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Psychiatry and Developmental Psychopathology: Unifying Themes and Future Directions

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Abstract

In the past 35 years, developmental psychopathology has grown into a flourishing discipline that shares a scientific agenda with contemporary psychiatry. In this editorial, which introduces the special issue, we describe the history of developmental psychopathology, including core principles that bridge allied disciplines. These include (1) emphasis on interdisciplinary research, (2) elucidation of multicausal pathways to seemingly single disorders (phenocopies), (3) description of divergent multifinal outcomes from common etiological start points (pathoplasticity), and (4) research conducted across multiple levels of analysis spanning genes to environments. Next, we discuss neurodevelopmental models of psychopathology, and provide selected examples. We emphasize differential neuromaturation of subcortical and cortical neural networks and connectivity, and how both acute and protracted environmental insults can compromise neural structure and function. To date, developmental psychopathology has placed greater emphasis than psychiatry on neuromaturational models of mental illness. However, this gap is closing rapidly as advances in technology render etiopathophysiologies of psychopathology more interrogable. We end with suggestions for future interdisciplinary research, including the need to evaluate measurement invariance across development, and to construct more valid assessment methods where indicated.

Keywords

psychiatry; developmental psychopathology; multifinality; equifinality; neurodevelopment; interdisciplinary

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1. Introduction

In 1974, Thomas Achenbach published his foundational text, which defined and named the emerging field of developmental psychopathology [1]. At the time, the new discipline was so nascent that the first sentence of Chapter 1 reads, “This is a book about a field that hardly exists yet” (p. 3). In the 35 years since, developmental psychopathology has burgeoned into a discipline with its own first-tier scientific journal [2], frequent special issues in journals from related disciplines [3,4,5], widely cited interdisciplinary texts and edited volumes [6,7], important scientific and theoretical advances [8,9], and dedicated graduate programs. Few disciplines enjoy such rapid proliferation and success. Although it is beyond the scope of this editorial to recount the full history of developmental psychopathology (others have done so in greater detail than limited space permits [10,11]), some historical context is necessary for any discussion of how the field aligns with and complements modern child, adolescent, and adult psychiatry.

2. The Emergence of a New Discipline

For those who were trained in the current interdisciplinary era, it may be difficult to appreciate structural forces that fostered the emergence of developmental psychopathology. In 1974—the same year Achenbach published his foundational text—Robert Spitzer was appointed to the DSM taskforce to update the *DSM-II*. Psychiatry was grappling with diagnostic validity concerns, and a major shift in philosophy was underway [12,13]. This shift, instantiated in publication of the Feigner Criteria [14,15], gravitated psychiatry away from rationally derived diagnosis toward an etiopathophysiological approach that was more consistent with modern medicine. At the time, child and adolescent disorders in the *DSM-II* were few in number, adevelopmental, and derived inductively rather than from empirical relations among and across syndromes [12,16]. Although this state of affairs has improved markedly since, at the time psychiatry was constrained by a diagnostic system that had yet to undergo significant revisions. In contrast to the adevelopmental, inductive approach of the *DSM-II*, from its inception developmental psychopathology was empirically driven, deductive, and transactional [17]. Several years prior to publication of the *DSM-III* in 1980 [18], Achenbach and colleagues published a series of papers in which they described a factor-analytic approach to assessing psychopathology in children and adolescents [19,20]. This effort culminated in development of the Child Behavior Checklist [21], which remains among the most widely used instruments for assessing child and adolescent psychopathology [22]. Although the CBCL is a complement to rather than a substitute for structured diagnostic interviews, its age-based, sex-based, and population-based norms provided a means of evaluating emergence and maintenance of psychopathology across intervals spanning toddlerhood to late adolescence, at a time when very little developmental research existed [23]. An enormous volume of research conducted since shows that population distributions of characterizing traits underlying major child, adolescent, and adult psychiatric disorders—as ascertained by the CBCL and related measures—are unequivocally continuous in nature. Boundaries between normal function and clinical impairment are therefore not carved in nature and instead are set rationally, consistent with the notion that most or all psychiatric disease states reflect severe manifestations of quantitative traits. Furthermore, longitudinal research conducted since the CBCL was developed shows that (1)

almost all psychiatric disorders have roots in childhood behavioral function, and (2) environmental enrichment often mollifies vulnerability, whereas environmental adversity often magnifies vulnerability. These observations have direct implications for prevention and reducing disease burden.

