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Seeing adolescents grow from many angles using a multilevel approach: A tribute to the contributions of Dante Cicchetti to the field of developmental psychopathology

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Abstract

Dante Cicchetti propelled forward the field of developmental psychopathology by advancing this framework and championing new methods, including emphasizing the central role that multilevel analysis holds for explicating pathways of risk and resilience. His work continues to change the face of existing science. It has also paved the way for the formation of new projects, like the Research Domain Criteria initiative. This paper uses our laboratory's work on multilevel approaches to studying adolescent depression, non-suicidal self-injury, and suicidal thoughts and behaviors to shine a spotlight on Dr Cicchetti's contributions. In addition, we review recent developments, ongoing challenges, and promising future directions within developmental psychopathology as we endeavor to carry on the tradition of growth in the field.

Keywords: adolescence; depression; developmental psychopathology; multilevel approach; multiple units of analysis; non-suicidal self-injury; suicide risk

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Introduction

A paradigm shift emerged in the 1970s and early 1980s (Achenbach, 1974; Sroufe & Rutter, 1984) with the birth of developmental psychopathology, a field that combines developmental and clinical sciences. Core features of developmental psychopathology include (a) considering the origins and course of behavioral adaptation and maladaptation across the life course, which may feature key principles of homotypic and heterotypic continuity, equifinality and multifinality, (b) identifying key drivers or causal mechanisms that underlie the salient developmental tasks relevant to the developing organism, (c) leveraging approaches that span across multiple levels of analysis (hereafter referred to as multilevel), and (d) considering applications to prevention and intervention (Cicchetti & Toth, 2009). Dr Dante Cicchetti played a pivotal role in defining and promoting this field of study since its inception (Cicchetti, 1984a, 1984b; Sroufe & Rutter, 1984). In addition to his paramount intellectual contributions, the current Special Issue recognizes his brilliant and tireless work throughout a 40-year editorship of *Development and Psychopathology*. Through these efforts, Dr Cicchetti shepherded the field from infancy to maturity by identifying and featuring key topics, highlighting advances, and fostering scientific discourse.

Dr Cicchetti's leadership contributions to developmental psychopathology provided a foundation for the work of generations of researchers in this field. He is resolutely committed to mentoring, encouraging, and providing opportunities for growth to emerging scientists. His own body of research is far-reaching and addresses many of the common psychological and behavioral mental health challenges faced by youth, including depression in adolescence (Cicchetti, 2016a). Yet, the core of his program of research is directed at understanding risk and resilience pathways in the context of maltreatment (Cicchetti, 2016b). Multilevel methods undergird much of this work, as he emphasizes how biology interacts with behavior, in turn impacting and being impacted by relationships at home, school, and other spheres of the environment (Cicchetti & Dawson, 2002; DePasquale et al., 2019). Using multilevel approaches, Dr Cicchetti and his colleagues examined critical biological mechanisms in these models including physiological and genetic indexes implicated in stress activation and regulation (DePasquale et al., 2019). Early on, Dr Cicchetti and colleagues outlined the history of interdisciplinary science, and the critical nature of systems neuroscience research, highlighting structure, mechanisms, and functions of neural systems (Albright et al., 2000; Cicchetti & Dawson, 2002). They also strongly advocated for multilevel approaches to understanding risk and resilience, noting that "psychopathology cannot be understood fully unless all levels are examined and integrated. Each level both informs and constraints all other levels of analysis" (Cicchetti & Dawson, 2002, p. 418). This idea subsequently emerged as a focus of the Research Domain Criteria (RDoC) framework, put forth by the National Institute of Mental Health (Cuthbert & Kozak, 2013; Insel et al., 2010). RDoC's "units" of analysis are synonymous with "levels," but include specified units of relevance delineated into genes, molecules, cells, circuits, physiology, behaviors, self-reports, and

paradigms. While overall the way that levels or units are defined and used across studies varies considerably, there is overwhelming agreement that multilevel approaches are critically important to advancing knowledge about risk and resilience, developmental cascades, and a host of other concepts central to developmental psychopathology. The deployment of optimally complex yet cogent multilevel approaches undoubtedly presents challenges; nevertheless, progress in understanding probabilistic pathways toward risk and resilience will be enhanced when multilevel approaches are used to inform science (Cicchetti & Dawson, 2002).

In this paper, we set out to highlight and honor Dr Cicchetti's contributions and to provide an example of how the foundational concepts that Dr Cicchetti spearheaded, paved the way for our work. To do so, in the first part of this paper, we concentrate on the progression of our own laboratory's research that uses multilevel approaches, to understand key biological mechanisms implicated in depression, non-suicidal self-injury (NSSI), and suicidal thoughts and behaviors (STB) in adolescents, and how these processes unfold over time. This part of the paper will show how, drawing on the framework that Dr Cicchetti put forward, we joined many others in standing on his shoulders to bring these foundational ideas to life and to further advance the field. In the second section of this paper, we point to future directions of this line of inquiry, many of which may be applied more broadly to developmental psychopathology research.

An illustration of the progression of our lab's multilevel work on adolescent depression, NSSI, and STB

A long-standing focus of our group has been to incorporate multilevel approaches to understand the biological underpinnings of depression in adolescents, considering key systems in the brain and the body. In the early days of our collaboration, we noted that research on the neurobiological correlates of adolescent depression were taking parallel and siloed approaches (Cullen, Klimes-Dougan et al., 2009). By then, there was a growing body of work focusing on the hypothalamic–pituitary–adrenal (HPA) axis in the context of adolescent depression (Klimes-Dougan et al., 2001; Lopez-Duran et al., 2009), although efforts to map functional brain activation and connectivity patterns associated with depression were just beginning (Greicius et al., 2007; Thomas et al., 2001), including in our work (Cullen, Gee et al., 2009; Cullen et al., 2010). Nevertheless, we argued for the importance of integrating these levels in research (Cullen, Klimes-Dougan et al., 2009). While the work in our lab encompasses a broader array of levels of analysis, including self-reported symptoms (experiences) and behavioral performance (expression), a central thread has been to examine the key features of threat system functioning in the context of the brain (structure, function, connectivity) and the body (endocrine system).

