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Abstract

Within the context of early infant–caregiver interaction, we review a series of pivotal transitions that occur within the first 6 months of typical infancy, with emphasis on behavior and brain mechanisms involved in preferential orientation towards, and interaction with, other people. Our goal in reviewing these transitions is to better understand how they may lay a necessary and/or sufficient groundwork for subsequent phases of development, and also to understand how the breakdown thereof, when development is atypical and those transitions become derailed, may instead yield disability. We review these developmental processes in light of recent studies documenting disruptions to early-emerging brain and behavior mechanisms in infants later diagnosed with autism spectrum disorder, shedding light on the brain–behavior pathogenesis of autism.

Neonatal Development in Context

At birth, the behavioral repertoire of human newborns is limited [1,2]. Within just days, weeks, and months, however, early reflexes and reflex-like predispositions give way to complex volitional behavior: infants acquire new vocal abilities [3]; change their feeding, sleeping, and waking patterns [4–6]; and acquire new control of their eyes, neck, hands, and feet [7–12]. Brain size at birth, approximately one-third that of an adult's [13], doubles during the first year [14] and increases by another 35% by year 3 [15]. Synaptic density quadruples in year 1 and will be 150–200% greater than that of an adult by year 3 [16,17] (to then be pruned or selectively strengthened in iterations that continue throughout the lifespan [17,18]).

This enormous postnatal change, however, does not happen in a vacuum [19]; in the absence of near-constant care, the infant's survival would be nonviable [20,21]. The infant enters the world in a state of utter fragility, and requires a parent or primary caregiver to provide for

survival needs. In playing that role, the caregiver serves as both partner and facilitator, matching his or her own behavior (in facial affect [22,23], vocal tone [24,25], and physical touch [26,27]) to the needs of the infant in a manner that serves as the foundation for further acquisition of abilities [27–29]. The behaviors of infant and caregiver are thus mutually adapted and mutually reinforcing [30]: the infant–caregiver dyad, iteratively changing itself through interaction, is an integral and inseparable unit of early development [31].

Within that context, we review a series of pivotal transitions in the first 6 months of typical infancy that depend upon the mutually reinforcing context of the infant–caregiver dyad, with emphasis on behavior and brain mechanisms thought to be involved in preferential orientation towards, and interaction with, other people. This topic is especially timely given recent reports demonstrating disruptions to early-emerging mechanisms of brain and behavior in infants later diagnosed with autism spectrum disorder (ASD) [32–34], highlighting early periods of infancy as key targets for future research. In reviewing this literature, we endeavored to link recent work to a broader set of seminal papers in neonatal behavior and development (additional references can be found in online supplemental materials). Only by intensively studying these periods and more fully understanding the growth trajectories that define normative development, will we be able to gain new mechanistic insights into the pathogenesis of autism and related disabilities.

Mechanisms of Social Adaptive Action Present Shortly After Birth

The prolonged period of caregiver dependency and biological immaturity of human neonates, lasting years longer than that of other primate species [35], has often been noted as a critical aspect of human adaptive success [36]. More than simply providing a longer period of postnatal plasticity in which to refine brain and behavior [37], the initial fragility and prolonged maturation of the human newborn provide an ineluctable 'initial task' (that of survival) as well as a highly specific context in which that task will be solved. That context, the specific setting in which changes in newborn brain and behavior will take place, is defined by nearly continuous interaction with other people.

Preferential Orientation and Reflexive Engagement

Shortly after birth, neonates already display remarkable attunement to their caregivers, demonstrating reflexive and reflex-like patterns of behavior that enable close physical contact [38], as well as distinct patterns of preferential orientation to the sights, sounds, and smells of their caregivers [39,40] (preferences that are present already despite extremely limited ex *utero* experience, with some preferences present already *in utero* [41]). These reflexive behaviors increase an infant's probability of initiating and/or maintaining direct caregiver interaction: the palmar grasp reflex enables holding [38]; the Moro reflex facilitates caregiver contact in the event of falling [42]; the rooting reflex aids neonates' efforts to find mother's nipple [9]; and the sucking reflex facilitates successful and continued feeding [4].

In addition to the presence of these reflexive actions, rather remarkable preferences are evident already at 10 minutes postpartum, when neonates will track a moving face-like pattern farther than a pattern of scrambled or inverted facial features [43]. Similar evidence

of preferential orientation has been replicated within the first hour [44] and the first 1–5 days of life [45,46], for cues ranging from biological motion [47] to others' eyes [48]. These preferences are highly specific (Figure 1), encompassing sight [48,49], sound [39], and smell [50,51] (touch, too, undoubtedly plays a critical role [52,53] but remains relatively and unfortunately less well studied).

Signaling Behaviors

In order to effectively increase the neonate's chances of survival, the predispositions described above must function as more than mere preference: viewed more broadly, these predispositions must serve not only to direct neonatal resources towards the caregiver, but also to elicit the response of those caregivers by serving as signaling behaviors [54]. Neonatal crying is a clear example of a reflexive behavior that functions as a highly effective signal to promote proximity and contact [55,56]. Crying reliably evokes perceptions of distress and discomfort on the part of most parents [55], is associated with distinct patterns of brain activity, and is believed to evoke distinct neuroendocrine responses (here the existing literature is sparse in humans [57,58] but more well-established in animal models [57]). Crying's efficacy as a signaling behavior is also found in parents' response: holding or cuddling the infant is a highly efficient means of reducing or ending infants' crying [59]. Crying thus signals the infants' state but also elicits parent response and precipitates additional opportunities for interaction.

Beyond the vocal domain, the neonate's own facial musculature also serves as a potent signaling system. Fully formed and functional at birth, neonates' facial muscles enable them to produce all but one of the discrete facial actions visible in adults [60]. Although these facial expressions are not initially contingent upon caregiver behavior (e.g., neonatal smiles are largely reflexive, occurring during sleep [61]), the muscle actions themselves clearly resemble interpretable facial expressions, including smiling, brow-knitting, and pouting [60,62], and are fully sufficient to evoke a caregiver's emotional response. By evoking that response (without in any way depending upon it), these noncontingent behaviors facilitate future (actually) contingent social interaction [20,63].

The fact that initially spontaneous, noncontingent actions can beget actual social interaction highlights a means by which adaptive solutions emerge from reoccurring couplings of infant and caregiver [64]. In the preceding example, the capacity of the neonate (the physical ability to form a smiling facial expression) combines with stable, recurrent features of the caregiving environment (the consistency with which the caregiver responds to facial actions that look like smiling). That coupling increases the joint probability of emergent social adaptive action, beginning moments after birth. Critically, the neonate's capacities and the functional significance of those capacities as signaling behaviors cannot be understood without examining them within the caregiving context into which neonates' behaviors are adapted. Through repeated interactions, solutions to the neonate's initial task of survival lead to mutually adaptive actions on the part of both neonate and caregiver.

Mutual Adaptation

The behaviors described above (behaviors that serve to preferentially orient neonates' attention towards their caregivers, as well as behaviors that then serve as signals to those caregivers) are adaptive precisely because they provide selective advantage within an environment that includes a caregiver. But those behaviors by themselves would not be sufficient for survival, even in a caregiver's presence. They require the reciprocal, complementary actions of the caregiver, actions that are themselves modified to optimally respond to the signals of the neonate and to then elicit further signals [20].

