

An agenda for 21st century neurodevelopmental medicine: lessons from autism

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Summary. The future of neurodevelopmental medicine has the potential of situating child neurology at the forefront of a broad-based public health effort to optimize neurodevelopmental outcomes of children born with high-prevalence and diverse genetic, pre- and peri-natal, and environmental burdens compromising early brain development and leading to lifetime disabilities. Building on advancements in developmental social neuroscience and in implementation science, this shift is already occurring in the case of emblematic neurodevelopmental disorders such as autism. Capitalizing on early neuroplasticity and on quantification of trajectories of social-communicative development, new technologies are emerging for high-throughput and cost-effective diagnosis and for community-viable delivery of powerful treatments, in seamless integration across previously fragmented systems of healthcare delivery. These solutions could be deployed in the case of other groups of children at greater risk for autism and communication delays, such as those born extremely premature or with congenital heart disease. The galvanizing concept in this aspirational future is a public health focus on promoting optimal conditions for early brain development, not unlike current campaigns promoting pre-natal care, nutrition or vaccination.

Key words. Autism. Autism spectrum disorder. Early brain development. Early detection. Early intervention. Neurodevelopmental medicine. Optimizing outcomes. Social visual engagement.

The promise of neurodevelopmental medicine: optimizing outcomes

Over 10 years ago, an editorial in *Developmental Medicine & Child Neurology* [1] proclaimed that the future of neurodevelopmental medicine ‘ain’t what it used to be’, that the demands upon physicians focused on the care for children with neurodevelopmental disabilities were changing rapidly, with trends towards narrow subspecialization against the backdrop of gravely concerning shortages of well-trained professionals in this field. In prescient fashion, the editorial stated: ‘it will be important to consider the ways that specialists’ roles may change in a system of care that shifts from a model based on reducing impairment to one focused on enhancing functional abilities and societal participation for those with disabilities.’

While a decade later child neurology is still many steps removed from public health, still confined to specialized practice and several referral steps downstream from primary care, its main subject matter –brain development– is emerging as a unifying concept capable of galvanizing public health policy across a wider range of childhood vulnerabilities than has hitherto been the main focus of child neurology. No longer confined to relatively lower-prevalence childhood epilepsy, cerebral palsy and severely debilitating genetic, metabolic or traumatic disabilities, neurodevelopmental medicine is expanding its horizons to the much higher-prevalence conditions that deleteriously impact early brain development. Possibly extending to 10-15% of the population of babies and toddlers presenting to primary care practice, these higher-prevalence conditions originate from etiologies ranging from complex genetic bases (e.g., autism spectrum disorder), to prenatal risks (e.g., prematurity, congenital heart disease), to post-natal environmental hardships (e.g., children growing up in low-income contexts). In agreement with this 2006 editorial, this review contends that the future of neurodevelopmental medicine will build on current science of early brain development in order to optimize outcomes of children born with a broad range of burdens likely to compromise neurodevelopmental trajectories that can result in lifetime disabilities.

This vision begins with a shift in scientific emphasis from causes of neurodevelopmental risk to prevention, or at least attenuation, of the deleterious effects of those risks upon early brain development. This suggestion stands in contrast to the model that has led to some of the greatest achievements in medicine. The most momentous health

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benefits originated from discoveries of causes of disease. Maybe the greatest medical achievement of all, the discovery of germs, led to antiseptic practices in surgical procedures, the discovery of antibiotics, and the development of vaccines, thus preventing or treating lethal infections and providing active acquire immunity to a host of devastating diseases among millions of people [2-4]. Similarly, advances in pharmacology have been guided by the discovery of diagnostic biomarkers that aid in identification and diagnosis and that can be used to monitor treatment response, thus tailoring interventions to cause of, or risk for, disease [5]. This model, however, has not been very fruitful in the management of complex neurodevelopmental conditions. On the one hand, there are several conditions for which the causes have been identified for several decades and yet our ability to minimize their impact on brain development is still limited. Examples are fragile X [6] and Rett [7] syndromes. On the other hand, the causes of highly prevalent neurodevelopmental conditions, such as autism, language and communication delays, and attention deficit hyperactivity disorder are extremely complex in their genetic bases and vastly heterogeneous in their symptomatic presentation, thus tempering hopes for momentous etiologic discoveries in the near future that could pinpoint treatments to the causes of associated early brain disruptions.