To move this line of investigation forward, we incorporated a multilevel approach that examined the threat system in a study of adolescents with and without depression (Klimes-Dougan et al., 2014), which leveraged data collection across multiple units of analysis: self-report (e.g., experienced stress), behavior (e.g., observed stress), and physiology (e.g., salivary cortisol), all within a lab-based social stress paradigm, the Trier Social Stress Test [TSST] (Kirschbaum et al., 1993); and brain structure, function, connectivity measures, collected via magnetic resonance imaging (MRI) (more specifically, amygdala volume and activation during an emotional face matching paradigm designed to stimulate the threat system) (Hariri et al., 2002). Although there were no differences in cortisol reactivity between the adolescents with and without depression in this sample, we found that across the whole sample, cortisol reactivity during the TSST was positively associated with greater amygdala reactivity while matching threatening faces in MRI. In addition, amygdala volume was positively associated with cortisol reactivity in adolescents with depression, but the opposite was true for those without depression. This set of findings highlighted how a multilevel approach can reveal how the synchronization of different branches (e.g., brain and body) of a given system (e.g., threat) may relate to psychopathology in adolescents.

During the time that this initial multilevel research on the neurobiology of adolescent depression was taking place, NSSI began to emerge as a highly prevalent concern in adolescence (Liu, 2019). While studying adolescent depression, we recognized that the prevalence of NSSI seemed to be increasing and that this behavior was notable in some of the adolescents in our studies. We began to wonder if NSSI might have a unique neural signature that distinguished it from depression and could be measured in adolescents. In a larger sample of 162 adolescents that included those in the prior study (Klimes-Dougan et al., 2014), we observed that among adolescents with depression, those with NSSI showed a blunted cortisol response on the TSST (Klimes-Dougan et al., 2018). This pattern of neurobiological stress system flattening in adolescents with NSSI was also demonstrated by other groups (Kaess et al., 2012; Plener et al., 2017), adding confidence that this pattern may be a consistent and replicable biological signature for NSSI in adolescents. We further considered how a multilevel approach might shed light on differences between adolescents with depression versus NSSI in patterns of coordination across and within neurobiological systems. While those without depression and NSSI showed a positive relationship between frontolimbic connectivity and HPA axis functioning, suggesting well-coordinated stress responding, we found tentative evidence that those with depression, particularly those with depression and NSSI, showed an opposite pattern (Thai et al., 2020). These discoveries encouraged us to broaden and deepen our examination of the neural correlates of NSSI. Additionally, we began to expand our conceptualization of NSSI as a transdiagnostic process that can occur across a wider range of clinical presentations.

Accordingly, we began examining the neurobiology of threat system functioning in NSSI (initially focusing on brain circuitry; R21MH094558) using a transdiagnostic approach aligned with the RDoC initiative (Cuthbert & Kozak, 2013; Insel et al., 2010). Rather than requiring a particular diagnosis, we recruited a sample of youth (aged 13–21) based on their history of engaging in NSSI and a sample of healthy control participants with no history of psychopathology. Implicating the threat system more centrally, compared to a healthy control group, we found lower connectivity between the amygdala and frontal cortex during an emotional face matching task (Westlund Schreiner et al., 2017), and widespread impairments in white matter microstructure, including fronto-limbic circuits (Westlund Schreiner et al., 2019) among those with NSSI. We also found that NSSI was associated with greater functional connectivity between the amygdala and the supplementary motor area (SMA) and dorsal anterior cingulate cortex (ACC) during rest, implicating areas of the brain involved in habit formation (Westlund Schreiner et al., 2017). These differences between a transdiagnostic sample of youth with NSSI versus those with no psychopathology prompted new questions about how neurobiological signatures of NSSI might vary across a spectrum of NSSI severity, across a broader array of neural circuits, and over the course of development.

We sought to broaden this multilevel RDoC-based approach in a larger study that would expand beyond the threat system to examine multiple relevant biological systems across a spectrum of NSSI severity, aiming to understand how these mechanisms interact and change over the course of adolescent development. In the Brain Imaging Development of Girls' Emotion and Self (BRIDGES) Study (NIH R01MH107394; National Data Archive #2401; (Nair et al., 2023), we examined the RDoC domains of Sustained Threat (an aversive emotional state caused by prolonged exposure to stimuli that signal danger), Cognitive Control (a system that modulates other cognitive and emotional systems in the service of goal-directed behavior and selects appropriate responses among competing alternatives), and Self-Knowledge (the ability to judge one's states, traits, and abilities) in a group of adolescents (aged 12–17) who were assigned female sex at birth oversampled for a history of NSSI (e.g., about 70% with a history of NSSI with varying levels of severity). A unique feature of this study was that participants without NSSI were not required to be "healthy controls," meaning that they could present with other forms of psychopathology. We utilized a multilevel approach by including multi-units of analysis (self-reports, behavior, physiology, brain structure, function, and connectivity) to assess multiple RDoC domains (Sustained Threat, Cognitive Control, and Self-Knowledge) at three time points, allowing us to examine relationships within and across domains concurrently and over time across mid-adolescence. Our primary aims were to confirm the relevance of these RDoC domains to NSSI and test their validity in an adolescent NSSI population; to establish biological predictors of clinical course; and, with our longitudinal analyses, to document typical and atypical developmental trajectories of these multilevel indices in adolescence.

