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Special Issue Article

The Future of Developmental Psychopathology: Honoring the Contributions of Dante Cicchetti

The future of intergenerational transmission research: A prospective, three-generation approach

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Abstract

Dr. Dante Cicchetti's pioneering theory and research on developmental psychopathology have been fundamental to the proliferation of research on intergenerational transmission over the last 40 years. In part due to this foundation, much has been learned about continuities and discontinuities in child maltreatment, attachment, parenting, and psychopathology across generations. Looking towards the future, we propose that this field stands to benefit from a prospective, three-generation approach. Specifically, following established prospective, longitudinal cohorts of children over their transition to parenting the next generation will afford the opportunity to investigate the *developmental origins* of intergenerational transmission. This approach also can address key outstanding questions and methodological limitations in the extant literature related to the confounding of retrospective and prospective measures; examination of mediators and moderators; and investigation of the roles of biology, environment, and their interplay. After considering these advantages, we offer several considerations and recommendations for future research, many of which are broadly applicable to the study of two or more generations. We hope that this discussion will inspire the leveraging of existing prospective cohorts to carry forward Dr. Cicchetti's remarkable contributions, with the ultimate aim to inform the development of preventions and interventions that disrupt deleterious intergenerational cycles.

Keywords: attachment; developmental origins; intergenerational transmission; maltreatment; psychopathology

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Introduction

As a founder and leader of the field of developmental psychopathology (DP), Dr. Dante Cicchetti's legacy is reflected in scientific progress towards understanding intergenerational transmission: how various behaviors and characteristics, from adaptive to maladaptive, are maintained or disrupted across generations.[1] Guided by DP theory, entire subfields of research in this area have emerged over the last 40 years, including in key domains such as the intergenerational transmission of caregiving behavior, attachment relationships, adverse childhood experiences, self-regulation, and psychopathology (see Bridgett et al., 2015; Madigan et al., 2019; Narayan et al., 2021; Verhage et al., 2016). Dr. Cicchetti's contributions to elucidating processes of intergenerational transmission are demonstrated not only in his establishment of DP theory and its namesake journal, but also in his seminal research on child maltreatment. Among Dr. Cicchetti's first papers is a proposed model to investigate the mechanisms through which maltreatment is transmitted across generations (Cicchetti & Rizley, 1981). This line of inquiry has persisted through his career: a recent publication from his research group elegantly illustrates an intergenerational cascades model of child psychopathology, with mothers' own histories of childhood maltreatment associated with their children's maltreatment experiences, which in turn related to greater symptoms of psychopathology in their children (Russotti et al., 2021).

Consistent with DP theory (Cicchetti & Lynch, 1993; Cicchetti & Toth, 2009), research has examined how the intergenerational transmission of behaviors involves the interplay of biological and environmental factors across multiple levels of ecology unfolding over development. The variability in outcomes observed in intergenerational transmission research (e.g., Madigan et al., 2019; Verhage et al., 2016) reflects DP principles of multifinality and equifinality (Cicchetti & Rogosch, 1996)- for example, not all children of parents with a history of depression go on to develop depression themselves (multifinality, or the same risk factor associated with different outcomes), while some children experience depression despite their parents having no such history (equifinality, or the same outcome arising from different risk factors across individuals; see Goodman, 2020). These findings underscore that development is probabilistic rather than deterministic, and any given outcome arises from interactions among multiple causal mechanisms (Cicchetti & Toth, 2009; Masten & Cicchetti, 2016). DP theory has directed the search for vulnerability factors than maintain or give rise

[1]Here, we use the term intergenerational broadly to refer to transmission across two or more generations, recognizing the use of distinct terminology in some contexts (e.g., intergenerational versus transgenerational transmission in epigenetics; see Scorza et al., 2019; Wang et al., 2017).

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to maladaptive outcomes across generations, as well as resilience factors that divert the transmission of unfavorable experiences (Langevin et al., 2021; Liu et al., 2023; Narayan et al., 2021).

Looking towards the future of DP and research on intergenerational transmission, what does this literature stand to gain, and what methodological advances are needed to maximize progress? Here, we highlight that the field of DP is at an exciting juncture- as a number of prospective, longitudinal cohorts with data collection spanning several decades are established, we have the opportunity to study the *developmental origins* of intergenerational transmission *prospectively across three generations* to address important knowledge gaps. Specifically, continuing to follow cohorts of participants (generation 2; G2) who were repeatedly assessed in childhood with their parents (generation 1; G1) affords examination of the emergence of intergenerational continuities and discontinuities- for G2, over their transition to parenthood, and for their children, generation 3 (G3), in early life (e.g., fetal and infancy periods). While the developmental origins hypothesis (Barker, 2004) has historically pertained to the persisting impacts of very early life experiences on later life mental and physical health, we extend this hypothesis to intergenerational transmission by considering, for example, how G2's early attachment behaviors and parenting from G1 influence these same processes in the next generation. Understanding the earliest manifestations of intergenerational transmission is critical to the development of targeted interventions aimed at optimizing well-being across generations.

