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FRONTIERS IN THE RESEARCH OF AUTISM PATHOGENESIS

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Abstract This review focuses on four interrelated teams and research lines that form the basis for new research on the pathogenesis of autism spectrum disorder (ASD) at the Marcus Autism Center, in Atlanta (US). These themes probe typical social behavior and brain development from birth, and disruptions thereof in babies later diagnosed with ASD. These four themes are: to leverage lifetime *maximal neuroplasticity*; to test the hypothesis that *developmental disruption of early-emerging mechanisms of socialization* drives pathogenesis and results in autistic social disability; the *focus on the infant-caregiver dyad*, and the iterative context associated with mutually reinforcing and adapted social and communitive inter-action, or emerging cycles of social contingency, from the first days and weeks of life; and the study of time-varying *neurodevelopmental transitions* in social behavior from *experience-expectant* (reflexive, endogenous) and subcortically-guided *to experience-dependent* (caregiver- and reward-driven) and cortically-guided, a transition that our work suggests is uniquely disrupted in babies later diagnosed with ASD. This science is opening a world of opportunities to optimize children's outcomes despite the genetic liabilities that they are born with. It provides the scientific grounding for new community-viable solutions for increasing access to early interventions using treatments that scaffold and strengthen infant-caregiver interactions, which is the platform for early brain development.

Key words: autism spectrum disorder, pathogenesis, neurodevelopment, neuroplasticity, socialization

Resumen ***Fronteras en la investigación de la patogenia del autismo.*** Esta revisión se centra en cuatro equipos y líneas de investigación interrelacionados que forman la base de nuevas investigaciones sobre la patogenia del Trastorno del Espectro Autista (TEA) en el Marcus Autism Center, en Atlanta (EE.UU.). Estos temas investigan el comportamiento social típico y el desarrollo del cerebro desde el nacimiento, y las alteraciones del mismo en los bebés a los que luego se les diagnostica TEA. Estos cuatro temas son: aprovechar la *neuroplasticidad* máxima en la vida; probar la hipótesis de que la interrupción del desarrollo de los mecanismos de socialización emergentes impulsa la patogénesis y da como resultado una discapacidad social autista; el enfoque en la díada bebé-cuidador, y el contexto iterativo asociado con la mutua interacción de refuerzo social y comunitario, o ciclos emergentes de contingencia social, desde los primeros días y semanas de vida; y el estudio de las transiciones del comportamiento social variable en el tiempo del neurodesarrollo desde la *experiencia-expectante* (reflexiva, endógena) y guiada subcorticalmente, a la *experiencia-dependiente* (cuidador e impulsado por la recompensa) y guiada corticalmente, una transición que nuestro trabajo sugiere que se interrumpe únicamente en bebés diagnosticados posteriormente con TEA.

Palabras clave: trastorno del espectro autista, patogenia, neurodesarrollo, neuroplasticidad, socialización

Autism Spectrum Disorder (ASD) is one of the most common forms of neurodevelopmental disability, with a prevalence of 1 in 44 reported in the most recent surveillance report by the (US) Centers for Disease Control and Prevention[1]. ASD is also one of the most strongly genetic and heritable of all complex neuropsychiatric conditions[2]. Little is known on how this genetic liability leads to the emergence of ASD in the first two years of a child's life. And yet, prospective and longitudinal studies from birth of younger siblings of children with ASD –who have a 20-fold increase in likelihood of also having ASD relative to the general population– are beginning to shed light on early pathogenesis, foreshadowing a future in which early treatment might be deployed to considerably optimize these children's outcomes, mitigating symptoms and augmenting social-communication and cognitive skills. This review covers the general themes and advances in the emerging developmental social neuroscience of ASD pathogenesis at the Marcus Autism Center in Atlanta, US, one of the five National Institutes of Health Autism Centers of Excellence.

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Four inter-related themes

We begin with the criticality of early diagnosis and intervention[3], and the need for much greater understanding of early ASD pathogenesis in social brain and social behavior in both typical and atypical development[4]. The American Academy of Pediatrics[3] strongly recommends universal early screening for ASD in the second year of life because early intervention significantly improves outcomes and may even normalize aspects of brain function in children with ASD. However, early intervention typically requires the diagnosis of ASD, which in turn awaits the emergence of symptoms that can only be identified as early as in the second or third year of life[4]. In the US, the median age of ASD diagnosis still hovers around 4½ years of age[1]. ASD is also a lifetime condition associated with economic burdens of over $2.4M per child/family and over $130B per year in the US alone, most of which is related to supports in adult life[5]. These facts have prompted the (US) National Institutes of Health Interagency Autism Coordinating Committee, which establishes the ASD research agenda in the US, to repeatedly prioritize this domain of research, in order to accelerate progress. At the Marcus Autism Center, several research themes have been pursued in the past five years to address these recognized challenges:

First, we aim to capitalize on *maximal neuroplasticity*. The first two years of human life represent the period of greatest brain transformation: a newborn's brain doubles in size in the first year of life, and will increase again by another 35% by year three; synaptic density, a marker of experience-dependent brain specialization, quadruples within year one alone, and will reach levels 200-300% greater than that of an adult by the end of the third year (with concurrent and subsequent pruning and strengthening)[6]. Of importance, longitudinal gene expression associated with synaptogenesis over the first two years of life, over a wide range of brain structures, is characterized by maximal values across the 6- to 12-month window, then decreases drastically after 15 months, or much before the time at which ASD symptoms emerge and the condition can be reliably diagnosed[6]. Therefore, treatment that is conditional on ASD diagnoses misses important windows of opportunity, and identified prodromal risks need to be addressed[7].

