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Annual Research Review: The power of predictability – patterns of signals in early life shape neurodevelopment and mental health trajectories

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The global burden of early life adversity (ELA) is profound. The World Health Organization has estimated that ELA accounts for almost 30% of all psychiatric cases. Yet, our ability to identify which individuals exposed to ELA will develop mental illness remains poor and there is a critical need to identify underlying pathways and mechanisms. This review proposes unpredictability as an understudied aspect of ELA that is tractable and presents a conceptual model that includes biologically plausible mechanistic pathways by which unpredictability impacts the developing brain. The model is supported by a synthesis of published and new data illustrating the significant impacts of patterns of signals on child development. We begin with an overview of the existing unpredictability literature, which has focused primarily on longer patterns of unpredictability (e.g. years, months, and days). We then describe our work testing the impact of patterns of parental signals on a moment-to-moment timescale, providing evidence that patterns of these signals during sensitive windows of development influence neurocircuit formation across species and thus may be an evolutionarily conserved process that shapes the developing brain. Next, attention is drawn to emerging themes which provide a framework for future directions of research including the evaluation of functions, such as effortful control, that may be particularly vulnerable to unpredictability, sensitive periods, sex differences, cross-cultural investigations, addressing causality, and unpredictability as a pathway by which other forms of ELA impact development. Finally, we provide suggestions for prevention and intervention, including the introduction of a screening instrument for the identification of children exposed to unpredictable experiences. **Keywords:** Unpredictability; development; early life adversity; cross-species; mood; parenting; entropy; neurodevelopment; psychopathology.

A complex sequence of events unfolds during the rapid transition from a single-celled zygote to a newborn with 100 billion neurons, to a toddler with complex neurocircuitry underlying cognitive and emotional behaviors. The maintenance or elimination of synaptic connections is an experience-dependent process during which certain synaptic connections are strengthened through activation while others are eliminated. Across mammalian species, patterned sensory input during sensitive developmental windows sculpts the formation of neural circuits in sensory systems (Espinosa & Stryker, 2012; Hackett, Barkat, O'Brien, Hensch, & Polley, 2011; Khazipov et al., 2004; Singh-Taylor, Korosi, Molet, Gunn, & Baram, 2015; Takesian, Bogart, Lichtman, & Hensch, 2018; Wiesel & Hubel, 1963). For example, dating back to the seminal work of Hubel and Wiesel, we have known that light patterns are necessary for the normative maturation of visual system circuits (Wiesel & Hubel, 1963). Similarly, patterned auditory input influences functional connectivity in language neurocircuits (Uchida-Ota et al., 2019). Our conceptual model, supported by empirical evidence, expands upon these foundational principles by proposing that patterns of sensory inputs are a fundamental influence on the development of cognitive and emotional neurocircuits as well (Birnie & Baram, 2022; Davis et al., 2017).

Caregivers are of primary importance during sensitive periods in early development, and thus, we have focused on patterned signals derived from parents as a key driver of neurodevelopment. From rodents to nonhuman primates and humans, we demonstrate that unpredictable patterns of parental sensory inputs have long-lasting implications for cognitive and emotional functions (Bolton et al., 2018; Davis et al., 2022; Levis et al., 2022; Short & Baram, 2019). The observed impact of unpredictable signals across these mammalian clades suggests that the role of unpredictable signals in neurocircuit formation is an evolutionarily conserved process with deep phylogenetic roots. Thus, we suggest that the principle that patterns of signals determine the strengthening and elimination of synaptic connections (Takesian et al., 2018; Wiesel & Hubel, 1963) applies to cognitive and emotional brain circuits, as is the case for sensory circuits.

Our work investigating unpredictability as a biologically plausible pathway that represents a proximal process shaping brain development benefits from contextualization among additional viewpoints that underscore the developmental importance of predictability in the environment at

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different timescales. Life history theory provides an important evolutionary lens for understanding how development unfolds across a range of environmental contexts and highlights the ability of the human brain to adapt to a multitude of environments (Ellis, Sheridan, Belsky, & McLaughlin, 2022). The hallmark of healthy attachment, an established predictor of child development, emphasizes consistent responsive parental behavior (Ainsworth, Blehar, Waters, & Wall, 1978; Bowlby, 1951; Feldman, 2007; Sroufe, 2005). The household chaos and family routines literature similarly document the developmental importance of patterns and routines in the home environment (Fiese et al., 2002; Marsh, Dobson, & Maddison, 2020). In learning theory, the predictive processing framework highlights the role of predictability in the infant's sensory input and in the consequences of their own actions as important for learning about their physical and social environment (Friston, 2010; Köster, Kayhan, Langeloh, & Hoehl, 2020).

In this review, we present evidence for a conceptual model, grounded in ecological theory and in biological principles documenting the impact of patterns of signals during sensitive periods on synaptic development and circuit formation (Figure 1). The central guiding premise is that unpredictability represents a critical determinant of child neurodevelopment and mental health, exerting effects that are observable across cultures and diverse populations and in multiple species. Further, the influences of unpredictability are both independent from and synergistic with other established early life influences. We begin by providing an overview of the literature comprising constructs and components of the child's environment at multiple timescales and contexts that are relevant to unpredictability. In particular, we highlight one focus of our research program – predictability of parental signals at a moment-to-moment resolution, which offers not only this novel contribution at a timescale that differs from previous work at the resolution of years, months, weeks, or days but also importantly provides a translational neuroscience model enabling testing of neurobiological mechanisms in a causal manner. Unpredictability both in multiple aspects of the environment (e.g. parental, family, neighborhood) and at varying timescales (from seconds to years) influences development. Further, contexts and timescales likely interact to influence development. In this review, we highlight a key strength of considering unpredictability of moment-to moment signals is that these signals occur on a timescale that is relevant for neuronal communication and thus may be most critical for neural circuit formation during sensitive developmental periods (Birnie & Baram, 2022). Finally, we offer guidance for next steps for research in this area, highlighting emerging themes related to the evidence for the importance of unpredictability in the early environment, a form of adversity that is amenable to intervention.

Unpredictability and development: Months to years

Much of the existing research on early life unpredictability has examined longer patterns of exposures that span months to years. Within this literature, researchers have focused on unpredictability in the family ecosystem that is contextually relevant to children's development including residential changes, financial stability, parental employment, household composition, school and child care, parental separation, parenting, and parental mood. We briefly overview these literatures here by beginning with studies examining unpredictability across multiple contexts conjointly and then summarize specific components of unpredictability. We highlight in this section that unpredictability exerts adverse consequences that are above and beyond any effects of level. The findings reviewed here are consistent with classic stress research documenting that unpredictable stressors have more adverse consequences than the same stressor administered in ways that can be predicted (Seligman, 1968; Selye, 1956).

Unpredictability across contexts

One common approach that demonstrates the importance of unpredictability is the examination of composite measures of unpredictability assessed across several domains including residence, household composition/parental cohabitation, parental employment, and parental separation. In several longitudinal studies, including those with large samples, such as the Future Families and Child Wellbeing Study (formerly known as Fragile Families and Child Wellbeing Study), children who experience more transitions show higher levels of externalizing behavioral problems and impulsivity and lower school readiness (Doom, Vanzomeren-Dohm, & Simpson, 2016; Doom, Young, Farrell, Roisman, & Simpson, 2022; Fomby & Mollborn, 2017; Li, Sturge-Apple, Jones-Gordils, & Davies, 2022). Such observations are present in cohorts with very different experiences and cultures. For example, adolescents from rural China who experienced unpredictability, including parental separation and chaos in the home, showed more aggression and risk-taking behaviors (Lu & Chang, 2019). In all these studies, associations with unpredictability persist after consideration of effects of established aspects of ELA such as experience of harshness. While it is an important observation that cumulative exposure to unpredictability is an important determinant of child development, it also raises the need to understand specific impacts of unpredictability within different domains.

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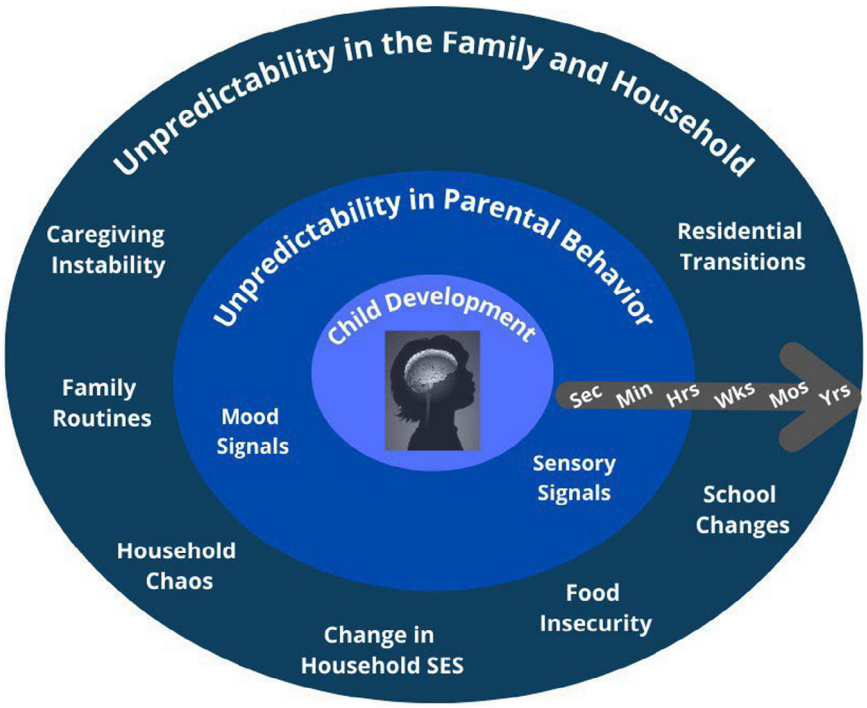

Figure 1 Pathways by which unpredictability shapes child development. Our model, grounded in an ecological perspective and fundamental biological principles, proposes that unpredictability across multiple timescales (e.g. seconds to years) and contexts (e.g. parental behavior, household) shapes developmental trajectories of cognitive and emotional development with implications for mental health. Our work identifies patterns of parental signals at a moment-to-moment timescale as a novel pathway shaping neural circuit development during sensitive periods

Residential/housing unpredictability

Housing instability is a lack of consistent residence including frequent moves that impacts millions of children worldwide. A nationally representative cohort study of US children born in 2001 indicated that 73% moved at least once between birth and kindergarten and 26% moved 3 or more times (Lawrence et al., 2015). In its most extreme form, housing instability includes homelessness which has pervasive effects on children's health, wellbeing, and educational attainment (Brumley, Fantuzzo, Perlman, & Zager, 2015; Coker et al., 2009; Muentner et al., 2019). Although homelessness is clearly linked to multiple components of adversity, the unpredictability of housing appears to be a key contributor to adverse outcomes beyond these other forms of adversity. For example, among preschoolers experiencing homelessness, the number of residential transitions predicted neurodevelopment (including both cognitive and socioemotional domains) beyond exposure to adverse childhood experiences (ACEs) (DeCandia, Volk, & Unick, 2022). Further in a nationally representative sample of 2,442 families with CPS involvement, children aged 4–14 who experienced two or more residential transitions with their families in a 12-month period showed cognitive deficits relative to their peers with fewer moves, beyond effects of socioeconomic status (Fowler et al., 2015). Of additional interest is the finding that children may be impacted by housing unpredictability even when it involves the parent with whom the child does not primarily reside. Children of divorced parents whose nonresidential parent moved frequently displayed more hostility and distress and rate their own emotional adjustment more poorly relative to children of divorced parents that maintain stable housing (Braver, Ellman, & Fabricius, 2003). Across different contexts, these studies suggest that lack of stable housing has long-term implications for development beyond effects of other components of adversity.