3. Developmental Psychopathology and Psychiatry: Selected Tenets and Unifying Themes

The need to consider development in the ontogenesis of mental disorders is of course a defining feature of developmental psychopathology [10,11]. However, early on, other principles also set the field apart from related disciplines. Several of these principles, although elegant theoretically, were difficult to verify or apply without soon-to-evolve advances in computing power, statistical modeling, psychiatric genetics, and neuroimaging. In addition, most samples in both developmental and psychiatric research were too small to map complexities and heterogeneities of human behavior—an issue now addressed by collaborative research consortia and publicly shared databases. As envisioned by Dante Cicchetti over 30 years ago [24], these advances in technology and methodology have melded disciplines with common scientific interests but different philosophical traditions into today's interdisciplinary approach. Indeed, one can browse the table of contents of virtually any developmental psychopathology or psychiatry journal and find common research questions addressing genetic, epigenetic, neural, neurohormonal, and environmental contributors to mental illness. Many of these papers are written by authors who cross disciplinary boundaries.

In sections to follow we review selected tenets of developmental psychopathology, some of which were novel when proposed, but are now infused in contemporary interdisciplinary thinking. Our intent is to outline how these principles contribute to current understanding of mental illness, and how they might be applied to improve future understanding of psychopathology—regardless of discipline. We focus on four interrelated principles, all of which acknowledge and embrace *etiological complexity*, an important theme in modern child, adolescent, and adult psychiatry [25,26]. These principles include calls for (1) *multidisciplinary* translational research [27,28], (2) specification of *multicausal* pathways to seemingly single diagnostic syndromes [26,29], (3) description of divergent *multifinal* outcomes from common etiological starting points [29,30], and (4) research conducted across *multiple* levels of analysis spanning genes to environments [31,32]. After discussing these principles, we turn our attention to the importance of disrupted neuromaturational processes in developing psychopathology. We propose that the relative value placed on neurodevelopment still differentiates developmental psychopathology from contemporary psychiatry, but this gap is narrowing quickly [33,34]. Although our descriptions are necessarily brief and illustrated by way of selected examples, extended discussions can be found in sources cited herein.

3.1 Multidisciplinary, Interdisciplinary, and Transdisciplinary Science

In the history of psychopathology research, multi-, inter-, and trans-disciplinary approaches are fairly recent developments that are sometimes attributed to emergence of the Research

Domain Criteria (RDoC) [28,35]. With its explicit matrix of behavioral and emotional constructs specified across units of analysis spanning genes to self-reports, RDoC represents an unambiguous paradigm shift away from historical emphases on pathognomonic signs, universal causes, and single levels of analysis in efforts to explain mental illness [31]. As noted elsewhere, however, RDoC thinking extends at least as far back as the mid-20th Century [36], with proponents in psychiatry, psychology, and related disciplines [37,38,39]. Yet it was not until Thomas Insel, Bruce Cuthbert, and others at the National Institute of Mental Health initiated RDoC that multidisciplinary and interdisciplinary science were formally recognized as essential to mapping pathophysiologies of major mental disorders [40].

Notably, multidisciplinary has always been a central tenet of the developmental psychopathology perspective [41]. A primary objective of editor Dante Cicchetti in establishing the journal *Development and Psychopathology* in 1989 was to encourage authors from a wide range of disciplines and theoretical viewpoints to contribute, with the explicit goal of synergizing scientific advances across child, adolescent, and adult psychiatry; child, adolescent, and adult clinical psychology, neuroscience, developmental psychology, and both behavioral and molecular genetics. In the past 30 years, *Development and Psychopathology* has published over 60 special issues in which experts from diverse fields and perspectives were invited to contribute. Cicchetti also edited all three editions of the highly influential interdisciplinary volume *Developmental Psychopathology* [6,42,43], which also attracted authors with diverse training and shaped the emerging multidisciplinary field. By 2006, these efforts yielded a science that, compared with other disciplines, was “more developmental, contextual, multilevel, dynamic, multidisciplinary, and collaborative” (p. 50) [44]. Developmental psychopathology also placed high value on translational animal research, from which epigenetic mechanisms of neural plasticity, neurohormone regulation, and other vulnerabilities to mental illness were initially discovered [45,46].