Second, our overarching hypothesis is that the *developmental disruption of early-emerging mechanisms of socialization drive pathogenesis and results in autism symptoms*[6]. For the past 15 years we have quantitatively characterized social visual engagement in ASD: this term captures what and when a child looks at, and learns about, in their surrounding social environment. Initially, we focused on preferential fixation to the eyes of others because the eyes and gaze are critical for extraction of socially adaptive information, and are potent enhancers of social information neural processing throughout the lifespan. Using eye-tracking methodology, we found increasing decline in eye fixation in babies later diagnosed with ASD, beginning at 2 months of age[8]; this declining curve in the first six months of life, were strong predictors of ASD and level of social disability at the age of 24 and 36 months. We also found that this skill, already present from the first days and weeks of life[6], is under strong genetic influence[9] in typically developing children and is considerable altered in toddlers with ASD. Given this starting point, our work has probed the hypothesis that both symptomatology and outcome levels result from these early disruptions, and as such, can be significantly attenuated and optimized[4]. Most cases of ASD are tied to highly complex polygenic profiles of vulnerability; already hundreds of common genetic variants having been implicated in ASD etiology[2]. In only a small minority of cases can single gene mutations be considered causal in ASD. We have thus hypothesized that the (vastly heterogeneous) nature of ASD is nevertheless well-captured by a syndrome-wide entity, reliably diagnosed by expert clinicians, *not* because of commonalities across the hundreds of initial causes (the so called "autisms") but because of *commonalities in what these causes disrupt*: infant-caregiver reciprocal social engagement, or social contingency, which is the universal platform for social and communication brain-behavior development[6]. In fact, disruptions in patterns of reciprocal social engagement may occur in children with other conditions, such as very early prematurity and congenital heart disease, who then develop ASD-related outcomes at higher-than-expected levels. Supporting this hypothesis of ASD etiology is recent work demonstrating that gaze aversion –a pathognomonic symptom of ASD included in the original description of autism– is not present in 2-year-olds, but is l learned over time as a result of insensitivity to the adaptive value of eye gaze[10] (as noted, a skill that is present in newborns). Additionally, using a measure of moment-by-moment social visual entrainment, in which we measure a child's ability to fixate on space-time "hot spots of socialization' (something of social importance at an exact moment in time) (Jones W. & Klin A. Entrainment to social context in typically-developing two-year-olds and absence thereof in autism. Under Revision), we showed that in 2-year-olds, cumulative divergences from normative benchmark (what typically developing children look at in typical social situations and when), is strongly predictive of levels of ASD symptomatology, verbal and nonverbal function one and a half years later. Children with ASD missed these momentary opportunities for social learning at rates of hundreds of times within a period of only 6 minutes of viewing videos of children interacting. The more they diverged from the way typically developing children watched these videos, the more social disabled and cognitively impaired they eventually became. Collectively, these insights form the basis for our choice of early treatment approach: if levels of symptomatology

and functional outcome can be predicted by deviations from normative socialization, then interventions aimed at normalizing social and communication engagement hold the promise of attenuating symptoms and optimizing outcomes[4]. Consequently, there should be no reason to await for clear symptoms of ASD as detected and diagnosed by clinicians for early treatment to begin, a consensus that is now shared by many investigators working on prodromal interventions for ASD[7].