Financial/income unpredictability

Both poverty and long-term income trends (increases and decreases) are linked to child health and achievement (Dearing, McCartney, & Taylor, 2006; Dufford et al., 2020; Johnson, Riis, & Noble, 2016; Miller, Betancur, Whitfield, & Votruba-Drzal, 2021; Miller & Votruba-Drzal, 2017; Votruba-Drzal, 2006; Zachrisson & Dearing, 2015). Far fewer studies have considered unpredictability in income. Income unpredictability both in terms of fluctuations in income over months and income shocks (substantial income increases or decreases) are linked to detrimental impacts on preschooler's cognitive performance (Sosu & Schmidt, 2022) as well as adolescent school engagement (Gennetian, Wolf, Hill, & Morris, 2015). These studies indicate that unpredictable changes in income are associated with cognitive and school performance from

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early childhood through adolescence beyond associations with income level.

Parental job unpredictability

Several aspects of unpredictable parental employment have been examined that unfold over the timescale of months to years, including both work schedules and lack of job stability. Clear evidence indicates that nonstandard parental work hours (e.g. night shift work) contribute to child behavioral problems (e.g. Kim, 2021; Wei et al., 2019), and this has been observed even in the context of within-family designs, which eliminate concerns about between family confounds (Gassman-Pines, 2011). Further, as discussed in a subsequent section, unpredictable work schedules (those that change on a daily or weekly basis) are also independently predictive of poorer child emotional development, and it may be that the combination of both nonstandard work schedules coupled with unpredictability of those schedules exerts negative effects on child development that are multiplicative (Hsueh & Yoshikawa, 2007; Johnson, Kalil, & Dunifon, 2012). This is an especially concerning observation because these two employment profiles often co-occur and are more prevalent among low-income families (Autor, Dorn, & Hanson, 2013; Presser, 2003). In addition to aspects of scheduling within a job, inconsistent employment (e.g. frequent job changes) is also predictive of child development. For example, in the Future Families cohort, inconsistent employment (e.g. shorter tenure, job churning), during the first five years of life, predicted child externalizing problems (Pilkauskas, Brooks-Gunn, & Waldfogel, 2018). Both nonstandard work schedules and inconsistent parental employment likely lead to increases in child exposure to unpredictability, such as disruptions in family routines and support structures. It is of note that a problematic feature of this literature is its almost exclusive focus on 'maternal' work.

Child-care unpredictability

Research focusing primarily on young children has consistently found that different forms of child-care unpredictability, including changes in caregiver arrangements over time, changes in providers within the same setting and experiencing multiple, concurrent arrangements, are associated with higher levels of behavior problems in preschool-aged children of diverse backgrounds (e.g. Claessens & Chen, 2013; Morrissey, 2009; NICHD Early Child Care Research Network, 1999; Pilarz & Hill, 2014). For example, the Future Families and Child Well-Being Study revealed links between these different types of child-care instability and children's internalizing, externalizing, and prosocial behaviors at age 3 (Pilarz & Hill, 2014).

Other studies have similarly confirmed that instability in providers may impact development. Children who experienced more changes in providers from 6 to 36 months were rated by their Pre-K teachers as less socially adjusted and this association was not accounted for by other important influences such as poverty status and quality of the home environment (Bratsch-Hines, Mokrova, & Vernon-Feagans, 2015). Overall, there is consistent evidence that instability in child care during the preschool years has implications for cognitive and emotional development.

Unpredictability in family household composition and relationships

Unpredictability in household relationships can include changes in the presence of parents and caregivers, changes in parental romantic partners, siblings, and other family members (e.g. grandparents). Unpredictability in parental presence, defined as separation from a parent (e.g. due to incarceration), is linked to internalizing and externalizing problems throughout childhood and adolescence (Geller, Cooper, Garfinkel, Schwartz-Soicher, & Mincy, 2012; Geller, Garfinkel, Cooper, & Mincy, 2009). Similarly, for children with Child Protective Service (CPS) involvement, a greater number of placements (more transitions) is predictive of poorer executive function performance (Fields et al., 2021; Lewis, Dozier, Ackerman, & Sepulveda-Kozakowski, 2007) and higher ratings of oppositional behavior (Lewis et al., 2007). Other types of household unpredictability such as individuals moving in or out of the household (e.g. parent's romantic partner) are linked to child mental health and school success, associations that remain after considering other covariates including household income, parenting quality, and other sociodemographic factors (e.g. Cavanagh, Schiller, & Riegle-Crumb, 2006; Davies, Thompson, Coe, Sturge-Apple, & Martin, 2019; Fomby, 2011; Lee & McLanahan, 2015) and other aspects of unpredictability such as parent job changes and residential changes (Hartman, Sung, Simpson, Schlomer, & Belsky, 2018). A significant limitation of this literature is a focus on instability related to presence or absence of a father or 'father-figure'. In making progress towards addressing this gap, a study conducted in Chilean families documented impacts of transitions in grandparent presence in the house on children's language. Specifically, separation from grandparents associates with impairments in language development (Reynolds, Fernald, Deardorff, & Behrman, 2018), illustrating the need for broader and more inclusive assessments of stability in family relationships. Further, recent evidence suggests that changes to family composition involving siblings may additionally contribute to child outcomes beyond

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changes in parent-partner relationships (Fomby, Ophir, & Carlson, 2021).

Unpredictable parenting: Parenting behaviors

Unpredictability in parental behaviors over the timescale of years has adverse developmental consequences beyond levels of these behaviors (Lippold, Hussong, Fosco, & Ram, 2018). Several studies, including ones with large samples and racially and ethnically diverse participants, have observed patterns of parenting across childhood and adolescence. Unpredictable parenting behaviors defined as lability (within-person fluctuations around developmental trends over years) in parental warmth and hostility has been linked to youth internalizing problems (Lippold, Hussong, Fosco, & Ram, 2021; Zheng & McMahon, 2022) as well as risky behaviors such as delinquency and substance use (Lippold et al., 2018) beyond effects of level of warmth and hostility. Similar to warmth and hostility, lability in parental knowledge of child activities from 6th to 8th grade is associated with higher delinquency behavior, substance use, and internalizing problems in ninth grade even after covarying for associations with level of knowledge (Lippold, Fosco, Ram, & Feinberg, 2016).

Overall, evidence indicates that unpredictable parenting behaviors contribute to internalizing and externalizing behavior problems during adolescence. In general, associations were stronger among girls (Lippold et al., 2016, 2018, 2021), although this gender-specific pattern was not observed in all studies (Zheng & McMahon, 2022). Overall, these studies suggest that unpredictability in parenting is a risk factor for developmental outcomes beyond any effects of level.

Parental mental health unpredictability

Instability in parental mental health across months to years similarly predicts child mental health beyond more commonly employed measures of level of maternal symptoms. Across continents and cultures, stable low maternal mental health symptoms are linked to more optimal child outcomes both in terms of child psychopathology and cognitive development (Bailey, Irwin, Davis, Sandman, & Glynn, 2021; Cents et al., 2013; Irwin, Davis, Hobel, Coussons-Read, & Dunkel Schetter, 2020; Rotheram-Fuller et al., 2018). Further, unpredictable maternal mental health defined as inconsistency in maternal depression symptoms from pregnancy to postpartum associated with less advanced children's cognitive development relative to predictable (stable) low or high symptoms (Sandman, Davis, & Glynn, 2012).

Similarly, Rinne and colleagues found that inconsistency in terms of both increases and decreases in depression symptoms across preconception, pregnancy, and postpartum predicts poor childhood effortful control compared to stable levels (Rinne et al., 2022). These findings indicate that unpredictability of parental mental health may exert consequences that cannot be explained by level of exposure and yet unpredictability is rarely tested in the existing literature.

Unpredictability and development: Daily to weekly

Family routines

One aspect of predictability in children's environments that has been embedded in the literature for some time is a focus on family routines. Nearly three-quarters of a century ago, Bossard and Boll (1950) made the observation that family routines are integral organizers of family life with the potential to protect families in times of uncertainty and adversity (see Moving Towards Causal Inference for more on the potential protective influences of predictability). Consistent with their conceptualization, there exists empirical work highlighting the positive effects of family rituals and routines for optimizing child health and development (Fiese et al., 2002). The majority of the literature focuses on health-promoting behaviors and physical health outcomes, demonstrating salutary effects on length of respiratory infections (Boyce et al., 1977), quality and duration of sleep (Mindell, Telofski, Wiegand, & Kurtz, 2009), asthma control (Schreier & Chen, 2010), obesity (Anderson, Andridge, & Whitaker, 2016), and general physical health (Mindell & Williamson, 2018).

A smaller literature has examined associations between family routines and indicators of child psychopathology, and these studies do indicate that routines portend better cognitive and emotional development (Ferretti, 2011; Kelly, Sacker, Del Bono, Francesconi, & Marmot, 2011; Turnbull et al., 2022). One theme that emerges from this small literature is that the presence of family routines is associated with augmented emotion regulation capabilities (Barton et al., 2019; Ferretti, 2011; Zajicek-Farber, Mayer, & Daughtery, 2012) and less negative mood lability (Miller et al., 2017), beginning in infancy through adolescence. Consistent with this observation, children who are raised in households with more structure in the form of routines are less likely to exhibit internalizing and externalizing symptoms in both childhood and adolescence (Bridley & Jordan, 2012; Brody & Flor, 1997; Glynn, Davis, Luby, Baram, & Sandman, 2021; Kelly et al., 2011; Manczak, Williams, & Chen, 2017).

To further underscore their potential significance, additional studies indicate that routines have broader implications for social and economic success, including greater school readiness (Ren, Boise,

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& Cheung, 2022; Zajicek-Farber et al., 2012), better academic achievement in grade school (Brody & Flor, 1997; Roche, Ghazarian, & Fernandez-Esquer, 2012; Zajicek-Farber et al., 2012), and higher rates of university enrollment and graduation (Barton et al., 2019). Indeed, Barton et al. (2019) report that every unit of increase in number of family routines experienced during adolescence is associated with a 10% increase in the likelihood of 4-year university enrollment or graduation. In sum, the small body of work on family routines and child cognitive and emotional development provides convincing support for the role of this form of unpredictability in child mental health. It is important to note that these positive associations with family routines appear to persist after accounting for other established influences on child development (e.g. SES, parental mental health) and in some cases, other indicators of unpredictability.

