

Genetic and environmental vulnerabilities in children with neurodevelopmental disorders

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One might expect that children with varying genetic mutations or children raised in low socioeconomic status environments would display different deficits. Although this expectation may hold for phenotypic outcomes in older children and adults, cross-syndrome comparisons in infancy reveal many common neural and sociocognitive deficits. The challenge is to track dynamic trajectories over developmental time rather than focus on end states like in adult neuropsychological studies. We contrast the developmental and adult approaches with examples from the cognitive and social domains, and we conclude that static models of adult brain lesions cannot be used to account for the dynamics of change in genetic and environmentally induced disorders in children.

autism | Down syndrome | infant development | number development | social cognition | Williams syndrome

This paper examines some of the key differences between two interpretations of genetic and environmental vulnerabilities in children: one interpretation inspired by static adult neuropsychological models and the other interpretation inspired by dynamic developmental accounts. This paper presents a rather unusual blend of theoretical and empirical issues, a blend that we deem critical to make our case. In the first section, we contrast the ways in which the static and dynamic paradigms have addressed research on neurodevelopmental disorders and show why a developmental account is crucial to understanding the dynamics of change. The next two sections use concrete examples to illustrate a dynamic developmental approach to the cognitive and social domains. One section focuses on a cognitive domain—infant sensitivity to numerical displays—in two neurogenetic syndromes and illustrates how the adult and developmental paradigms yield very different interpretations of exactly the same data. The other section takes a similar approach by examining examples from the social domain—the effects of differences in parent-child interaction. Throughout the paper, we argue that the adult neuropsychological model should no longer be applied to genetic and environmental vulnerabilities that dynamically change over developmental time.

Static vs. Dynamic Approaches to Neurodevelopmental Disorders

Research on neurodevelopmental disorders has often been inspired by models of adult neuropsychological patients (1, 2), which is illustrated by the following quotation: “Williams syndrome can be explained in terms of selective deficits to an otherwise normal modular system” (ref. 2, p. 347). By contrast, we have consistently stressed the dynamic nature of neural and cognitive development over time:

[B]rain volume, brain anatomy, brain chemistry, hemispheric asymmetry, and the temporal patterns of brain activity are all atypical in people with Williams syndrome. How could the resulting system be described as a normal brain with parts intact and parts impaired, as the popular view holds? Rather, the brains of infants with WS

develop differently from the outset, with subtle, widespread repercussions (ref. 3, p. 393).

We termed this latter approach neuroconstructivism (3–6), recognizing that the infant brain is not only less differentiated and less modular than the adult brain but that, early on, it is highly interconnected. Only through experience and pruning do brain circuits gradually become increasingly specialized and localized (i.e., relatively modularized) over the course of development (3, 7–9). Environmental factors play a key role in ontogenesis (10), affecting both gene expression and progressive neural specialization. In sum, the application of the static adult neuropsychological model to developmental disorders ignores the ontogenetic history of the organism, and the roots of development are often critical for understanding the dynamic trajectory that leads to the socio-cognitive end state (11).

With this distinction between static and dynamic paradigms to development in mind, we present cross-syndrome comparisons of infant cognitive data, which lend themselves to two very different interpretations. We then go on to extend similar reasoning to the social domain.

Two Interpretations of Infant Sensitivity to Number in Neurodevelopmental Disorders

Studies of adult neuropsychological patients have yielded a double dissociation between numerical abilities that affects different intraparietal circuits—one circuit for computing exact number and the other circuit for computing approximate numerical quantities (1, 12, 13). Research on typically developing (TD) infants reveals two similar systems that develop at different rates (14–18). Small exact number discrimination involves the computation of precise differences between one, two, three, or four items. Large approximate number discrimination is the ability to judge whether two quantities (e.g., 8 vs. 16 items) are different without being able to count them; this ability relies on magnitude judgments. Whether these two systems are innately specified or emerge as the product of gradual brain specialization remains a topic of considerable debate (19–21).