In this paper, we first propose how prospective, three-generation designs that examine the developmental origins of intergenerational transmission are uniquely poised to advance intergenerational transmission research. Specifically, we outline how such work can address key outstanding questions and methodological constraints in the field related to 1) conflating retrospective and prospective measures, 2) examining mediation and moderation, and 3) understanding the roles of biology, environments, and their interplay. We then offer recommendations for future intergenerational transmission research, many of which are broadly applicable to the study of two or more generations. We hope that our discussion will encourage a leveraging of existing prospective cohorts to advance the science of intergenerational transmission. Such research has the potential to directly inform the development of policies and practices that have cascading benefits for current and future generations.

Addressing methodological limitations with prospective, three-generation approaches

As is common in intergenerational research, we use G1 to refer to the parents of G2 participants, with G2's children being G3, the third generation (see Figure 1). The prospective, three-generation design we advocate for here would involve following an existing cohort of G2 participants, longitudinally assessed as children with their parents (G1), into adulthood and as they transition to parenting G3. Such an approach would allow researchers to test novel research questions about the emergence of intergenerational phenomena using robust methods that attend to methodological challenges in the literature.

Retrospective versus prospective measurement

Intergenerational transmission research can benefit in several ways from prospective, three-generation designs that use multi-informant data (e.g., observational, self-report, parent-report) to assess G2's childhood experiences *both* prospectively over childhood and retrospectively in adulthood over the transition to parenthood and G3's early life. We adopt the perspective that these reflect unique and valuable as opposed to unbiased and biased sources of information. In addition to more objective measures that identify and quantify experiences, individuals' perceptions and interpretations, both as events are occurring in childhood, and later in life when parenting one's own children, are likely to account for additional, important variance in intergenerational transmission processes (see Smith & Pollak, 2021b).

Prospective and retrospective measures are commonly regarded as interchangeable in research on the intergenerational transmission of adverse childhood experiences ("ACEs," e.g., childhood maltreatment; family instability) and parenting, a major limitation of this work. For example, G2's retrospective reports of parenting or maltreatment experienced in their own childhood from G1 are often examined for their relations with G2's observed (or self-reported) parenting of G3. This practice is ubiquitous in the growing number of studies interested in the influence of G2's ACEs on G3's fetal development and postnatal experiences, *independent* of current prenatal exposures (e.g., maternal prenatal psychological distress, current life stressors or events; see Souch et al., 2022). In these studies, G2 retrospective recall of childhood adversities is typically collected concurrently with pregnancy factors. Yet, mounting empirical evidence has revealed minimal overlap between prospective data and retrospective self-report measures (see Coleman & Baldwin; Nivison et al., 2021). Findings underscore that these methods capture different information and distinct groups of individuals, likely accounting for some of the inconsistencies in findings and modest effect sizes in the intergenerational transmission literature see Madigan et al., 2019; Verhage et al., 2016). Within a prospective, three-generation study, a "both/and" approach to prospective and retrospective measurement of G2's experienced parenting, parental psychopathology, and maltreatment from G1 would allow for an evaluation of their convergence, as well as their specific correlates (e.g., retrospective reports with G2's concurrent mental health symptoms and family relationships; Danese & Widom, 2020; Nivison et al., 2021). The unique variation explained by each of these perspectives in relation to a single outcome (e.g., parenting of G3), as well as their potentially distinct associations with different outcomes, also could be examined (see Newbury et al., 2018; Reuben et al., 2016). Further, repeated, prospective assessments of all three generations would provide the opportunity to examine the significance of features like the timing, severity, chronicity, and predictability of parental psychopathology or childhood trauma in intergenerational transmission (Glynn & Baram, 2019; Goodman, 2020; Madigan et al., 2019; Smith & Pollak, 2021a), which are often not captured in reductive, present versus absent retrospective variables.

An additional benefit of a three-generation design with both prospective and retrospective accounts of G2's early life is that the same prospective measure(s) can be administered in G3, ideally at the same developmental stage. Some percentage of the discrepancy between prospective and retrospective measures is very likely because these are simply different measures of the same construct, or, in some cases, different constructs altogether. Related is the principle of heterotypic continuity- that the behavioral manifestation of an underlying process is likely to change over development and thus cannot be assessed the same way across time (see Cicchetti & Rogosch, 2002; Petersen et al., 2020). This issue is perhaps especially relevant to research on the intergenerational transmission of attachment, as attachment is operationalized differently over the lifespan. In infancy, internal working models

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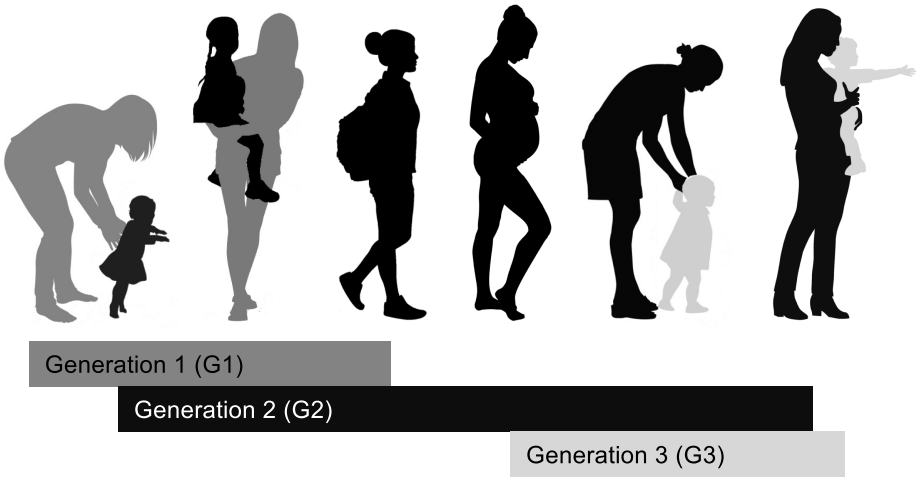