Household chaos

A review of unpredictability and its influences on the developing child would not be complete without consideration of the construct of chaos in the household. Usually described as a home environment consisting of high levels of ambient stimulation, crowding, frenetic activity, unpredictability, and a lack of family routines (Matheny, Wachs, Ludwig, & Phillips, 1995), this umbrella concept certainly encompasses the concept of unpredictability, but the two are not synonymous. Chaos is often conceptualized as comprising two dimensions (Andrews, Atkinson, Harris, & Gonzalez, 2021): disorganization (clutter, crowding) and instability (inconsistent family routines, changes in household members and activities), with the latter being more closely aligned with unpredictability. There is a robust literature implicating the role of household chaos in child mental and behavioral health. Among the most common findings are those linking higher levels of household chaos to poorer self-regulation (Andrews et al., 2021) and increased behavioral problems in the externalizing domain. For example, higher levels of household chaos predict poorer inhibitory control and attentional focusing (Dumas et al., 2005), general conduct problems (Deater-Deckard et al., 2009; Shamama-tus-Sabah, Gilani, & Wachs, 2011), and aggression (Delker et al., 2020) throughout childhood and into adolescence. Additionally, there are a handful of studies implicating increased household chaos in a higher probability of adolescent substance use (Chatterjee, Gillman, & Wong, 2015; Delker et al., 2020; Kim-Spoon et al., 2019). There are fewer investigations of internalizing symptoms and disorders; however, these phenotypes do not appear to escape untouched. Higher household chaos predicts negative infant temperament (Bridgett, Burt, Laake, & Oddi, 2013), as well as internalizing symptoms in childhood and adolescence (Deater-Deckard et al., 2019; Richie et al., 2021; Wilhoit et al., 2021). Finally, youth residing in chaotic home environments exhibit poorer nonverbal cognitive development (Dumas et al., 2005; Pike, Iervolino, Eley, Price, & Plomin, 2006), compromised language development (Lecheile, Spinrad, Xu, Lopez, & Eisenberg, 2020), and lag behind their peers in academic achievement and performance (Berry et al., 2016; Shamama-tus-Sabah et al., 2011). Across this literature, these influences not only appear to predict child development beyond other indicators of childhood adversity but also may represent a pathway through which other forms of ELA, such as poverty, shape development (Marsh et al., 2020).

Unpredictable parenting: Parenting behaviors

As discussed above (Unpredictability and Development: Months to Years), unpredictability or lability in parenting from year-to-year predicts child mental health indicators above and beyond level. Rarer are studies that investigate day-to-day unpredictability in parenting behaviors. However, Fosco, Mak, Ramos, LoBraico, and Lippold (2019) have argued that day-to-day fluctuations in parenting practices may constitute a unique risk factor for child maladjustment. There are empirical demonstrations derived from daily diary studies with both parents and youth as reporters supporting this suggestion. Parent reports of greater daily fluctuations in parenting practices and in knowledge of their youths' activities predicted more child depressive symptoms as well as increased likelihood of substance use (Fosco et al., 2019; Lippold et al., 2016). Similarly, adolescent reports of greater day-to-day variability in parental warmth predicted higher self-reports of depressive symptoms (Lippold et al., 2016). Each of these studies provide evidence that these associations persisted after accounting for absolute levels of these constructs, further indicating that daily unpredictability in parenting may provide additional insights into child mental health. It is worth noting however, that to date, it is not known whether day-to-day unpredictability provides additional predictive validity or insight beyond those provided previously by unpredictability on longer timescales in the same constructs.

Unpredictable parental work schedules. Several studies provide evidence that unpredictable or 'precarious' work schedules characterized by schedules that vary from day to day or week to week, on-call work, frequent last-minute changes to shift timing and short advance notice of weekly schedules, exert negative developmental consequences on children (Johnson et al., 2012; Schneider & Harknett, 2022). For example, the Shift Project which includes over 2,500 mothers and their children aged 2–15 years documented that unpredictable maternal

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work schedules were associated with both internalizing and externalizing child behavior problems (Schneider & Harknett, 2022).

Fortunately, fair work week policies are effective at decreasing unpredictability in parental work schedules and are emerging with increasing frequency in the United States (Ananat, Gassman-Pines, & Fitz-Henley, 2022).

Early life unpredictability and development: Moment to moment

Unpredictable parental sensory signals

Parental care is an altricial species-expected stimulus that plays a foundational role in neurocircuit formation. Decades of research documents that parental care during sensitive windows is a critical regulator of offspring development (Ainsworth et al., 1978; Bowlby, 1951; Harlow, 1964; Hofer, 1973). Our work in this domain differs from other important work examining patterns at a moment-to-moment timescale between the two actors (parent and child) in a dyad (e.g. Beebe & Steele, 2013; Feldman, 2007) by evaluating predictability of signals produced by the parent, independent of the child's behaviors and responses.

Characterizing unpredictable parental sensory signals. Our approach quantifies unpredictability of parental sensory signals by computing entropy rates. Entropy is associated with randomness and used in numerous scientific fields ranging from the study of interacting particles, to heat and energy to the transmission of information. We have applied entropy to the study of parental behavior utilizing Shannon's definition, which was used initially to characterize predictability of a symbol or word transmitted in communication (Cover & Thomas, 2006). In the context of parental signals, entropy rate of a sequence of parental sensory signals provides a quantitative measure of the randomness or unpredictability of the next observation in the sequence.

Sensory signal entropy: We briefly describe here the computation of entropy rate to characterize unpredictability of parental signals derived from observations of parent-child interactions. In Figure 2, we detail the process with humans, noting that the same basic approach has been successfully applied cross-species (e.g. mice, rats, and monkeys) with the primary difference being the selection of species-appropriate behaviors. In humans, sensory signals (visual, tactile, and auditory) are derived by coding observations of parents interacting with their children in a play episode.

These sensory signals are coded continuously in real time, and then, an index of unpredictable sensory inputs, an entropy rate, is computed, with higher scores indicating more unpredictability. Importantly, this entropy rate is stable within a given mother-child play session (entropy derived from the first and second half of a 10-min play period have correlation 0.5) and across sessions from when the infant is 6–12 months of age (Vegetabile, Stout-Oswald, Davis, Baram, & Stern, 2019). Further, unpredictable patterns of parental signals, rather than counts of behaviors or counts of transitions, are predictive of outcomes described below (Davis et al., 2017).

Unpredictable parental sensory signals and cognitive development. We have reported that the unpredictability of sensory signals early in life, characterized by entropy, associates with cognitive development (Davis et al., 2017). Initial observations using a standardized measure of cognitive function, the Bayley Scales of Infant Development, revealed that exposure to unpredictable patterns and sequences of parental signals in infancy predicted mental development at 2 years of age. Building on these findings, we now have documented that two aspects of cognitive function have been consistently related to unpredictable sensory signals early in life: memory and effortful control.

Unpredictable parental sensory signals and memory: Cross-species findings: Our cross-species research highlights that memory is susceptible to early life exposure to unpredictable signals in rodents, monkeys, and humans. We show that exposure to unpredictable maternal sensory signals during infancy predicted poorer child recall memory at 6 years and poor memory performance in adolescent rats on an object recognition task (Davis et al., 2017). Building on this finding and to further test the hypothesis that the impact of unpredictable parental sensory signals on the developing brain is an evolutionarily conserved process with importance for maturation of biological systems, we tested the link between unpredictable parental signals in infancy and memory function in rats, mice, rhesus monkeys, and humans (Davis et al., 2022). Higher entropy predicted poor performance on a continuous memory recognition task in humans, a delayed non-match-to-sample task in monkeys, as well as spatial memory (water maze) and object recognition tasks in rodents. Notably, in humans, associations with unpredictability persisted after covarying for maternal mental health, maternal sensitivity, and socioeconomic status. Together these data highlight the fundamental biological importance of exposure to patterns of parental signals during sensitive windows for neurodevelopment. That such associations are observed across species with very different environmental contexts and including observational and experimental work provides compelling evidence that patterns of parental signals exert causal influences on the developing brain.

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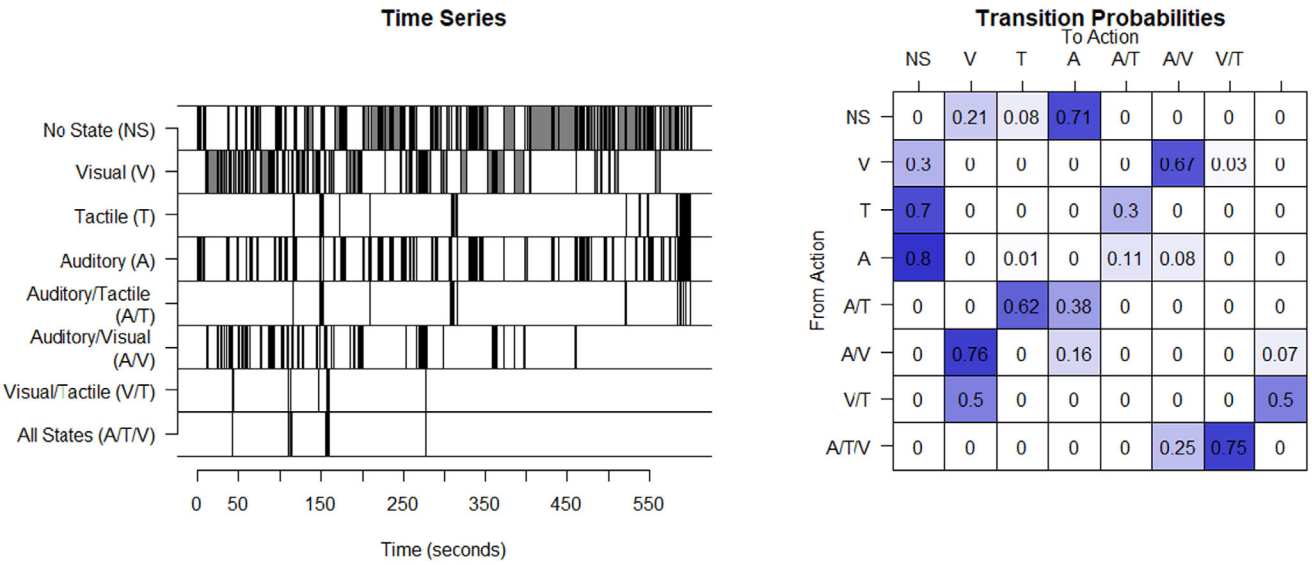

Figure 2 Parental sensory signal entropy. In humans, sensory signals (visual, tactile, and auditory) are derived by coding observations of parents interacting with their children in a play episode (typically a 10-min period). Parental provision of auditory (A; e.g. any speech or laughter), visual (V; e.g. showing an object while the child is attending to the object), or tactile (T; e.g. any touch such as stroking or holding the child) signals to the child are coded continuously in real time. For each dyad, a timeseries of these three types of behaviors is created for the play period. Panel A shows the time series for one example parent given the three types of sensory signals. Because signals can occur at the same time (e.g. talking while showing an object) from the three channels of sensory signals coded (A, T, and V), there are eight categories of sensory signals the parent can provide; these include one signal at a time (A, T, or V) any combination of two signals (e.g. T and V), all three of these signals (A, T, and V) at the same time, or no input. This time series is used to compute a transitional probability matrix seen in Panel B. This matrix shows the percent of times a parent transitions from one state to another. For example, as shown in this example, 76% of the time this parent transitions from providing both auditory and visual stimuli to visual stimuli on its own. Entropy rate is then calculated. The entropy rate of the process (Cover & Thomas, 2006) measures the unpredictability and randomness of the distribution of transitions with higher entropy rate indicating less predictable parental signals. Additional details of the coding scheme and computation of the entropy rate estimates (including the Rcode) are described in more detail in Davis et al. (2017) and at https://contecenter.uci.edu/

Unpredictable parental sensory signals and effortful control: As discussed further in Unpredictable Early Life Experiences and Effortful Control, effortful control is a domain in which we observe consistent links to unpredictable parental signals among children from varying backgrounds and cultures. Effortful control is a core component of executive function that is involved in the purposeful regulation of attention and behavior (Moffitt et al., 2011; Putnam, Gartstein, & Rothbart, 2006).