More recently, cross-disciplinary collaboration has progressed at a remarkable pace, extending well beyond what was envisioned a generation ago. Distinctions between unidisciplinary, multidisciplinary, interdisciplinary, and transdisciplinary science are depicted in Figure 1 [35]. Over the past several decades—and particularly since the turn of the last century—disciplinary boundaries have become increasingly diffuse as psychiatry leverages scientific discoveries across related fields. As just three examples, (1) modern neuroimaging cannot be conducted without advanced scanning sequences and new imaging modalities devised by physicists, (2) modern psychiatric genetics cannot be conducted without experts in both molecular genetics and Bayesian statistics, and (3) neurogenetics, which specifies neural functions that mediate relations between multifactorial genetic burden and behavior, cannot be conducted without expertise in all these domains [47]. Given such developments and other important technological advances, the value of transdisciplinary research is likely evident to readers, so we turn our attention to other principles.

3.2 Multicausal Pathways to Common Behavioral Syndromes

In a 1996 editorial for a special issue of *Development and Psychopathology*, Cicchetti and Fred Rogosch noted how *equifinality*—a term used in developmental psychopathology

research to describe multiple causal pathways to apparently single behavioral syndromes—has always been a hallmark of the discipline [48]. In that special issue, equifinal pathways to antisocial behavior, depression, disruptive behavior disorders, schizophrenia, and other mental health outcomes were considered. As a concept, equifinality originated in biology to describe how open living systems can and often do reach similar developmental endpoints through diverse and complex causal processes—including stochastic effects—across functional levels of analysis[49,50]. In modern psychiatric genetics, multifinal outcomes are often referred to as *phenocopies*. At the time, however, equifinality was not an influential concept in mainstream psychiatry. Instead, searches for distinct causes of mental disorders and associated pathognomonic signs predominated given how useful the approach had been in modern medicine [31,36,37].

Although there was always recognition in psychiatry of heterogeneity within diagnostic classes, equifinality and associated developmental processes were typically not invoked as causal explanations. One likely reason is that without yet-to-emerge technological advances discussed above, specific mechanisms of equifinality could not be observed directly. In child and adolescent psychiatry, this state of affairs began to change in the early 1990s, when both the *DSM-IV* field trials and a landmark paper by Terrie Moffitt suggested two developmental pathways to conduct disorder [51,52,53]. Moffitt proposed that those who initiate delinquency in early childhood suffer from heritable neuropsychological vulnerabilities that persist across the lifespan, whereas those who initiate delinquency in adolescence suffer from no such impairment. Neuropsychological testing largely upholds this distinction, demonstrating at least two equifinal pathways to conduct disorder [54]. The resulting *DSM-IV* subtyping of *life-course persistent* vs. *adolescent-onset* conduct disorder embeds equifinality in the modern psychiatric nomenclature. These subtypes are carried forward to the *DSM-5* [55].