Figure 1. Illustration of a prospective, three-generation study.

of attachment, thought to develop based on the history of infant-caregiver interactions (Bowlby, 1969/1982; Sroufe & Waters, 1977), are typically measured with the Strange Situation (Ainsworth et al., 1978), a laboratory paradigm designed to activate infants' attachment *behaviors*. According to attachment theory, in adulthood, attachment information is organized as a mental representation (Main et al., 1985) which reflects one's psychological adaptation to attachment experiences, distinct from the "actual" quality of childhood attachment relationships (remembered or not; see Verhage et al., 2016). With the Adult Attachment Interview, *states of mind* regarding attachment are assessed, operationalized as the coherence of an adult's narrative of their childhood experiences as opposed to the concrete information provided. Most studies on the intergenerational transmission of attachment examine how adult states of mind are associated with their child's attachment behaviors (often measured concurrently), with meta-analytic evidence that the former explains about 10% of the variance in the latter (Verhage et al., 2016). This linkage, while undoubtedly important to understanding attachment over generations, is distinct from that which relates one's own attachment in infancy to one's infant's attachment. We are aware of only one prospective, longitudinal study that has collected two generations of Strange Situation data (Raby, Steele, et al., 2015). Ongoing for over 40 years, the Minnesota Longitudinal Study of Risk and Adaptation (MLSRA) recruited G1 mothers in pregnancy, with repeated assessments of G1 and G2 spanning G2's infancy into their adulthood and parenthood of G3. Collected in a subsample of 55 dyads, G2 and G3 infant attachment disorganization in the Strange Situation were positively associated, with a positive but smaller effect size evident for organized attachment patterns. Similar analyses in larger samples can seek to replicate these findings and further clarify intergenerational patterns of early attachment. Again, we emphasize the value of capturing both prospectively assessed G2 and G3 early attachment behaviors *and* G2 adult states of mind regarding attachment in G3's early life, as these both are likely to shape parenting and parent-child relationships (see also Narayan et al., 2019; Swerbenski et al., 2023 regarding the potential roles of G2's positive childhood memories and childhood trauma resolution in parenting).

Related is the need for prospective, observational assessment of the intergenerational transmission of processes in the sensitive developmental periods of infancy and early childhood (as well as the *in utero* environment), which requires a three-generation design (=prospectively following G2 from early life into parenthood of G3). For experiences such as early parenting and attachment security, self-report is not possible, and G1 reports (e.g., of parenting of G2) can be confounded not only by factors like psychological distress and socioeconomic disadvantage (see Herbers et al., 2017), but also measurement error due to a shared-method bias (e.g., if G1 reports on both own and child's experiences). Furthermore, some early sensory inputs are not possible to capture with self- or parent-report and must be assessed observationally (see Glynn & Baram, 2019). Very few studies have early observational data for both G1–G2 and G2–G3 to be able to address important questions regarding the intergenerational transmission of early experiences (Kerr & Capaldi, 2019). Two studies using data from the MLSRA have linked G1 observed parenting quality of G2 at age 2 to G2 parenting of G3 at age 2–3, using observational and interview-based assessments of G2 parenting (Kovan et al., 2009; Raby, Lawler, et al., 2015). Adjusting for factors including socioeconomic disadvantage, intelligence, and stressful life events, G1 observed parenting was modestly associated with both G2 observed and interview-based parenting.

New, prospective, three-generational studies can seek to replicate these findings and address novel questions related to the intergenerational transmission of very early life experiences such as attachment security and parenting quality. These approaches also could examine the involvement of early life experiences in the neurobiological changes that occur over transition to parenthood (see Cárdenas et al., 2020), with the opportunity to examine within-person change through repeated assessment of G2 from before parenthood to early parenthood. As another possibility, three-generation research studies can inform screening efforts to identify G2 individuals vulnerable for psychopathology and parenting difficulties over the transition to parenthood. Retrospective reports of childhood trauma are related to perinatal psychopathology independent of other salient risk factors (e.g., prior history of psychopathology, sociodemographics), but findings are mixed as to whether this association persists when also considering adulthood trauma (e.g., intimate partner violence; see Choi & Sikkema, 2016). Prospective data are needed to better understand the potential unique contributions of childhood risks (and protective factors), above more proximal experiences. Beyond identification, these approaches can inform the development of personalized and appropriately timed interventions to support G2 and G3.

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Examining mediation and moderation

Intergenerational transmission research is principally interested in identifying mediating mechanisms as well as moderators that maintain or disrupt transmission, based in various theoretical and empirical perspectives (e.g., genes, environments, and their interplay; social learning theory; attachment theory; neurobiological models; see Alink et al., 2019; Branje et al., 2020; Goodman, 2020; Narayan et al., 2021; Van IJzendoorn et al., 2020). Here we consider how prospective, three-generation studies which follow G2 over the transition to parenthood of G3 can strengthen conclusions regarding mediators and moderators previously identified in the literature and pose unique questions to further understanding of these processes.