The third theme is that *the unit of scientific focus and of treatment target is the infant-caregiver dyad*, and the iterative context associated with mutually reinforcing and adapted social and communicative *inter*-action[11]. Innate predispositions to orient to social stimuli serve as strong engaging signals to caregivers, who at once constrain the world around the child and strengthen the infant-caregiver context (by their reciprocal engagement); upon this foundation, ever increasing and more complex cycles of contingency evolve, from birth over the course of the first two years of life[6]. As noted, in the domain of social visual engagement, genetic control is exercised over macroscales – e.g., patterns of visual fixation over minutes of social visual experiences; and over microscales – e.g., moment-by-moment predispositions to react to and seek social information in the surrounding social world, such as when to shift one's visual attention, in which direction, and onto which targets, measured in milliseconds[9]. In essence, via these predispositions, infants and toddlers create their own individual niches, which both constrain the environmental realm within which they will learn, and intensify inter-actions with these preferred aspects of the world[4]. Genetic influence, however, is limited to predispositions to engage, or not, with the social world, from birth. We, therefore, can alter the environment which the infant experiences: the social world with which infants engage, and which transforms infants, can be deliberately altered via social and communication transactional supports effected by the caregiver. This principle is fundamental to several lines of early intervention research, which prioritize caregiver-mediated treatments[12]. In these approaches, parents are trained to compensate for a child's attenuated social sensitivities by scaffolding social engagement through interventions that promote shared attention, reciprocal communication, and social-emotional reciprocity[13]. Such transactional supports, when deployed sufficiently early in development, can achieve higher levels of mutual social-communication engagement and reduce prolonged deviations from normative social experiences, thus attenuating the formation of symptoms and subsequent burdens of autism, which, as noted, evolve with time. The importance of early social contingency to the development of social behavior and social brain provides the scientific rationale for caregiver-mediated treatments, which is a community-viable solution for increased access to early intervention for children and families affected by ASD and related developmental disabilities, including among traditionally under-served communities[4].

The fourth theme relates to an important *neurodevelopmental shift in which experience-expectant, reflex-like, and subcortically-guided social behavior, transitions, within the first 4 to 16 weeks of life, into experience-dependent, voluntary, and cortically-guided social behavior*[14]. The relevance of this hypothesis to research of ASD relates to a surprising finding from our earlier work: eye fixation in babies later diagnosed with ASD is not immediately reduced at birth, but in fact begins at levels that are even higher than those observed in typically developing babies, with mean decline beginning at 2 months of age[8]. This observation contradicted prior hypotheses (including our own) of congenital absence of social adaptive orientation[11], and suggested, instead, that some social adaptive behaviors may initially be intact in newborns later diagnosed with ASD. If confirmed, this finding would offer a remarkable opportunity for treatment: innate predispositions that are initially intact suggest a neural foundation that may be built upon, offering far more positive possibilities than if that foundation were absent from the outset. Equally exciting, these data fit well within the framework of long-studied animal models of the neural systems subserving filial orientation and attachment[14]: they highlight a narrow period for investigation spanning the transition from experience-expectant to experience-dependent mechanisms originally proposed in the context of accumulating findings in research on face processing in human infants[6] and cross-species analogs[14].

For the past four years, we have probed the hypothesis that filial predispositions may initially be intact in newborns later diagnosed with ASD, but that a second phase of neurodevelopment, in which initial perceptual predispositions are superseded by interaction-based learning, fails. With remarkable consistency across domains of adaptation, including social adaptive action, reflex-like actions transition to voluntary actions within the first few weeks of life[6]. In our data on social visual engagement[8] and on social vocal behavior in infancy (precursors of speech)[15], unfolding reflexive behaviors in general and human smiling and infant vocalizations in particular, together with the remarkable analogy of these processes in infant monkeys[16], all serve to outline a resolvable hypothesis of ASD pathogenesis positing disruption of transitions from primarily subcortically- to primarily cortically-guided behavior within a delimited time window in the first 16 weeks of a child's life. Our data suggest syndrome- and time-specific hypotheses of pathogenesis, which may highlight the role of proteins critical in anchoring, stabilizing and maintaining synaptic communication[17,18], a common thread in genetic findings in ASD. Armed with strong preliminary data, and studying multiple domains of social and other functions across species, this research is moving forward via mapping and quantification transitions

in brain connectivity and tractography over the period of birth through 6 months in human infants, and from birth through 2 months in infant monkeys. Its goal is to advance understanding of the brain-behavior reciprocal transitions occurring this early in life, a period which, as discussed, predicts ASD diagnostic classification and levels of disability 2 ½ years later[8].

Early brain science meets public health challenge

The national priority in the US to advance early detection and intervention for children with autism spectrum disorder (ASD) has not reduced the late age of ASD diagnosis over several consecutive (US) Centers for Disease Control and Prevention surveillance cohorts, with traditionally under-served populations accessing diagnosis later still. The science of social behavior and brain development, from birth, and its disruptions in babies later diagnosed with ASD, is transforming our understanding of ASD pathogenesis. This science is opening a world of opportunities to optimize children's outcomes despite the genetic liabilities that they are born with. This view is countering outdated notions that potentially devastating disability is determined the moment a child is born, and that these burdens are inevitable, with opportunities for improvement being constrained to only alleviation of symptoms or limited improvements in adaptive skills. Instead, this new developmental social neuroscience is already providing the grounding for new community-viable solutions for increasing access to early interventions, which hold the potential of improving children's lifetime outcomes. Based on quantitative, prospective and longitudinal measurements of social development, and discoveries of early disruptions in babies later diagnosed with autism, the emergence of social contingency between infants and their caregivers is viewed as not only the platform within which the development of social brain takes places, but also as the focus of treatment intended to scaffold infant-caregiver interaction, and in this way, attenuate symptoms and promote higher-level social-communication and cognitive skills.

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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