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TRANSLATING ADVANCES IN DEVELOPMENTAL SOCIAL NEUROSCIENCE INTO GREATER ACCESS TO EARLY DIAGNOSIS IN AUTISM SPECTRUM DISORDER

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Abstract Early identification and diagnosis of autism spectrum disorder (ASD) is necessary to promote access to early treatment, a critical factor in optimizing children's lifetime outcomes. And yet, diagnosis is often late, delaying interventions to a time in which symptoms have aggravated and communication skills already show impairing differences. This review illustrates progress in developmental social neuroscience that shows promise in generating novel tools for objective and cost-effective early diagnosis of ASD. We focus on research of social visual engagement, which is the way infants and toddlers look at and learn from their social environment. Moment-by-moment quantification of social visual engagement is yielding measures that are beginning to approximate best-practice procedures used by experienced clinicians in the assessment of young children. This progress and potential solutions have public health importance because experienced clinicians are limited in number, and specialized clinical assessment services tend to be lengthy, costly, and plagued by extended wait time, all of which contributing to limited access, particularly in the case of low-resource families. The research reviewed here illustrates a wider effort to advance biomarker-based measurements intended to develop better and more efficient tools and procedures for screening, diagnosing and monitoring treatment response in children with ASD. The advent of such tools could increase access to early diagnostic services and promote efficiencies in early treatment delivery, with the ultimate goal of ensuring that children with ASD are afforded the services they need to thrive.

Key words: autism spectrum disorder, neurodevelopment, socialization

Resumen ***Repercusión de los avances en la neurociencia social del desarrollo en un mayor acceso al diagnóstico temprano en el trastorno del espectro autista***

La identificación y el diagnóstico temprano del trastorno del espectro autista (TEA) son necesarios para promover el acceso al tratamiento temprano, un factor crítico para optimizar los resultados de por vida de los niños. Y, sin embargo, el diagnóstico suele llegar tarde, lo que retrasa las intervenciones hasta un momento en el que los síntomas se han agravado y las habilidades de comunicación ya muestran diferencias perjudiciales. Esta revisión ilustra el progreso en la neurociencia social del desarrollo que se muestra prometedora en la generación de herramientas novedosas para el diagnóstico temprano objetivo y rentable de los TEA. Hacemos énfasis en la investigación del compromiso visual social, que es la forma en que los bebés y los niños pequeños miran y aprenden de su entorno social. La cuantificación momento a momento del compromiso visual social está generando medidas que comienzan a aproximarse a los procedimientos de mejores prácticas utilizados por médicos experimentados en la evaluación de niños pequeños. Este progreso y las posibles soluciones tienen importancia para la salud pública porque los médicos con experiencia son limitados en número y los servicios de evaluación clínica especializados tienden a ser largos, costosos y están plagados de tiempo de espera prolongado, todo lo cual contribuye a un acceso limitado, particularmente en el caso de familias con bajos recursos. La investigación revisada aquí ilustra un esfuerzo más amplio para avanzar en las mediciones basadas en biomarcadores destinadas a desarrollar herramientas y procedimientos mejores y más eficientes para la detección, el diagnóstico y el seguimiento de la respuesta al tratamiento en niños con TEA. El advenimiento de tales herramientas podría aumentar el acceso a los servicios de diagnóstico temprano y promover la eficiencia en la entrega del tratamiento temprano, con el objetivo final de garantizar que los niños con TEA reciban los servicios que necesitan para prosperar.

Palabras clave: trastorno del espectro autista, neurodesarrollo, socialización

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Autism unfolds in the first two years of life as a result of the accumulation of thousands of missed opportunities for social learning, learning that is foundational for the development of speech, language and communication skills in typically developing children. The moment-by-moment quantification of looking behavior to others in infants and toddlers with autism is beginning to yield measures that approximate diagnostic and assessment results generated by best-practice procedures used by experienced clinicians. This progress is likely to advance cost-effective solutions to achieving increased access to early diagnostic services, access that is presently very limited and constitutes a public health challenge that effectively deprives the majority of autistic children of the benefits of early treatment.

