regression as being a feature of autism, the question of whether regression has always been a part of autism or is something more recent arises. Autism has evolved over the years as knowledge about the condition has increased and technologies offer new insights into the label. One would have thought, however, that had regression been a significant part of autism in the years prior to the 1990s, it would have been more prevalent in previous scientific and clinical descriptions. The question, therefore, is whether the autism of more recent decades is necessarily the same as the autism of yesteryear?\(^ {37}\)

**Optimal Outcome And Growing Out Of Autism**

The second part of our paper focuses on another important clinical and scientific phenomenon highlighted in relation to some cases of autism: the abatement of autistic features to the point where previously reached diagnostic cut-off points are no longer met. Such discussions are framed in the context that alongside the heterogeneity in presented features, so also there is diversity in the developmental trajectories of autism.\(^ {38}\) Such differing trajectories inevitably means that the behavioural core features of autism and associated issues will ebb and flow according to factors such as environment, biology and maturation.

Much like the issue of regressive autism, the idea that autism for some is not a lifelong condition is a fairly recent addition to the knowledge of autism. Isolated reports\(^ {19}\) talking about children “growing out of autism” peppered the research literature in the 1980s and 1990s following some earlier initial interest in this topic.\(^ {40}\) These reports, however, were few and far-between. Such findings were also to some degree explicable as mistakes in the initial diagnosis of autism or autism being diagnosed in lieu of other conditions. Some authors also detailed how the use of various interventions for autism may also have impacted on the expression of autism.\(^ {41}\) But alongside such explanations, words like “spontaneous recovery” have also been used to denote an idea that autism or the presentation of autistic features are not always fixed and lifelong for all.

The editorial by Ozonoff\(^ {42}\) marked an important point for discussions about autism not necessarily being lifelong for all. Mentioning the seminal paper by Fein and colleagues\(^ {43}\) which coined the term “optimal outcome”, the dogma around the lifelong aspect to autism was lifted to be replaced by something seemingly better reflective of that seen in clinical practice. Fein et al observed that alongside “a clear documented history of ASD,” their cohort also met strict criteria for the optimal outcome on the basis of results from several standardised autism measures. Ozonoff\(^ {42}\) further described how the mention of the word “recovery” as in a recovery from autism should not necessarily be the taboo that it had previously been.

Further research from Fein and colleagues\(^ {44-46}\) and other independent researchers\(^ {47}\) has provided more detailed information about those who lose their diagnosis of autism and other associated features. Such collected findings suggest that the early presentation of autism may provide some important clues about the likelihood of such an optimal outcome. Specifically that less severe autistic behaviours during infancy coupled with “stronger adaptive skills” may be important features of such a grouping.

Insofar as the estimated numbers of people who undergo such a reversal of symptoms, there is some preliminary data available. Moulton et al\(^ {48}\) talked about 9% of their cohort showing what they described as optimal progress. Other data show a similar figure.\(^ {48}\)
This 1 in 10 figures should be viewed as preliminary in view of the lack of large-scale studies specifically examining this issue. A similar lack of prospective longitudinal data further hampers such estimates.

Another important focus of some of the studies in this area is the impact of such a loss of symptoms on other important features that seem to be overrepresented in cases of autism. Taking into account the increasingly important finding that a diagnosis of autism rarely appears in a diagnostic vacuum and the idea that the term “comorbidity” may not be entirely appropriate for every additional diagnosis appearing alongside autism, several themes have emerged. Primary among these is the observation that loss of a diagnosis of autism may, in some cases, also translate into a loss of other important co-occurring conditions too. Gillberg et al reported findings based on 50 males diagnosed with ASD (Asperger syndrome) followed for almost 20 years. They observed that those who no longer met criteria for “a full diagnosis of an autism spectrum disorder” were more likely to be free of other comorbidities, specifically psychiatric comorbidity. Bearing in mind how prevalent psychiatric comorbidity such as depression, anxiety and other features are when it comes to autism and the often profound effects they can have on a person, freedom from such clinical conditions is a welcomed state. That being said however, other data have not been so positive with regards to loss of an autism diagnosis being linked to an improved comorbidity profile. The requirement for continuing support to be in place it seems should not be underestimated.

Discussion

Without giving the impression that regression in skills accompanying acquired autism or “growing out of autism” are generalisable to all autism, there is a growing research evidence base indicating that autism is not innate or lifelong for everyone. Such sentiments potentially have far-reaching implications when it comes to several important issues including the continuing search for early behavioural and biological markers for autism and the requirement for further investigation of what happens to the expression of autism into middle and older ages. Such information will also have sociological effects too. The increasingly vocal voices from the autism spectrum discussing autism as an identity over and above just a clinical diagnosis will no doubt be affected by discussions about autism not being innate and/or life-long for everyone.

Another area likely to be impacted by such findings relates to the conceptualisation of autism in research and clinical terms. In one of the most widely used diagnostic characterisations, the label autism or autism spectrum disorder has moved away from including previous diagnostic subcategories to include everyone under one single umbrella. Such a singular label includes massive heterogeneity. Heterogeneity around the presentation of autism is to some degree covered by the use of levels of support but such a singular label offer little or no details on how someone arrived at such a diagnosis. In that respect, the use of a singular label includes those who present with more idiosyncratic autism and where autism is secondary to another clinical issue and does not distinguish between them. For research purposes, such a singular label covering such heterogeneity makes it almost impossible to come up with universal truths about autism. Regression and resolution in relation to autism or autistic traits point to the need to more closely examine how autism is conceptualised. Such variables, alongside the differing developmental trajectories already known about in relation to autism and the different comorbidity profiles co-occurring alongside autism, provide some important anchors for looking at autism as a more plural condition: the autisms.

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