Here, we discuss findings (details in *SI Text*) from a study of large approximate number discrimination and small exact number discrimination in infants with Down syndrome (DS) and

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compare them with our previous work on infants with Williams syndrome (WS) (20, 21). We set the stage by first summarizing earlier findings from which we generated a prediction. Our initial cross-syndrome design had examined only small exact number discrimination in infants with WS and DS as well as two groups of TD controls matched on either chronological age or mental age. That study revealed that, like TD controls, infants with WS succeeded in discriminating changes in small exact number, whereas those infants with DS failed (21). We contrasted this finding with the serious numerical deficits that emerge in later WS development (22–24) as well as a cross-syndrome study showing that, although both syndromes are impaired relative to TD controls, older children/adults with DS significantly outstrip those individuals with WS on a battery of mathematical tasks (24). This finding would suggest that successful small exact number discrimination in infancy does not predict subsequent mathematical outcome.

At that juncture, data on large approximate number discrimination in TD infants were emerging. It turned out that TD infants can discriminate not only small numbers (one, two, and three) as early as 3 mo but subsequently, large approximate quantities; at 6 mo, they differentiate 8 dots from 16 dots (i.e., a ratio of 1:2), and by 9–10 mo, they distinguish 8 dots from 12 dots (i.e., a ratio of 2:3) (25, 26). Because infants with WS performed like TD controls on small number but had serious problems with subsequent mathematics, we hypothesized that their deficits might originate in early problems with large approximate quantity discrimination. With a new group of infants/toddlers with WS, we showed this hypothesis indeed to be the case (20). Just like the WS infant group in the earlier study, the new WS infants succeeded in discriminating small numbers. However, they showed significantly weaker discrimination of large approximate quantities (20), even with the easy 1:2 ratio and despite being significantly older than the age at which TD infants succeed.

A cross-syndrome comparison was, however, critical to a hypothesis (i.e., that large approximate number discrimination in infancy might be more predictive of subsequent mathematical abilities than small number discrimination). We, therefore, individually matched a new group of infants/toddlers (Table S1) with DS to our previous infants/toddlers with WS (20), and we tested them on the same two tasks measuring small (2 dots vs. 3 dots) and large (8 dots vs. 16 dots) number discrimination (Figs. S1 and S2). We predicted that infants/toddlers with DS would yield the opposite pattern as the infants/toddlers with WS.

Our results yielded a double dissociation between small exact number and large approximate number in infancy in the two neurogenetic syndromes. We replicated our previous findings that infants/toddlers with DS have serious difficulties discriminating small exact numbers, but this time, we used a different group of DS children of a similar age range, indicating that the current DS group is a representative sample. Most interesting was our demonstration that, unlike those children with WS (20), infants/toddlers with DS, who failed small number discrimination, succeeded in discriminating differences in large approximate quantities (SI Text and Fig. S3). We argue that the DS infant ability with large approximate quantities contributes to an explanation of why older children with DS subsequently go on to have better, albeit not normal, numerical abilities than their chronological age- or mental age-matched WS counterparts (24).

One might object that the DS findings can be explained by the fact that the small number task (2 dots vs. 3 dots) involved the harder 2:3 ratio, whereas the large number task (8 dots vs. 16 dots) used the easier 1:2 ratio. Two reasons discount such an explanation. First, the WS infancy data yield the opposite pattern, and therefore, one of the tasks cannot be intrinsically more difficult than the other. Second, the TD literature has clearly shown that small exact number discrimination is not subject to

ratio constraints, whereas large approximate number discrimination is subject to such constraints (14, 17, 25, 26).

At first blush, our findings yield a double dissociation between two neurogenetic syndromes, typical of findings in the adult neuropsychological literature, that points to two separable numerical subsystems, which some might claim to be innately specified as either intact or impaired. Everything seems clear: for WS, one or more of the 28 genes deleted on one copy of chromosome 7q11.23 contributes to a domain-specific deficit in large approximate number discrimination, while leaving intact the small number system, and for DS, one or more of the extra genes on chromosome 21 contributes to a domain-specific deficit in small exact number discrimination, while sparing the large number system.

However, concepts like double dissociation, intact, and sparing are borrowed from the adult neuropsychological literature. Are they appropriate for developmental syndromes (3, 4, 27)? Do numerical systems start out prespecified in the infant brain, already dissociated into separate subsystems, or do these subsystems emerge over time through early cross-domain interactions as different brain circuits progressively specialized for different numerical functions (3, 4, 19)?