Evidence of this iterative mutual adaptation (Table 1) is found even upon first contact with the neonate, when mothers display orderly and predictable patterns of species-specific behaviors that include touch and an intense interest in establishing eye-to-eye contact [65]. The mother's interest in the neonate's eyes matches the neonate's ability to attend to mother's eyes [48,49] and appears to play an important role in establishing affective ties [65]. In addition to seeking eye contact, caregivers use slow and exaggerated speech patterns, facial expressions, and body movements that are well matched to the newborn's restricted perceptual capacities [20,66,67]. These are also the actions that appear to optimally engage young infants [66,68].

In another instance of parity between infant and caregiver, newborn crying elicits picking-up and soothing [20], but newborn crying also occurs most frequently when newborns lose visual, auditory, or physical contact with their caregivers [55]. Parental response thus serves to reinstate that which was lost. Picking up the infant not only soothes and promotes state regulation but also increases newborn arousal and visual attentiveness [20,59]. Likewise, touching the infant has the effect of increasing infant eye contact with the caregiver [69]. Each of these mutually adapted actions facilitates still further forms of interaction [70].

Caregivers are, of course, highly motivated to engage their newborns socially. Reflexive actions of the newborn, such as grasping, are often interpreted by caregivers as signals of actual social recognition, affection, or emotional expression, well before such actions are consciously controlled or contingently deployed [20,63]. This perception creates rich opportunities for newborn learning: the meaning that caregivers ascribe to newborns' actions, and the way in which caregivers then modify their own reactions accordingly, creates the ideal framework for newborns to learn the meaning of their own actions: that is, through the reactions of their caregivers [71,72].

Early patterns of imitative behavior reveal this exact form of interactional meaning-making. Mothers imitate their babies' gestures soon after birth and continue to increase their degree of imitation in the following first 3 days [54]. Imitation is a form of mutual adaptation and another strong signaling behavior for both partners. Maternal imitation increases infants' gazing towards the mother, and an infant's reflexive orienting towards the eyes of a caregiver reliably elicits increased caregiver response [54,73].

Typical Transitions in Social Adaptive Action After 2–3 Months' Experience

Neonates' success in the social adaptive tasks described above (i.e., their success in preferentially directing biological resources towards a caregiver; the success with which their predispositions serve as signaling behaviors; and the success with which those signaling behaviors then become mutually adapted to those of their caregivers) creates, in turn, a set of new conditions that will further facilitate development. The initial acts of orienting, signaling, and adapting establish myriad opportunities for extended social interaction. These new avenues for social interaction present the infant with new tasks to be learned and put to use, setting the stage for a cascade of transitions in behavior (Figure 2).

Early Adaptive Action Constrains Later Learning

The iterative process of early infant learning, whereby 'each [ability] is first of all an effect of the preceding [ability], and itself becomes the cause of the following [ability]' ([74], p. 112), is well illustrated by the learning that transpires in Rovee-Collier's classic 'infant conjugate reinforcement' paradigm [75]. In this experiment, an infant lies on her back, with a string connecting her foot to a mobile that hangs above. Given the direct coupling between foot and mobile, movements of the infant's foot induce movement in the mobile, providing the child with novel reinforcement of what were initially only spontaneous leg movements. Importantly, infants discover this relationship themselves: as infants spontaneously kick their feet they learn the contingency between their own movements and the movement of the mobile. Once this link is discovered, the act of kicking, initially spontaneous and unrelated to the mobile, acquires new meaning: kicking becomes an instrumental act for effecting control over the external world. As a consequence of this newfound adaptive value, more precise and vigorous instrumental kicks increase while spontaneous and undirected kicks decline [76].

These data illustrate two key points about developmental change. First, infants play an active role in discovering their own new tasks: in this case, they discover a direct but previously unknown link between their own actions and those of the external world, and they then learn to control and exploit that link. Second, learned volitional behaviors can emerge from and/or depend upon behaviors that were initially spontaneous or reflexive.

Together, these two points demonstrate highly specific constraints that specify and guide subsequent skill acquisition: both the spontaneous initial actions (kicking rather than, for example, hand-waving) as well as the learned solution to that task (kicking with specific magnitude and direction) have the direct effect of limiting and specifying future instances of, and opportunities for, learning. If no initial kicks occurred, or the relationship between kicking and mobile never discerned, the contingency would not be learned. Likewise, by learning to control the mobile with specific kinds of kicks, the probability of other actions (e.g., trying to use hand-waving for the same purpose) declines, while the probability of the newly learned kicking increases (see [77] for an additional elegant example of how early experiences precipitate changes in infants' subsequent activities).

In short: by selectively exploiting specific actions that successfully yielded past adaptive results, infants transform not only their own future behaviors but also their own future

possibility of behaviors (i.e., altering the probability that other related behaviors will be more or less likely to occur) [78].

Reflex-like Behaviors Give Way to Volitional Actions

The kicking-to-mobile-movement contingency is by no means the only case in which learned, volitional behaviors replace, emerge from, and/or depend upon behaviors that were initially spontaneous or reflexive. A host of such transitions occur in a variety of different developmental domains in an infant's first months (Figure 3).

For instance, the side-to-side head turning reflex, a variant of the rooting reflex, is thought to play an important role in feeding by providing an opportunity for the neonate's mouth to come into contact with the mother's nipple [9]. As neonates gain increasing experience with feeding, this initially spontaneous action transitions to a directed head turning reflex at approximately 2–3 weeks of age [4,9], and then transitions again to volitional directed head turning at approximately 3 months [11]. The hand grasping reflex, present at birth, begins to disappear at approximately 4–5 months of age, coinciding with the emergence of voluntary reaching and grasping [38]. Similarly, the toe grasping reflex, also present at birth, begins to fade as infants gain voluntary control over feet and legs and begin to crawl [10].

These transitions from reflexive behaviors to volitional actions do not appear to progress according to lockstep chronological timers; instead, they depend more heavily on individualized experiences that are necessary to facilitate later transitions. For instance, the directed head turning reflex persists longer in infants who are breast-fed compared with infants who are bottle-fed [4]; voluntary reaching and grasping emerge earlier in infants who are afforded the experience of picking up objects [77]; and the decline of the toe grasping reflex is more closely related to the acquisition of voluntary control of the feet than to chronological age [10]. Each of these examples can be thought of as an individualized timescale of development: initial behaviors provide pivotal opportunities that enable subsequent learning, in highly individualized fashion. (For more on individualized timescales of development, and recent statistical advances in the measurement thereof, see Figure 4.)

Infant–Caregiver Adaptation Guides Developmental Transitions

The developmental learning processes described above are equally applicable to transitions in social learning. Just as infants discover a physical linkage in the foot and mobile example, infants also discover links connecting them to their social partners [79,80]. Research on infant–caregiver dyads reveals that infants' facial movements, head movements, and vocalizations are coupled, often tightly, to the facial expressions and sounds of their caregivers [54,79]. As infants discover and exploit the links between their own actions and the actions and reactions of others, the spontaneous and reflex-like behaviors of the neonate are transformed.