This shift in emphasis does not mean that we advocate for the abandonment of research on the etiologic bases of complex neurodevelopmental disorders. Rather it calls for near-term action that can promote early brain development despite the burdens with which, or within which, a child is born, whether the burdens correspond to genetic susceptibility, adverse medical condition, or environmental challenges. Maybe an analogy would be to state that there is a need to continue research on the causes of poverty if we are to advance the health and well-being of children in the world; but we should not discard the tremendous benefits of immediate action focused on finding clear sources of drinking water, supplying mosquito nets, and changing policy promoting more favorable social determinants of health.

In this review, we begin by covering some principles of early brain development because it provides a unifying context to promote optimized outcomes. We do so in the context of autism because it is maybe the quintessential neurodevelopmental disorder, providing a framework for understanding other conditions marked by disruptions in early brain development, such as extreme prematurity

and congenital heart disease. In this context, it is of interest that diagnostic and intervention solutions emerging from research on autism may also have beneficial applicability to a much wider range of complex neurodevelopmental conditions. The availability of solutions, however, will only benefit the next generations of children at risk for compromised neurodevelopmental outcomes if they are readily accessible, cost-effective, and community-viable. We, therefore, conclude by outlining an agenda for implementation science –the translation of brain science into tangible benefits for pediatric healthcare delivery– in which child neurology, or neurodevelopmental medicine more generally, has a critical role to play.

Some key principles of early brain development associated with outcomes in children with autism

The challenge and the opportunity

The American Academy of Pediatrics [8,9] strongly recommends universal early screening for autism in the second year of life because early intervention significantly improves outcomes [10-13] and may even normalize aspects of brain function [14,15]. However, early intervention typically requires the diagnosis of autism, which in turn, awaits the emergence of symptoms that can only be identified by expert clinicians as early as in the second or third year of life [16,17]. Nationally in the US, the median age of autism diagnosis still hovers around 4½ years of age [18], and later still in low-income families [19]. Autism is also a lifetime condition associated with economic burdens of over \$2.4M per child/family [20] and over \$130B per year in the US alone, most of which is related to supports in adult life [21,22]. These costs are primarily a result of the cost of care required to alleviate the impact of language and intellectual disabilities, as well as of severe behavior challenges, which commonly accompany autism. And yet, early intervention may in fact significantly attenuate the emergence and effects of these associated disabilities. These facts have prompted the prioritization of early detection and intervention as priorities in autism research by the (US) National Institutes of Health [23].

More broadly, the criticality of early diagnosis [24,25] and intervention [26,27] in promoting better outcomes for individuals with autism has highlighted the need for much greater understanding of early autism pathogenesis in social brain and social

behavior [28-31], a discussion that has built on the following themes:

Capitalizing 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 [32,33]; 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) [34,35]. 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 autism symptoms emerge and the condition can be reliably diagnosed [36,37]. Therefore, treatment that is conditional on autism diagnoses misses important windows of opportunity, and identification of prodromal risks need to be addressed [29,30,38-41].

Autism results from divergences from normative early brain development

Developmental disruptions of early-emerging mechanisms of socialization appear to drive pathogenesis and results in autism symptoms [28,29,39,42]. In the past 15 years, our group has quantitatively characterized social ability and social disability in autism [39,43-50]. While using a range of social stimuli, we eventually focused on preferential eye fixation because the eyes and gaze are critical for extraction of socially adaptive information [51], and are potent enhancers of neural processing of social information throughout the lifespan [52,53]. Through this work we ascertained reliable and replicated quantitative markers of prodromal autism, which span the spectrum of social-communication symptoms [39], represent variable instantiation of genetic vulnerability that likely represents dosage and timing of disruption [54], focus on a skill that is present from the first days and weeks of life [52,55-57], and are population-wide quantitative traits under stringent genetic control [50].