The importance of early diagnosis and treatment

Autism spectrum disorder (ASD) is a neurodevelopmental disability diagnosed behaviorally by the presence of early-emerging, persistent deficits in social interaction and communication skills, and by the presence of restricted and repetitive patterns of behavior[1]. Early identification and treatment are two of the most important factors promoting improved lifetime outcomes for children with ASD[2, 3]. Because up to 80% of parents recognize developmental concerns in their children subsequently diagnosed with ASD by age 2 years[4], the American Academy of Pediatrics recommends universal screening for ASD at 18 and 24 months[5]. And yet, the median age of ASD diagnosis in the US has been late, between 4 and 5 years of age[6]. This public health challenge moves eligibility and access to intervention services from within the period of maximal neuroplasticity[7] –the period from birth to 3 years– 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[8]. Age of diagnosis is later still in minority, low-income and rural communities[9]. Several factors account for late ages of diagnosis of ASD, including primary care clinicians' time restrictions, lack of accurate and cost-effective screening and diagnostic tools, limited number of expert clinicians, and a general "wait and see approach" that results in ASD diagnosis being made only when symptomatic presentation is obvious, typically when the child is older[10].

One solution explored in the research literature has been the use of eye-tracking technology to generate quantitative biomarkers that could serve as objective, standardized, quantitative and cost-effective tools for the diagnosis of ASD[11]. For eye-tracking studies of ASD in infants and toddlers, the focus of research has been on looking behavior in social situations because disruptions in this domain represent one of the core features of the condition[8]. Here we summarize some advances in this area of research.

Social visual engagement in ASD

Social visual engagement (SVE) refers to the way that children look at and learn from the social environment, moment-by-moment, as they interact with others or view scenes of social interaction such as children's play or people talking[8]. In the past decade, several discoveries have placed SVE at the core of programmatic research aimed to understand the mechanisms underlying the unfolding of autism in infancy and toddlerhood:

SVE emerges early in typical development and is disrupted in ASD: SVE is a foundational mechanism of socialization, attracting babies' attention to others from the first days and weeks of life[12]. Babies' attention is attracted to caregivers' eyes, setting in motion a mutually reinforcing choreography of contingent, back-and-forth social interaction that is critical for the development of speech, language and communication skills. In babies later diagnosed with autism, this response is disrupted from as early as 2-months of life; developmental trajectories of eye looking show that deviations from normative patterns in the first 6 months of life are both predictive of an ASD diagnosis and of levels of autistic social disability at 24 and 36 months[13].

SVE is under strict genetic control: ASD is one of the most strongly genetic and heritable complex neurodevelopmental conditions. Although several hundred genetic variants have been found to be implicated in ASD, the vast majority of cases result from polygenic combinations of genes with small effect sizes, resulting in highly complex genetic vulnerabilities. To date, research has not yet revealed how molecular vulnerabilities can lead to the behavioral symptomatology that defines ASD. One approach to this problem has been the stance that rather than leading directly to symptoms, this genetic liability leads to disruptions in normative socialization, and thereof become ASD symptoms, which emerge in the second and third year of life[8]. Critical in this effort has been to establish what behaviors that are core symptoms of ASD are influenced by genetic variation and whether such behaviors are specific to the condition. In a large study involving identical twins (monozygotic or MZ) and fraternal twins (dizygotic or DZ), the former sharing 100% of their DNA whereas the latter sharing 50% of their DNA, typically developing MZ toddlers showed 91% agreement in eye looking behaviors relative to only 35% agreement in eye-looking behaviors in typically developing DZ toddlers. This large gap in agreement demonstrates that eye looking behaviors are under strict genetic control[14]. Moreover, this study also showed that, when watching naturalistic scenes of social interaction, MZ toddlers are more likely

than DZ toddlers to make saccadic eye movements at the same time, in the same direction, and onto the same social content, with within-twinset concordant behavior happening at microscales of tens of milliseconds. Finally, this study also showed that SVE behaviors that are most strongly genetically determined are also the behaviors that segregate toddlers with ASD from typically developing peers, thus indicating that SVE is both genetic in origins and diagnostic for ASD.