One notable example of such a transition is the case of orienting towards faces. Preferential tracking of faces (as described above) is initially a reflex-like, spontaneous, stimulus-driven form of orienting, observed from the first hours after birth [43]. Notably, however, this neonatal orienting response declines after 4–6 weeks postpartum, reaching a relative low

point, before preferential attention to faces then increases at approximately 2 months [29,81]. This would appear to be a transition from a more reflex-like response (i.e., not socially contingent) to a more volitional, truly social, form of orienting. Evidence of this transition is also supported by other changes at approximately 2 months. First, the physical characteristics of face-like stimuli that most effectively elicit preferential attention also change: while neonatal preference for faces can be elicited by simple schematic stimuli [44], real faces are preferred by 1–2-month-old and older infants (reviewed in [82,83]).

In addition, the 2nd month also marks the first time in which clear evidence exists that infants engage with other people in an interactive, socially meaningful manner. At approximately 2 months, infants begin smiling and cooing in response to faces [84]. Prior to this point, neonatal smiling is endogenous, happens most often during sleep, and shows little evidence of linkage to external stimulation [61,84]. At 2 months, however, smiles begin to be contingently linked to changes in caregiver vocalization and affective state, indicating not only the emergence of social smiling but also indicating that infants' preferential visual attention (in this case, directed towards faces) now also functions as a form of communication [84]. Newborn vocal development also undergoes marked change shortly thereafter: prior to approximately 3 months, crying is reflexive, undifferentiated, and marked by an absence of vowel production; after 3 months, cries become interactive, intentional [85], and increasingly reflective of the infant's psychophysiological state [3] (note that the timing of these changes, in contrast to smiling, is partially constrained by anatomy: at 3 months, the larynx descends [3] and the ribs reconfigure [86], altering the infant's capacity for vocal production).

Finally, there are also large changes at approximately 2 months in infants' expectations of other people. New capacities for active social engagement are evidenced by several classic studies: in the still-face paradigm [87], when a formerly interactive partner becomes unresponsive, 1.5- and 3-month-old infants (but not neonates) become upset, with signs of distress including crying, general negative affect, and shifts in visual attention away from the caregiver [88]. In addition, infant social bids during the still-face phase increase at 2 months of age [80], offering evidence that infants have now become active agents in dyadic interaction, developing specific expectations of the ways in which social interactions should unfold.

As infants exploit the links between their own actions and those of their caregivers, caregivers, in turn, modify their behavior to progressively advance cycles of learning. During the infant's second month, mothers spend more time talking and smiling with their infants, and less time displaying neutral facial expressions [89]. Regularities in face-to-face play (such as turn-taking) are established, repeated, and then extended during this period [54], with the peak in face-to-face play occurring between 3 and 6 months [90]. Evidence suggests that mothers of 3-month-olds display an average of approximately eight changes in emotion-related facial expressions per minute [54]. With even 3 hours per day of direct interaction, and with as little as 25% of that time spent directly attending to mother's face [91], an infant would be exposed to approximately 360 changing emotional cues in a single day, or more than 32 000 between the ages of 3 and 6 months.

Co-occurring Changes in Early Infant Brain and Body Systems

Relative to our knowledge of infant behavioral transitions, detailed information about co-occurring changes in brain are still limited. Existing knowledge does, however, suggest a substantial transition also occurring at approximately 2 months, shifting from largely subcortical to increasingly cortical control [92].

At birth, reflexive visual orienting appears to be supported by the subcortical visual system, which is differentially responsive to low-spatial frequency information [81], top-heavy vertically asymmetric patterns [93], and high contrast polarity [94]. Notably, these are all properties also strongly represented in the faces and eyes of conspecifics, and much like other mutual adaptations between infant and caregiver (Table 1), this match between signal and receiver may be a means of increasing the probability that neonates orient towards conspecifics rather than other competing stimuli [81,95].

As the neonate enters her second postnatal month, existing models suggest that reflexive orienting responses, subserved by subcortical structures, decline due to developing inhibition by cortical circuits (as visual preferences come under increasing cortical control) [96]. This theory is supported by the relative immaturity of primary visual cortex at birth [97] and also by developmental changes in orienting. Newborn orienting is most effectively elicited by face-like stimuli presented in the peripheral visual field [45] (the area that feeds more directly into subcortical visual pathways [98]), whereas preferential orienting in 2-month-olds is more effectively elicited by stimuli presented in the central visual field (which feeds more directly into cortical visual pathways [97]). Further evidence comes from the fact that retinocortical pathways become fully functional at approximately 2 months [99], and signs of adult-like cortical specialization for face processing are also first observed at 2- to 3-months in both event-related potential (ERP) [100] and positron emission tomography studies [101].

Generally speaking, however, much is still to be learned about infant brain development and the manner in which behavioral milestones are coupled with brain changes. Newly available resources (e.g., the Allen Human Brain Atlas [102] and BrainSpan [103,104] projects) and ongoing projects (Human Connectome [105] and Developing Human Connectome [106] Projects) are likely to transform our understanding of infant brain development in the coming years (Figure 5). Currently, however, data from infant behavior and brain development showcase a system that undergoes enormous developmental change in a matter of months: neonatal preferences and reflex-like responding give way to remarkably sensitive and contingent volitional action. We now review some of the emerging literature regarding what is currently known about the derailment of such action in children with ASD.

Disruptions in Social Adaptive Action in Autism Spectrum Disorder

A striking developmental contrast in autism is that older children, and even adults, on the autism spectrum often exhibit deficits in social adaptive action that are otherwise present in typical infancy. For example, while typically developing infants preferentially orient to the eyes of others [48,49], 2-year-olds [107], 10-year-olds [108], and even adults [109] with ASD do not.

Unfortunately, direct observation of infant development in autism is still limited. Given the late average age of conventional diagnosis [110], and the extent to which diagnosis currently depends upon behaviors that emerge in toddlerhood [111], a large gap in current knowledge remains. To fill that gap, the past 10 years have seen a substantial increase in prospective studies of the infant siblings of children with ASD, whose risk of also having the condition is approximately 20% [112], a substantial increase relative to infants in the general population [113].

Social Adaptive Action and Brain Specialization in Autism Spectrum Disorder

Recent studies examining the course of early social development in high-risk infant siblings have focused primarily on measures of social attention, interaction, and/or more general aspects of social development, using standardized assessments as well as experimental tasks (see online supplemental materials for references). A wide array of between-group differences have been identified among infants subsequently diagnosed with ASD, including, among others, differences in frequency of shared smiles, vocalizations, and gaze to faces [114,115]; attention to social scenes and images [116]; attention to and engagement with objects [117]; ERP amplitude differences in relation to observed eye gaze [118]; temperament profiles [119]; responsiveness to distress in others [120]; mutuality of infant–caregiver interaction [121]; and social smiling and joint attention [122,123].

Related differences are also found in brain structure [34,124,125] and function [33], with differences in extra-axial cerebrospinal fluid volume [125], cortical surface area [34], white matter fiber tracts [124], and functional connectivity [33] all identified as possible predictors of autism in the first year of life. Some studies have also highlighted ways in which similar overt behaviors were accompanied by notable differences in measures of underlying brain function [118,126].

Across these varied studies, one relatively consistent finding is that although indications of earlier differences are present, between-group differences are more easily identified at later ages (see online supplemental materials for references). This pattern of results is consistent with the notion reviewed above that development is iterative, with an infant's own actions and experiences guiding and constraining future learning [78]. Such a model predicts that even small disruptions of early social adaptive action can yield progressively greater between-group differences over time, culminating later in the marked symptomatology of ASD. Importantly, recognition of development as an iterative process means that differences observed at later times must be underway already at earlier ones.