At present, nowhere is the principle of equifinality more evident than in psychiatric genetics. In merely 15 years since the human genome was sequenced [56], molecular geneticists have migrated away from conducting candidate gene studies with dozens to hundreds of participants toward large-scale genome-wide association studies (GWAS) that include tens of thousands of people [57]. As power of GWAS increases and methods such as genomewide complex trait analysis (GCTA) and approximate Bayesian polygenic analysis (ABPA) become mainstream, it is increasingly clear that hundreds and even thousands of genes affect complex behavioral traits, and that few if any particular genes are necessary or sufficient for psychiatric impairment [26,31]. Furthermore, epigenome-wide association studies (eGWAS) are providing insights into environmentally mediated gene regulation [58], and central roles for both *de novo* mutations and heritable copy number variants (CNVs) in the pathogenesis of psychiatric disorders have become clear [59]. Thus, in little more than a decade, oligogenic and polygenic theories have been largely abandoned in favor of complex, multifactorial models that include heritable, epigenetic, and stochastic effects [31,60]. Although the importance of genomewide significant single nucleotide polymorphisms (SNPs) in pathophysiologies of psychopathology should not be understated, they individually account for limited proportions of liability [61,62].

Importantly, even though psychiatric disorders may be more complex genetically than many other medical conditions, any such distinction is a matter of degree. Figure 2 depicts ABPA relations between numbers of syndrome-relevant GWAS SNPs and proportions of phenotypic variation explained for several complex diseases [62]. Over 8,300 SNPs—almost all of very small effect size (i.e., well below genomewide significant)—are required to explain 50% of population-based phenotypic variation in schizophrenia liability. By comparison, 1,000 or more SNPs are required to explain similar levels of phenotypic variation in myocardial infarction and type II diabetes [63]. Thus, genetic vulnerabilities to schizophrenia and other psychiatric and medical disorders may be orders-of-magnitude more multicausal than envisioned only a decade ago [26]. Furthermore, polygenic risk score analyses indicate considerable overlap in genetic vulnerability to major psychiatric disorders [64,65]. Although validity of ABPA and related methods is still being evaluated, complex multifactorial genetic vulnerability is indisputable. It is important to note, however, that etiological complexity is not confined to molecular genetics. In remaining sections we discuss additional levels of analysis that mediate and interact with genetic influences to eventuate in psychopathology [66].

3.3 Multifinal Outcomes from Common Etiological Start Points

As a construct, *multifinality* can be defined in at least two ways. A common yet perhaps overly general definition refers to different long-term functional outcomes (e.g., well-adjusted, psychopathological) given similar rearing contexts (e.g., maltreatment, poverty). By this definition, a wide range of moderating and contextual variables, including genetic burden, temperament, and trauma exposure might explain diverse outcomes. In this article, we use a more restrictive definition of multifinality—different long-term functional outcomes given equivalent, pre-existing vulnerabilities (e.g., genetic, neural). Of particular interest are mechanisms through which the same neurobiological vulnerabilities eventuate psychopathology only for those who are exposed to impinging environments (i.e., Gene $\times$ Environment interaction) [32,66]. This form of multifinality overlaps with the concept of *pathoplasticity* in psychiatry. Notably, although multifinality is a founding principle of developmental psychopathology [1,29], psychiatry has been more cautious toward adopting the construct, perhaps because pathoplastic outcomes can only be inferred when common etiological start points are assumed—a highly implausible supposition in most psychiatric research given the complexity of genetic and other vulnerabilities to psychopathology.

Appropriate caution notwithstanding, four important developments bolster arguments for multifinality. First, elegant animal models, including those articulated by Michael Meaney and colleagues and extended by others, reveal stress-induced, epigenetically-mediated changes in neural structure and function in brain regions implicated in motivation, mood regulation, and social affiliation [45,46]. Many of these changes confer long-lasting behavioral adaptations, including impairments that persist into rodent homologues of adolescence and adulthood [67]. Such findings provide unambiguous evidence of pathoplasticity given genetically identical rodent strains and tight experimental control over environments.

Second, in a landmark study with humans, Mario Fraga and colleagues reported diverging DNA methylation patterns across the lifespan for monozygotic twin pairs [68]. Whereas twin toddlers showed almost no epigenetic differences, middle-age twins showed highly distinguishable epigenome profiles of 5-methylcytosine and histone acetylation. These findings complemented extensive animal research by demonstrating environmentally moderated gene expression in humans, and initiated the current explosion of studies on the epigenome and psychopathology. In fact, psychiatry has witnessed profound advances in and proliferation of psychiatric epigenetics in only 13 years since the Fraga paper.