Early disruptions of SVE in ASD leads to accumulation of missed opportunities for social learning: The clinical implications of these findings became clear when space-time distributions of SVE were created, quantifying moment-by-moment deviations of social attention in individual toddlers with ASD relative to large databases of SVE in typically developing toddlers[8]. When watching complex scenes of social interaction, groups of children may show dispersed visual focus (when there is no element of great social salience in the scene), or they may show group convergence on a particular element of importance to understand that social situation (these are sometimes called "hot spots of socialization", because the attention of an entire group of children is entrained to that spot of the screen at that moment in time). The resulting effect on space-time measurements of visual attention is called an "attentional funnel", because the group as a whole, during free viewing of the video, momentarily focus on the same spot of the screen at the same time. These attentional funnels are naturally occurring and data driven, amounting to hundreds of statistically significant attentional space-time convergences, thus representing "experimental presses" against which it is possible to compare the time-varying visual fixations of children with ASD. This line of research has revealed that within a 6-minute free viewing of video depicting social scenes, toddlers with ASD diverge over 500 times from the space-time focus of their typically developing peers. Each one of these divergences represents a missed opportunity for social learning, since social looking behavior reflects the child's social learning from scene content. The social attention of toddlers with ASD does not diverge from normative patterns only during this kind of experiment; it diverges in their real-life social experiences. As a result, toddlers with ASD appear to miss opportunities for social learning many thousands of times in a week of social exposure, accruing these deviations in ever larger numbers in the first three years of life. The accumulating consequences of these deviations is the emergence of social disability in ASD[8].

In summary, SVE is early emerging in development, is under strict genetic control, and is disrupted in ASD from the first months of life, pointing to a mechanism of social disability that impacts social learning at microscales of tens of milliseconds and that accrues by rates of thousands of times in the first 2-3 years of life. Because SVE behavior segregates toddlers with ASD from their peers, it has diagnostic value and could possibly be used for the purpose of advancing objective diagnostic tools, thus contributing to ongoing efforts to reduce the age of diagnosis of ASD and to increase access to diagnostic services.

Translating measures of social visual engagement into solutions for objective and accessible early diagnosis of ASD

Best practices in the diagnosis of ASD in young children require experienced clinicians who administer standardized procedures for measuring autistic symptoms (such as the *Autism Diagnostic Observation Schedule, 2nd edition*, or ADOS-2[15]) and for measuring developmental skills such as verbal and nonverbal learning ability (such as the Mullen Scales of Early Learning[16]). Together with medical, family and developmental histories, these clinicians use the totality of this clinical information in order to make the diagnosis. The great challenge in the field is that experienced clinicians are scarce, and because this process may take several hours and is very costly, large portions of the population wait many months, at times years, to access diagnostic services, and this challenge is particularly acute among low-resource families in the US[10]. Therefore, there are several efforts underway to use objective, performance-based procedures to develop tools that will increase access to diagnosis by circumventing the need for experienced clinicians conducting lengthy and costly clinical procedures[17]. The following is such an effort that capitalizes on the findings of research on social visual engagement summarized above.

A social visual engagement (SVE) diagnostic classifier: Using moment-by-moment measures of SVE, our group has been able to assemble large datasets of social looking behavior to complex social scenes in typically developing toddlers. These datasets become data-driven norms against which one can compare the SVE measures for a single toddler with ASD. Because, as noted, the normative datasets contain many hundreds of statistically significant attentional funnels (moment-by-moment space-time normative convergences in SVE), this procedure can quantify a single child's divergences from these normative patterns many hundreds of times over the period of 10-minute free viewing of complex social scenes (such as in the case of videos of toddlers playing and interacting). This level of quantification allows us to test whether the sum of these divergences for a single toddler with ASD –a measure of "relative entrainment" to normative SVE– could perform the function of a diagnostic classifier, in essence matching a child's ASD or non-ASD diagnosis given by experienced clinicians.