Cross-sectional assessments of each domain in the BRIDGES study confirmed their relevance to NSSI, and, in particular, to NSSI severity (calculated from lifetime NSSI episodes) (Başgöze et al., 2021). Within the Sustained Threat domain, we again confirmed that NSSI was associated with a blunted cortisol response to the TSST, showing that this pattern is associated with NSSI severity (higher the severity, flatter the cortisol response). Moreover, higher NSSI severity was associated with lower resting-state functional connectivity (RSFC) within amygdala-frontal circuitry (Başgöze et al., 2021). Within the Cognitive Control domain, higher NSSI severity was associated with lower RSFC within an *a priori*-defined cognitive control network (CCN) in the brain, as well as lower accuracy while inhibiting behavioral impulses in the context of positively-valenced images during an emotional Go/NoGo task (Başgöze et al., 2023). Moreover, the relationship between NSSI severity and brain activation of CCN regions during the inhibition task showed opposite patterns depending on the region and emotional context of the inhibition. For example, for the right medial prefrontal cortex, higher NSSI severity was associated with greater activation during inhibition within negative contexts, but lower activation during inhibition within positive contexts, while the opposite pattern was seen for the right dorsolateral prefrontal cortex (Başgöze et al., 2023). Within the Self-Knowledge domain, greater NSSI severity correlated with lower global self-worth, more frequent and faster negative self-evaluations, fewer positive self-evaluations, and greater activation in the posterior medial cortical network (Thai et al., 2024). Together these cross-sectional findings illustrate the complexity of these systems and how systematic measurement of these domains across levels of analysis can inform our understanding of adolescent NSSI. The longitudinal trajectories and implications of these patterns are only now beginning to

emerge, as analyses of the longitudinal data are underway by our group and (we hope) by other researchers around the world who can now access the public dataset for the BRIDGES study through the National Data Archive (Collection ID: 2401).

Our multilevel longitudinal data collection with a subset of participants who were enrolled in the BRIDGES study has further allowed us to better understand adolescent engagement in NSSI at the onset of the global COVID-19 pandemic, a novel and pervasive stressor, especially for youth. Our work was among the first to identify that youth who had previously engaged in NSSI followed two separate trajectories during the pandemic: persisting and desisting in this behavior (Carosella et al., 2021). We went on to better understand risk markers for these groups by examining whether they demonstrated differences in multilevel pre-pandemic predictors (e.g., cortisol reactivity to the TSST, amygdala volume, amygdala activation to threatening faces, and frontolimbic RSFC; Carosella et al., 2023). We found that lower pre-pandemic cortisol reactivity to stress and lower pre-pandemic amygdala activation to threatening faces predicted desistance of NSSI rather than persistence during the early months of the pandemic. While requiring further replication, this work is a first step toward identifying risk markers that may inform individualized intervention approaches and needs at the onset of a novel stressor.

As we continued to embrace this multilevel approach to data collection and analysis, our team recognized the need to incorporate new analytical techniques into our work that would highlight the richness of our data and lend new clinical insights. Recent developments have acknowledged that traditional variable-centered methods are not always successful in capturing complex patterns of interaction among systems at the individual level, especially for research on neurodevelopmental differences, where traditional group averaging has reached an impasse (Astle et al., 2024). Person-centered approaches, which characterize variability across indexes of interest *within* individuals through various clustering methods, may hold promise for addressing this issue (von Eye & Bergman, 2003). For example, previous studies using multi-trajectory modeling (Nagin et al., 2018) demonstrated biological profiles characterized by distinct patterns of stress response and brain circuitry with distinct clinical characteristics in adolescents (Bendezú et al., 2021, 2022) and adults (Simon et al., 2022).

Inspired by this work, we applied a person-centered approach to characterize multilevel stress response data (self-reported/ experienced stress, observed/expressed stress, physiological stress response) from the TSST in our earlier study of adolescent depression (Bendezú et al., 2022). We aimed to determine whether correspondence (e.g., consistency in the degree and direction of response) across these multilevel indicators of the stress response is common, as may be assumed theoretically (e.g., Campbell & Ehlert, 2012), and whether lower correspondence across levels may be indicative of dysregulation and risk for depression, NSSI, and STB. Results from this work demonstrated that stress responses were best characterized according to four profiles, three with high correspondence across levels (e.g., High Experience, High Expression, High Physiology; Low Experience, Low Expression, Low Physiology; Moderate Experience, Moderate Expression, Moderate Physiology) and one with low correspondence across levels (e.g., High Experience, High Expression, Low Physiology). In this study, youth with a low correspondence profile were more likely to be characterized by elevated depressive symptoms, engagement in NSSI, and experiences of suicide ideation (Bendezú et al., 2022).

We have since replicated similar patterns of multilevel stress responses in our BRIDGES study, which includes a different

sample composition than the prior study of adolescent depression (e.g., adolescents assigned female sex at birth, oversampled for a history of NSSI engagement). Again, we identified four profiles, this time two with high correspondence (e.g., High Experience, High Expression, High Physiology; Low Experience, Low Expression, Low Physiology) and two with low correspondence (e.g., High Experience, High Expression, Low Physiology; High Experience, Low Expression, Moderate Physiology) across levels (Carosella et al., 2023). Similar to the prior study, adolescents who had a stress profile characterized by low cortisol reactivity and high observed and self-reported stress exhibited generally higher levels of depression and STB. Importantly, youth across profiles did not differ in their history of NSSI, allowing us to determine that group differences in depression and STB were not driven by the overrepresentation of "control" participants in the concordant groups in this sample (Carosella et al., 2023). These studies demonstrated the utility of person-centered approaches for identifying patterns that mark risk for psychopathology. For example, despite having similarly low physiological responses to the TSST, the subgroup of adolescents with the High Experience and Expression compared to those with Low Experience and Expression profiles had significantly higher depressive symptoms and suicide ideation severity. Such nuances about the synchrony across systems are important though might be missed with variable-centered approaches. While much of our work to date has focused on understanding developmental patterns related to risk, following in the footsteps of Dr Cichhetti who championed research on resilience in the field of developmental psychopathology (Luthar et al., 2000; Southwick et al., 2014), we have also applied multilevel approaches to examine patterns of recovery and well-being in adolescence. To do this, we examined whether the previously identified person-centered profiles from the BRIDGES sample might predict future positive outcomes. Specifically, we wondered whether the two concordant profiles might incur resilience, given that they might indicate consistent, commensurate responses to the stressor. We showed that teens with the baseline High Experience, High Expression, High Physiology stress response profile not only demonstrated relatively consistent patterns of symptom reduction in depression and suicide ideation over three years, but also showed increases in positive affect and self-worth over this period, which differed from patterns observed among those with discordant response profiles (Wiglesworth et al., 2023). Taken together, our findings suggested that, while relatively high responses to stress may be associated with concurrent psychopathology, some configurations of concordant responding across systems may be a marker of adaptive processes that can promote resilience during the course of adolescence even after the onset of psychopathology (Wiglesworth et al., 2023).