To address these questions, it is critical to examine which other aspects of development interact with infant sensitivity to numerical displays. In adopting this more dynamic developmental perspective (5–7, 28, 29), we related our DS numerical findings to earlier data on infant/toddler attention and saccadic eye movement planning in the two syndromes (30). The attention studies identified deficits in both syndromes—problems with attention shifting in WS and problems with sustained attention in DS. The eye movement research revealed that infants/toddlers with DS had similar patterns to TD infants (i.e., efficient saccadic eye movement planning), whereas those infants/toddlers with WS displayed severe deficits (30). We, thus, hypothesized that infants/toddlers with WS might be impaired with respect to their scanning of large numerical displays. To further explore this hypothesis, after the experiment, we used the Tobii Infrared 1750 Eye Tracker (31) and were able to subsequently collect data from some of the atypical infants while they were viewing numerical displays on the computer screen. Unfortunately, as can be the case when testing atypical infants, it was often difficult to calibrate their eye movements and thus, obtain sufficient data for statistical analysis. Nonetheless, an initial examination of scanning patterns of the few infants who did provide useful eye tracking data indicates that, like our studies of eye movement planning and attention (30), those children with DS tended to scan the overall array, whereas those children with WS tended to remain fixated on a few individual items (illustrations of WS and DS scanning patterns for large approximate number are in Fig. S4).

We, therefore, argue that the numerical deficits in WS may be rooted in basic level visuoattention problems that cascade over developmental time on other emerging cognitive level domains, such as number. For WS, a serious deficit in rapid saccade planning (30) causes problems in visually disengaging from individual objects in displays. This finding likely explains why WS infants/toddlers succeed at small exact number discrimination but have difficulty discriminating large approximate quantities. The opposite is true for infants with DS, because their problems lie in difficulties with sustained attention (32, 33), which makes it difficult for them to individuate objects in small displays. Thus, rather than identifying a double dissociation between the syndromes, a single basic level problem for each syndrome—attention shifting in WS and sustained attention in DS—contributes to the explanation of both the proficiencies and deficits in each syndrome concerning early sensitivities to differences in small and large numerical displays.

It is possible that an even more basic problem contributes to these differences, one which is again more domain-general and outside the domain of number. The work by Dakin et al. (34)

reinterpreted numerosity processing in terms of the ratios between low and high spatial frequencies (LSF/HSF) in displays. Interestingly, individuals with WS have difficulty with LSF displays, and individuals with DS have problems with HSF displays (35, 36). Irrespective of whether the numerical problems are directly in the HSF and LSF demands on the visual system and/or related to differences in attention mechanisms, it is clear that the deficits and proficiencies of each syndrome (and perhaps, the different onset timing of small and large number discrimination in TD infants) do not entail an explanation solely in terms of domain-specific number abilities.

Clearly, these early cross-syndrome differences should not be interpreted in the adult neuropsychological terms of a double dissociation in numerical abilities, with small number impaired and large number spared in DS and vice versa in WS. Rather, the differences are likely to be traceable to basic level deficits or proficiencies in the visual and attention systems early in development, which have cascading effects on cognitive level outcomes over ontogenetic time.

Our studies highlight the need for syndrome-specific intervention. Importantly, training for number should not start out being domain-specific (i.e., focused on number per se). For WS, we suggest that training initially targets rapid visual saccade planning very early in the developmental trajectory, which could lead to an enhancement of their scanning abilities and encourage a focus on global quantities rather than only individual objects. For DS, by contrast, training in sustained attention might be more appropriate, leading to a focus on individual objects with better discrimination of small number displays. Our future research will coregister high-density event-related potentials (ERP) and eye tracking in older toddlers to ascertain whether such syndrome-specific training regimens impact on brain specialization over developmental time in these neurodevelopmental syndromes.

Our findings alert scientists to the limitations of some traditional developmental research focused on single age groups or single syndromes. They highlight the theoretical and applied importance of a neuroconstructivist approach [i.e., tracing cognitive level functions back to their basic level roots in infancy and then probing their ontogenetic progression (4, 6, 37), which elucidates how number abilities initially interact with other developing capacities, such as attention and visual scanning]. They also underline the critical role that cross-syndrome comparisons play in the planning of syndrome-specific intervention. Crucially, the cross-syndrome number study challenges the use of neuropsychological models of adult brain lesions for explanations of early proficiencies or deficits in neurodevelopmental syndromes.

