

Measurement and Mismeasurement of Social Development in Infants Later Diagnosed with Autism Spectrum Disorder

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Abstract: Autism spectrum disorder (autism) is a common and heterogeneous neurodevelopmental disorder of genetic origins defined by challenges in social communication and clusters of restrictive and repetitive behaviors. An emerging hypothesis of autism pathogenesis describes symptoms as the results from deviations from normative developmental processes. In this account, symptoms represent the outcome of variable instantiation of genetic liabilities – in terms of dosage and timing – leading to disruptions in the developmental trajectories of foundational social adaptive skills. Given the fast pace of change in behavior and brain development in the first two years of life, we pose that the currently prevalent cross-sectional experimental designs are ill-suited to capture changes from normative benchmarks that might be small at any data point but which inexorably and cumulatively increase divergences in developmental trajectories that ultimately culminate in the unmistakable cluster of atypical behaviors we now call autism. We argue that only densely-sampled longitudinal experimental designs can capture the underlying dynamic processes moving the individual child's development towards or away from normative benchmarks. We illustrate this phenomenon *via* a detailed example in which a cross-sectional comparison between a clinical and a control cohort failed to find differences, which could only be detected by ascertaining that the developmental trajectory of one cohort was moving upwards while the other was moving downwards, with the developmental lines intersecting at the cross-sectional data point. We conclude by magnifying Karmiloff-Smith's assertion, oft-quoted but seldom followed, that "development itself is the key to understanding developmental disorders" [1].

Keywords: Autism, Autism Spectrum Disorder, Social Visual Engagement, Eye Fixation, Infancy, Prodromal, developmental trajectories, growth curve, growth charts.

INTRODUCTION

Autism Spectrum Disorder (autism) is a biologically-based but highly complex neurodevelopmental disorder [2]. It is one of the most heritable of psychiatric conditions [3] but no single molecular marker defines its diagnosis. Instead, research estimates suggest that greater than three to five hundred distinct genes—the majority of which are still unknown—may each play a role in etiology [4-6]. No single gene has yet been associated with more than a fraction of patient cases (<1% [7]), and the extent to which any pattern or patterns of gene variants or expression can reliably indicate risk of the condition remains unclear. There are numerous insights into the developmental neurobiology of autism [8], but the condition is still diagnosed behaviorally by the presence of early-emerging, persistent deficits in social interaction and communication skills, and by the presence of restricted and repetitive behavior [9]. The most robust markers for early diagnosis of autism include reduced interaction with and attention to others [10,11]; reduced attention to others' eyes; failure to respond to the calling of one's own name; and inability to join in

imitative games and reciprocal vocalizations [12-14]. Autism affects approximately 1 in every 68 individuals [15].

The early identification and early treatment of children with autism are consensually regarded as two of the most important factors for improving lifetime outcomes for individuals impacted by the disorder [16-19]. The earlier a diagnosis can be established, the better the long-term outcome [16]. Because symptoms of autism are present already by 18 and 24 months in the majority of cases [20-22], the American Academy of Pediatrics recommends universal screening for autism at 18 and 24 months [23]. Unfortunately, the median age of diagnosis in the US remains 5.5 years of age [24]. In all children, delay in diagnosis leads directly to delayed intervention and treatment. Thus the point at which a child can be accurately diagnosed with autism moves from within a window of tremendous neuroplasticity [25]—the period from birth until age three—to a point several years hence, when many years of development have already played a large role in shaping the course of a child's condition [26]. This marks the loss of a potentially critical opportunity for improving treatment efficacy and associated outcome [19].

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The field's focus on reducing the age of diagnosis of autism has given rise to a large number of research

projects aimed at identifying developmental markers in infancy capable of predicting later diagnosis in objectified, quantitative fashion. These projects often involve the younger siblings of children with autism – or “baby siblings” [18] – who are at a substantially increased risk of also developing the condition [27]. While this cohort of children could, in principle, be followed intensively from birth through the period of diagnostic ascertainment at the ages of 24 to 36 months, most studies obtain only one measure during the first year of life and attempt to ascertain the utility of that measure by comparing cohorts of affected and unaffected children, defined as such on the basis of diagnostic outcome later on [28]. Here we argue that such an approach might not be sufficient to fully capture fast-paced developmental processes during the period of greatest change in behavior and brain development [25, 28].