The translational implications of multilevel approaches are paramount if this line of work will have clinical utility in altering the course of psychopathology (Cicchetti & Toth, 2006). This consideration has been at the forefront of our thinking since the onset of our collaboration, though our group has only just begun to garner preliminary evidence in small samples for the role of multilevel processes in intervention outcomes among adolescents with depression. For example, we found that, after eight weeks of antidepressant treatment, clinical improvement was associated with decreased activation to threat in rostral and subgenual ACC, but increased activation in insular, middle frontal, parahippocampal, and cerebellar regions, together with increased amygdala RSFC with right frontal cortex, but decreased amygdala RSFC with right precuneus and right posterior cingulate cortex (Cullen et al., 2016).

In this same sample, baseline predictors of favorable treatment response included lower amygdala connectivity with left SMA and with right precentral gyrus, and greater amygdala RSFC with right central opercular cortex and Heschl's gyrus, and greater activation of bilateral ACC and left medial frontal gyrus, and higher cortisol in the TSST (Klimes-Dougan et al., 2018). Additionally, greater amygdala activation to threat and greater amygdala-ACC RSFC are also implicated in predicting favorable responses to Interpersonal Psychotherapy in a small study of adolescents (Klimes-Dougan et al., 2022). These findings from our studies with small samples represent the early stages of considering biological mechanisms of treatment response, underscoring the need for large-scale intervention studies that include more assessment waves to identify mechanistic actions that combine multilevel response patterns. So too are we at the early stages of considering avenues for personalization of interventions, as this early work with adolescents has only considered predictors of treatment response, and has not used analytic approaches that examine moderators (Papke et al., 2023). By including multiple treatments and multilevel assessment waves in randomized control trials, we can learn more about pretreatment characteristics that can more optimally determine treatment assignment as well as mechanistic features that may underlie treatment response.

In summary, inspired by the work spearheaded by Dr Cicchetti, our group and countless others have embraced the core principles of developmental psychopathology as we have applied multilevel approaches to advance the field to understand how deviations from typical development arise in the context of youth depression, NSSI, and STB. We are honored that much of our work has been published in *Development and Psychopathology*, and count ourselves among the many researchers that Dr Cicchetti has influenced, inspired, mentored, and encouraged. Our hope is that we continue to honor the legacy of Dr Cicchetti by continuing to make progress in explicating risk and protective processes and encouraging innovation in the service of helping those youth who are suffering.

Celebrating progress and highlighting recommendations for future research

As we endeavor to understand the factors that precede, maintain, stave off, and alter psychopathology, it is critical to recognize and celebrate the advances made in our field to date while considering new horizons. As science has advanced, so have the opportunities to more carefully consider sample characteristics, nuanced measurement strategies, and advanced analytical approaches. And yet, we are still faced with addressing the limitations of our current body of knowledge. While the issues raised subsequently are from the lens of those researching adolescent depression, NSSI, and STB, the topics are relevant to other areas of developmental psychopathology. Further, our intent here is to highlight some future directions for the field that hold tremendous promise for the continued refinement of the core principles of developmental psychopathology. Here we do not only consider foundational questions for multilevel research, but also apply our lens to the broader state of the field of developmental psychopathology, celebrating key areas of advancement, taking stock of gaps in our existing knowledge, and practices, and making recommendations for future research. Hence, our discussion will be guided by the following critical steps of the research process: (a) ensuring that the research question is embedded in a sound conceptual framework,

(b) designing the research protocol, (c) considering measurement issues, and (d) analyzing and interpreting data.

Conceptual framework

While the principles of developmental psychopathology shape all stages of the research process, developmental psychopathology encourages the application of diverse theories and frameworks to ground research. That is, there is no one "right" theory that should apply to all developmental psychopathology research. However, having a conceptual framework or theory is paramount for scientific advancement. Indeed, considerations of sampling, sample diversity, protocol selection, and study interpretations can all be linked back to the conceptual framework. Even in cases where research approaches are primarily data-driven, conceptual frameworks shape the research protocol by determining who and what will be assessed, how they will be assessed, and how the data produced will be optimally analyzed and interpreted. Such approaches may have distinct advantages as well as unique (though not new) challenges (e.g., Lever et al., 2016), particularly when viewed as *atheoretical*. The importance of identifying a conceptual framework or grounding theory for a study *a priori* is highlighted in the Open Science movement, which outlines a number of processes and procedures that increase the transparency of research (e.g., pre-registration of study methods and hypothesis; publicly available code; (Shrout & Rodgers, 2018)). Open science practices provide a safeguard against problematic research practices such as HARKing ("hypothesizing after results are known" (Kerr, 1998); and other problems of inference, see (Syed, 2021)) and p-hacking (e.g., (Wicherts et al., 2016) and can be leveraged to promote equity in our field (Syed & Kathawalla, 2022)).

Yet, there are some instances in which our ability to lean on a conceptual framework or theory, or otherwise make strong *a priori* hypotheses, may be limited by the current state of knowledge in our respective subfields. In this vein, some have called attention to the "theory crisis" in psychology, where psychology as a discipline lacks solid theories and faces barriers in theory building (Eronen et al., 2021). Such circumstances motivate the need for more basic science research that can ground future questions related to psychopathology and contribute to theory building. To illustrate this idea, we highlight below one example where additional basic science research is needed to bolster conceptual frameworks of typical and atypical neurodevelopment to advance our understanding of developmental psychopathology.