Extending the Neuroconstructivist Approach to the Social Domain: Need for In-Depth Studies of Environments

This same neuroconstructivist, cross-syndrome approach can be extended to the social domain. Hitherto, experimental research into social impairments in, for example, autism spectrum disorders (ASDs), has often focused on older children and adults compared with TD controls (38, 39). However, the social deficits in ASD are likely to be rooted in early infancy (40, 41). We believe that a comparison between infants with WS and infants with ASD might constitute a fruitful avenue of research, despite the obvious syndromic differences. Genetically, the two syndromes are indeed different, with ASD likely to be caused by multiple genes of small effect and WS caused by a heterozygous deletion of some 28 contiguous genes on chromosome 7q11.23. Phenotypically, individuals with WS seem to have the opposite social profile of individuals with ASD (6, 38). Individuals with ASD are aloof and find looking at eyes and faces disconcerting, whereas individuals with WS are socially disinhibited and fascinated by eyes and faces. Individuals with ASD prefer to interact with objects, whereas individuals with WS actively seek engagement with people. Individuals with ASD fare better on spatial

tasks compared with language and communication, whereas individuals with WS are more proficient at linguistic than spatial tasks. In sum, the two syndromes seem to present with very different sociocommunicative profiles in both childhood and adulthood (6, 38). However, if we assess their profiles during infant and toddler development, numerous cross-syndrome similarities emerge. Both syndromes have difficulty with rapid eye movement planning. Both have problems with attentional disengagement. Both display atypical eye gaze following and atypical referential pointing, and both are poor at triadic attention (6, 40, 41). From a neural perspective, both have atypical cortical maturation, corpus callosum abnormalities, impaired orbitofrontal cortex/amygdala connectivity, and dorsal and ventral stream vulnerabilities, with gray and white matter integrity being compromised in both (42). There are, of course, differences between the syndromes, particularly in later neuro- and sociocognitive outcomes, but tracing their increasingly diverging developmental outcomes back to their commonalities in infancy could reveal more subtle deficits than the more obvious comparison with TD controls. This is particularly true when start states are similar but sociocognitive end states are different.

A number of teams worldwide are carrying out longitudinal studies of infants within families in which an older sibling has already been diagnosed with ASD. The studies aim to uncover neural, cognitive, and behavioral markers of ASD not only in toddlerhood but in early infancy before the age at which the syndrome is normally diagnosed (40, 41). However, before a marker can be identified as autism-specific, cross-syndrome comparisons are crucial. Ongoing research in our laboratory is using the same protocol as the London British Autism Study of Infant Siblings (41)—behavioral experiments, eye tracking, resting state EEG, ERP, questionnaires, and standardized tests—with infants with other syndromes as well as infants from low socioeconomic status (SES) backgrounds. Our studies will be addressing the following questions. (i) Which processes are syndrome-specific, and which are syndrome-general? (ii) Which are modality-specific vs. -general? (iii) Are the neural and sociocognitive processes different, even when overt behavior is similar? (iv) Over time, is there compensation or compounding of effects? It will be critical to follow each syndrome's trajectory over developmental time at multiple levels of analysis, including changes in gene expression, neural circuit activation, and sociocognitive processes.

One question to emerge from cross-syndrome comparisons is why the positive effects of high SES are not greater in families with infants with genetic disorders. Unlike children from low SES environments (43–47), many children with neurogenetic syndromes are well-nourished, grow up in a caring environment, receive considerable cognitive stimulation, and do not suffer the physical and mental abuses that exist in some contexts of early social adversity. Therefore, why do such positive environments not compensate for genetic vulnerabilities? Is it just the severity of the genetic mutations that constrains environmental effects? Or is it possible that this finding is not only because of a genetically compromised computational system but also the fact that early environments differ in more subtle ways than is commonly realized? Having a neurodevelopmental disorder not only involves genetic mutations; it also modifies the environment in which the atypical infant develops. We hypothesize that the moment that a parent is informed that their child has a genetic disorder, the parent's behavior subtly changes. As a result, the baby's responses within the dyadic interaction will also be subtly modified.

A couple of examples serve to illustrate this hypothesis. The first example is from motor development. Observational data from families who visit our laboratory reveal that parents of infants/toddlers with genetic syndromes often find it difficult (compared with parents of TD infants) to allow their atypically developing offspring to freely mouth objects to explore their properties with the sensitive nerve endings in the mouth or crawl/

walk uninhibited around the laboratory to fully discover their environment. We speculate that this reticence is because of a natural fear of accidents in vulnerable infants, but it nonetheless results in a less richly explored environment. The second example is from vocabulary learning (48). When TD toddlers start to name things, their parents allow them to overgeneralize. By contrast, in the case of toddlers with DS, for instance, parents veto overgeneralizations and correct immediately (48). We speculate that this finding is because they fear that their child with lower intelligence will never learn the right term if allowed to overgeneralize. However, initial overgeneralization in the TD child encourages category formation (e.g., by calling different animals cat, the child starts to create an implicit animal category), and categorization is known to be impaired in several neurodevelopmental disorders. We propose that such unconscious assumptions about what atypical children can and cannot learn may unwittingly lead parents to provide less variation in linguistic input and in general, a less varied environment to explore. These quite subtle environmental changes are likely to compound over time.