Mediation

Prospective, three-generation designs will allow for the appropriate temporal ordering of measures that is essential when investigating mediators of intergenerational transmission. Of course, causation cannot be inferred from even the most rigorously designed observational, longitudinal study of a proposed mechanism, as it is impossible to adjust for all possible confounds, and developmental processes are expected to be multiply determined. Studies have attempted to statistically account for other continuities that might account for intergenerational patterns, considering them as covariates (e.g., to show that G1 parenting is associated with G2 parenting independent of socioeconomic disadvantage) or as mechanisms of transmission (e.g., socioeconomic disadvantage as a pathway by which G1 parenting relates to G2 parenting). Appropriate temporal sequencing at a minimum allows for interpretation of results somewhat closer to the level of causal inference, by adjusting for the potential confound of time (O'Laughlin et al., 2018). Cross-sectional studies are highly prevalent in the intergenerational transmission literature (e.g., G2 retrospective reports of their parenting from G1 collected concurrently with observational measurement of their parenting of G3), as are what are referred to as "half-longitudinal designs" (two of the three variables assessed contemporaneously, for example, time has elapsed between the measurement of G2 adversity and G2 psychopathology, or G2 psychopathology and G3 adversity, but not both; see O'Laughlin et al., 2018 for discussion). With prospective, three-generation models, predictor (e.g., prospectively assessed G2 early life attachment behavior), mediator (e.g., G2 early parenting of G3), and outcome (e.g., G3 early life attachment behavior) could be examined prospectively across three different timepoints, serving as a more robust test of mediation.

Prospective, three-generation designs also will be better equipped to empirically test the DP conceptualization of intergenerational processes as "cascade effects" involving multiple, interacting causal mechanisms across levels and systems which unfold over development and spread across generations (Masten & Cicchetti, 2010). Models which account for multiple possible mediators and their interplay over time are likely to better address what are referred to as "transmission gaps" (e.g., proposed mediators accounting for minimal variance in intergenerational associations; see Verhage et al., 2016). To our knowledge, only a few existing studies have tested cascade models of the intergenerational transmission, specifically regarding G2–G3 childhood maltreatment e.g., Choi et al., 2019; Russotti et al., 2021). These studies have yielded results in support of both independent and cascading (e.g., via G2 maternal depressive symptoms) pathways of G2 maternal history of childhood maltreatment on G3 childhood maltreatment experiences and psychopathology. However, they are limited by issues related to contemporaneous measurement, retrospective reporting of G2 experiences of maltreatment from G1, and/or shared-method variance for many of the variables. Studies with prospective, longitudinal assessments of G1 and G2 over G2's childhood and of G2 and G3 can replicate and expand upon these findings. Repeated assessment of factors hypothesized to contribute to intergenerational transmission also is important because mediators of interest are often not static, and, as alluded to above, their timing in development is likely to be relevant. While Cicchetti and his colleagues (Cicchetti & Lynch, 1993; Cicchetti & Rizley, 1981) outlined the importance of distinguishing between risk and protective factors that are transient versus those that are enduring with regards to the intergenerational transmission of maltreatment, for example, this has rarely occurred in empirical practice.

In addition to considering pathways of transmission from G1 to G3 via G2, three-generation designs also can consider the additive contributions of G1 and G2 on G3, as well as G1 influences on G3 that are *independent* of G2. Studies have pointed to the value of direct assessment of three generations for identifying risk for psychopathology. For example, Weismann et al., (2016) found that G3 children with both G1 and G2 major depressive disorder (MDD) histories were at very high risk for MDD. Several studies have documented G1 to G3 psychopathology associations independent of G2 (over and above or in the absence of G2 psychopathology), highlighting then need to consider that transmission can "skip" generations (Kendler et al., 2018; Olino et al., 2008; Pearson et al., 2019). Environmentally mediated G1 to G3 effects independent of G2 may be more salient in sociocultural contexts in which grandparents tend to be highly involved in caregiving (Pearson et al., 2019). Collectively, these findings underscore the importance of including not only parental but also grandparental history and involvement when evaluating familial risk for psychopathology. This small literature is limited by design features such as retrospective recall of (grand)parental history and, in some cases, shared-method variance (G2 report of own and G3 symptoms of psychopathology). Thus, findings would be bolstered by replication in future prospective, three-generation studies with prospective measures of psychopathology across multiple generations.

Moderation

Intergenerational transmission researchers are interested in identification of moderating factors that may account for continuities and discontinuities in transmission, with a motivation to identify modifiable factors as potential targets for prevention and intervention (see Langevin et al., 2021). Findings suggest that safe, stable, nurturing relationships, such as supportive caregivers in childhood or romantic partners in adulthood, may buffer the transmission of ACEs, maltreatment, and negative attachment patterns (Narayan et al., 2021; Raby, Steele, et al., 2015; Schofield et al., 2013). For example, G2 mothers who reported a history of childhood maltreatment from G1 were more likely to "break the cycle", evidenced by no documented history of G3 maltreatment, if they reported more access to family support and less intimate partner violence (St-Laurent et al., 2019).