Building an understanding of typical and atypical development

A core tenet of developmental psychopathology is that advances in understanding arise from an iterative process where understanding typical development informs work on pathways toward and away from psychopathology, and vice versa (Cicchetti, 1984a). This framework helps us determine what period(s) of development should be studied to address the question of interest, producing new ways to describe these complex linear, nonlinear, and cascading developmental progressions (Masten & Cicchetti, 2010). In some cases, our ability to operationalize a conceptual framework is dependent upon this iterative characterization of typical/atypical development being realized.

For example, the stress acceleration hypothesis continues to hold tremendous promise for elucidating patterns of atypical development that might influence psychopathology (Belsky et al., 1991; Callaghan & Tottenham, 2016). The stress acceleration model purports that in childhood and adolescence, the context of high stress drives a process of accelerated development of the brain and the body that is advantageous for survival from an evolutionary perspective. This model has potential relevance to the disproportionate burden of psychopathology, and in particular suicide ideation and attempts, among minoritized youth who experience chronic stressors related to their minorized racial and sexual/gender identities (Wiglesworth et al., 2022). Notably, understanding whether aging is accelerated directly depends on understanding typical developmental processes and developmental cascades. In cases where our knowledge of these processes is limited, so is our ability to operationalize them in research.

This is true when considering the state of the field in characterizing normative structural brain development, which may provide a foundation for research on accelerated neurobiological aging. A foundational study by Giedd and colleagues (1999) provided the first substantial longitudinal data to inform normative longitudinal changes in gray and white matter in 145 young people ages 2–22 (total number of scans = 244). Results revealed nonlinear, spatially heterogeneous (e.g., across the frontal, temporal, parietal, and occipital lobes), and sex-different changes in gray matter from childhood to early adulthood. Subsequently, trajectories of cortical thickness and surface area were shown to differ substantially across age and sex in 647 healthy individuals aged 3–30 (total number of scans ≈ 1,250; (Raznahan et al., 2011)). Through this foundational work, the field began to reach a consensus about the asynchronous, regionally-specific nature of brain development, which has since been consistently demonstrated in developmental neuroscience research (e.g., Ball et al., 2019; Wierenga et al., 2014; Vijayakumar et al., 2021). However, this early, foundational research included wide age ranges, with only about half of the participants having data at two or more time points, which presents two problems: first, participants at the upper and lower end of the age range are entirely non-overlapping, limiting the ability of the data to speak to longitudinal change across adolescence; second, the limited number of timepoints constrains the ability to characterize nonlinear developmental trajectories. Notably, finer-grained analyses have highlighted the need to account for pubertal development when examining associations between age, sex, and cortical development (e.g., Herting & Sowell, 2017; Vijayakumar et al., 2018; Wiglesworth et al., 2023). Further, future research considering developmental trajectories for cortical volumes, thickness, and surface area, and how they differ across neural networks will undoubtedly provide needed information for outlining a fuller picture, as these indices have not yet been systematically examined in tandem in the same sample (Koolschijn & Crone, 2013; Tamnes et al., 2017; Wierenga et al., 2014).

Taken together, the extant research contributing to current knowledge on normative brain development has limitations, leaving gaps in the foundation for research. Further basic science research is needed to better understand normative developmental trajectories in order to situate hypotheses about accelerated development. These issues pertaining to brain development serve as just one example of how our theories or conceptual frameworks may be constrained by the current state of knowledge in the field. Nevertheless, it is this process of research on typical and atypical development, the building of conceptual frameworks, and continuous, iterative refining of this knowledge alongside advancements in our science (e.g., the introduction of new methods, amelioration of past limitations) that hold promise for building a science of developmental psychopathology that positively impacts the trajectory of youths' lives.

Designing the research protocol and selecting relevant measures

Sample size

While micro-trials and pilot data offer critical advantages such as the agility to advance and evaluate promising developments, it is increasingly recognized that for far too long, research has relied on findings based on underpowered samples, especially in the fields of neuroimaging and molecular genetics (e.g., Marek et al., 2020). One of the most exciting new developments in the field is the initiation of large-scale collaborations and designs that compile data to identify reliable, reproducible, and meaningful markers, mechanisms, and correlates of psychopathology across different samples and populations. Systematic reviews, meta-analyses, mega-analyses, and umbrella reviews (compiling results from many reviews) of existing data provide an approach to compiling and synthesizing findings across studies, not only by leveraging greater information than is available in any one study to characterize the state of the literature on a particular research question, but also combining more than one complementary fields that may otherwise operate in silos (e.g. clinical neuroscience and psychopathology). For example, in a recent literature review of research on children at risk for depression by virtue of being born to and raised by a mother with mood disorders, we concluded that basal cortisol and, to some extent, cortisol in the context of stressors was elevated in those at high versus low risk for depression (Klimes-Dougan et al., 2022). Other large-scale scientific efforts involve coordination between study sites around the world to establish and harmonize data sets that focus on developmental processes and clinical samples. Pooling different samples through collaborations like the ENIGMA consortium (Thompson et al., 2014) and other pooled mega-analytic techniques (Koenig et al., 2021) provides exciting new opportunities with a high yield in advancing the understanding of depression in youth and adults. Large-scale single-site or multisite efforts that use the same study protocol require significant investments from funding agencies; noteworthy examples aiming to compile large, longitudinal, epidemiologically informed datasets that include key biological measures in youth, including hormonal assays, brain scans, and genetic testing are needed to answer today's most pressing questions. Examples include the UK Biobank (Sudlow et al., 2015), Generation R (Jaddoe et al., 2006), the Adolescent Brain and Cognitive Development (ABCD®) study (Karcher & Barch, 2021) and the HEALthy Brain and Cognitive Development study (Jordan et al., 2020). Further, translational implications of our field have been borne out in large-scale studies on the treatment of depression, NSSI and STB in adolescence such as the Treatment for Adolescent Depression study (March et al., 2004), the Treatment of Resistant Depression in Adolescents study (Brent et al., 2008), and a randomized control trial of dialectic behavioral therapy versus individual and group supportive therapy (McCauley et al., 2018). Efforts that integrate relevant multilevel biological indicators into intervention studies such as these will undoubtedly prove to be an important advancement. These large-scale projects can increase power to examine questions of interest, foster sharing data and analysis codes, and encourage collaboration between researchers of different disciplines, contributing to the generation of new perspectives and creative approaches to solve our most pressing problems.