THE DEVELOPMENTAL NATURE OF AUTISM

One approach attempting to narrow the gap in autism research between advancements in molecular genetics and the instantiation of this genetic liability as a cluster of symptoms during the toddlerhood years has posed the following hypothesis: variable etiologies disrupt normative processes of socialization with different force or dosages, and at different time points, leading eventually to the emergence of symptoms. In this light, symptoms result from cumulative and ongoing divergences from typical developmental trajectories [29]. Following from the experience-expectant/experience-dependent model of child development [reviewed in 28], genetically determined schedules of neural maturation match the timing of adaptive tasks; therefore, disruptions of socialization processes occurring at different times are likely to result in different outcomes. Thus, although the homogeneity of autism may originate from shared failings in the process of socialization as a whole, the heterogeneity may stem from variable timing in the onset of individual disruption [29]. In typical development, success in social adaptive tasks prompts further development in an iterative process that builds on older structures to generate new ones. This process is ever ongoing, resulting in successively more complex social cognitive development. In the case of autism, this model of pathogenesis [28] draws from the fact that developmentally early-emerging, foundational social skills appear to be absent or markedly reduced in children with autism.

In no other developmental area is this contrast more pronounced than in social engagement skills. Within

the first hours of life, typically-developing babies attend preferentially to people. They distinguish and prefer their own mother's voice to that of an unknown woman, but prefer the sound of even an unknown woman's voice to that of silence [30]. Human newborns preferentially fixate on faces gazing at them rather than faces looking away [31], and by 3 months they are drawn to the eye region when viewing speaking faces [32]. Infants are also capable of imitating the facial gestures of a person [33] while not mimicking similar movements made by a mechanical device [34]. This evidence suggests that typically-developing babies have a predisposition to engage with the social aspects of the world around them: the social dimension is what is most behaviorally salient and what consequently commands the greatest portion of the typically-developing child's attention.

For infants with autism, the available evidence suggests that this is not the case. The most robust markers for early diagnosis of children with autism center on disruptions to typical engagement with the social world: reduced interaction with and looking at others [13]; failure to respond to the calling of one's own name; diminished eye contact; and inability to join in imitative games and reciprocal vocalizations [26,35]. While, until recently, most insights into the first two years of the lives of children with autism were gained *via* retrospective parental reports and analyses of home movies made by parents prior to their children's diagnosis [13], in the past 5 years we have witnessed a surge of prospective studies of children at high-risk for autism [36-39]. While most of the studies so far have focused on the emergence of early symptoms [40,41], several experimental studies have focused on abnormalities in normative processes of socialization. Using behavioral probes, eye-tracking, electrophysiological, functional and diffusion tensor magnetic resonance imaging, investigators have been attempting to document derailment of fundamental social engagement processes from the first year of life [28,42-46]. However, there have been conflicting results, and many have questioned the extent to which there are any markers at all of prodromal autism – that is, before symptoms are visible and can be reliably diagnosed, particularly in the first year of life [47].

We propose that a key reason accounting for the confusion in this area of research has to do with the cross-sectional nature of prevalent experimental designs. The main premise of these designs is that an emerging skill thought to be a precondition for subsequent social development can be measured at

one data point: if there is a statistically significant difference in the given measure across the clinical and the comparison group, the construct is deemed a prodromal feature of autism; if not, the construct is judged not to be so, and the early development of children with autism in this domain is concluded to be intact. And yet, there are many reasons to question these assumptions: First, there is tremendous heterogeneity across children (in both typical and atypical development) in the emergence of discrete behaviors and skills, in terms of both timing and magnitude; Second, there is great variability in expression of behaviors and skills by the same child across time and across contexts; and Third, experiments that collect limited amount of data over a limited window of time (e.g., a few probes, a few seconds of eye-tracking data, a limited number of trials measuring evoked potentials) are unlikely to achieve enough sampling of the construct and of the children's expression of the construct to adequately cover the heterogeneity, variability and inconsistency that are hallmarks of behavioral and brain measures in the infancy period of life. This is probably why the vast majority of studies published to date report group results and do not attempt to probe the utility of their constructs as potential "biomarkers", that is markers of risk for autism that have relevance to individual children. Such biomarkers are of critical importance – e.g., for the development of objectified and quantitative tests for screening and early diagnosis -- but to date, with only one exception [48], studies have not shown measurements that are sufficiently robust, consistent, reliable and stable that could be used to predict subsequent diagnostic outcome and eventual level of ability or disability for an individual child.