Leveraging two prospective international cohorts, we demonstrated that unpredictable sequences of parental signals during infancy predicted poorer effortful control throughout infancy and childhood, assessed via both parent report and performance on a response inhibition task (Davis et al., 2019). A subsequent study extended these findings with 5-year-old Finnish children showing similar links between unpredictable sensory signals and effortful control (Holmberg et al., 2022b). In both studies, associations persisted after covarying maternal mental health and socioeconomic factors.

Unpredictable parental sensory signals and neural circuit development: Experimental animal research has demonstrated that unpredictable patterns of parental sensory signals alter brain circuit maturation. We recently demonstrated similar findings in humans. Using diffusion tensor imaging (DTI), we showed that early life exposure to unpredictable parental signals is associated with aberrant development of corticolimbic pathways. Specifically, unpredictable parental sensory signals in infancy predicted integrity of the uncinate fasciculus as assessed with generalized fractional anisotropy. Further, alterations to these circuits partially mediate links with memory function in children (Granger et al., 2021). Notably, associations persisted after covarying maternal sensitivity, mental health, and household income.

Unpredictability of sensory signals in the home environment. A complementary approach to our examination of patterns of parental sensory signal unpredictability considers the role of patterns of auditory signals from the home environment. Using auditory recordings, Werchan and colleagues show that predictability of moment-to-moment auditory signals (from both parents and other sources in the home) is linked to development. Infants who are exposed to unpredictable patterns of auditory signals in the home show poorer sustained attention during a laboratory task at three months and decreased frontal theta power during that attention task (Werchan, Brandes-Aitken, & Brito, 2022). Importantly, associations with unpredictability

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remained after covarying total auditory input as well as metrics of language input such as word count. Consistent with our work described in this section, this study provides important evidence that patterns of sensory signals early in life sculpt neurodevelopment above and beyond level or amount of exposure.

Unpredictable parental mood signals

Our focus on unpredictable maternal mood as a determinant of child cognitive and emotional development was inspired not only by our observation that predictability of parental sensory signals plays a causal role in rodent offspring neurodevelopment, but also by the observation that mood variability or unpredictability (independent from level or valence) represents a meaningful individual difference. Analysis of intraindividual variability or patterns in behaviors and attitudes is rooted in personality psychology (c.f. Bem & Allen, 1974; Fiske & Rice, 1955; Mischel & Shoda, 1995) and has been most commonly characterized as either intraindividual variability in item scores on a questionnaire or intraindividual fluctuations across situations and time (Eid & Diener, 1999; Penner, Shiffman, Paty, & Fritzsche, 1994). Further, for the past 50 years, emotion theory has recognized that variability of mood patterns, independent of level, are central components of affective experience in their own right (Larsen & Diener, 1987; Wessman & Ricks, 1966). More recently, the significance of patterning of emotions has been considered in the context of mental health, linking increased mood variability across hours or days, to a number of distinct clinical disorders including bipolar disorders (Bonsall, Wallace-Hadrill, Geddes, Goodwin, & Holmes, 2012; Depue et al., 1981), borderline personality disorder (Mackinnon & Pies, 2006), and to clinical and sub-clinical depression (Costello, Benjamin, Angold, & Silver, 1991; Kuppens, Van Mechelen, Nezlek, Dossche, & Timmermans, 2007; Thompson, Berenbaum, & Bredemeier, 2011). In spite of the fact that predictability or lability of mood has implications for mental health, little attention has been paid to whether unpredictable parental mood profiles have implications for child development. This is somewhat surprising given the extensive literature linking parental prenatal and postnatal parental mood and psychopathology to child cognitive and emotional development (Netsi et al., 2018; Rogers et al., 2020). As discussed below, we now have shown that unpredictable parental mood, independent of level or valence, is associated with less optimal child cognitive and emotional development.

Measurement of mood unpredictability. Emotion regulation: A related, but indirect measure: Although not a direct measure, in some respects parental ability to regulate emotion may help inform our understanding of how mood predictability affects offspring development, particularly in light of the dearth in the existing literature. Emotion regulation comprises components of emotional lability and temporal components of affective experiences (i.e. patterning of emotions; c.f. Aldao, Nolen-Hoeksema, & Schweizer, 2010; Gross & John, 2003). In a recent meta-analysis of 32 studies, Holzman, Kennedy, Grassie, and Ehrenreich-May (2022) reported consistent positive associations between poor parental emotion regulation and risk of child mental health symptoms (overall effect size estimate, $r = .25$). Similarly, an intervention that improved maternal emotion regulation was associated with enhancements in child self-regulation, which in turn predicted subsequent teacher reports of fewer child externalizing problems (Byrd, Lee, Frigoletto, Zalewski, & Stepp, 2021). These studies provide only indirect evidence supporting the premise that parental mood unpredictability may shape child cognitive and emotional development, as these studies do not separately examine components of emotion regulation, but rather broad summaries, precluding insights into what components account for the relations with child mental health.

Ecological momentary assessment: Perhaps most intuitive method for assessing unpredictable mood is experience sampling methods (Csikszentmihalyi & Larson, 1987) or ecological momentary assessment (EMA; Stone & Shiffman, 1994). These approaches are characterized by repeated collection of moment-to-moment, real-time measures of individuals' experience and behaviors in the natural environment. The advantages of EMA for the assessment of mood and affect include increased accuracy and reduced recall bias, enhanced generalizability due to assessment in naturalistic settings, and characterization of dynamic processes in real-time (Shiffman, Stone, & Hufford, 2008). EMA generates a large number of data points from which indices of mood unpredictability can be computed that are either temporally dependent (e.g. mean squared successive difference) or independent of temporal sequencing (e.g. flux and spin; Ebner-Priemer, Eid, Kleindienst, Stabenow, & Trull, 2009).

To date, we are aware of only one study that has examined the link between patterns of parental mood assessed with EMA and child emotional development. MacNeill et al. (2023) employed EMA over 14 weeks in 72 pregnant individuals, examining whether baseline stress level, average stress level, and/or stress lability (quantified as mean squared successive differences) predicted infant negative affect at 3 months of age. Results indicated that greater stress lability was associated with higher infant negative affectivity and this effect persisted after adjusting for mean stress levels.

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Mood entropy: While the strengths of EMA are clear for assessment of mood predictability or variability, given its relatively high participant burden, in many research settings EMA is not feasible. Faced with this challenge, we developed a new index of moment-to-moment unpredictable mood that can be derived from existing validated mood measures (e.g. depression, anxiety) measured once. The result of this work was a measure of mood dynamics – mood entropy – comprising an application of Shannon's entropy to the distribution of responses on standardized mood questionnaires (Cover & Thomas, 2006). Critically, we have shown that this measure of mood entropy is associated with concurrent EMA measures of mood unpredictability (Howland et al., 2020), providing strong evidence that it is an indicator of momentary fluctuations in mood throughout the day. Another important observation is that identical entropy scores calculated from nonmood-related measures (e.g. physical activity) do not predict child development, providing further evidence that our mood entropy measure is indexing unpredictability of mood, rather than some sort of individual difference in questionnaire response style (Glynn et al., 2018). A detailed description of the calculation of mood entropy is provided in Figure 3.

Unpredictable maternal mood signals and internalizing disorders: Our initial investigation of whether unpredictable maternal mood was associated with child mental health profiles was assessed in two prospective longitudinal cohorts in which mood entropy was measured both pre- and postnatally (Glynn et al., 2018). Vulnerability to internalizing disorders was assessed by maternal report of child negative affectivity at 1, 2, and 7 years of age. At 10 and 12 years of age, youths self-reported on their anxiety and depressive symptoms. Higher maternal prenatal and postnatal mood entropy each were independently predictive of increased child negative affectivity at 12 months through 7 years of age. Notably, these associations persist through age 11 (new data presented in Figure 4). Consistent with these maternal reports, higher prenatal and postnatal mood entropy also were independently associated with increased child self-report anxiety and depressive symptoms. These effects persisted after adjusting for gestational age at birth, child age at assessment, socioeconomic status, cohabitation with the child's father, maternal race/ethnicity, as well as pre- and postnatal mood level. Thus, in a prospective sample followed for 13 years from pregnancy through early adolescence, we show that unpredictable maternal mood is associated with internalizing problems beginning in infancy.

Unpredictable maternal mood signals and internalizing disorders: New data: In a third independent cohort of 183 children, we have replicated the links between prenatal mood entropy and negative affectivity. This cohort differs from prior investigations in that that the families were more likely to be Latinx (54%) and were lower income on average than the cohorts described above (e.g. 61% of these families had incomes below the estimated living wage in their area of residence). Consistent with our previous findings, prenatal and postnatal mood entropy predict child negative affectivity at 6, 12, and 24 months of age (Figure 4), and these effects remain statistically significant when modeling prenatal and postnatal mood entropy together, suggesting that exposures to both prenatal and postnatal mood unpredictability have implications for development. Also of note, when modeling adjusting for concurrent level of negative affect (a composite of maternal perceived stress, anxiety, and depressive symptoms) both pre- and postnatal mood entropy continue to predict negative affectivity at each age (all p's $< .05$).