Participant characteristics

Increased focus on equitable research practices is needed to ensure that the findings are generalizable, to clarify *for whom* research findings are relevant, and to fill remaining knowledge gaps regarding youth who are not well represented in existing research. Similar to the broader field of behavioral sciences, developmental psychopathology has increasingly recognized the severe limitations introduced by research that focuses on samples from Western, Educated, Industrialized, Rich, and Democratic societies, which has been ubiquitous and led to findings that are not generalizable to the broader global population (Coll et al., 2000; Henrich et al., 2010). Moreover, the exclusion of those who are Black, Indigenous, and People of Color from research, or positioning White racial identity as the default, has been pervasive (Dupree & Kraus, 2022; Guthrie, 2004), including within developmental science (Syed et al., 2018). Recognizing the fallacy and injustice of this approach (American Psychological Association, 2021, 2023; Buchanan et al., 2020), the past decade has seen increased efforts striving for samples to be more representative of the broader human population and advocacy for within-group rather than between-group comparisons across race, ethnicity, and culture (e.g., Williams & Deutsch, 2016). Dr Cicchetti and his colleagues at Mount Hope Center were early leaders of this initiative. Indeed, for decades they persevered to develop a sustained program of research that prioritized understanding factors related to childhood maltreatment and best-practice intervention approaches among primarily Black/African American families embedded in under-resourced communities who have often been overlooked in research (Vachon et al., 2015). Relatedly, researchers have recently taken greater care to use accurate and specific terminology for describing additional aspects of identity (e.g., gender identity, gender presentation, sexual orientation) and differentiate those from other characteristics (e.g., sex assigned at birth; see (Eliot et al., 2023)). Moreover, in the decades following Crenshaw's foundational work on intersectionality and Black women's experiences in the carceral system (Crenshaw, 1991), there has been an increasing recognition that individual identities do not exist in isolation, but instead intersect to produce an individual's experiences (Buchanan & Wiklund, 2020; Cyrus, 2017). However, there is room to grow in incorporating intersectionality theory into developmental science, including generating and employing best practices for collecting and analyzing identity-relevant data (e.g., Buchanan & Wiklund, 2021; Watson-Singleton et al., 2023). Finally, developmental psychopathology has seen a more widespread discussion of how research pertaining to marginalized youth is framed (e.g., as in "representational ethics" (Haarlammert et al., 2017)), recognizing the risk of pathologizing individuals and communities in how research is designed and reported, and emphasizing the societal-level factors that influence health/well-being (e.g., discrimination, social determinants of health; (Kirkbride et al., 2024) along with promoting strengths-based approaches (e.g., Fish et al., 2023; Nair et al., 2024; Opara et al., 2023). Moreover, going beyond the individual and more often using an ecosystemic perspective (Bronfenbrenner, 2000) allows us to identify societal, community, and familial-level factors that contribute to psychopathology and well-being. This progress builds on decades of work by developmental psychologists who have long been interested in the role of context in development (Spencer et al., 1997; Spencer, 2023).

Measurement selection

What we have learned so far is inherently related to the measures that we have selected for our research protocols, while gaps in knowledge arise from measures left out. Of course, researchers can not include all possible measures of interest due to both logistical

constraints (e.g., funding limits, minimizing participant burden) and scientific constraints (e.g., current theoretical framework does not support measurements that would help advance the field, or lack of reliable methods to measure the desired phenomenon). Therefore, the act of protocol design can be painstaking and involve informed decisions based on prior research (which is, in turn, inherently limited), and at times speculating about which measures will be most informative.

Given that decisions for measurement selection are typically made based on past theory and findings, protocol selection can at times contribute to a homogenizing of constructs studied in the field at large, which furthers potential biases in our knowledge base. Though it makes good sense to study areas where preliminary research has provided a "signal," the practice of limiting our approaches to these leads may create an increasingly narrow view of what is important for understanding and intervening on psychopathology. This phenomenon of homogenization is illustrated in a meta-analysis of 50 years of research focused on risk factors for STB (Franklin et al., 2017), where the authors note that the risk factors studied in the literature have grown more homogenous over time, with the five most common risk factor categories (demographics, internalizing symptom, externalizing symptoms, prior STB, social factors) comprising over 70% of the factors studied in the literature. Though likely unintentional, such narrowing may marginalize perspectives that are not aligned with this dominant view (e.g., Fish, 2022), thwart appreciation of cultural differences, and hinder progress in understanding developmental psychopathology from a comprehensive standpoint.

Timing of measures

Another important decision in the design of studies in developmental psychopathology is the selection of the best timescale for data collection. Again applying the lens of our own research area, while the bulk of extant longitudinal research has measured NSSI, STB, and related correlates at timescales of one year or more, recent work examining finer timescales has revealed important new insights to our field. For example, this work has illuminated the momentary relationships between affect and NSSI thoughts and behaviors (Kiekens et al., 2020) as well as the course of suicide ideation, where elevated states of suicidal thinking last 1–3 hours on average (Coppersmith et al., 2023).