To draw stronger conclusions about moderating factors and more promptly impact families, future three-generation research could leverage the DP "intervention as a test of mechanism" approach (Cicchetti & Gunnar, 2008; Masten & Cicchetti, 2010) to test whether a prevention or intervention targeting a hypothesized

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moderator decreases the likelihood of intergenerational transmission of harmful experiences from G2 to G3. This could involve building an intervention into an ongoing, prospective, longitudinal study- an evidence-based modality for G2 perinatal mental health, early G2 parenting, and/or G2–G3 relationship quality could be delivered to test whether intervening disrupts transmission and results in more optimal outcomes for G3's development (see Cicchetti et al., 2006; Davis et al., 2018; Guild et al., 2017). A quasi-experimental, three-generation design also could be formed out of an existing prevention/intervention study that has continued to follow children who received interventions into adulthood to see if effects persist (see Hill et al., 2020; Rothenberg et al., 2023). For example, the Seattle Social Development Project, a longitudinal study of a universal preventative intervention called Raising Healthy Children delivered to G2 elementary school children and their G1 parents and teachers, has examined whether intervention effects are sustained into the next generation, 20 years later. Using multi-informant measures collected across 7 timepoints, G3 children (ages 1–13 at first assessment) whose G2 parents received the intervention showed more optimal early development, lower behavioral problems, higher academic performance, and lower drug use, compared to G3 children of parents in the control group. As a further option, researchers could examine the effects of temporal variations in policies (e.g., related to income supplementation, healthcare) on intergenerational transmission as a form of quasi-experimental study of potential moderating influences to support intergenerational resilience (see Howland & Cicchetti, 2021).

Understanding biology, environment, and their interplay

From a DP perspective, intergenerational transmission is very likely a result of both biological (e.g., genetic, hormonal) and environmental influences, as well as their interplay (see Wilson & Rhee, 2022). To date, research has sought to disentangle biological and environmental effects to understand direct and indirect pathways of transmission, with a newer interest in epigenetic mechanisms by which experiences and exposures can "get under the skin" to alter patterns of gene expression across generations (see Bos, 2017; Branje et al., 2020 for review). Other work has examined how biological and environmental factors interact to influence transmission. In this section, we propose several ways that prospective, three-generation models can advance our understanding of the unique and synergistic influences of biology and environment in intergenerational transmission.

Disentangling genes and environments

Genetically-informed, two-generation research studies have endeavored to isolate genetic and environmental contributions to the intergenerational transmission of multiple behaviors and characteristics from G2 to G3, by addressing shared genetic and environmental confounds (reflected in gene-environment correlations; see Sellers et al., 2022). A genetically-informed three-generation design could be developed by continuing to follow prospective twin cohorts (e.g., ABCD twin subsample; Fan et al., 2023) into parenthood, as an extension of the children of twins (CoT) design (see McAdams et al., 2018; Sellers et al., 2022). In this framework, G2 twins would be followed longitudinally, beginning in childhood with their G1 parent(s) and then with their G3 children. A prospective, longitudinal CoT design would address key limitations of existing genetically-informed intergenerational research.

Briefly, as a form of family-based, quasi-experimental design, CoT studies allow for tests of competing causal hypotheses based on differences in the degree to which family members share genes and environments (for detailed discussion, see Sellers et al., 2022; Wilson & Rhee, 2022). Children of monozygotic (MZ) twins are as genetically related to their parent as there are their parent's co-twin, with 50% of their genes shared. In contrast, children of dizygotic (DZ) twins share 25% of their genetic variance with their parent's co-twin. Comparing correlations between a child and their parent and between a child and their parent's MZ twin allows for examination of the influence of living with one's parent beyond simply inheriting 50% of their genes, while also adjusting for environmental confounds that twins share. Further, contrasting the strength of correlations between MZ versus DZ twin pairs and their children estimates the extent to which intergenerational phenotypes (e.g., psychopathology) are due to genes, environments, or both. Existing intergenerational CoT studies have been cross-sectional. For example, Singh et al., (2011) interviewed an Australian sample of 445 MZ and 598 DZ twins and their children (age 14–39 years). Depression histories were compared among cousins who were differentially exposed to parental depression (one co-twin reported a history of depression and the other did not). Analyses suggested that the intergenerational transmission of depression was partially due to "direct" environmental influences (e.g., social learning, parenting; see also Eley et al., 2015). In addition to the previously referenced issues related to cross-sectional design (retrospective vs. prospective measurement and temporal ordering issues), these CoT models assume that the same genes influence adolescent and adult anxiety phenotypes. Singh et al., (2011) authors note that this assumption could be empirically tested with measures from adolescence for the adult twin parents, pointing to several existing longitudinal child twin studies in which the children are entering young adulthood.

A prospective, longitudinal CoT study which follows G2 into parenthood represents only one of a number of possible family-based, genetically-informed designs that characterizes three (or more) generations. As another option, extended family designs (e.g., recruitment of participants and their extended family members) can be used to ask questions related to intergenerational transmission (for example, see Pittner et al., 2019).