Early Patterns of Preferential Orientation in Autism Spectrum Disorder and Transitions Therein

Given the foundational nature of social skills disruption in ASD, as well as the profound transitions in typical social development happening in early infancy, changes in preferential orientation, engagement, and adaptation during the first weeks and months after birth are a critical area of future ASD inquiry.

Existing data in infants later diagnosed with ASD suggest that one such mechanism, preferential orientation to the eyes, is not immediately diminished [32]. Levels of early eye-

looking are relatively high in infants with ASD. To be clear, the presence of these relatively high levels does not necessarily indicate 'normative' or 'intact' function [32]; to the contrary, while the magnitude of eye-looking at 2 months is relatively high, the underlying developmental processes are clearly already different: rate-of-change in eye-looking, from at least 2 months onwards, differs significantly between outcome groups. Moreover, infants later diagnosed with ASD exhibit a slight but statistically significant increase in eye-looking at 2 months, which then declines (Figure 3D); by contrast, typically developing infants exhibit a relative low point in eye-looking at 2 months, which then increases.

As reviewed above, the timing of these differences may relate directly to important transitions in adaptive behavior: preferential orientation to faces (present at birth [43]) typically declines between 4 and 6 weeks [44] before beginning to increase at approximately 2 months [81]. Similar transitions during this same period are observed in orienting to auditory sounds [127] and imitating others [128]. At a neural level, these changes are thought to be accompanied by a shift from subcortical to cortical control, with initial reflex-like predispositions (subserved by subcortical structures) declining as cortical control matures [81].

Taken as a whole, a very specific hypothesis emerges (Figure 3D): reflex-like orienting to the eyes of others may be initially, at least superficially, present in newborns with ASD, while the latter phase of preferential eye-looking is disrupted. More broadly, in a wide range of other sensory and behavioral domains, preferential orientation may initially be present in these infants, whilst early pivotal transitions (transitions that depend upon the way in which initial preferential orientation is integrated into mutually adaptive interaction) are disrupted. Critically, this hypothesis focuses scientific attention on key developmental transitions very early in life, and specifically on the progression from a reflexive/'experience expectant' phase of development (largely subcortically mediated), to an interactive/'experience dependent' phase (with greater dependence on cortical control) [96,97].

To be clear, there is little evidence to suggest an outright failure of cortical control of voluntary preferential visual attention in ASD; to the contrary, data at later age points suggest a co-opting of those cortical mechanisms by attention to other features of the environment, such as nonsocial, physical cues [107,129]. These data suggest future lines of inquiry, focused in these first few months, on how early predispositions transition into mutually adapted social interaction. This line of inquiry should benefit from a direct link to decades of work from pertinent model systems [130], work that can now be brought to bear in guiding gene–brain–behavior hypotheses of the pathogenesis of autism. Likewise, the role of other sensory systems in these processes remains understudied; given the early development of the auditory and tactile systems (affective touch in particular [53]), their role in constraining and influencing early development is a key area for future study.

Concluding Remarks

Collectively, the data reviewed above, from both behavior and brain development in typical infancy, showcase a system that is remarkably attuned to the social world, is mutually adapted to caregiver behavior, and becomes progressively more so overtime. From the first

moments of life, neonates exhibit a wide range of socially adaptive preferences and reflex-like responses that serve to orient their attention towards caregivers as well as behaviors that serve as important signals to those caregivers. These behaviors are adaptive because they occur within an environment that depends upon a caregiver, one whose own actions are adapted to optimally respond to the neonate's and to further elicit such actions. This mutually adapted, mutually reinforcing context of the infant–caregiver dyad is both the platform and the catalyst for subsequent development: initially spontaneous reflex-like responses transition into remarkably sensitive and contingent social action, all within the first months of life.

These findings, together with evidence from early normative transitions, provide an important framework for future research in ASD by constraining hypotheses about what specific developmental transitions may be disrupted in ASD and when. For instance, rather than suggesting a complete absence of preferential orientation to others from birth (as was hypothesized dating back to Kanner [131]), these data identify a specific transitional period of early infancy, around the second month of life, as a critical focus for future investigation, both for systems level neuroscience research (in both human and model systems) and for genetics research (guiding and providing the quantitative traits for developmental gene expression and methylation studies). These data further suggest that future analysis of potential disruptions in autism might productively focus on mechanisms of preferential orientation, signaling, and, critically, mutual adaptation between infant and caregiver, particularly during this transitional period (see Outstanding Questions). The pursuit of these constrained hypotheses holds great promise for yielding insight into the specific developmental processes that are disrupted in ASD and for discovering new opportunities for innovative early interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

From the first moments of life, neonates exhibit a range of socially adaptive preferences and reflex-like responses that serve to orient their attention towards caregivers, as well as behaviors that serve as important signals to those caregivers.

Within the first 6 months of typical infancy, a series of pivotal transitions occur within the context of early infant-caregiver interaction, as initially spontaneous reflex-like responses transition into remarkably sensitive and contingent social action.

Recent reports suggest that these developmental transitions may be disrupted in autism spectrum disorder, opening a critical theoretical insight into understanding the brain-behavior pathogenesis of autism.

Outstanding Questions

How do neonatal reflexive actions and predispositions transition into mutually adapted social interaction in the first months of typical development? What changes at the level of brain networks and gene expression accompany such transitions?

How do infants' early behaviors facilitate later attainment of normative social developmental milestones?

How do earlier-developing systems (e. g., touch), as well as disruptions in such systems (e.g., potential disruptions in affective touch in infants with ASD), have the potential to constrain and canalize the development of later-emerging systems?

For children with delays in specific milestones, is there a corresponding delay in offset of related reflexes? Or, alternatively, do reflexes decline on their own timeline, irrespective of other subsequent delays?

Is the transition from 'experience expectant' reflexive action to 'experience dependent' social interaction accompanied by a shift from subcortical to cortical control?

Are typical predispositions for conspecific orienting present in newborns with ASD?