When defining timescales, theory, and descriptive phenomenological research, can ground longitudinal research designs in outlining what patterns of change are expected for the developmental period of interest. To provide a concrete example, if we are interested in understanding how aberrant development of neural circuitry as measured by RSFC development may relate to the onset of depression in adolescence, it is critical to design studies that capture the timescales at which we expect RSFC to demonstrate meaningful change in a particular network. Past research provides us with an understanding that neural networks become more integrated from childhood to adulthood and that the trajectory of this integration is specific within each network or within nodes of a network (Gao et al., 2013; Uddin et al., 2011). Understanding where youth are developmentally along that trajectory at a given study time point can provide insight into the patterns of expected change in RSFC in normative development, which will inform the desired time between follow-up periods to capture deviations in patterns. Moreover, beginning such a study early relative to the typical onset of depression for youth is critical to allow the capture of potential changes in RSFC before and after the onset of symptoms.

Measurement feasibility

There are additional feasibility challenges with measurement selection strategies inherent to multilevel research and other study designs that require considerable participant burden. To use an example from our lab, the BRIDGES study (Nair et al., 2023) ambitiously aimed to examine three RDoC domains using a longitudinal multilevel approach. The combination of multiple levels within multiple domains led to a large number of measures critical to our research questions. Reducing participant burden required us to exclude many measures of interest. Even so, the participant burden of the resulting protocol, which included three study visits at each time point to collect self-report, parent-report, clinical interview, behavioral, and neuroimaging data, (in addition to the onset of the COVID-19 pandemic during the mid-point of the study) likely contributed to drop-out rates (24% drop-out for those returning the second time, 42% drop-out for those returning the third time). This example illustrates the need to carefully balance the importance of including measures across units of analysis that are critical for answering rich and nuanced research questions versus the risk of attrition due to participant burden.

Issues specifically pertaining to multilevel research

Many of the considerations we have discussed apply when advancing multilevel research, specifically, including the importance of theory, measurement selection, and so on. However, there are unique considerations when discussing multilevel designs that require refinement conceptually and practically. As a starting point, what is considered a level? Undoubtedly, one measurement such as salivary cortisol under stress conditions could not fully capture all the critical components of acute threat. Even if we were to limit our examination of the physiological units involved in negative affect to cortisol, how do we go about measuring cortisol? Do we focus on cortisol response (e.g., area under the curve - ground), reactivity (e.g., area under the curve - initial), slope, or other metrics? If we were to consider broadening the question slightly to include other physiological responses to acute threat, there would undoubtedly be a host of measures including heart rate, heart rate variability, vagal tone, alpha-amylase, skin conductance, and so on. Further careful consideration needs to be paid as to what might be mechanisms implicated in chronic stress and what measures may be likely to provide insights into the body's effectiveness to avoid predation. When hypotheses are supported, we can gain confidence that we have identified relevant constructs and measures that advance our knowledge. And yet, a continual revision of theory, protocol, constructs (as well as measurement), and analytic strategies may be needed when hypotheses are not supported.

Furthermore, we must acknowledge that some of the lines we draw about a "level" may be arbitrary. Some equally useful methodologies may be characterized more accurately as multimodal rather than multilevel. That is, in some regards, assessing key constructs of relevance may be a priority rather than considering the boundaries of levels per se. For example, much of our multimodal work has included a range of brain metrics, from structure, to connectivity, to activation (e.g., Başgöze et al., 2021). Indeed, we could argue that these are all relevant to brain "circuits" based on the RDoC framework. While in theory these modalities should tap into similar underlying processes in that structure belies function (Hebb, 1949), in practice this is rarely the case. Nevertheless, both multiple divergent or multiple convergent indexes may increase prediction and suggest that there is considerable utility in considering both multilevel and multimodality approaches to better understanding

youth development and psychopathology. As Cicchetti (Cicchetti, 2013) so aptly stated, "The ultimate criterion of what constitutes a level of organization is its utility in elucidating the understanding of a particular biological or psychological phenomenon."

When using multilevel data to study specific processes, we are often faced with a lack of coherence observed across domains. While we would not expect indexes across levels of analysis to be perfectly correlated, given that the hope in looking across levels is that they may provide unique insights into the processes of interest, we do expect some degree of relatedness that demonstrates that they are providing insight into a common process or mechanism. However, when these indicators are not significantly correlated, as is often the case (e.g., Creswell et al., 2019), we are confronted with findings that do not fit into our hypothesized frameworks. This suggests that continued evaluation and reevaluation of our assumptions of how levels within a domain operate is needed. In a recent commentary, Joyner & Perkins discussed these issues and articulated ways forward, particularly in relation to defining constructs through research that integrates levels of analysis at the outset (Joyner & Perkins, 2023).

Analysis and interpretation

With the emerging opportunities provided by large-scale, multilevel, and longitudinal datasets comes the need for applying statistical methods that can handle these rich, highly dimensional data and reveal useful information about youth development and psychopathology. Developmental computational psychiatry, a recently proposed framework for studying brain maturation and cognitive development that proponents believe will lead to a richer understanding of psychopathology, is one example of using advanced methods to make sense of highly complex phenomena (Hauser et al., 2019). Other advances in statistical methods that provide opportunities to better understand complex patterns have already been highlighted here, such as person-centered approaches that incorporate multilevel data in a way that considers the child "from all angles." Additional computational approaches hold further promise for charting developmental paths and highlighting the directionality of effects while others may advance our ability to predict outcomes of interest including treatment response.