The exception so far has been one study that took a very different approach: it probed development prospectively and longitudinally using a densely-sampled design comprising 10 data points over the first two years of life, 5 of which within the first 6 months of life [48]. In so doing, its results contradicted several studies focused on similar constructs but which had been conducted cross-sectionally, over one data point only. The key difference, however, has to do with the way that these two kinds of approaches conceptualize developmental constructs: the former makes developmental trajectories the variable to be studied – e.g., a skill can only be captured as it unfolds over time, and the parameters of such unfolding should be the focus of our studies; the latter assumes that one-point samplings of the given construct are sufficient to corroborate or discard its relevance to pathogenesis –

e.g., what is measured are the parameters of that construct at one point in time, not how it became so, nor what it is likely to become subsequently.

These differences in approach are probably best illustrated through a stark comparison between two studies: the first [44] measured eye fixation in infants later diagnosed with autism relative to infants later ascertained as unaffected in one data point only at the age of about 8 months; the measure of relevance was magnitude of eye fixation – that study concluded that infants later diagnosed with autism show no abnormalities in eye fixation during the prodromal stages of autism; the second [48] measured eye fixation in similar cohorts but, as noted, over 10 data points; the measure of relevance was the developmental trajectory of eye fixation – that study concluded that infants later diagnosed with autism show decline in eye fixation beginning at the age of 2 months.

EYE GAZE IN INFANTS LATER DIAGNOSED WITH AUTISM

In autism, deficits in eye gaze are a defining feature of the condition [9] and a key item in standardized diagnostic tests [49]. These deficits have been extensively demonstrated in eye-tracking studies [42,50,51]; in electrophysiological reports [44,52], including intracranial recordings [53]; and also in functional MRI studies [54-56]. The conserved nature [57,58], early onset [31,32], and critical role of eye fixation in socialization [57,59] have prompted several studies focused on detecting eye fixation abnormalities in the prodromal stage of autism, namely during the first year of life.

In one prominent paper [44], eye-tracking data were obtained while 6 to 10-month-old infants viewed two video sequences of different female faces (with alternating gaze shifts towards and away from the viewing infant). Average total looking time per child in that study was 7.7 (3.3) seconds, 8.0 (3.3) seconds, and 7.3 (3.2) seconds for low-risk typical controls, at-risk no-ASD infants (i.e., "baby siblings" who were ascertained as unaffected), and at-risk confirmed-ASD infants (i.e., "baby siblings" who were ascertained as having ASD), respectively. When percent fixation time on the eyes was compared across the three groups, no significant differences were detected, leading to the conclusion that the expression of risk for autism within the first year is subtle when measured using overt behavioral markers (as predicted by 60).

This conclusion was in conflict with the results of a subsequent paper, described here in detail [48]. Infants who were later diagnosed with autism and typically developing infants were shown pre-recorded video scenes of actresses playing the role of caregivers while engaging their children in infancy games. The children’s visual scanning was measured by eye tracking. As noted, data were collected monthly, from two to six months of age, and then every three months until the age of 18 months, with a final data point at 24 months (10 time points overall). Ascertainment of diagnostic status and its stability happened at 24 and 36 months, respectively. Eye-fixation data for the typical children delineated “growth charts” of social visual engagement (Figure 1A) against which we compared the data for the infants later diagnosed with autism (Figure 1B). Typically developing children, from two to six months, looked more at the eyes than at any other region of the screen (mouth, body, objects); eye fixation increased steadily during this period and remained rather stable until the age of 24 months.

Given our hypothesis that children with autism have a congenital deficit impairing their ability to preferentially orient to others’ eyes [43], our expectation was that their levels of eye fixation would be reduced relative to those of typically developing infants from the earliest time of data collection (Figure 1C). Our results falsified this hypothesis (Figure 1DE): eye fixation began at a level similar to typically developing controls but then declined steadily from the two-month starting point, arriving at a level that was approximately half that of controls by the 24-month endpoint. This decline in eye fixation was already underway within the first 6 months.