More recently, our work began to probe the hypothesis that both symptomatology and outcome levels result from these early disruptions, and as such, can be significantly attenuated and optimized [38,58]. Most cases of autism are tied to highly complex polygenic profiles of vulnerability; already hun-

dreds of common genetic variants having been implicated in autism etiology [59,60]. In only a small minority of cases can single gene mutations be thought of as causal in autism [61]. We have thus hypothesized that the (vastly heterogeneous) nature of autism is nevertheless well-captured by a syndrome-wide entity, reliably diagnosed via standardized instrumentation, not because of commonalities across the hundreds of initial causes (the so called 'autisms' [62]) but because of commonalities in what these causes disrupt: infant-caregiver reciprocal social engagement, the universal platform for survival that is also co-opted as a platform for social and communication brain-behavior development [54]. In fact, disruptions in patterns of reciprocal social engagement may occur in children with other conditions, such as pre- and peri-natal suboptimalities (e.g., NICU graduates [63]) and diseases (e.g., congenital heart disease [64]), who then develop ASD-related outcomes at higher-than-expected levels. Supporting this hypothesis of autism etiology is a recent study [49] in which we demonstrated that gaze aversion – a pathognomonic symptom of autism included in the original description of autism [65] – is not present in 2-year-olds, but is likely learned over time as a result of insensitivity to the adaptive value of eye gaze (a skill that is present in newborns [55]). Additionally, using a measure of moment-by-moment social visual engagement [40] – the way in which infants visually explore, engage, and ultimately learn from and adapt to their surrounding world – we showed that cumulative divergences from benchmark, typical social visual experiences at the age of two years, are strongly predictive of autism symptomatology, non-verbal, and verbal cognitive function levels 1.5 years later; in fact, this experimental measure had much greater predictive power for ASD outcomes than the standard diagnostic measures taken at two years of age and repeated at follow-up [66]. Collectively, these insights point to a choice of treatment approach [11]: 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 [11,38]. This research goal is consistent with, and provides firm developmental social neuroscience grounding for, field-wide aspirations [67,68] for early treatment in autism.

Treatment should target infant-caregiver social-communicative interactions

The emerging insights outlined above suggest 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 interaction [37]. 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 [37]. 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– [40]. In essence, via these predispositions, infants and toddlers create their own individual niches [69,70], which both constrain the environmental realm within which they will learn, and intensify inter-actions with these preferred aspects of the world [29,37,42].

The level of genetic determinism, however, is limited to predispositions to engage, or not, with the social world, from birth [40]. 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 [10,11,71,72], which includes the most influential approaches to date: the Early Start Denver Model, Project ImPACT, and Early Social Interaction, and parent-delivered Pivotal Response Treatment. 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 [67]. Current data suggest that such transactional supports, when deployed sufficiently early in development, can achieve higher levels of mutual social-communication engagement, can reduce prolonged deviations from normative social experiences, and in this way, can attenuate the formation of symptoms and subsequent burdens of autism, which, as noted, evolve with time. That this approach is now the keystone for an entire system of early detection, diagnosis and intervention being deployed in several states in the US –www.autismnavigator.com and www.firstwordsproject.com– is emblematic of these approaches’ translational and implementation science potential.

The explanatory and translational potential of these principles is also evident in work focused on social vocal engagement, although data in this domain of research are not yet published. And yet, current results are very promising. Much before reduced vocalizations and speech delays can be detected in the second year of life in toddlers with autism, disruptions over developmental trajectories of infant-caregiver contingent vocal engagement can be reliably measured, beginning around the sixth month of life; these are causally connected to the eventual delays appearing some 6 to 12 months later. In other words, speech delays, a common burden in autism, appear to emerge over time, as a result of breakdowns in early reciprocal vocal engagement. These findings strengthen the scientific rationale for parent-delivered interventions focused on social interaction, and suggest that speech and language delays can be attenuated in ways that are community-viable since an interventionist is not needed to provide highly intensive treatment as previously prescribed [73] –a prescription that is too expensive and unrealistic in most settings– as their scarce talent can be used to train caregivers, who in turn, can deploy the approach using every daily experience they share with the infant, thus reaching the level of desired intensity.