Epigenetic transmission

Prospective, three-generation studies are especially well-suited to advance scientific understanding of epigenetics, a form of gene-environment interplay by which environmental exposures or experiences can induce long-term alterations in gene expression and associated phenotypes without changing the underlying genetic sequence (see Scorza et al., 2019; Yehuda & Lehrner, 2018). Epigenetics is a primary proposed mechanism by which experiences in one generation can influence the next, even in the absence of continued exposure (though many exposures are not limited to a single generation in humans, creating challenges for disentangling inherited and current effects). Here, distinct terminology is needed- *intergenerational* epigenetic inheritance refers to the transmission or persistence of this modified pattern of gene expression into the next generation (e.g., G1 to G2, or G2 to G3); in other words, parents transmit not only genetic but also epigenetic characteristics. For example, G2's experiences of childhood maltreatment from G1 can impact G3 even in the absence of G2 maltreatment of G3, via changes in G2's germline. While well-established in animal models (see reviews by Breton et al., 2021; Scorza et al., 2019), little evidence exists in humans

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regarding intergenerational epigenetic transmission. As one of several exceptions, Yehuda et al., (2016) showed that Holocaust exposure was associated with differences in methylation of the FKBP5 gene, a key regulator of stress system function, in both Holocaust survivors and their adult children, relative to a non-exposed, comparison group. The authors advocated for future, prospective longitudinal studies which follow trauma survivors before conception, during pregnancy, and into the postpartum period to examine pathways of epigenetic transmission from one generation to the next (e.g., changes in gametes, *in utero* effects, early parenting, or other early life experiences influenced by parental history of trauma; see also Yehuda & Lehrner, 2018). One study in mice has demonstrated that the intergenerational transmission of early life trauma-induced epigenetic changes can be prevented by environmental enrichment in G2's adulthood, before conception of G3 (Gapp et al., 2016). Parallel findings in humans could come from a prospective, three-generation study which provides an intervention to G2 (as suggested above), for example, to G2 individuals who experienced childhood maltreatment from G1, with measures of G2 epigenetics collected pre- and post-intervention in G2 and then in G3.

In addition to epigenetic transmission from one generation to the next, epigenetic inheritance across more than two generations is possible (see Wang et al., 2017), the study of which necessitates characterization of three or more generations. The timing of exposure and sex differences must be taken into account to test for such patterns. An exposure (e.g., traumatic event) in a G1 pregnant female can directly impact the G2 fetus as well as G2's primordial germ cells, the future G3. Therefore, an epigenetic effect from a G1 female can be considered to reflect *transgenerational* inheritance only if it is evident in the absence of direct exposure (observable in G3 if G1 was not pregnant when exposed, or in G4 if exposure was in G1's pregnancy). In contrast, an exposure-induced epigenetic change in a G1 male only directly affects his germline, the future G2, so G3 and subsequent generations can be examined for evidence of transgenerational epigenetic inheritance. To our knowledge, no previous study has documented transgenerational epigenetic inheritance in humans. Epigenetic data in three or more generations would offer unprecedented opportunities to explore the potential for isolated exposures in one generation to have cascading biological effects on future generations, as well as the likely cumulative, biological impacts of experiences spanning multiple generations (e.g., structural racism, historical trauma; see Hankerson et al., 2022).

Neurobiological influences

Three-generation studies can investigate how G2 neurobiological factors (e.g., endocrine profiles; Bos, 2017) shaped in early life (e.g., childhood or fetal period if G1 is recruited in pregnancy) relate to the onset and course of their parenting or maltreatment of G3. Bolstered by extensive non-human animal evidence, studies of human parenting, thus far primarily among mothers, support the role of hormones, neuropeptides, and neurotransmitters in the intergenerational transmission of parenting and maltreatment (see Bos, 2017; Lomanowska et al., 2017). Bos (2017) articulates a model by which G2 *in utero* exposures and experienced early parenting from G1 influence patterns of endocrine sensitivity, which then shape the quality of the intrauterine environment and parenting provided to G3. Findings from a few human studies are aligned with this perspective, though they are typically limited by their reliance on G2 mothers' retrospective reports of childhood experiences (e.g., G1's parenting) collected concurrently with measures of neurobiology and parenting of G3. The aforementioned literature on the *in utero* environment as a mediator of the intergenerational transmission of early adversity (see Souch et al., 2022) would similarly benefit from prospective characterization of maternal childhood experiences and from accounting for maternal pre-pregnancy biological profiles.

Towards prospective, three-generation designs: considerations and recommendations

The design and execution of any prospective, longitudinal study involves numerous considerations, and one that attempts to span three generations adds further complexities. Several lead investigators of existing three-generation studies have offered detailed guidance (Kerr & Capaldi, 2019; Thornberry et al., 2012; Thornberry, 2016). We draw from and expand upon these insights here to offer several recommendations and action items, acknowledging that we do not address the full range of possible strengths and limitations of this work (not the least of which are the financial and logistical hurdles involved). A few of our recommendations are broadly applicable to any study involving more than one generation, while several others are specific to prospectively following existing cohorts of G2 as they transition to parenthood.