Two additional observations added significance to this finding. First, the decline in eye fixation within the first six months alone was strongly and significantly associated with diagnostic outcome at the age of 36 months. Thus developmental differences in level of preferential attention to the eyes of other people was a strong marker of later diagnosis one and a half years

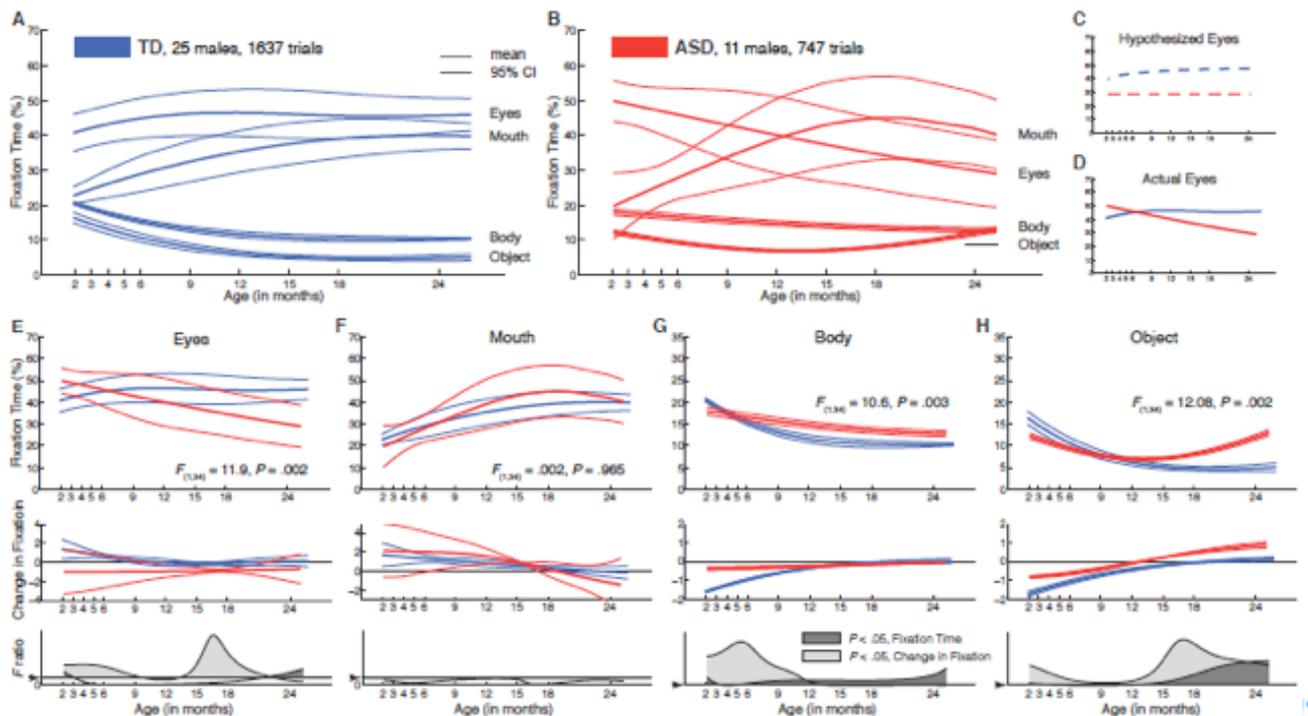


Figure 1: Growth charts of social visual engagement for typically-developing children (TD) relative to children diagnosed with autism spectrum disorder (ASD). (A) Fixation to eyes, mouth, body, and object from 2 until 24 months in TD males (in blue) and (B) in males with ASD (in red). Contrary to a hypothesis of congenital reduction in preferential attention to the eyes in ASD, infants with ASD exhibit mean decline in eye fixation from 2 until 24 months of age. Hypothesized (C) and actual (D) mean eye fixation curves are plotted in blue for TD children and in red for children with ASD. Longitudinal change in fixation to (E) eyes; (F) mouth; (G) body; and (H) object regions. Dark lines of each color represent mean growth curves, while light lines indicate pointwise 95% confidence intervals. Top panel in each section plots percent fixation over time; middle panel plots change in fixation over time (the first derivative, in units of % change per month); and the bottom panel plots F value functions for pointwise comparisons of fixation and change in fixation between groups. Pointwise comparisons with F values greater than F_{crit} (for 1,34 dof = 4.13, $P = 0.05$, marked by arrowhead on F ratio axis) are shaded in medium gray (for comparison of fixation data) and light gray (for comparison of change-in-fixation data). [Courtesy of Nature].

before the children could be diagnosed conventionally and two and half years before they would be diagnosed stably [48]. Second, in the children with autism, the degree of decline in eye looking was a strong predictor of level of social disability at outcome (as measured with standardized clinical instruments): children whose levels of eye looking declined most rapidly were also most socially disabled in later life [48].