In summary, these principles of early brain development in the social and communication domains –the opportunity afforded by early neuroplasticity to change developmental trajectories; the concept that autism is the result of early divergences from normative brain development in the social-communicative domains; and effective treatment can be deployed by engineering social engagement via parent-delivered treatment– collectively, not only provide a model of pathogenesis of autism [29], but also point to the direction in which community-viable treatment might significantly attenuate the burdens of the conditions. In other words, while advances are made on the science of causes of autism, there is enough developmental social neuroscience already to focus on opportunities to optimize outcomes of children born with genetic liabilities associated with autism. And given the field’s consensus on the beneficial effects of early intervention, there is a bioethical imperative to actualize this potential now for the maximal number of children as over 60,000 children are born every year, in the US alone, who will have autism [74]. It is in this context that neurodevelopmental medicine can play a central role, building on its focus on early brain development as a catalyst of change in patterns of healthcare delivery.

Autism and related disabilities via different etiologies

Autism as a syndrome refers to a highly complex family of conditions defined by early-onset impairments in social interaction and social communication accompanied by a wide range of behavior rigidities [75], with lifetime consequences for language and learning skills, independent-living skills, and, potentially, the presence of severe behavior challenges [76,77]. It is one of the most highly-heritable of all complex neuropsychiatric conditions [78] but, as noted, no single molecular marker defines its diagnosis. Instead, current estimates suggest that hundreds of genetic and genomic disorders [79] –the majority of which are still unknown– may play a role in etiology, including rare and common variants [60,80]. No single gene has yet been associated with more than a fraction of patient cases (< 1% [81]), 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 hoped-for future insights into the developmental neurobiology of ASD [82], but the condition is still diagnosed behaviorally by the presence of its defining characteristics, via direct behavioral examination and historical information [77]. There is, however, vast phenotypic heterogeneity, spanning the entire range of IQ and language function, with variable profiles of strengths and deficits, symptom characteristics, change over time, and comorbidities with common psychiatric conditions such as anxiety, mood and attentional disorders [83]. The most robust markers for early diagnosis of autism include reduced interaction with and attention to others; 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 [29,84,85], all failures in normative skills that represent milestones in the development of social interaction and social communication skills, which in turn, become causative factors in subsequent atypical developmental trajectories and in the emergence of more severe symptomatology [42]. Given these multiple layers of complexity, there has been great interest and investments in the identification of biological markers or biomarkers for ASD, with the hope of identifying more homogeneous groups for biological study, of aiding in diagnosis (including early detection prior to the emergence or exacerbation of symptoms), and of developing more robust and sensitive markers for individualization of treatment and for measurement of treatment response [86,88].

This effort is not distinct from the search for biomarkers in other neuropsychiatric conditions, in which there is an emerging consensus that clinical phenomenology, while still the primary means for classifying individuals into diagnostic categories, does not capture biologically meaningful differentiations [89,90].

The genotypic and phenotypic heterogeneity of autism, combined with the notion that autism is the result of atypical social brain development preceding visible clinical symptoms, opens the possibility of multiple pathogenetic paths to the condition. This is an important possibility because, if so, lessons accrued from research on autism, and solutions for optimizing these children's outcomes, would also be relevant to a much wider group of vulnerable infants. Here we focus on two of these conditions –extreme prematurity and congenital heart disease– although the arguments made here apply to many other conditions resulting from pre- and peri-natal suboptimality, or from adverse environmental conditions including poverty.

Extreme prematurity

The prevalence of ASD in the general population is 1.47% [74] (1:68) whereas the prevalence of actionable communication delays (i.e., delays requiring treatment, which include delays in speech-language function and/or verbal and nonverbal communication) is estimated at 12-15% of the general population [91]. In contrast, in extremely preterm (EP) infants, numerous studies have now suggested markedly increased prevalence of autism [92-96], with wide variability in estimates ranging from 20-41% –in studies using screening tools only– or from 3.6-12.9% in studies using expert-clinician-based diagnostic procedures, with more recent studies yielding higher prevalence rates. Several critical reviews have indicated that studies deploying only screening tests identify a large number of false-positives because of the EP population's high rates of severe neurologic and cognitive impairment, although the rate of positive screens is still several-fold higher among unimpaired EP children compared with unselected populations. Of importance, excluding children with severe neurological impairments, several studies show that a large proportion of children screening positive for autism actually have communication delays without meeting criteria for autism, as revealed in studies comparing autism screening tools vs. 'broadband' communication delay screening tools, or in studies that include expert-clinician diagnostic ascertainment [95,96].