Unpredictable maternal mood signals and cognitive development: Given the findings from both our human studies and animal models examining

	1	2	3	4	5	6	7	8	9	10
Random	b	a	a	c	b	a	b	d	c	c
All a's	a	a	a	a	a	a	a	a	a	a
Mostly d/c	d	c	c	d	d	d	d	c	d	c

Figure 3 Parental mood entropy. Calculation of mood entropy involves a quantification of unpredictability of the item-by-item responses to dimensional assessments of mood states (e.g. depression, anxiety). The responses at a single assessment are tabulated over the items within each scale into probability distributions based on the relative frequency of each response choice, and these distributions represent empirical estimates of the propensity of a study subject to respond across items in a consistent way. In this sense, mood entropy quantifies the degree of predictability of the item-specific response. An individual who generally reports highly worried or never secure on a dimensional anxiety scale, for example, would be considered very predictable and thus have a very low entropy score (see response pattern in middle row above), whereas an individual who completes the mood questionnaire items entirely at random would have a very high entropy score (row 1 above). The mood entropy for a given scale ranges from zero (perfectly predictable) to a maximum value that depends on the number of points on the scale. To facilitate application of the approach across the different mood questionnaires, we normalize the entropy score by expressing it as a percentage of the maximum value. Thus, normalized mood entropy scores range from 0 to 100. Additional details of the computation of mood entropy (including the Rcode) are described in more detail in Glynn et al., 2018 and at https://contecenter.uci.edu/

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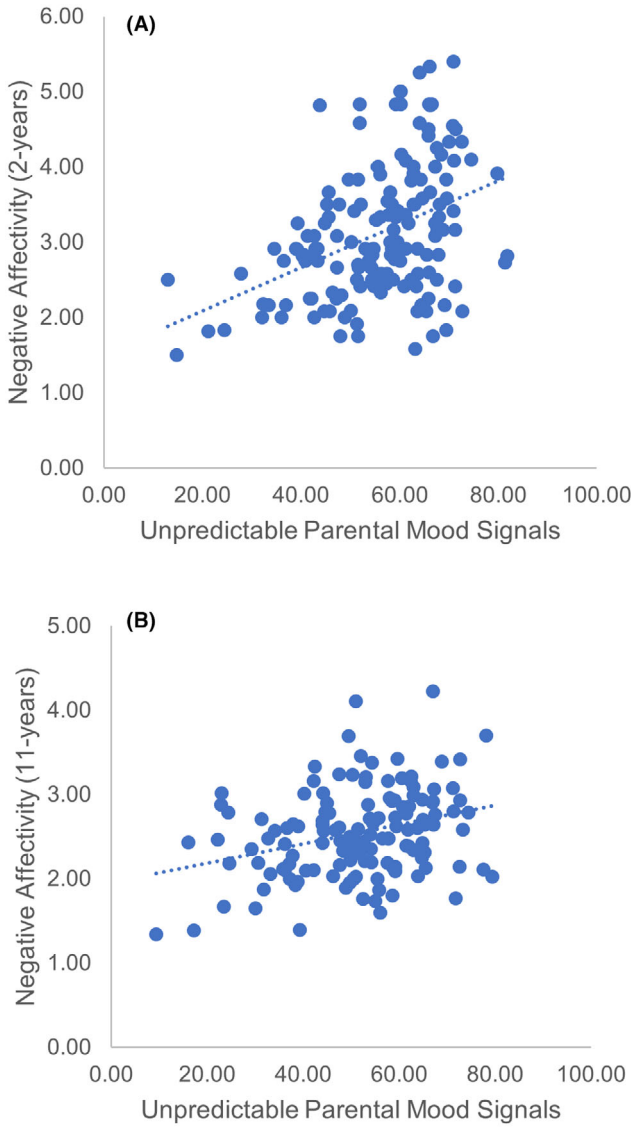

Figure 4 Mood entropy predicts negative affectivity. Panel A. In a cohort of 183 children followed from birth, higher levels of prenatal and postnatal mood entropy predict child negative affectivity at ages 6 months (*r*'s .36 and .37, respectively, both *p*'s < .01), 12 months (*r*'s .38 and .30, respectively, both *p*'s < .01) assessed with the Infant Behavior Questionnaire, and 24 months with the Early Childhood Behavior Questionnaire (*r*'s .40 and .30, respectively, both *p*'s < .01). Data at 24 months are shown. Panel B. Among 135 11-year-olds, greater exposure to prenatal and postnatal maternal ME is associated with increased negative affectivity assessed with the Temperament in Middle Childhood Questionnaire (*r*'s .31 and .24, respectively both *p*'s < .01)

unpredictable parental sensory signals and cognitive development, we next examined whether exposure to unpredictable maternal mood might portend poorer cognitive development (Howland et al., 2020). Child cognitive vulnerability was assessed with the Mental Development Index of the Bayley Scales of Infant Development at 2 years of age and expressive vocabulary at 7 years. As predicted, higher prenatal mood entropy was associated with poorer cognitive and language development. These associations persisted after adjusting for relevant sociodemographic variables (child age, maternal age, socioeconomic status, cohabitation with child's father), maternal intelligence, and prenatal and postnatal maternal mood level.

Unpredictable maternal mood signals and neural circuit development: Because of the links between mood entropy and child cognitive and emotional development, a next step was to begin to examine whether exposure to unpredictable maternal mood is associated with child brain development. In a cohort of 138 youths (mean age 13.5 years), we showed that prenatal mood entropy was associated with salience network integrity and with amplitude of low-frequency fluctuations (ALFF) of the network (Jirsaraie et al., 2023). Importantly, the associations remained after accounting for both prenatal mood level and income-to-needs ratio. Taken together, these findings indicate that exposure to unpredictable maternal mood is associated with a weakened and inflexible salience network, which is significant given the role of the salience network in socio-emotional regulation (Toller et al., 2018).

Development of a comprehensive measure: Questionnaire of unpredictability in childhood

Although prospective longitudinal examination of early life influences on development represents the gold standard, it quickly became apparent that to advance examination of unpredictability, self- and parent-report measures would be useful. Although as discussed in Unpredictability and Development: Daily to Weekly, there do exist measures that tap specific components of predictability (e.g. family routines, household chaos), a comprehensive measure was lacking. To meet this need, we developed the Questionnaire of Unpredictability in Childhood (QUIC), a 38-item questionnaire that assesses unpredictability in social, emotional, and physical domains across multiple timescales. The QUIC assesses the presence or absence of events prior to the age of 18 (similar to the ACEs scale; Felitti et al., 1998). It comprises five subscales: Parental Predictability, Parental Involvement, Parental Environment, Safety and Security, and Physical Environment. It has strong psychometric properties with excellent internal consistency (Cronbach's alpha = .89) and test-retest reliability ($r = .92$) (Glynn et al., 2019). The validity of the QUIC is further supported by its associations with prospective measures of unpredictability. In a cohort followed beginning prenatally, adolescent self-reports on the QUIC were correlated with unpredictable parental signals in infancy and childhood, as well as prospective measures of frequent residential moves, demonstrating both the association with moment-to-moment assessments of parental signals and the validity of self-report on this measure.

In the validation study (Glynn et al., 2019), which examined the QUIC's utility in three independent

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cohorts, male veterans, adult women and male and female adolescents, we established two important observations (in addition to the excellent psychometric properties described above). First, higher scores on the QUIC were associated with mental health profiles (depression, anxiety, and anhedonia) in each of the three cohorts. Second and critically, these associations could not be accounted for by other well-established indicators of childhood adversity including income-to-needs ratio, exposure to stressful life events, household chaos, and harsh parental discipline.

Two more recent studies have investigated mental health and unpredictability assessed via the QUIC in the context of clinical populations. Gillespie and Rao (2022) examined the association between QUIC and depressive symptoms in adolescents, half of whom had a clinical diagnosis of major depressive disorder. Consistent with expectations, adolescents exposed to higher levels of unpredictability exhibited greater depression symptom severity. Our group examined early-life unpredictability assessed with the QUIC, in trauma-exposed adults, two-thirds of whom had sought treatment for anxiety, mood, and/or posttraumatic stress disorder (Spadoni et al., 2022). Results indicated that exposure to early life unpredictability was associated with higher depression, anxiety, and anhedonia symptoms and that these associations were independent from exposure to childhood trauma. Further, we documented for the first time that exposure to unpredictability in childhood is associated with suicidal ideation.

In light of the promising findings related to the QUIC, and in recognition that a 38-item instrument may not be feasible in many clinical and research settings, we subsequently developed a brief 5-item version of the scale in English and Spanish (QUIC-5; Lindert et al., 2022). The predictability of the QUIC-5 was compared to the full QUIC in four independent cohorts, and it predicted internalizing symptoms (anxiety and depressive symptoms) with very similar effect sizes and beyond other forms of adversity, indicating that it is a valid alternative in time-limited settings.

An additional unmet need we addressed was the development of parent report versions of the QUIC, both full-length and short versions, that allow assessment of unpredictability in the home environment for infants and children too young to complete self-report versions (Glynn, Stern, Baram, & Davis, 2023). The predictive validity of the parent report QUIC and the parent report QUIC-5 was tested in three independent cohorts. First, we show that the parent report QUIC and QUIC-5 produce similar associations with very similar effect sizes with internalizing symptoms (anxiety and depression) as the self-report QUIC and QUIC-5 described above (Glynn et al., 2023).

Second, in three cohorts we show that the parent report QUIC and QUIC-5 predict effortful control during infancy, early childhood, and middle childhood with similar effect sizes as the self-report QUIC (See Table 1) (Figure 5).

In sum, the QUIC represents a feasible, low-burden measure to assess unpredictable childhood experiences across multiple aspects of the home environment. A key advantage of the QUIC is that it has been linked to prospective measures of unpredictability including moment-to-moment assessments (i.e. sensory and mood entropy).