Our group has conducted two large trials to date. The first was a feasibility trial involving 1,089 toddlers including both children with clinician-based diagnoses of ASD and of non-ASD (this group includes primarily children with non-

autistic developmental delays as well as children without a diagnosis). Two-thirds of this sample's data were used to develop a computation model for the diagnostic classifier (the discovery cohort), whereas one-third of this sample's data were used for independent testing (the replication cohort). In this replication testing, by comparing outputs of the eye-tracking procedure to best-practice clinician-based diagnoses, one can measure the accuracy of the diagnostic classifier. Encouraging results in this study led to a multi-site pivotal trial of this diagnostic procedure involving 505 toddlers. The pivotal trial followed the Standards for Reporting of Diagnostic Accuracy Studies (STARD[18]), which provide best-practice parameters to improve the completeness and transparency of reporting of studies of diagnostic accuracy. This study was pre-registered in the US repository of clinical trials (accessed at www.clinicaltrials.gov, protocol NCT03469986). Results for this second, multi-site replication cohort, reproduced the encouraging results of the feasibility study, and led to a clearance issued by the (US) Food & Drug Administration (FDA) for this tool and procedure to be used in the clinical realm.

Social visual engagement (SVE) indices of severity: While a diagnosis is critical for eligibility for, and access to, early treatment and intervention services, treatment planning for a given child also require measurements of disabilities and abilities, such as levels of autistic social disability and levels of verbal and nonverbal learning, since appropriate treatment programs need to not only address a child's challenges (social disability) but also to build on the child's assets (their ability to learn via verbal and nonverbal means)[2,3]. Because SVE is one of the foundations of language acquisition and learning from others[12], our group explored the possibility of mining the SVE datasets generated by the feasibility trial described above for the development of eye-tracking-based proxies to measures of social disability, and of verbal and nonverbal ability resulting from clinician-based assessments using the ADOS-2 and the Mullen. In other words, we used the normative SVE datasets to identify the moments of the video that best predicted social function and verbal and nonverbal ability (each one modeled separately) in these typically developing toddlers. Once the computation model was built, we tested its ability to proxy ADOS-2 and Mullen scores in toddlers with ASD. Results of the replication sample in the feasibility trials revealed that the eye-tracking-based indices of social disability and verbal and nonverbal ability could capture over 70% of the variance in scores of the ADOS-2 and the verbal and nonverbal subtests of the Mullen, respectively. In effect, therefore, these eye-tracking indices were good approximations of the clinical measures and could be used to replace the clinical procedures. These results were replicated in the pivotal, multi-site trial described above.

The future of biomarker-based tools for the early diagnosis of ASD

Results of the trials reviewed briefly here offer a science-based solution to increasing access to early diagnostic services while maintaining high quality parameters for the assessment of young children. The community uptake of this and other biomarker-based solutions, however, will depend on our collective success in overcoming systemic barriers that continue to delay diagnosis and make it less accessible, including the ways in which developmental concerns are identified (and often missed) in young children at a population level, and inadequate levels of reimbursement for early detection and diagnosis. To overcome these barriers, however, there will be a need for community-wide awareness and understanding of the profoundly deleterious public health implications of late diagnosis to the almost 90,000 children born in the US every year who will have ASD.

Conflict of Interest: Dr. Klin is inventor of technologies that are thematically related to scientific concepts covered in this review. These technologies are licensed to EarliTec Diagnostics. EarliTec Diagnostics is a company that develops medical technologies for early diagnosis of autism and gives revenue to support treatment of children with autism. Dr. Klin is an equity holder in EarliTec Diagnostics.

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