The elevated prevalence of autism and communication delays in EP children signify both a major burden on their families and an opportunity to considerably improve their outcomes. Many stressors—developmental, medical and environmental—may have deleterious impact on brain development and on social-emotional experiential learning of EP children, impeding deployment and/or limiting the impact of treatment meant to mitigate neurodevelopmental effects and to optimize outcomes. When considering the global burden of disease, autism is the leading cause of disability in children under 5 years of age [97], and the effects of autism have lifetime implications. The magnitude of the public health challenge associated with autism outcomes in EP children is reflected in the fact that 1.42% of all births registered in the US in 2012 were EP births [98], corresponding to 56,130 such births per year. Considering survival rates at 70–85% [99], and 10% with severe visual, hearing or cerebral palsy impairments [100], an estimated 40,000 EP births/year survive without these severe neurodevelopmental impairments but are at risk for other neurodevelopmental vulnerabilities. Considering prevalence of autism in EP children at 3.6–12.9%, a range of 1440 to 5160 EP children may develop autism per year in the US. Considering also that most EP studies that probed the prevalence of communication delays in this population also identified comparable, if not larger, rates of such delays in this population, autism and communication delays are likely to represent major burdens on EP children and their families, and probably contribute to poorer lifetime outcomes.

Despite major advances in care of EP children in the past several decades [101], neurodevelopmental outcomes over various epochs have remain unchanged [102]. As noted, in autism, the criticality of early diagnosis and intervention to optimize outcomes has been repeatedly demonstrated, and represent a priority in the field. Also, as noted, there is a public health imperative to better understand barriers to the translation of early screening and diagnosis into improved access to appropriate early intervention services. In this context, although utilization of early intervention services is reported to be relatively high among EP children in the small number of extant studies [103–106] (32–55%), opportunity remains to improve early intervention uptake, particularly in families with social and parental psychosocial risk [107]. Identified gaps include need-specific referral, family receptivity, service provision and coordination with medical care, and inadequate funding; simple oversights or com-

munication failures between hospitals, early intervention providers and families; services may be delayed or terminated early, and early intervention providers may have little specialized training to address need-specific challenges. Importantly, it is unknown whether EP children with autism and related communication delays receive individualized, need-specific services. One study reported, for EP children in general, that while the use of medical specialties, neurodevelopmental services, and occupational therapy and physical therapy were widely used, speech-language services were used the least [103]. Given that speech-language-communication services are the most common types of early intervention for infants and toddlers with autism [67], there is an opportunity to improve access to, and utilization of, need-specific services in the population of EP children, with a focus on those at risk for autism and related communication delays. A major concern is that speech-language services for EP children appear to be primarily focused on oral-motor needs rather than language-communication needs, a likely critical challenge for EP children displaying symptoms of autism and communication delays [104,106].

Congenital heart disease

Survivors of neonatal surgery for congenital heart disease (CHD) exhibit a high prevalence of compromised neurodevelopmental outcomes [108–111], which have lifetime implications and represent a major contributor to disease burden [109,112]. Among these neurodevelopmental challenges are speech-language-communication delays in general [109,113–119], and autism in particular [109,120–125]. These conditions compromise early brain development, and likely contribute to late-diagnosed neuropsychological burdens (such as visual construction and perception, intelligence, attention and executive functioning, and academic performance) and neuropsychiatric burdens (e.g., psychosocial maladjustment, internalizing and externalizing problems) known to be highly prevalent in the lives of children, adolescents and adults with CHD [109]. Despite high levels of severe developmental delays by age 3 years reported by parents of children with CHD requiring early surgery, early intervention service utilization is low [126]. Of concern, if families do not access services in the first year of life, they may never receive them [126], suggesting that services for ‘low severity’ developmental delays may be underutilized because these conditions may go undetected without formal neurodevelopmental

evaluation [126]. And yet, 'low severity' delays are the most common finding in children with CHD [127], are unlikely to be identified in the first year of life, and are more amenable to remediation early in life [126] relative to more severe medical, motor or psychomotor concerns. Hence a scientific statement from the American Heart Association on neurodevelopmental outcomes in children with CHD [109] has recommended universal screening and systematic evaluation for autism and related communication delays in children with CHD at ages 18 and 24 months, consistent with the American Academy of Pediatrics recommendations for the general population [8].