Cross-cutting themes and future directions

Unpredictable early life experiences and effortful control

Executive functions emerge early in life with a protracted developmental trajectory across childhood and adolescence (Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989; Rueda et al., 2004) and are clearly shaped by early life experiences. EF enables individuals to engage in intentional planning and goal-directed behavior, and its key components comprise cognitive flexibility/rule shifting, updating/working memory, and inhibitory/effortful control (Miyake et al., 2000; Rothbart, Ellis, & Posner, 2006; Santens, Claes, Dierckx, & Dom, 2020). A cross-cutting theme emerging from this work is that in varying timescales and contexts there appears to be specificity of effects of unpredictability on individual executive function components, with some showing more vulnerability. Our work and that of others demonstrate that exposure to a range of indicators of unpredictability is consistently associated with decreased effortful control. Table 1 overviews studies showing that unpredictable childhood experiences characterized both by moment-to-moment signals, such as sensory and mood entropy, and unpredictability at longer timescales in the home and family environment (QUIC), predict poor childhood effortful control from infancy through adolescence assessed with laboratory observations, self-report, and parent report. These observations have important implications as poor effortful control is a transdiagnostic risk factor for psychopathology, including risk for both internalizing and externalizing disorders (Beauchaine & Thayer, 2015; Joseph, McKone, Molina, & Shaw, 2021; Nigg, 2017; Santens et al., 2020) as well as poor physical health and decreased productivity and material success across the lifespan (Johnson, Voegtline, Ialongo, Hill, & Musci, 2022; Moffitt et al., 2011). Intriguingly, a handful of findings indicate that although exposures to unpredictability predict reduced effortful/inhibitory control, cognitive flexibility may be spared, or even enhanced following these exposures (Fields et al., 2021; Gillespie & Rao, 2022; Mittal, Griskevicius, Simpson, Sung, & Young, 2015; Rinne et al., 2022). The possibility that unpredictability affects executive function in targeted ways (by

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Table 1 Early life exposure to unpredictable signals in the parental and home environment is associated with effortful control across ages and multiple forms of assessment

Study	Participants	Primary EC finding	Sex differences
Observational measures of unpredictability			
1. *Sensory signal entropy and early childhood delay of gratification (New Data)	59 mothers and their 2-year-old children (25 female)	Exposure to greater unpredictability in parental sensory signals during the first postnatal year associates with shorter latencies to grab a treat on a snack delay task ($r = -.27$ $p = .04$).	None
2. *Sensory signal entropy and early childhood delay of gratification (New Data)	40 mothers and their 3-year-old children (21 female)	Higher levels of unpredictable parental sensory signals during the first year of life predict shorter waiting times on a snack delay task (Figure 5, $r = -.33$; $p = .047$).	None
3. Davis et al. (2019). Across continents and demographics, unpredictable maternal signals are associated with children's cognitive function. *EBioMedicine*, 46, 256–263.	135 mothers and their 2-year-old children (67 female) from Turku, Finland and 192 mothers and their children from 1 to 9 years (91 female) from Irvine, CA, USA	Unpredictable parental sensory signals during the first postnatal year (high sensory entropy) associates with low effortful control assessed with the Flanker task and parent report in the United States and Finland.	None
4. Holmberg et al. (2022b). Unpredictable maternal sensory signals in caregiving behavior are associated with child effortful control. *PLos One*.	133 mothers and their 5-year-old children, (63 female)	Unpredictable parental sensory signals (high sensory entropy) measured in infancy associates with low effortful control	Stronger in males
5. *Mood entropy and child inhibitory control	127 mothers and their children (54 females) 9.6 years	Unpredictable parental mood during infancy (mood entropy) correlates with poor performance on the Go, No-Go task, a measure of response inhibition. Specifically, high mood entropy was associated with lower accuracy ($r = -.24$, $p = .006$) and poorer ability to discriminate 'Go' from 'No-Go' trials, d' ($r = -.22$, $p = .012$).	None
6. *Mood entropy and child effortful control	135 mothers and their children (59 female) 9.6 years	Unpredictable parental mood both during the prenatal and infant periods associates with poor child effortful control on the TMCQ. More unpredictable maternal mood both during the prenatal ($r = -.280$, $p = .001$) and infant periods ($r = -.256$, $p = .004$) predicted low childhood effortful control.	None
Questionnaire of Unpredictability in Childhood (QUIC)			
7. *QUIC and infant and childhood effortful control	89 mothers and their children (46 female) 6.2 months and 3.4 years	Higher unpredictability assessed with the parent report QUIC-5 associates with effortful control during infancy (IBQ; $r = -.24$, $p = .025$) and early childhood (CBQ; $r = -.23$, $p = .033$).	None
8. *QUIC and middle childhood inhibitory control	104 participants (48 female) 9.6 years	Higher unpredictability correlates with poorer performance on the Go, No-Go task, a measure of response inhibition. Specifically, high QUIC was associated with lower accuracy ($r = -.20$, $p = .041$), and d' ($r = -.188$, $p = .055$). Associations were stronger among females (per cent correct $r = -.271$, $p = .06$. d' $r = -.296$, $p = .04$) relative to males (per cent correct $r = -.10$ $p = .46$ and d' $r = -.051$, $p = .71$). For d' Fishers r to z transformation revealed that the correlation was significantly stronger for girls relative to boys ($p = .039$).	Stronger in females

(continues)

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Table 1 (continued)

Study	Participants	Primary EC finding	Sex differences
9. *QUIC and middle childhood effortful control	106 mothers and their children (55 female) 9.6 years	Higher unpredictability assessed with the QUIC (both parent and self-report), predicts poor childhood effortful control on the TMCQ (r − .39, p < .001 and self-report r = −.38, p < .001, respectively). Fisher r to z transformation revealed the correlations were significantly (p < .001) stronger for girls (r = −.49, p < .001) relative to boys (r = .22, p = .09).	Stronger in females
10. *QUIC and adolescent self-regulation	158 youth (83 female) 14.3 years	Higher unpredictability assessed with the QUIC, predicts poor self-regulation based on self-report on the Barrett Impulsivity Scale, version for adolescents (r = .219, p < .006) (Mathias et al., 2018). Notably, the association was stronger among girls (r = .34, p = .002) relative to boys (r = .71, p = .54; Fisher r to z p = .041).	Stronger in females

CBQ, Childhood Behavior Questionnaire; ECBQ, Early Childhood Behavior Questionnaire; IBQ, Infant Behavior Questionnaire; TMCQ, Temperament in Middle Childhood Questionnaire.
Sensory signal entropy and mood entropy were calculated as described in Unpredictable Parental Sensory Signals and Unpredictable Parental Mood Signals, respectively. Studies with * indicate new data not previously published statistics more detail are presented in the Supporting Information.

preserving or enhancing cognitive flexibility while impairing inhibitory/effortful control) is consistent with conceptual models emphasizing the role of ELA in shaping both risk and resilience in cognitive phenotypes and represents an important direction for future investigation (Belsky, Schlomer, & Ellis, 2012; Ellis & Del Giudice, 2019; Frankenhuis, Panchanathan, & Nettle, 2016; Munakata, Placido, & Zhuang, 2023; Mushtaq, Bland, & Schaefer, 2011). In sum, the emerging literature indicates that effortful/inhibitory control is particularly susceptible to unpredictability early in life. Future research is needed to characterize how specific components of EF are differentially affected by early life unpredictability.

Sensitive periods

As we work to understand the impact of unpredictability, it will be critical to consider the likelihood that how and what aspects of unpredictability influence development varies based on maturational stage. During the prenatal and infant periods, the central nervous system develops at an extraordinary pace whereby the foundation of neural structures and circuits are formed, laying the groundwork for future functions (Demers et al., 2021, 2022). During such sensitive periods, experiences drive the strengthening and eliminating of synaptic connections, and thus, the brain may be particularly impacted by unpredictable signals (Tottenham, 2020). Critical periods have been clearly defined for sensory circuits, such as vision, when patterns of visual input are critical for normative development. Higher order cognitive and emotional circuits build hierarchically on sensory and motor circuits, and it is likely that sensitive periods similarly exist for these domains. Rodent work has begun to delineate sensitive windows during the first postnatal weeks when unpredictability impacts specific functions such as stress responses and memory (Molet, Maras, Avishai-Eliner, & Baram, 2014). Consistent with this experimental research, human studies provide compelling evidence that patterns of sensory information during infancy are important for development of cognitive and emotional functions (Aran et al., 2024; Davis et al., 2017, 2022; Norona-Zhou et al., 2020). The timing of this sensitive period for unpredictable parental signals has yet to be established in humans. However, experimental human research from the Bucharest Early Intervention Project documents that parental presence (foster placement vs. institution) during the first two postnatal years is critical for maturation (Reh et al., 2020; Zeanah, Gunnar, McCall, Kreppner, & Fox, 2011) consistent with the likelihood that infancy may be a sensitive period for exposure to patterns of parental signals. Future work is needed to determine developmental periods when patterns of sensory information are needed for development of cognitive and emotional circuits.

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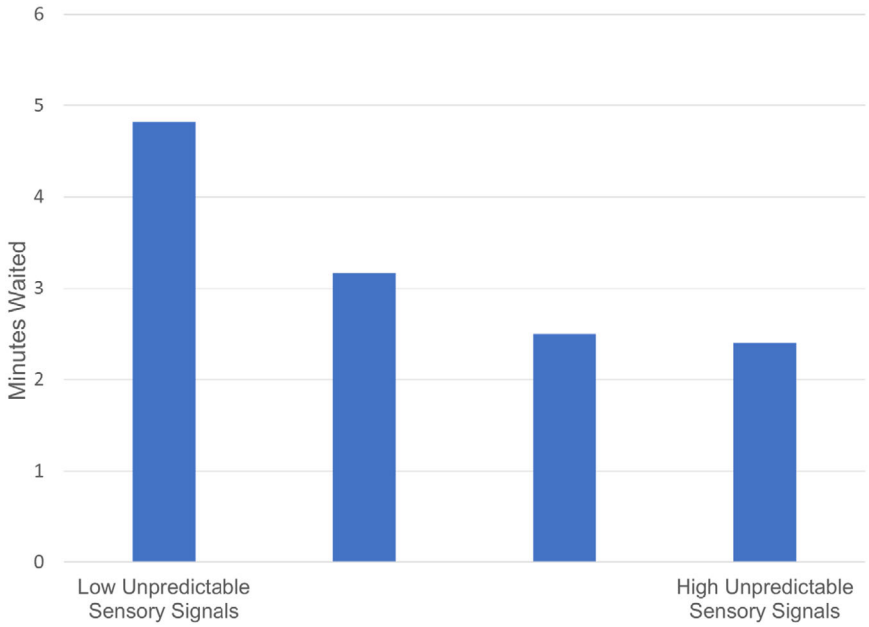

Figure 5 Unpredictable parental sensory signals predict delay of gratification. Three-year-old children who were exposed to more unpredictable sensory signals in infancy exhibit shorter waiting times in a snack delay task ($r = -.33$; $p = .047$). Bars represent quartiles of sensory signals

While it is likely that the sensitive period for patterns of sensory information resides during infancy (or earlier in the prenatal period), it is probable that other aspects of unpredictability are impactful during other stages of life. For example, adolescents may be susceptible to predictability in social relationships, particularly those involving peers. The prenatal and infant periods are clearly times of susceptibility to unpredictability in parental mood as periods when parental signals are of primary importance (Glynn et al., 2018; Tottenham, 2020). It is likely however, that unpredictable parental mood influences developmental outcomes throughout childhood and adolescence (Glynn et al., 2018; Howland et al., 2020) as exposures that are unique to the adolescent period have long-term developmental implications (Tottenham & Galvan, 2016). Further work is needed to evaluate the differential impact of aspects of unpredictability based on the developmental stage.