How and when do mechanisms of preferential orientation, signaling, and infant-caregiver adaptation become disrupted in infants with ASD?
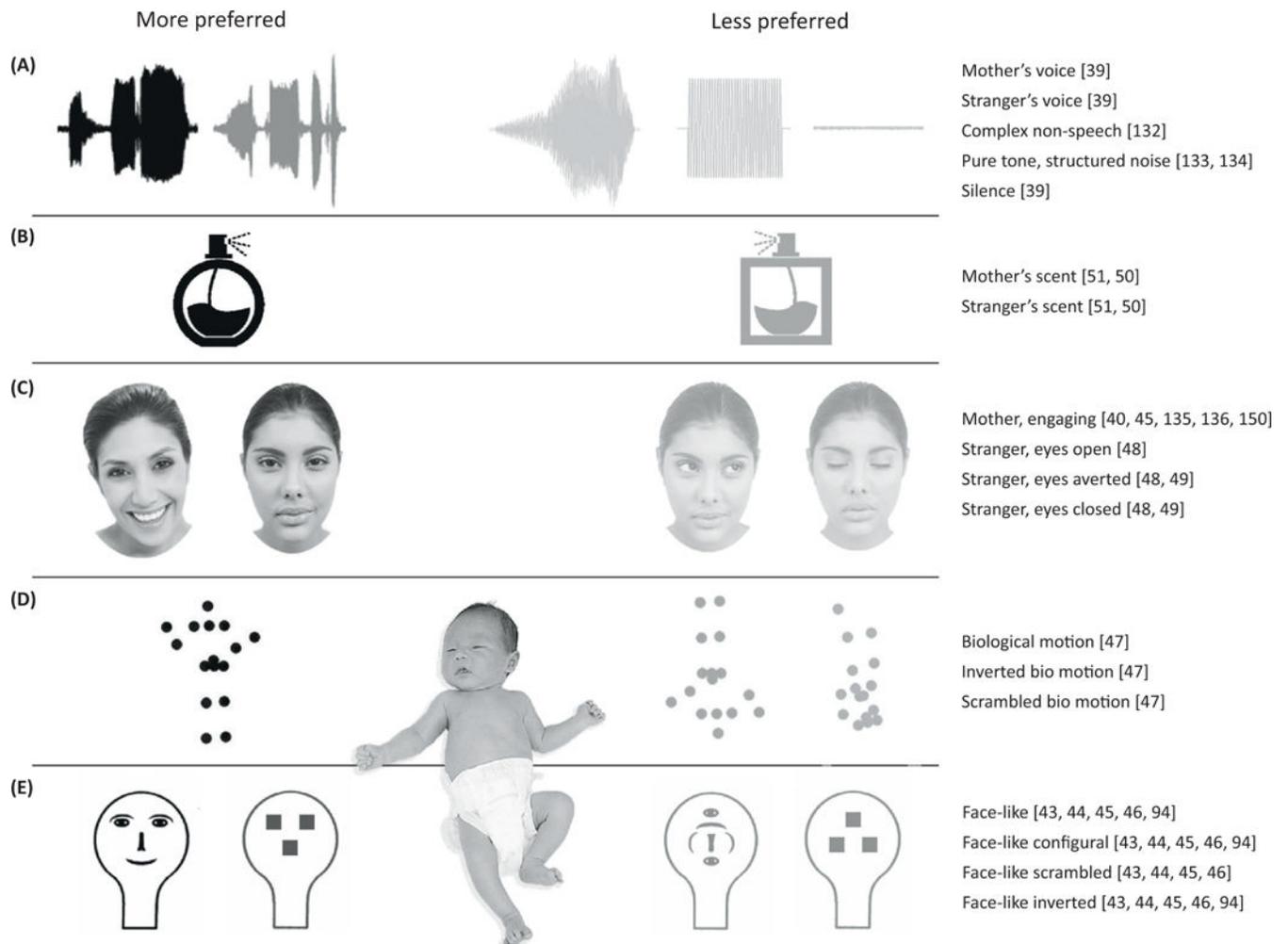
Figure 1. Neonatal Preferential Orientation to Caregiver Sounds, Smells, and Sights.
Preferential orienting is observed already in the first days after birth in the auditory domain
(A), in response to olfactory cues (B), and in visual attention to faces (C), biological motion
(D), and face-like stimuli (E). At 5 days, neonates show distinct preference for looking at
faces that have eyes open rather than closed and even distinguish, despite relatively poor
visual acuity so soon after birth, between faces with eyes directed towards them rather than
away. Similarly, neonates distinguish and prefer their own mother's voice to that of an
unknown woman, but prefer the sound of even an unknown woman's voice to that of silence.
In addition, neonates recognize their mother's smell and will selectively head-turn at 2–7
days after birth towards the scent of their own mother's breast. Examples of more preferred
stimuli are pictured in the left column while less preferred stimuli are pictured in the right
column. Stimulus descriptions and citations are given at far right. Data are from references
[39,40,43–51,94,132–136,150].
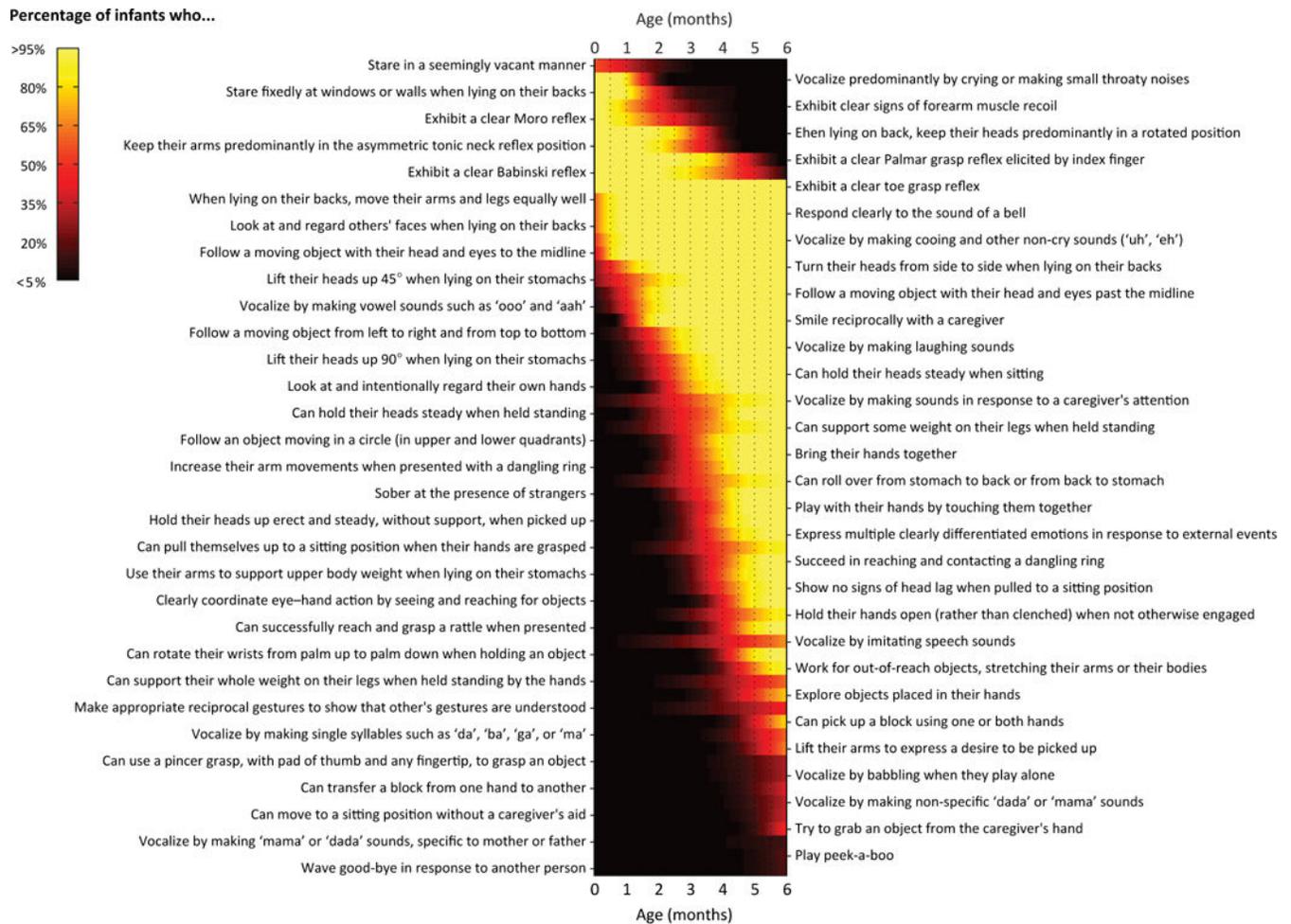
Figure 2. Developmental Milestones in Infants' First 6 Months.