While neurodevelopmental disability is the most common, and potentially the most damaging [128-130], complication for survivors of surgery for CHD [111], early neurodevelopmental outcomes have improved only modestly over time, and only after adjustment for innate patient risk factors; and as more high-risk CHD infants undergo cardiac surgery and survive, a growing population will require significant societal resources [109,111]: for example, children with CHD are 50% more likely to receive special education services than children without birth defects, often qualifying in multiple exceptionality categories [131]. Currently known risk factors explain only ~30% of the observed variation in neurodevelopmental outcome after cardiac surgery in infancy [129], and few modifiable risk factors for adverse neurodevelopmental outcomes have been identified [128-130]. Like in children with autism and communication delays without CHD, early intervention services might greatly optimize outcomes for at-risk children with CHD if these conditions are identified, diagnosed and singled out for treatment. This is a priority not only highlighted by the American Heart Association Scientific Statement [109], but also by other expert panels providing practice parameters for similarly at-risk children, such as those born extremely premature [132], as described above, and whose early brain development share precisely the early brain development vulnerabilities found also in children with CHD [133,134].

While children born extremely premature or with congenital heart disease present with more clear-cut cases in which there is an opportunity to deploy solutions emerging from autism research in early brain development, other cohorts of children may present with similar opportunities, including those with other neurogenetic etiologies such as children with fragile X and Williams syndromes, or children

born in adverse conditions such as poverty: in all of these cases, there is a higher than expected prevalence of autism-related social and communication disabilities [135-137].

An agenda for neurodevelopmental medicine

If we are to capitalize on current knowledge of early brain development for the purpose of optimizing outcomes of children born with a wide range of genetic, medical and environmental burdens –if the vision proposed in this review is to become a reality– there will be a need for several advancements in systems of healthcare delivery and the associated implementation science required to effect such change. These will include:

Integration of neurodevelopmental considerations in pediatric healthcare systems

From primary care practices to highly specialized complex medical treatment centers to population-based healthcare programs, the focus of medical practice is on alleviating current medical concerns rather than strengthening conditions for future brain development. Primary care physicians need to treat common infections, monitor general growth and to act as gatekeepers for specialized care. But they are often unable to secure referrals for diagnostic and intervention services that will address cognitive, speech-language and communication delays that will eventually determine their patients' lifetime outcomes [9]. Pediatric cardiologists strive to increase survivability of children born with cardiac defects by improving surgical and post-surgical procedures, by decreasing ischemic injuries on brain, and by achieving medical stabilization while reducing hospital stay. But they are often unable to secure the early identification and remediation of developmental delays likely to lead to future neuropsychological, academic, and neuropsychiatric vulnerabilities in their patients [126]. While immediate medical concerns require immediate medical interventions, best-practice parameters in pediatric medicine, across sub-disciplines, have all emphasized the lifetime benefits of early detection of neurodevelopmental vulnerabilities and of improved access to early treatment and intervention.

Inter-professional healthcare delivery

There has been an increase of referrals of children with neurologic disorders, and disorders previously

managed by general practitioners are often seen in child neurology clinics [138]. At the same time, there is a shortage of physicians practicing neurodevelopmental medicine, and inadequate training in management of non-acute neurodevelopmental concerns [139,140]. And yet, chronic burdens associated with long-term compromised development are not amenable to short consultations or 'one-off' interventions; in fact, most developmental risks are multifactorial and involve social determinants, thus requiring a team approach requiring professionals with different areas of expertise and different levels of access to affected families, all working in concert to address the child's global needs [141]. These facts necessitate a change in child neurology practice, from being an isolated point of care to an element of expertise within a nexus of healthcare professionals, ranging from physician colleagues in other disciplines, to nursing personnel, speech-language pathologists, psychologists, care coordinators, home visitation providers and others [142].