Therefore, two prominent papers [44,48] reached apparently contradictory (and far-reaching) conclusions. The former suggested that eye fixation abnormalities were not a feature of the prodromal stage of children with autism whereas the latter promoted it as a “biomarker”, already noticeable in the first 6 months of life, and with significance for individual children given the predictive relationships with both subsequent diagnostic outcomes and levels of disability. One possible reason for this conflict could be the amount of data collected in both studies. The latter [48] contained more than 500 times the amount of eye-tracking data collected, per child, with more than 50 times as much data collected at any single cross-sectional time point. But the more important aspect of the comparison between these two studies is that results were actually consistent in both studies: inspection of the growth charts of eye fixation (Figure 1E) in the latter study [48] indicates that cross-sectional comparisons of gaze behavior within the period from 6 to 9 months – the period of development during which the cross-sectional eye-tracking sampling was obtained in the former study [44] are *unlikely* to distinguish the groups. In other words, looking at the longitudinal growth charts, at that cross-sectional comparison, the lines intersect – i.e., there is no cross-sectional differences between the two experimental groups – but the lines or growth curves are actually going in different directions – upwards for the typically developing group, downwards for the group later diagnosed with autism.

This example forcefully argues for a longitudinal approach to developmental constructs such as the unfolding of social visual engagement. Were we to be blind to what happened before and after the cross-sectional comparison, it would have been fully justified to conclude that eye fixation abnormalities are not a feature of prodromal autism.

NOVEL QUANTITATIVE TOOLS FOR MEASURING DEVELOPMENT

Novel concepts focused on capturing unfolding human development in infancy have emphasized the importance of emergent dynamic systems that are

individual and self-referential – individual to a given child [61]. In other words, each child may follow her own developmental timing and pace. An example of this phenomenon in later life is the time in development in which children reach pubescence: while different children may show a slightly different “growth chart” for when puberty begins, underlying this variability is a prototypical curve that signifies pubescence for the species. We believe that this concept needs to be applied to early development as well, particularly because we still do not know what are the underlying phenomena (or curves) that we are seeking. Therefore, it is critical to “align” variable curves obtained for individual children in order to shed light on the regularities that characterize these unfolding phenomena for groups of people – not cross-sectionally but as defining parameters of developmental curves. Recently, there has been a concerted effort to create and refine quantitative methodologies to achieve just that, particularly given the expected challenge of missing data in densely sampled experimental designs that involve subjects that might not be fully cooperative (such as human infants).

In the study reviewed in detail above [48], we adopted such a novel approach. We used Functional Data Analysis (FDA) [62] and Principal Analysis by Conditional Expectation (PACE) [63-66]. We favoured the FDA approach over more traditional growth curve analyses because the latter can be confounded by individual differences in developmental timescale (which smear statistical variation across time), and by the need with many methods to correctly assume an underlying parametric or semi-parametric model rather than allowing this to be determined in a data-driven fashion [67]. In contrast, FDA methods explicitly model statistical variation in both time scale as well as amplitude [64,66], and determine curve shape empirically [63,65]. In addition, the PACE method of FDA is designed specifically to overcome a common problem for longitudinal studies: non-uniform sampling particularly in the case of missing values [63,65]. PACE characterizes statistical ensembles of irregularly-sampled longitudinal data in terms of entire curve shapes on the basis of conditional expectation. This maximizes the ability to detect patterns of correlation across an ensemble and minimizes the impact of data sampled at discrete intervals with varying number of measurements per participant [63]. This approach significantly improves both the detection of common features in trajectory shape as well as the identification of individual spurts or delays relative to group data.

“DEVELOPMENT ITSELF IS THE KEY TO UNDERSTANDING DEVELOPMENTAL DISORDERS” [1]

Development in the first two years of life unfold at dizzying pace; it is profoundly individual in its most important parameters of magnitude and timing; it reflects a dynamic in which simpler processes are co-opted into more complex ones; and it defies static measurements because the essence of its nature is the way it unfolds over time. To capture developmental phenomena, and disruptions thereof, we need concepts and methodologies that move us away from discrete measures obtained at cross-sectional points and onto continuous and highly quantitative measures obtained over encompassing developmental periods. We briefly outlined here some pertinent concepts and relevant quantitative methodologies. Clearly, densely-sampled experimental designs are costly along several factors, from the level of investment of children and families in research studies, to the level of resources needed in order to accomplish such an intensive research plan for a sufficiently large number of subjects. And yet, we contend that these costs are worth the investment given the potential rewards associated with the discovery of hitherto unknown developmental phenomena and disruptions thereof that could shed light on pathogenesis of neurodevelopmental syndromes such as autism.

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