Plotted data, showing the percentage of infants who display each listed behavior between birth and 6 months. Behaviors are plotted sequentially, with behaviors that emerge (and, in some cases, decline) earlier in development at the top and behaviors emerging later in development at the bottom. This sequence of developmental milestones highlights the cascading process of infant development, whereby an infant's own emerging abilities lead the infant towards new ways of exploring and experiencing the world, prompting further development in an iterative process. Developmental milestone data were scanned or transcribed from published texts and manuals [8,10,12,137–142]; data were fitted with a sigmoid function to describe the cumulative proportion of children displaying each behavior (common milestones were averaged across sources). The fitted functions are color-scaled from generally absent (black) to present in 50% of children (red) to present in most children (yellow).
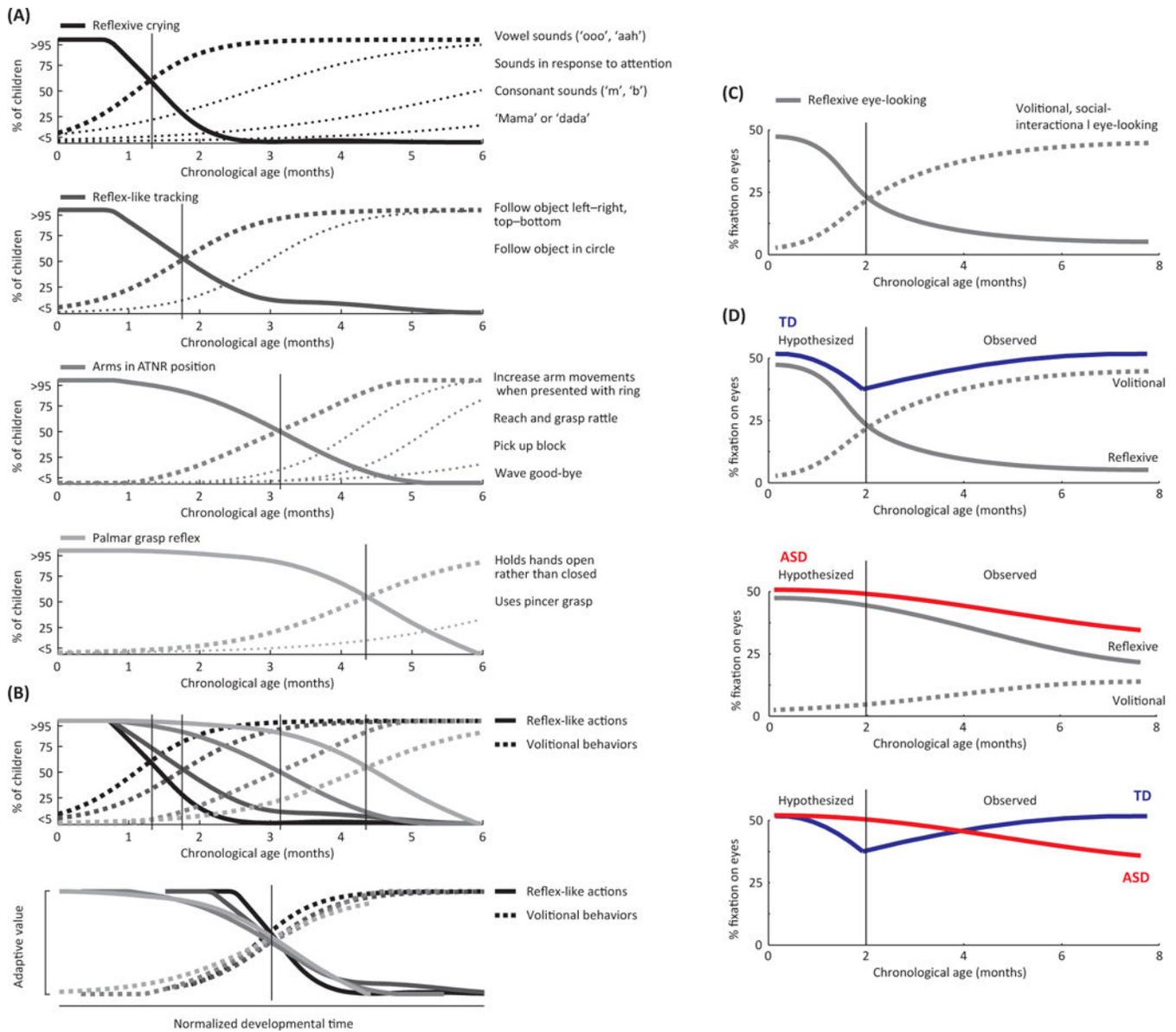
Figure 3. Transitions from Reflex-like Actions to Volitional Behaviors.
Behavioral transitions in the first6months of life, with implications for early social behavior
in autism. (A) Data from references [8,10,12,137–142] showing examples of declining
reflex-like actions (unbroken lines) and emerging volitional behaviors (broken lines) in the
vocal, visual, and motor domains. Approximate transition times are marked by vertical lines.
(B) Top, trajectories of reflex-like actions and volitional behaviors from (A) are plotted
against chronological age. Bottom, trajectories are aligned at the time of transition to
illustrate the idea that learned, volitional behaviors may replace, emerge from, and/or depend
upon behaviors that were initially spontaneous or reflexive: as new volitional behaviors are
acquired, the adaptive value of simpler reflex-like actions decreases, as does the action. (C)
In typical face perception, existing normative data [44,45,81,92] suggest a similar transition
at approximately 2 months: reflex-like eye-looking declines (unbroken gray line) while
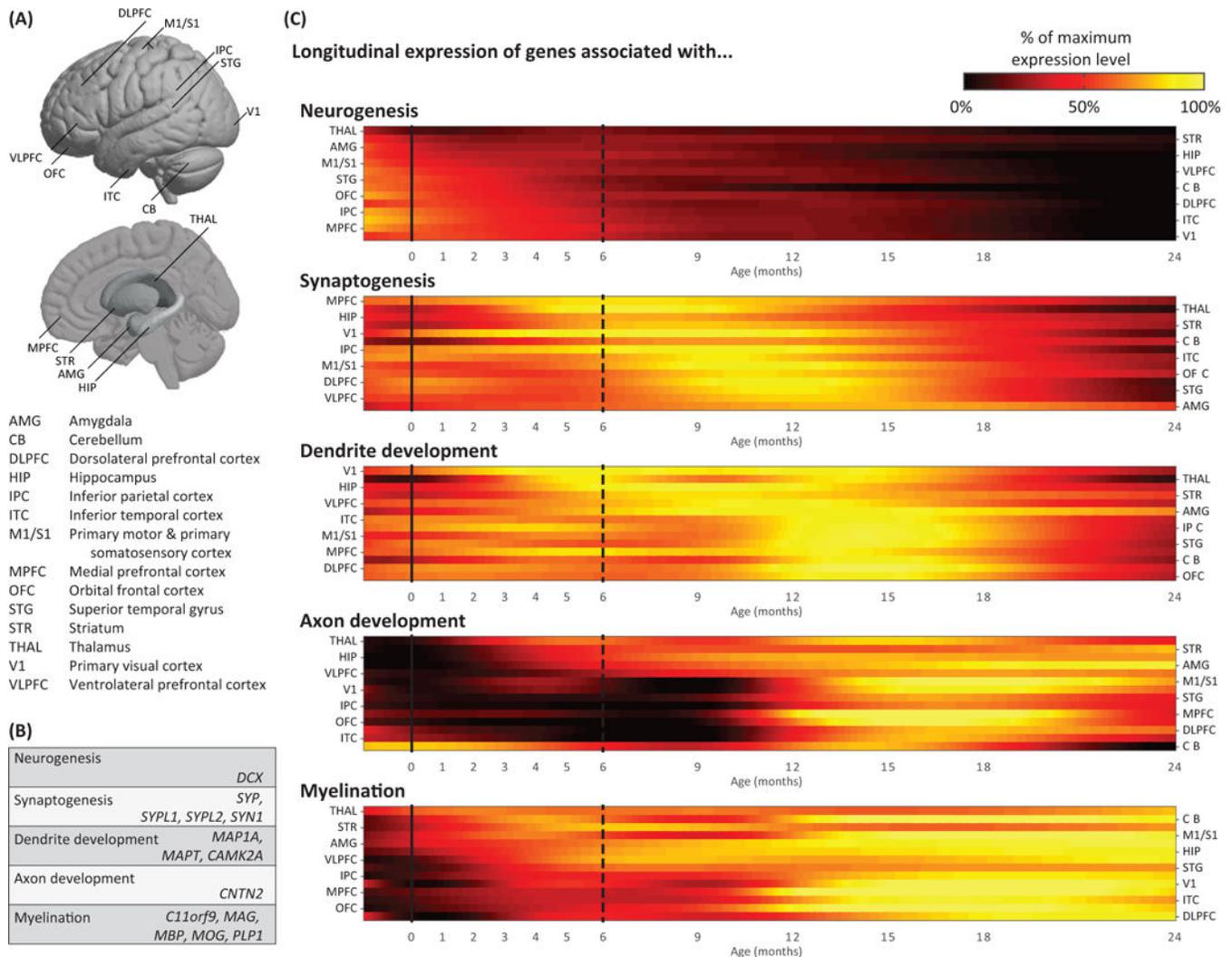
volitional eye-looking increases (broken gray line). Reflexive eye-looking is believed to be experience-expectant and subcortically mediated, while volitional eye-looking is believed to be experience-dependent and largely cortically mediated. (D) A corresponding reduction in amount of eye-looking by typically developing (TD) infants has been observed at the hypothesized time of transition, shown in the top panel (blue line, sum of percentage fixation on eyes). Observed data from months 2–8 replotted from [32]. Trajectories from 0–2 months represent hypothesized levels of eye-looking in keeping with existing normative data [96,97]. In observed data from [32], infants with autism spectrum