Better and more cost-effective diagnostic tools and more accessible interventions

Whether in primary care, or in specialized child neurology or child psychiatry practices, physicians' ability to address children's developmental concerns are significantly hindered by the fact that early diagnosis of cognitive or speech-language and communication delays typically require the costly deployment of experts, whose availability is scarce; or depends on procedures that are subjective in nature, or which are limited to information provided via parent report. This state of affairs contrasts markedly with medical conditions for which there are objective and quantitative markers of disease and of response to treatment. An MRI scan of the brain may pinpoint and quantify a brain tumor; cluster of differentiation markers may classify white blood cells and diagnose and monitor lymphomas and leukemias. In contrast, no such markers are available for conditions such as autism or language delays. With limited time to see a child and poor reimbursement for 'non-medical' developmental procedures, it is well-nigh impossible for physicians to embrace their role in neurodevelopmental health. This challenge has provided our group with the impetus to transform our lab-based experimental procedures, now shown to have diagnostic utility, into an investigational device undergoing large field testing. This device aims at providing diagnostic and developmental information about a child within the context of a 12-minute procedure conducted by a

technician, not unlike other medical tests capable of quickly providing the clinical provider with the information they need in order to operationalize an action plan, and execute it, on behalf of their patients, all of which within parameters of viability within the context of busy clinical practices.

Physicians also often face the dilemma that, were they to sound a diagnostic alarm, it is still the case that securing treatment and intervention remains a challenge, as treatment providers are in short supply, or financial coverage might not be available. Some are also unaware of the availability of evidence-based treatments that can benefit children greatly despite their chronic conditions. In this light, many would feel that it is unethical to convey a concern to a family, or to make a diagnosis, if there were little for them to offer to that family. And yet, as noted, effective and viable treatments are available, and community update is on an upward trajectory as implementation science studies continue to expand showing the effectiveness of these interventions in clinical settings, including low-resource ones, and the successful implementation of systems of care that coordinate communications across various settings, linking, for example, families, primary care physicians and early intervention providers, thus ensuring successful referrals, family engagement, and access to services.

For these accomplishments to become the norm in our communities, they will require change at multiple levels of the ecosystem of care in which child neurology plays but a limited role to date, but in which it could effect a much more pervasive and beneficial role were it to unpack the beneficial implications of current science of early brain development into tangible policies and models of healthcare delivery. Major advancements are already being made in all areas touched in this review, including better tools, more integrated inter-professional communication systems, and community-viable interventions, as we described in greater detail in a previous piece for this journal [38]. These advancements raise the prospect of a near-future neurodevelopmental medicine that goes beyond the treatment of acute or chronic brain symptoms –thus alleviating suffering– to a focus on preventing or significantly attenuating the deleterious impact of early burdens on brain development, thus promoting optimized outcomes. For this scenario to become a reality, child neurologists will have to expand their roles and become thought leaders in the domain of neurodevelopmental health, as well as architects of their own healthcare systems.

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Una agenda para la medicina del neurodesarrollo en el siglo XXI: lecciones aportadas por el autismo

Resumen. El futuro de la medicina de los trastornos del neurodesarrollo posee el potencial de situar a la neurología infantil en la vanguardia de un amplio esfuerzo de la sanidad pública con miras a optimizar los resultados del proceso de neurodesarrollo en los niños nacidos con diversas cargas genéticas, pre y perinatales y ambientales, de prevalencia elevada, que ponen en riesgo el desarrollo temprano de su cerebro y acaban provocando incapacidad durante toda la vida. Construida sobre los avances de la neurociencia del desarrollo social y de la ciencia traslacional, esa transformación ya está teniendo lugar en el ámbito de un trastorno del neurodesarrollo emblemático como es el autismo. Aprovechando la neuroplasticidad temprana y la cuantificación de las trayectorias del desarrollo comunicativo y social, están viendo la luz nuevas tecnologías de diagnóstico con alta capacidad, rentables y viables para administrar potentes tratamientos en el ámbito comunitario, en perfecta integración entre redes de atención sanitaria que en el pasado estaban fragmentadas. Estas soluciones son susceptibles de utilizarse para atender a otros colectivos de recién nacidos y niños con un riesgo acusado de autismo y retraso de la comunicación, como los prematuros extremos o los niños con cardiopatías congénitas. La idea motriz de este futuro ambicioso es que la sanidad pública se concentre en la promoción de las condiciones óptimas para el desarrollo inicial del cerebro, de modo similar a las actuales campañas de fomento de la atención prenatal, la nutrición o la vacunación.

Palabras clave. Autismo. Desarrollo cerebral temprano. Detección precoz. Interacción social de carácter visual. Intervención precoz. Medicina del neurodesarrollo. Optimización de los desenlaces. Trastorno del espectro autista.