Third, molecular genetic studies of rare neuropsychiatric conditions have long established the phenomenon of *pleiotropy*, whereby a rare variant known to exert deleterious causal influences does so to varying degrees of severity across individual carriers. Such variation may emerge from interacting environmental influences (see below) and/or interactions with variable elements of family genetic background, as observed in 22q11.2 and 16p11.2 deletion syndromes [69,70]. The concept of pleiotropy also applies to heritable behavioral expressions of multiple dimensions of psychopathology, including liability to internalizing disorders, externalizing disorders, and psychotic disorders [71,72].

Fourth, behavioral genetics research indicates strong non-shared environmental effects on mental health outcomes. Large twin studies show that common molecular genetic risk is often shaped by non-shared environmental influences into alternative expressions of psychopathology (e.g., major depression, generalized anxiety) [71]. These studies are critically important because they include monozygotic twins reared together vs. reared apart, and therefore demonstrate impinging effects of unique environmental experience for those with identical DNA sequences and identical epigenetic profiles at birth. Notably, magnitudes of effects of *shared* (common) environmental influences are relatively low for most though not all psychiatric syndromes in childhood, suggesting that (1) social and rearing influences within typical ranges of variation in the population (to the extent that such variation is represented in a given study and when considered independently of other domains of causation) are not as influential on psychopathology as genetic and non-shared environmental factors; (2) their effects may nevertheless be pronounced when interacting with genetic or non-shared environmental factors (rather than being analyzed as isolated main effects; see below); and (3) may exhibit non-linear associations with psychopathology [73]. Thus, whereas common environmental influences across typical ranges of variation exert modest effects, severe disruptions of environment—as in deprivation and maltreatment—exert profound deleterious effects, even when controlling for genetic variation. Children with genetic liability who incur severe environmental risk are therefore more vulnerable to psychopathology than children without genetic liability who incur the same environmental risk [74].

Finally, in the 1990s Sandra Scarr proposed a reconciliation of genetic and environmental hypotheses regarding individual variation in behavior by advancing the notion that in given environmental contexts, genetic variation guides *reconstruction* of experience to optimize what children assimilate from that experience to meet their individual developmental needs [75]. Recently, an example of this phenomenon was observed serendipitously in research on early autism endophenotypes: Variation in normal infants' visual engagement of dynamic

social scenes ascertained by eye tracking exhibits wide variation in the population, is under stringent genetic control (on a time scale of tens of milliseconds), and is comprised an enduring trait-like feature in which eye gaze patterns specify highly-individualized approaches to assimilating information from the social environment [76].

Taken together, evidence from animal, behavioral genetic, epigenetic, and molecular genetic research converge on a conclusion of multifinal Gene $\times$ Environment causation of psychopathology [32,61,66]. This provides an ideal segue into our next section.

3.4 Multiple Levels of Analysis Spanning Genes to Environments

Given the clear migration toward interdisciplinary and transdisciplinary research noted above and depicted in Figure 1, it may seem unnecessary to promote science that transcends levels of analysis spanning genes to environments. Historically, however, developmental psychopathologists, psychiatrists, and other behavioral scientists have tended to focus on 1 or 2 variables (e.g., symptoms, candidate genes)—and by extension 1 or 2 levels of analysis—in their research. This approach is exemplified in both main effects and two-way interaction models of psychopathology, the latter of which originated in mid-20th Century diathesis-stress theories of schizophrenia [77]. Although groundbreaking at the time, these theories assumed either monogenic or oligogenic inheritance of liability to a discretely distributed disorder [78]. Such models are straightforward and therefore easy to test and interpret, but they cannot capture the etiological complexity of psychopathology discussed herein [25,26,31]. In fact, they can obscure associations between predictors and outcomes when diagnostic cut points are specified incorrectly or arbitrarily [79]. Nevertheless, main effects and simple interaction models predominated across disciplines until recently [24] and are still well represented in published research.