disorder (ASD) exhibited relatively high levels of eye-looking at 2 months, which then declined. By contrast, TD infants showed relatively low levels of eye-looking at 2 months, which then increased. Relatively high levels of eye-looking at 2 months in ASD (red) suggests reflex-like eye-looking that is not supplanted by volitional eye-looking and, instead, persists atypically. Rather than an outright failure of cortically controlled voluntary preferential attention in ASD, eye-tracking data suggest a co-opting of experience-dependent cortical mechanisms by attention to other, nonsocial features in the environment. As a result, reflex-like eye-looking gradually declines as it is supplanted by attention to other (non-eye) features. Abbreviation: ATNR, asymmetrical tonic neck reflex.
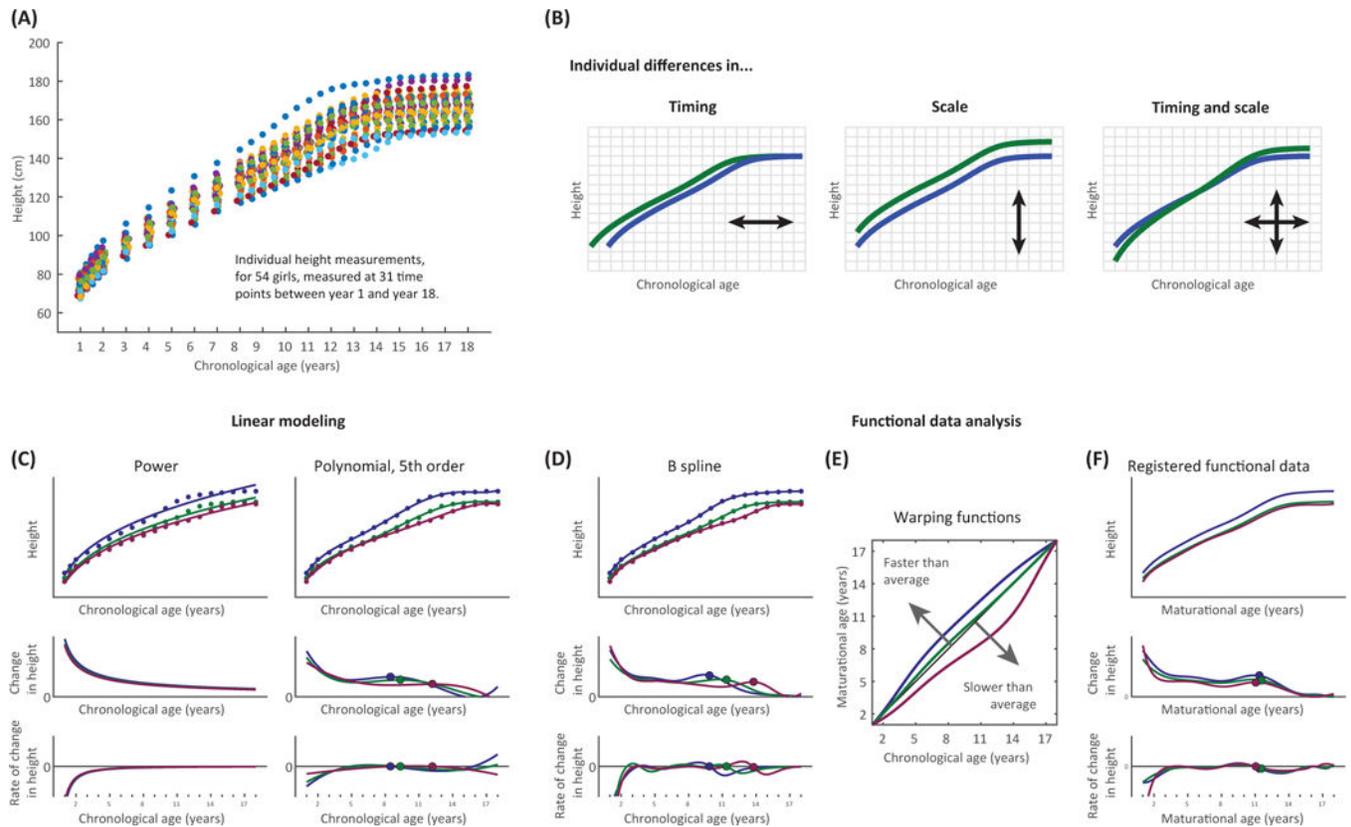
Figure 4. Developmental Methods: Quantifying Individualized Timescales of Growth.
Functional data analysis is a relatively new method of analyzing time series data that places greater emphasis on individual trajectories of data, considering the trajectory itself to be a single observation and quantifying that function's variability in terms of both timing and scale [143,144]. This is an important methodological as well as conceptual shift in how longitudinal data are analyzed and understood, with exciting implications for studies of child development and for the conclusions we may draw about underlying biological processes. A good example of this shift can be seen when analyzing a very literal example of a child's growth: change in height. (A) Shows height measurements of girls from 1 to 18 years of age (from the classic Berkeley Growth Study [145]). The underlying biological process of growth is of course nearly identical in all children, but exactly when the pubertal growth spurt occurs and how large it is varies considerably by individual. (B) Individual differences can be expected in timing (when a particular change occurs), in scale (how large or small a given change may be), and in both timing and scale. With conventional growth curve modeling, (C) fitting individual data with a power function (left panels) yields a relatively good fit in statistical terms ($R^2 > 0.98$ for each of the three example curves); however, it also eradicates all signs of the pubertal growth spurt, as seen especially in the plots of change in height and in rate of change in height (the 1st and 2nd derivatives, respectively). Fitting the same data with a 5th order polynomial [right panels of (C)] improves the picture somewhat, but parameter estimates of when the pubertal spurt occurs in individual children (colored dots) are as much as 2 years earlier than estimates observed in a more data-driven fashion, as in (D), using B-spline basis functions. (D) In functional data analysis, variation in both