Sex differences

As early as conception and meiosis, sexually dimorphic strategies can be observed in response to environmental signals (Hunt & Hassold, 2002). Throughout the embryonic and fetal periods, males and females show dramatically differentiated responses to adversity in terms of growth trajectories (Clifton, 2010; Clifton & Murphy, 2004; Murphy et al., 2003), methylation patterns (O'Connell, Moritz, Walker, & Dickinson, 2013), and placental function (Walker et al., 2012). These sexually dimorphic responses to ELA contribute to sex-specific phenotypes during infancy, childhood, and adolescence (see Sandman, Glynn, & Davis, 2013 for review). Despite these observations, much of the human ELA literature does not systematically consider sex differences until adolescence and adulthood. A critical step for future research evaluating unpredictable early life experiences is the systematic testing of sex differences in responses to unpredictability. In both our experimental work with rodent models and our human studies, we see growing evidence that males and females are differentially responsive to unpredictable early life experiences. In rodents, early life unpredictability differentially impacts males and females in anhedonic and reward-seeking behaviors, with females exhibiting increased propensity for substance seeking and addiction and males evidencing increased anhedonia (Birnie, Levis, Mahler, & Baram, 2022; Levis, Baram, & Mahler, 2022; Levis, Birnie, et al., 2022; Levis, Mahler, & Baram, 2021). Further, sex-specific patterns of responses to ELA including unpredictability are observed in CRH-related gene expression, critically associated with stress responding and risk for psychopathology (Demaestri et al., 2022).

There are fewer human studies of sex-specific responses to unpredictability. However, we show in Table 1, compelling evidence that males and females display differentiated response patterns. Specifically, our analyses of responses to unpredictability assessed with the QUIC document stronger consequences for effortful control among females relative to males from childhood through late adolescence, perhaps reflecting a greater sensitivity to unpredictability in the parenting and home environment. We have further shown that unpredictability exerts a stronger influence on the development of fronto-

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limbic white matter tracks among females relative to males (Granger et al., 2021). Of note, these findings are broadly consistent with evidence by Lippold and colleagues that unpredictability in parental warmth and hostility trends examined over years is more strongly related to mental health outcomes for females than males (Lippold et al., 2018, 2021). In contrast, in humans we did not observe consistent sex differences in responses to moment-to-moment signals on effortful control (see Table 1) or negative emotionality (see Household Chaos). An important area for future research is to ascertain how unique components of unpredictability differentially sculpt the developing male and female brain.

Continued examination of the relevance of unpredictability across cultures and diverse groups

The majority of the literature examining the links between ELA, including unpredictability, has focused on White, middle-class populations. It is therefore critical to consider whether unpredictability in childhood represents a meaningful predictor of child neurodevelopment and mental health among more diverse populations. Our observations of the cross-species relevance of unpredictability (Davis et al., 2022) coupled with perspectives describing its evolutionary significance (Ellis, Figueredo, Brumbach, & Schlomer, 2009; Hartman et al., 2018; Szepsenwol & Simpson, 2019) strongly predict that it would be a significant developmental influence across diverse groups and cultures, but this requires empirical substantiation. In Table S1, we present a survey (albeit not an exhaustive one) of studies examining unpredictability and child cognitive and emotional development in populations that are racially and ethnically, demographically, and economically diverse. The studies summarized had to meet one or more of the following criteria: 1. Participants were either solely or majority participants from racially and ethnically minoritized backgrounds; 2. Participants resided in households that were primarily or entirely low income; 3. Participants were from a country other than the United States.

Examination of the table indicates that predictability is associated with child cognitive and emotional development from infancy through adolescence when examining populations that are under-resourced financially or living in poverty and those from racially and ethnically diverse backgrounds. Finally, the developmental significance of unpredictability is observed in both urban and rural contexts, as well as across the globe including in the United Kingdom, Northern Europe, South America, Africa, and Asia.

The fundamental importance of unpredictability across contexts and cultures suggests that unpredictability may represent one pathway through which structural determinants of health such as poverty and racism influence development (see empirical examples of this potential pathway described below). As is the case with many other forms of ELA, unpredictability is likely unevenly distributed across populations and therefore could be one contributor to existing health disparities. For example, the long history of discriminatory policies in the United States such as residential segregation and redlining laws have resulted in an overrepresentation of families of color in neighborhoods characterized by a number of risk factors in both the built and social environments (Mitchell & Franco, 2018; Schwartz, Onnen, Craigmile, & Roberts, 2021). Some of these neighborhood features specifically include elements of unpredictability such as housing instability, crime, increased police surveillance, immigration raids, and physical disorder (Ursache, Barajas-Gonzalez, & Dawson-McClure, 2022). It is critical moving forward that examinations of the developmental significance of unpredictability for child health and development consider exposures and pathways that may uniquely explain mental health disparities.

How does unpredictability get under the skin?

A body of rigorous empirical work has made strides in identifying the neural underpinnings of exposure to ELA and has clearly documented that ELA gets under the skin (McLaughlin, Sheridan, Humphreys, Belsky, & Ellis, 2021; Sheridan et al., 2022; Tottenham, 2020). In contrast, very few human studies have specifically examined how unpredictability uniquely impacts neural systems (Dufford et al., 2020; Granger et al., 2021; Jirsaraie et al., 2023) or peripheral physiology that could have implications for brain development and function (Doom et al., 2018; Manczak et al., 2017; Manczak, Leigh, Chin, & Chen, 2018; Norona-Zhou et al., 2020). Given the strength of the evidence for developmental consequences of ELA including unpredictability, there have been a number of recent calls, highlighting the need for tests of specific aspects of ELA with biologically testable mechanistic pathways (Boyce & Hertzman, 2018; Gee, 2021; Luby, Baram, Rogers, & Barch, 2020; McLaughlin et al., 2021; Smith & Pollak, 2020). We propose that predictability of patterns of parental signals is a proximal process that occurs at a moment-to-moment time scale that is relevant for synaptic firing and may be a direct process by which early life experiences sculpt the developing brain, providing a framework for understanding pathways by which ELA shapes development.

To highlight the power of cross-species models to identify mechanistic pathways, we consider the example of unpredictability and learning and memory. Patterns of sensory information sculpt the hierarchical integration of sensory and memory circuits and thus patterns and signals impact development of systems underlying learning and

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memory (Birnie & Baram, 2022). The identification of these biological pathways in experimental systems makes evident the biological importance of unpredictability as a driving force in shaping the developing brain. In rats, exposure to unpredictable signals from the dam has been linked to attenuation of long-term potentiation (a hallmark of learning) and with impoverished dendrites and synapses in the dorsal hippocampus (Brunson et al., 2005; Ivy et al., 2010; Short & Baram, 2019), reflected in reduced dorsal hippocampus volumes (Molet et al., 2016). These experimental studies provide causal evidence for the neuroanatomical consequences of patterned parental sensory inputs and then link these anatomical changes with function. Building on these experimental studies, we leverage the power of cross-species research to test parallel observational models in nonhuman primates and humans. We show that unpredictable patterns of parental signals during infancy are associated with deficits in memory performance in rodents, nonhuman primates, and humans (Davis et al., 2017, 2022). Further, using diffusion tensor imaging (DTI) we show that early life exposure to unpredictable parental signals impacts development of corticolimbic circuits partially mediating links with memory function in children (Granger et al., 2021). The exciting consistency in the impact of unpredictability across species and in both experimental and observational studies supports the hypothesis that unpredictable patterns of parental signals are of biological importance as part of the process by which early life experiences shape developmental outcomes.

Evidence from experimental systems and humans is now also beginning to shed light on the mechanisms by which unpredictable parental signals impact neural circuits involved in emotion (Birnie et al., 2022). We have shown that exposures to more unpredictable maternal mood predicts decreased flexibility in the salience network of their adolescents (Jirsaraie et al., 2023). Additional new work identifies an inhibitory basolateral amygdala to nucleus accumbens projection that is responsible for deficits in reward behavior resulting from early-life unpredictability (Birnie et al., 2023). This exciting finding, in conjunction with human research linking unpredictable early life experiences to anhedonia and reward processes (Glynn et al., 2019; Spadoni et al., 2022), inspires our current cross-species work evaluating impacts of unpredictability on anhedonia and reward behaviors and underlying processes and mechanisms.

Moving towards causal inference

A challenge with human observational research is its limited ability to make causal inferences (Pingault et al., 2018). Perhaps the two most common alternative explanations raised are that observed associations between unpredictability and child development could be due to genetics and/or that the child is causing unpredictability in their environment. There are three strategies that can be employed to address this challenge: (a) genetically informed designs (e.g. twin studies), (b) quasi-experimental research, and (c) experimental research. We will briefly review the potential for these approaches along with emerging evidence indicating the experience of unpredictability contributes to developmental outcomes.

First, research employing genetically informed twin designs provides evidence that environmental components of unpredictability contribute to child outcomes even after consideration of shared genes (Hanscombe, Haworth, Davis, Jaffee, & Plomin, 2011; Jaffee, Hanscombe, Haworth, Davis, & Plomin, 2012). A second line of evidence that exposure to unpredictability is a driver of child developmental outcomes can be obtained from quasi-experimental designs or natural experiments. For example, there now is compelling evidence that implementation of fair work week policies reduces unpredictability in parental work schedules (Ananat & Gassman-Pines, 2021; Harknett, Schneider, & Irwin, 2021). Emerging evidence further suggests that implementation of these policies also is associated with improvements in parental mental health and sleep quality (Ananat & Gassman-Pines, 2021; Harknett et al., 2021). Future research can leverage these natural experiments to document how reductions in unpredictability in the early environment affect child mental health and development as well. Third, the strongest test of whether unpredictability in early life causes changes in developmental outcomes comes from experimental intervention. Rodent studies where experimental designs involving cross-fostering control for shared genes and eliminate genetic explanations for links between unpredictable experiences and child outcomes. The concordance between experimental translational and observational human work provides compelling evidence that exposure to unpredictability of parental signals contributes to child outcomes beyond genetic factors (and other alternative explanations). The extent to which conclusions from rodent work can be applied to humans remains an obvious limitation. An important next step for identifying the role of predictability on child outcomes is the implementation of randomized controlled trials (RCTs) in the context of intervention research. Although not focused on predictability, prior intervention work clearly has demonstrated that changing the child's environment has the potential to change child behavior (Bick, Palmwood, Zajac, Simons, & Dozier, 2019; Dozier, Roben, Caron, Hoye, & Bernard, 2018; Drozd, Leksbø, Størksen, Wilhelmsen, & Slinning, 2022; Hwang, Chao, & Liu, 2013; Mountain, Cahill, & Thorpe, 2017). We now need to develop and evaluate interventions that increase predictability in the child's environment.

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Unpredictable parental signals as pathway to child neurodevelopment

As we have described, unpredictable patterns of parental signals sculpt circuit development in experimental systems and humans. Given translational evidence for this mechanism, we further raise the possibility that unpredictable parental signals may be a process by which other forms of ELA influence development. For example, aspects of ELA such as poverty or domestic violence may impact the child in part through increasing unpredictability of parental signals such as unpredictability in mood and sensory signals. We provide here examples of our initial tests of this hypothesis by evaluating whether unpredictable parental signals are one of the paths by which household income and other previously established influences shape development.