There are several likely reasons for lingering influence of research that assesses main effects and simple interactions. These include intuitive appeal of causal models that are easy to communicate, test, and interpret [80]; limited statistical power to test higher-order interactions in small samples [81]; expertise required to implement methods that parse variance across nested levels of analysis [82]; highly specialized training in single disciplines [83]; difficulties measuring environments with precision in large scale genetics studies [84]; pressure to disaggregate interrelated findings into multiple publications [85]; and the human tendency to overvalue one's preferred methods and research questions and undervalue research from outside one's area of expertise [86].

These considerations notwithstanding, more basic models of mental illness are clearly giving way to complex characterizations that subsume established findings into rapidly evolving discoveries across levels of analysis [26]. In our own work, for example, we have advanced a neurodevelopmental model of externalizing behavior in which genetic burden, epigenetic regulation of neural function, neurohormonal influences, and impinging exogenous risk exposures (e.g., in utero stress exposure, hypoxic events) combine/interact in complex ways to disrupt both resting striatal activity and striatal reactivity while anticipating appetitive stimuli [87,88]. Such neural response patterns characterize a wide range of impulse control disorders, including ADHD, conduct disorder, intentional self-injury, and both active and remitted addiction [89,90,91]. A multiple levels of analysis depiction of this model appears

in Figure 3. Although space constraints preclude full elaboration, several points are worth noting.

First, the temporal sequence of externalizing progression depicted in the bottom panel of Figure 3 has been described for over 50 years by scientists across disciplines including sociology [92], psychology [52], psychiatry [93], and criminology [94]. Notably, however, only a subset of children who exhibit ADHD early in life progress to more severe externalizing behavior across development. Thus, although ADHD is a serious mental health concern that confers lifelong impairment in educational, occupational, and other functional outcomes [95], it need not eventuate in antisociality. Traditionally, psychiatry has interpreted multifinal outcomes of ADHD as evidence for discrete disorders, but an alternative view is one of common liability, with differences in symptom expression emerging at various levels of disease progression, in interaction with exogenous risk and protective factors [96,97]. Thus, similar to medical conditions such as type II diabetes, (1) early vulnerabilities present very differently than end-state structural and functional outcomes, (2) disease progression is potentiated by environmental risk, and (3) disease progression may be halted in protective environments. Such an interpretation is supported by findings of common behavioral genetic, molecular genetic, and neural vulnerabilities across externalizing disorders [96,98], with broadening neural dysfunction later in ontogenesis, as discussed below [99].

Specific environmental risk mediators of externalizing progression are well characterized. Impulsive children, including those with ADHD, are more vulnerable to externalizing progression when they are exposed to authoritarian parenting and maltreatment [100], when they are reared in low SES neighborhoods with high rates of violence and criminality [101], and when substances of abuse are readily available [102], among other risk factors. Such findings underscore the need to avoid biological reductionism in modeling and treating psychopathology [80]. Indeed, psychopharmacologic treatment of ADHD symptoms in childhood often does not spare affected individuals from downstream adverse outcomes of these protracted biological vulnerability $\times$ environmental risk interactions [103], even though sustained treatment in adulthood reduces criminal activity [104]. Taken together, these findings and others suggest that as with physical diseases, biological vulnerabilities and environmental risk factors interact complexly across time to yield observed psychopathological endpoints [10,26,87,105].

Figure 3 also emphasizes a fundamental role of emotion in externalizing behavior. Neither genetic influences nor neural functions exert direct effects on behavior. Rather, they confer behavioral biases *through* their indirect effects on temperamental, emotional, and psychological states. Many forms of psychopathology—including externalizing disorders—are characterized by emotional and psychological responses that are either too intense or too enduring to be adaptive [106]. Contemporary models of externalizing behavior specify a central role of anhedonia and irritability— affective byproducts of striatal under-responding—in motivating impulsive, reward-seeking, and substance-abusing behaviors [87,107,108].