Developing prospective, three-generation cohorts

We encourage continued assessment of any prospective, longitudinal cohort of G2 individuals who have been followed with their G1 parents into the next generation, even if capturing G2 over pregnancy and early parenting of G3 is not feasible. Ideally, this work would involve large scale, representative studies and/or harmonization across smaller cohort studies, a practice already well-reflected in the approximately one dozen existing prospective, three-generation studies (see Branje et al., 2020; Breton et al., 2021; Kerr & Capaldi, 2020; Scorza et al., 2019). Two of these are part of the larger United States (U.S.) National Institutes of Health's Environmental Influences on Children's Health Outcomes (ECHO) study, a 7-year initiative which draws on 84 existing cohorts to prospectively examine the role of early experiences on child health and development (Scorza et al., 2019). One of the ECHO cohorts, the Pittsburgh Girls Study (PGS), is a longitudinal, community sample of 2,450 G2 girls (approximately half White and half Black, 33% living in poverty). They were assessed over childhood with their G1 caregivers, for seventeen annual assessments from G2 ages 5–8 through 21–24 years (with a mean retention of 90%). Assessments have included an array of measures spanning multiple levels of analysis (biological and environmental, including family, school, and neighborhood contexts). Scorza et al. (2019) report that PGS sub-studies have now collected perinatal data on G2 and G3 (see Hipwell et al., 2023), including brain imaging of G3 to examine early brain development. Beyond the two ECHO cohort studies described in Scorza et al. (2019), the Netherlands-based TRacking Adolescents' Individual Lives Survey (TRAILS) study (Branje et al., 2020) and the United Kingdom's Avon Longitudinal Study of Parents and Children (Lawlor et al., 2019) also are following G2 cohorts into the next generation. TRAILS has involved ongoing multi-informant, multiple-levels-of-analysis data collection from 2,773 G1–G2 families over bi- or triennial follow-up assessments from G2 age 11 into adulthood (ages 25-29). The study is now inviting G2 participants and their partners to join TRAILS-The Next generation when they are pregnant, with at least 5 assessments planned (from pregnancy to 78 months postpartum). Data collection includes self-report and

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observational measures (e.g., of G2–G3 parent-child interactions; G2 psychopathology and early precursors in G3; life events; home environment) as well as biological samples (e.g., buccal cells for genotyping). As of Branje and colleagues' 2020 publication, over 300 TRAILS-Next G3 children were born, with many more expected to be recruited in the years to come. These trailblazing studies will be important exemplars for future three-generation investigations and will be able to provide lessons learned.

In addition to following ECHO cohorts into the third generation, the Adolescent Brain and Cognitive Development (ABCD) study (abcdstudy.org; see Karcher & Barch, 2021) represents another possible future target. ABCD has enrolled over 11,000 G2 children and their G1 caregivers across 21 sites in the U.S., with an aim to develop a sample approximately representative of sociodemographics of U.S. population. Beginning with the baseline assessment at ages 9–10 years, G2 children are prospectively followed every 6 months to a year, with planned assessments through ages 18–19 (concluding in years 2025–2027). The ABCD protocol is comprehensive and includes a rich array of repeated measures, including brain imaging and genotyping, as well as assessments of psychological and physical health, neurocognition, and contextual factors like family environment, socioeconomic status, neighborhood quality, and cultural values. ABCD includes genetically-informative components, as the study enrolled G2 children along with their eligible siblings, as well as a subsample of 860 same-sex G2 twin pairs (Fan et al., 2023). That all ABCD participants were recruited at the same chronological age points to a major challenge with prospective, three-generation studies regarding cohort development. Using their Rochester Intergenerational Study, Thornberry and colleagues (see Thornberry, 2016) demonstrate how a prospective, three-generation study produces a very diffuse age distribution across three generations- G2 may all be born within several years of each other but become parents of G3 over the span of 20 plus years. They offer helpful guidance around clustering G3 participants of similar ages into "birth cohorts" for adequate statistical power and appropriate statistical modeling, which yields a variant of a cohort sequential or accelerated longitudinal design. Of course, there are other ways to assess three or more generations in a shorter time frame, but this is the design likely to result from the prospective, three-generation approach we propose.

As present and future intergenerational transmission researchers consider cultivating three-generation cohorts, we urge reflection on several other key factors related to cohort design and management. First, researchers should approach following G2 into parenthood with a sensitivity to diverse pathways to parenting (e.g., LGBTQ + parenthood, single parenthood, adoption, stepparenting), as well as the decision not to parent. If resources are available, we advocate for studies to follow all G2 parents, not just birthing parents. G3's other parent(s) also could be included in data collection when possible. Involving all parents can address a number of outstanding questions and limitations in the extant literature, including the role of informant, as well as concurrent and intergenerational influences from the other parent(s).

Issues of participant attrition and retention will be critical to consider across phases of study design, implementation, and data analysis. While following G2 into parenthood of G3 offers the benefit of not needing to recruit an entirely new parent-child cohort, at the same time, this may create limitations if the representativeness of the sample changes over time with attrition. In our experience, retention of participants over sensitive transitions in their lives and over many subsequent years is made possible by strong rapport between researchers and participants, bolstered through continuity in research staff and representation of participant identities and language preferences among staff. Strategies to maximize retention also should include appraisal of participant burden and direct benefit when designing study protocols, proper compensation, as well as efforts to address barriers such as lack of transportation and resources. As an example, in one of our studies, we provided participants with smartphones to support full participation in ecological momentary assessment protocols. Further, integrating community-engaged research approaches to include the voices of participants and relevant stakeholders in the research process can help refine research questions, design, and implementation, as well as empower and affirm community members.