timing and scale are quantified, and curve shape is determined empirically. (E) Rather than being confounded by individual differences in maturational rate (individualized developmental timescale), functional data analysis measures the extent of these differences as 'warping' or registration functions, explicitly comparing and correcting for differences in chronological time versus individual maturational time. (F) When data are analyzed as functional trajectories, registered according to measures of individual difference in developmental timing, the ability to estimate the shape of the actual developmental process improves substantially.

(A)

DLPFC
M1/S1
IPC
STG
V1
VLPFC
OFC
ITC
CB
THAL

MPFC
STR
AMG
HIP

AMG	Amygdala
CB	Cerebellum
DLPFC	Dorsolateral prefrontal cortex
HIP	Hippocampus
IPC	Inferior parietal cortex
ITC	Inferior temporal cortex
M1/S1	Primary motor & primary somatosensory cortex
MPFC	Medial prefrontal cortex
OFC	Orbital frontal cortex
STG	Superior temporal gyrus
STR	Striatum
THAL	Thalamus
V1	Primary visual cortex
VLPFC	Ventrolateral prefrontal cortex

(B)

Neurogenesis	DCX
Synaptogenesis	SYP, SYPL1, SYPL2, SYN1
Dendrite development	MAP1A, MAPT, CAMK2A
Axon development	CNTN2
Myelination	C11orf9, MAG, MBP, MOG, PLP1

(C)

Longitudinal expression of genes associated with...

% of maximum expression level

0%   50%   100%

Figure 5. Longitudinal Expression of Genes Associated With Neurodevelopmental Processes.
Recent advances in studying the spatio-temporal dynamics of gene expression in the human brain augur a new frontier for studies of infant and child development, connecting well-studied behavioral and cognitive milestones to multiple measures of infant brain biology. One example is the BrainSpan Atlas of the Developing Human Brain[i] [104], offering a transcriptional architecture of the human brain from early fetal development through adulthood. While longitudinal expression patterns for more than 17,500 genes were analyzed, the gene expression trajectories plotted here are for genes whose differential expression is associated with key neurodevelopmental processes. (A) Fourteen brain regions in which expression was measured are highlighted. (B) Five sets of genes are highlighted, the expression levels of which are associated with neurogenesis, synaptogenesis, dendrite development, axon development, and myelination, respectively. (C) Longitudinal expression levels of genes associated with each process are plotted, for each brain region, as a

[i]Resources
www.brainspan.org

percentage of the minimum and maximum lifetime levels of expression. Brain regions are sorted according to peak expression levels between 0 and 24 postnatal months of age. Note the clear waves of expression during these periods of early child development: high levels of expression associated with neurogenesis continue through the first 6 months of life, with marked decline thereafter, followed by waves of increased expression associated with synaptogenesis, dendrite development, axon development, and finally myelination. Given the enormous developmental change occurring in these time periods, data like these, coupled with densely sampled behavioral and neuroimaging data, are likely to transform understanding of infant development in the coming years. See online supplemental materials for additional related references.

Table 1.

Mutual Adaptation of the Infant–Caregiver Dyad

Infant capacity/action	Caregiver action/capacity	Refs
Neonates have strong rooting and sucking reflexes.	Rooting facilitates breastfeeding; sucking triggers maternal prolactin and oxytocin release (prolactin stimulates milk synthesis and oxytocin produces milk release). Amount and frequency of sucking determines the amount of breast milk produced; without suckling, milk production ceases.	[9]
Neonatal sound production is limited (by state of vocal tract development and brain maturation) to crying and vegetative noises (sucking, sneezing, breathing).	Crying reliably elicits caregiver actions, including closer physical proximity, increased holding, and increased cuddling; in lactating women, infant crying stimulates blood flow to the areolar area and milk flow from the breast.	[55,56]
Neonates significantly reduce their crying and become more alert when …	caregivers provide proprioceptive-vestibular stimulation (holding and cuddling).	[59]
Neonates demonstrate varying states of alertness.	Caregivers respond to periods of neonate alertness with affection: looking enface, smiling, talking, humming, singing, cuddling, and kissing.	[59]
Infants are differentially sensitive to sounds encompassing and modulated across a broader frequency range (150–550 Hz) than to sounds in narrower, lower frequency ranges (150–275 Hz) or to nonmodulated, lower frequency tones.	Infant-directed speech ('motherese', with characteristically exaggerated pitch contours) covers a broader frequency range inclusive of higher frequency sounds.	[68,146,147]
Newborns demonstrate increased responsiveness to voice sounds.	Newborn responsiveness to voice sounds encourages caregiver interaction.	[20]
Neonates demonstrate differential neural processing of sounds modulated over timescales of 25–50 ms.	Sounds modulated over timescales of 25–50 ms are particularly relevant for spoken communication.	[148,149]
The infant visual system has greater sensitivity to visual signals with high-contrast polarity.	The faces and especially eyes of caregiving conspecifics contain multiple sources of high-contrast visual information.	[94]
The infant visual system has greater sensitivity to low (rather than high) spatial frequency information.	The faces of caregiving conspecifics are replete with low spatial frequency information; facial affect cues are communicated predominantly via low spatial frequencies.	[81]
Infants attend more to top-heavy, vertically asymmetric patterns.	Human faces are vertically asymmetric with features concentrated in their upper portion; mothers display intense interest in establishing eye contact with their infants.	[93]
Neonates spontaneously produce a broad range of facial expressions and gestures.	Spontaneous facial expressions evoke emotional responses in caregivers, and caregivers imitate newborn gestures which, in turn, increases infant gaze towards the caregiver.	[20,60–62]
Infants produce voluntary, intentional facial gesturing.	Caregivers respond to voluntary infant facial gesturing with 'modified imitation': producing contingent responses or producing different but related expressions; caregivers then wait for infant to respond, initiating further cycles.	[54]