Charting developmental paths

Common approaches to examining developmental pathways such as path analyses and structural equation modeling continue to hold great promise for understanding how features of risk and resilience unfold across development. A particular strength of path and structural equation models is that the application of a conceptual framework or theory is baked into the model specification process in a way that is less true or explicit for traditional regression approaches. Cross-lag path analytic models (Grimm et al., 2021) have been used to further elucidate longitudinal relations between variables, particularly regarding the directionality (e.g., often unveiling bi-directionality) of effects of interest (e.g., Del Toro et al., 2021; Tak et al., 2017). For example, in a study from the Mount Hope data, Flynn and colleagues showed that the number of subtypes of maltreatment a child experienced predicted low self-worth and relationship quality as well as high emotional and behavioral symptoms in early- to mid-adolescence (Flynn et al., 2014). Cross-lagged effects between early and mid-adolescence showed that low self-worth and low relationship quality also predicted internalizing but not externalizing symptoms. Researchers are also using cross-lagged approaches in large, longitudinal data

sets such as the ABCD Study, to understand pathways of psychopathology in early adolescence (Funkhouser et al., 2021).

Causal discovery analysis represents another approach that can take very rich data (both cross-sectional and longitudinal) to identify causal pathways in complex systems (Rawls et al., 2022; Stevenson et al., 2021). Causal discovery analyses have distinct advantages over traditional regression frameworks, particularly in their ability to leverage highly dimensional data, which actually improves the algorithm by providing additional information through which causality can be determined (Nogueira et al., 2022). This advantage starkly contrasts concerns in a traditional regression framework, where a large number of variables risks being underpowered and producing multicollinearity. Causal discovery analysis is being leveraged in many areas of clinical science to uncover individual paths to psychological disorders and develop personalized intervention approaches (e.g., Anderson et al., 2023).

Predicting outcomes

Machine learning models provide additional opportunities to develop theories in developmental psychopathology and gain insight into the onset, progression, and treatment of mental health symptoms (Luby et al., 2019; Van Lissa, 2022). These methods are being applied across the translational spectrum, including in animal research to study neurobiological mechanisms that underlie naturalistic behaviors (e.g., Shemesh & Chen, 2023). Machine learning approaches are also being leveraged to better understand how risk factors for psychopathology fluctuate on a momentary basis, as in ecological momentary assessment and passive sensing research. For example, Coppersmith and colleagues found that suicidal thoughts varied considerably from hour to hour as well as from minute to minute (Coppersmith et al., 2023). They also used Markov models to analyze subtypes of suicide ideation (desire, intent) and found that they varied considerably across time scales. Translational approaches using computationally intensive machine learning approaches have also revealed demographic, clinical, and psychosocial predictors of treatment responses for adolescents (Gunlicks-Stoessel et al., 2020). There is great promise in applying these approaches to datasets that include key biological indexes of potential relevance. However, it is important to note that computational approaches are not impervious to bias, much like our research methods in general, and great care is needed in developing and employing these approaches in ways that do not further solidify systemic biases or inequities (Hitczenko et al., 2022).

Interpretation of multilevel data

As the lasting influence of Developmental Psychopathology approaches is carried forward in the RDoC era, we are pushed to evaluate and reconsider our theoretical assumptions of how information will or should come together across levels of analysis. Additionally, future research should consider more carefully the question of interplay. Multilevel approaches commonly consider key indexes in parallel. Pushing the field forward requires considering the interaction among levels of relevance. There is an emerging body of literature that is starting to look at how patterns of synchronization differ across groups, though in some cases this work uses timescales for this data that introduce additional error in the models (for example when assessments of threat are measured on different days; e.g., Klimes-Dougan et al., 2014). Measuring how transactional processes unfold across development is needed as potentially one level serves to modify another level (Cicchetti & Dawson, 2002). Future research is needed to better understand what processes of synchronization

across levels lead to favorable and unfavorable outcomes. Further, how does this synchronization help to explicate developmental trajectories? Or, does this line of inquiry inform treatment selection (personalization) and treatment development? With rapid changes in the field related to computational methodologies and biostatistics, we are looking forward to the new discoveries that are just on the horizon of our knowledge as we integrate these analytic techniques with the foundational principles and frameworks of developmental psychopathology.

Conclusion

We are honored to be a part of the celebration of Dr Cicchetti's four-decade tour at the helm of both the field of developmental psychopathology and the journal, *Development and Psychopathology*. We began by narrating the progression of our work on adolescent depression, NSSI, and STB, which provides one window into the application of the core tenets of developmental psychopathology. In particular, our work provides an illustrative example of how a multilevel approach can be applied to descriptive, longitudinal, and intervention science approaches, and how analytic techniques link constructs across individuals (variable-centered approaches) as well as examine a constellation of constructs within groups of individuals (person-centered approaches). In the second part of this paper, we contemplated how we as scientists can continue these efforts of moving the field(s) of developmental psychopathology forward. Celebrating recent advances is especially warranted when turning an eye toward the future. It is critical to acknowledge the courage it takes to ignite a new paradigm shift in the field. Key advances evident in each phase of the research process have come through interdisciplinary approaches, examination of biological substrates that are deeply embedded in experiences of the individual within their environment, and approaches to produce knowledge that is clinically useful. We also discussed where significant gaps persist in this field, calling for an increased focus on defining a conceptual framework (or frameworks) and discussing critical issues for research related to sample characteristics, designs, measures, analytic approaches, and interpretations. We hope that these reflections may accelerate the pace of progress as we move towards understanding risk and resilience trajectories, outlining mechanisms of psychopathology, and considering applications of precision medicine. Simple solutions to complex problems are unlikely.

Multilevel research represents a (relatively) new horizon for developmental psychopathology. It is without a doubt that technological advances and interdisciplinary science have already hastened the pace of integrating biological processes with behavioral, emotional, and social features of the individual. However, this work needs to continue to proceed in a thoughtful manner to result in an optimal yield. In many of the methods we have outlined here, we have emphasized the importance of characterizing many pieces of the individual, pulling out features of their environmental contexts, neurocircuitry, physiological responses, and emotional experiences. Nevertheless, the critical task for developmental psychopathologists is to put the pieces back together after pulling them all apart, considering human experience holistically at the core of this work. We are deeply grateful for Dr Cicchetti's resolute leadership in the field of developmental psychopathology. The impact of his leadership will undoubtedly continue to guide important scientific advances that will improve lives in the future.

Competing interests. None.

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