Unpredictable parental signals mediate associations between poverty and child outcomes: New data. As expected, household income is correlated with child effortful control and negative affect. Notably, as shown in Figure 6A,B, the associations between income to needs ratio (INR) and both child effortful control and negative affect are partially mediated by unpredictable parental signals. These novel findings suggest that unpredictability may be a proximal pathway by which poverty impacts development, identifying a previously unrecognized pathway by which this potent form of ELA may affect neurodevelopment.

Unpredictable parental signals mediate associations between established measures of parenting and child outcomes: New data. In investigations of the role of parenting in child development, two of the most influential factors identified to date include parenting characterized by high in intrusiveness coupled with low sensitivity and warmth (hereafter referred to as parental sensitivity) and parental mental health. It is plausible that these well-established parenting profiles influence the child in part because they increase unpredictability of parental signals.

We have previously established that parental sensory signal unpredictability is correlated with parental sensitivity (Holmberg et al., 2022a) and that unpredictable parental signals partially mediate the link between parental sensitivity and child cognitive development (Davis et al., 2017). Consistent with these data, new findings presented in Figure 6C illustrate that unpredictable sensory signals partially mediate the association between parental sensitivity and effortful control. These published and new findings indicate that not only do sensitivity and unpredictability contribute unique variance to child outcomes, but that patterns of parental signals may represent part of the pathway by which parental sensitivity influences the child.

In parallel to quality of parental care, decades of research have demonstrated the profound impact of parental mental health on a range of child outcomes (Netsi et al., 2018; Rogers et al., 2020). We suggest that one of the pathways by which parental mental health may impact child outcomes is via unpredictable parental mood. Parental mental health (mood level) and unpredictable parental mood are correlated, and each contributes unique variance to child outcomes (Glynn et al., 2018; Howland et al., 2020; Jirsaraie et al., 2023). Figure 6D shows that mood unpredictability partially mediates the association between parental mental health and child negative affect, providing evidence that patterns of parental signals may play an important role in shaping the developing brain.

Unpredictable parental signals as a pathway to child outcomes: Leveraging translational models. The examples provided above lend support to our hypothesis that unpredictable parental signals represent a pathway by which other forms of ELA influence development. A key strength of the focus on parental momentary signals is its clear connection to translational animal models. These experimental studies allow identification of the causal role of unpredictability in shaping neural mechanisms and thus advance the field with a new approach to understanding how commonly studied aspects of early life experience, such as parental mental health, sensitivity, and poverty, shape child development.

Prevention and intervention

There are several features of unpredictability that distinguish it from many other forms of ELA, rendering it a promising target for prevention and intervention. First, examination of Figure 1 highlights that there are multiple opportunities for prevention and intervention, including the prospect of multilevel intervention (Paskett et al., 2016). These range from the level of the individual (e.g. altering parental attitudes regarding the importance of predictability), at family system level (e.g. implementing family routines), and at the public policy level (e.g. adoption of Fair Work Week regulations that address precarious work schedules). Addressing structural drivers of unpredictability such as poverty should be a top priority to improve the well-being of children and families. However, in tandem, there are other opportunities that can be pursued, such as the encouragement of family routines, which have the additional advantage of being relatively low cost. Second, although we do conceptualize high unpredictability as a form of ELA, low unpredictability (i.e. predictable environments) may have the potential to exert salutary influences on development. As we have comprehensively reviewed, there is a strong literature to support the positive developmental impacts of predictability on child cognitive

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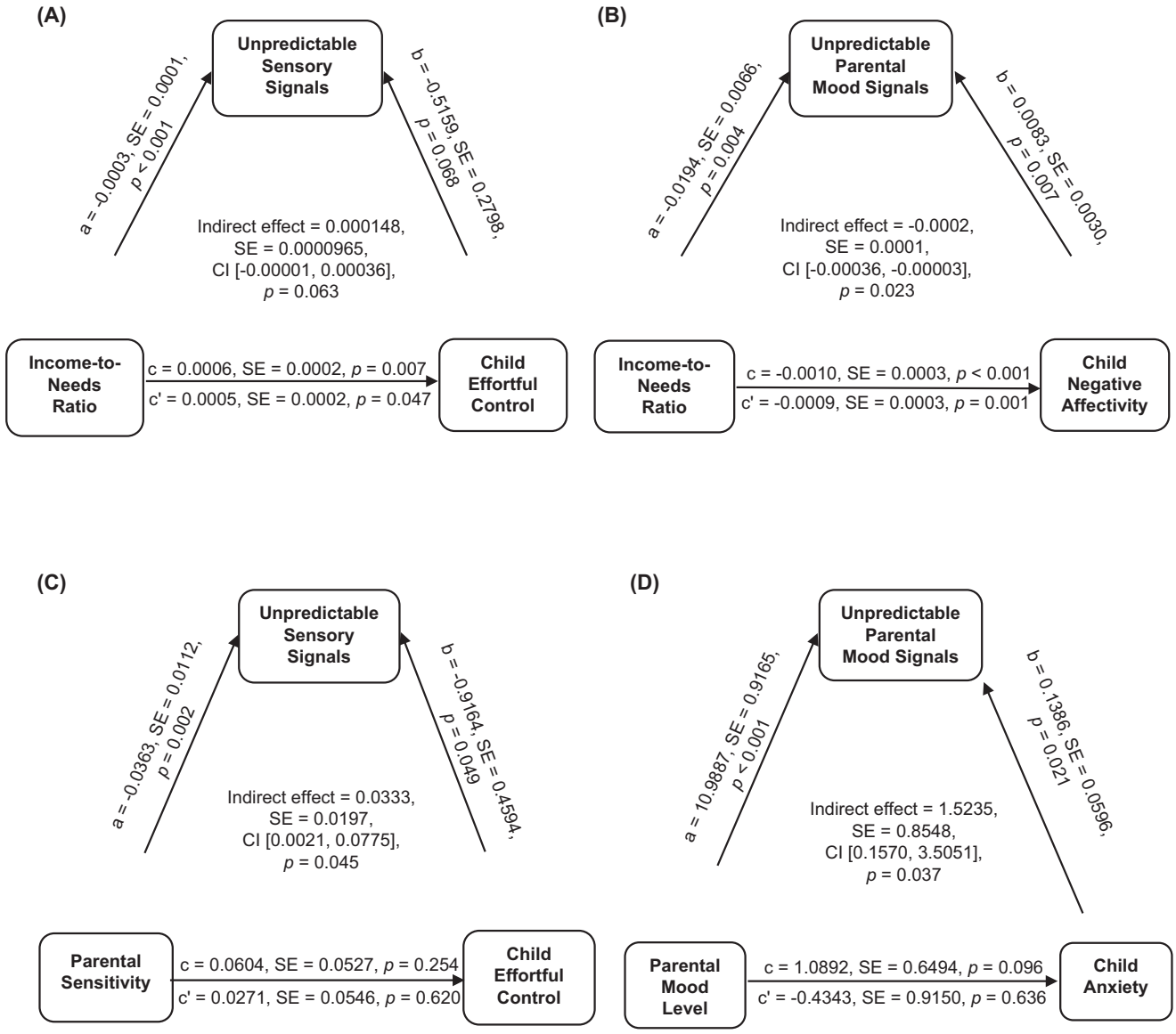

Figure 6 Unpredictable parental signals represent a pathway accounting for the association between established forms of ELA and development. Unpredictable sensory signals (Panel A; *N* = 121) and mood signals (Panel B; *N* = 124) during infancy partially mediate the association between income to needs ratio and child outcomes (effortful control and negative affect at 9 years of age). Further, unpredictable sensory signals in infancy partially mediate the association between parental sensitivity and effortful control at 12 months (Panel C; *N* = 103) and prenatal parental mood signals partially mediate the association between prenatal parental mental health and child self-report of anxiety symptoms at 9 years of age (Panel D; *N* = 139)

and emotional development. One important direction for future research is to further determine whether creating structure in the environment may additionally serve to protect or buffer children in the context of adversity and challenge. Consistent with this possibility, Bridley and Jordan (2012) report that although family routines are associated with fewer mental health challenges among youths, for those experiencing higher levels of daily stress, the protective effects of routines are more potent. Similarly, in families experiencing poverty, parental substance use disorders, chronic illness, or divorce, family routines predict child resilience (Betancourt, Meyers-Ohki, Charrow, & Hansen, 2013; Crespo et al., 2013; Guidubaldi, Cleminshaw, Perry, Nastasi, & Lightel, 1986; Wolin & Bennett, 1984). It also seems clear that predictability has the potential to promote child development in the context of larger, community or societal-level disruptions such as global pandemics (Bates, Nicholson, Rea, Hagy, & Bohnert, 2021; Gadermann et al., 2021; Glynn et al., 2021; Gordon-Hacker, Bar-Shachar, Egotubov, Uzefovsky, & Gueron-Sela, 2023; Rosen et al., 2021).

Third, in addition to leveraging a strengths-based perspective, it is possible that interventions seeking to promote predictability are clearly amenable to culturally responsive approaches. It is clear that what is an appropriate intervention target, or even feasible for some families, may not be so in others.

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For example, while there are clear benefits for child development of family rituals such as holiday traditions or celebrations, the potential to tailor these to the individual family is obvious and while not all families can facilitate a consistent dinner time together, there are other routines that could be adopted that would be feasible in that family context. In other words – promotion of predictability in the individual household need not utilize a one-size-fits-all approach.

Given the developmental importance of unpredictability and the amenability to prevention and intervention, as described above we have developed a short (5-item) screening instrument, the QUIC-5, available in multiple languages including Spanish and English (Glynn et al., 2023; Lindert et al., 2022), to facilitate identification of children who may benefit from preventive efforts. The QUIC-5 is currently being administered in pediatric clinics in Southern California to test the benefits of screening for unpredictability in addition to standard ACEs.

Conclusions

Patterns and signals in the early environment exert potent influences on development and represent a unique dimension of ELA deserving of investigation. These influences are independent of other forms of ELA, but importantly unpredictable parental signals at the moment-to-moment timescale also appear to constitute a pathway through which other ELAs determine developmental trajectories. That unpredictable parental moment-to-moment signals during early life predict neurodevelopment across diverse species provides compelling evidence that the sensitivity of the developing brain to patterns of signals is an evolutionarily conserved feature. A significant advantage of our translational neuroscience model of unpredictable parental signals is that it leverages a cross-species approach to enable causal testing of mechanisms down to the cellular level. Further, there exist many opportunities to address unpredictability in the early environment and increasing predictability may scaffold or enhance child development, perhaps even with the potential to provide a buffer against other forms of ELA.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. A survey of studies examining the relevance of unpredictability across cultures and diverse populations.

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Key points

- Unpredictability is an understudied dimension of early life adversity with pervasive effects on child development.
- The effects of unpredictability are observable across cultures and diverse populations, and its effects are independent from and synergistic with other established early life influences.
- Because unpredictability is an evolutionarily conserved process, translational models exist that enable probing the biologically plausible mechanistic pathways by which unpredictability impacts the developing brain.
- Unpredictability is a form of early life adversity that is amenable to prevention and intervention and further predictability has the potential to exert salutary influences on development.

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