Measurement considerations

Drawing from our above review of measurement issues in intergenerational transmission research, we recommend, when possible, to collect both prospective and retrospective measures of constructs of interest, and from multiple informants, both objective (e.g., CPS records, observer ratings) and subjective (e.g., self-report, parent-report). Multi-informant measurement can bolster reliability and predictive validity, adjust for shared-method variance, and allow for a more nuanced examination of factors involved in intergenerational transmission (see Coleman & Baldwin, 2023; Hendriks et al., 2018; Madigan et al., 2019; Smith & Pollak, 2021b; Widom et al., 2015).

While considered best practice in intergenerational transmission research (Kerr & Capaldi, 2019; Thornberry, 2016), it is often impossible, even for longitudinal studies spanning several decades, to administer the same measures at the same age or developmental stage in both G2 and G3, both because of the long span of time in which G2 may become parents and the desire to use improved measures as the field advances. We suggest collecting both the "old" and "new" measures when possible. At a minimum, intergenerational research must recognize the impact of the type and timing of measures used when interpreting findings (Kerr & Capaldi, 2019; Petersen et al., 2020; Thornberry, 2016). Kerr & Capaldi (2019) highlight a related, rarely acknowledged point in terms of analytic approach: most intergenerational research uses methods which capture stability and instability (correlations between G2 and G3 which reflect rank ordering across generations) rather than continuity and discontinuity (similarities or differences in mean levels of behaviors), the latter of which is difficult to examine if disparate measures are used in each generation. This distinction is critical to consider when interpreting intergenerational research findings.

When paired with sound measures, researchers can leverage statistical methods to strengthen inferences about transmission across generations. For example, from a DP ecological-transactional perspective (Cicchetti & Lynch, 1993), developmental processes are understood to involve bidirectional and reciprocal influences between the child, caregivers, and broader environment, yet these transactional relationships are rarely (if ever) accounted for in empirical studies on intergenerational transmission. To isolate a unique transmission effect from one generation to the next, disentangling of potential reciprocal parent and child effects is needed, which includes appropriately accounting for the stability over time within measures (e.g., parenting behavior across time and generations) and the covariance of parent and child measures assessed at the same timepoint within statistical models (see Berry & Willoughby, 2017; Masten & Cicchetti, 2010). As another

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possibility, application of causal inference methods such as propensity score matching can be used to strengthen conclusions about intergenerational processes, by "matching" participants on as many covariates of interest as possible to better isolate the effect of interest (e.g., maltreatment; see Thornberry & Henry, 2013).

Finally, intergenerational transmission is likely to involve environmental influences not only at the microsystem level (e.g., parents, family) but across all levels of the ecosystem, including the macrosystem and exosystem (e.g., neighborhood, socioeconomic factors; Cicchetti & Lynch, 1993). Intergenerational stability or continuity in processes such as parenting or psychopathology may arise as much, or more, from consistency in broader environmental factors across generations (e.g., socioeconomic (dis) advantage; structural barriers), relative to more direct pathways of transmission (Cheng et al., 2016; Conger et al., 2009; Scorza et al., 2019). While undoubtedly challenging methodologically to account for factors across multiple levels of ecology in a single intergenerational study, at minimum, we encourage further consideration of more distal, systemic factors that may mediate or moderate intergenerational transmission and contribute to the undue perpetuation of adverse experiences in marginalized populations.

Conclusions

Dr. Dante Cicchetti's foundational theoretical and empirical contributions to the discipline of DP over his prolific career have fundamentally informed research on the intergenerational transmission of core developmental phenomena, including parenting, attachment relationships, child maltreatment, and psychopathology. *Development and Psychopathology* has served as a home for much of this literature, with multiple special issues dedicated to intergenerational transmission (e.g., Alink et al., 2019). As we have considered here what has been learned and what remains to be understood about intergenerational processes, we are excited about what gains we believe can be seen with a prospective, three-generation approach. By leveraging carefully developed existing prospective cohorts, future DP research can seek to replicate existing findings with more robust methods and answer exciting, unexplored questions about intergenerational cascades across multiple generations.

Prospective, three-generation research can and should work to directly inspire policy and practice transformation. We echo Kerr and Capaldi's (2019) prediction regarding the influence of three-generation empirical findings (over and above two-generation evidence): "the telescoping lens of intergenerational research demonstrates the potential for parenting influences to ripple across the life span, spread to coparents and other close relationships, and cascade across subsequent generations" (p. 473). Ultimately, drawing inspiration from Dr. Cicchetti's legacy of preventive intervention research (Cicchetti et al., 2006), three-generation empirical evidence can be translated to *three-generation preventions and interventions*. Cheng and colleagues' (2016) call for a paradigm shift to focus on a three-generation approach to disrupting intergenerational cycles of socioeconomic disadvantage provides an excellent illustration of this potential. By extending program and policy focus beyond G1 parenting and G2's early childhood into G2's parenthood of G3, the reach of interventions can be expanded to "break" detrimental intergenerational cycles and promote the health and well-being of both current and future generations.

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