There is, therefore, a vital need for a more dynamic notion of environment (e.g., how having a neurodevelopmental disorder may subtly change the social, cognitive, linguistic, emotional, and physical environments in which the atypically developing child grows).

What about typical development? Are environments basically the same for those TD infants who suffer neither genetic nor environmental vulnerabilities? In fact, subtle individual differences in social interaction, even in the TD case, are ubiquitous and just as likely to become biologically embedded. Our study of the effects of differences in typical mother–infant interaction on the timing of infant cognitive milestones addressed this point (49). Healthy monolingual infants each underwent testing at 6- and 10-mo of age in several experimental tasks (i.e., processing of speech, human goal-directed actions, physical events, etc.) as well as videotaped recordings of mother/infant dyadic play with a structured set of toys. Our findings highlight the effects of differences in mother–infant interaction styles on the timing of the onset of cognitive milestones. At the group level, 6- and 10-mo-olds displayed all of the expected effects found in previous research. However, when we reanalyzed our data according to mother–child interaction ratings, the quality of dyadic interaction style—sensitive vs. controlling—turned out to subtly foster or delay development.

One might have expected that it would be dyads high on the sensitivity rating whose achievement of cognitive milestones would be advanced across all domains (i.e., that the positive effects of contingent mother–infant interaction would be domain-general). However, this expectation was not the case. For the domains of both physical event and speech processing, the infants from dyads with high sensitivity were, indeed, in advance of their peers (i.e., sensitive, contingent interaction fostered earlier specialization). By contrast, the opposite held for the processing of human goal-directed actions. In the latter case, it was the infants of the more controlling mothers who displayed earlier specialization.

Why are the infants of controlling mothers the ones who show earlier success in processing human goal-directed actions? Our

analyses of the details of the dyadic play sessions revealed that controlling mothers tended to impose their own choice of toy on their infants and keep changing the toys, without showing sensitivity to the infant's current focus of attention. In this way, the more controlling mothers force their infants to frequently process the mother's goals rather than focusing on their own goals. By contrast, the sensitive mothers altered their own goals to follow their infants' focus of attention. These subtle variations in dyadic interaction style, we contend, place different processing demands on infants when interpreting human social interaction, helping to explain the differences in onset timing of the infants' understanding of human goal-oriented actions (49).

The reason why infants from sensitive dyads show earlier specialization in speech processing is in the fact that the dyadic play sessions showed that such mothers provide their offspring with a greater variety of appropriate level input. The more controlling mothers, by contrast, varied their speech less, without taking into account the progressively changing nature of their infants' vocalizations. Much the same applied to physical event processing. The controlling mothers tended to interrupt their infants' exploration of objects and offer them a succession of new toys, whereas the sensitive mothers left their infants sufficient time to fully explore the properties of objects, which would, we believe, enhance their growing knowledge of physical objects.

If such subtle differences in early mother–infant interaction in TD infants growing up in nonadverse environments can have such effects on the timing of cognitive milestones (49), the developmental trajectories of those infants who grow up with genetic or environmental vulnerabilities are likely to be even more heavily influenced. Nothing is static in biology or psychology, and this finding holds equally for the environment.

Conclusions

Infant research has tended to raise static questions reminiscent of those questions asked of adult neuropsychological patients. Which modules are impaired, and which are intact? In which regions of the brain are they located? How are syndromes dissociated? By contrast, throughout this paper, we have advocated a more dynamic set of questions. How do phenotypic outcomes originate in infancy? How do neural circuits change over time? Which domains interact across their developmental trajectories? How can we use the cross-syndrome design to reveal more subtle differences than comparisons with TD controls? How do the multiple aspects of the dynamically changing environment affect development? Indeed, rather than the static approach of much of adult neuropsychology, scientists' basic question in studying genetic or environmental vulnerabilities should always be: is there a developmental explanation?

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