4. Neurodevelopment and Psychopathology

Thus far in this editorial we have considered themes that unify, dovetail, and bridge the research agendas of developmental psychopathology and psychiatry. All of these themes are well represented in contemporary interdisciplinary research. By comparison, neurodevelopmental theory—which is central to the developmental psychopathology perspective—fits less neatly into this mold. Despite longstanding exceptions in the psychiatry literature [109], particularly in research on autism and schizophrenia [26,110,111], broad application of neurodevelopmental theory in psychiatric research is a more recent development [32,33,34]. This may be an instance of psychiatry waiting for advanced technology—in this case neuroimaging and genetics—to verify otherwise difficult-to-test neuromaturational models [112].

Literature on the neurodevelopment of psychopathology is complex and therefore cannot be reviewed herein. Instead, we focus on three important considerations, including (1) differential neuromaturation of subcortical vs. cortical structures, (2) increasing contributions of cortically-mediated executive function, self-regulation, and emotion regulation deficits to psychopathology across adolescence and young adulthood, and (3) effects of endogenous insults including substance use and correlates of poverty on cortical development.

Neuroscientists have known for many years that neuromaturation of frontal brain regions including the orbitofrontal cortex, the anterior cingulate cortex, and the dorsolateral, ventrolateral, and ventromedial prefrontal cortices (PFCs) lags behind neuromaturation of deep, subcortical brain regions [113,114]. PFC neuromaturation is of course critical for executive function, including self-regulation of behavior and affect [115]. Among other mechanisms, such regulation occurs through top-down-inhibition of subcortically-generated impulses and emotions [116,117]. Notably, typically developing children and adolescents show stronger subcortical responses but weaker and more diffuse PFC responses to emotion-eliciting events than adults [118]. According to contemporary neurodevelopmental theory, age-related increases in self-regulation occur in part through improved connectivity and improved top-down inhibition of subcortical structures by functional subdivisions of the PFC [33,106,112]. Although specific neural networks differ, both neuromaturation of the PFC and efficiency of subcortical-cortical connectivity become increasingly compromised across development in internalizing and externalizing disorders [119]. Given space constraints, we focus here on externalizing disorders, building on our discussion from previous sections.

Volumetric prefrontal neuromaturation among children and adolescents with ADHD lags about two years behind that of typically developing controls [120], and adolescent males who develop severe conduct disorder fail to exhibit normative gray matter pruning in the orbitofrontal cortex and anterior cingulate cortex (ACC) from ages 10 to 14 years [121]. Furthermore, volumetric deficiencies in the ACC are accompanied by disrupted connectivity with subcortical structures implicated in reward processing [122,123]. Although a more thorough summary of this literature is not possible here, several recent reviews suggest that

conduct disorder is associated with structural and functional deficiencies that both subsume and extend beyond those observed in ADHD [87,117].

Taken together, such findings suggest that externalizing progression may be in part attributable to persistent underdevelopment of prefrontal regions implicated in self-regulation and executive function [120,121,124]. Thus, as depicted in Figure 4, multifactorially derived striatal (subcortical) vulnerabilities that predispose to impulsivity and ADHD are amplified across development if coupled with deficient PFC neuromaturation. According to this perspective, disrupted PFC development potentiates vulnerability to externalizing progression by compromising volitional control over subcortically generated affect and impulses [87,105].

From a developmental psychopathology perspective, a crucial point concerns effects of environment on neural structure and function across development. Research conducted in the past decade shows strong effects of adversity in childhood and adolescence on neurodevelopment—not only in prefrontal regions implicated in executive function and self-regulation, but also in subcortical structures implicated in impulsivity. For example, children reared in poverty show reduced volumes in a wide range of cortical and subcortical brain regions compared with their peers, effects that are larger the poorer children's families are [125,126]. Furthermore, family stress and adversity measured in childhood are associated in dose-response fashion with reduced functional neural responding to incentives in adulthood in both cortical subcortical regions [127].

Compelling neurodevelopmental research on substance use and addiction is also emerging. Consistent with animal models articulated many years ago, longitudinal work now demonstrates that (1) low striatal responding to incentives predicts vulnerability to marijuana, cocaine, and methamphetamine abuse and addiction three years later [128]; and (2) heavy drinking in adolescence induces faster gray matter loss and slower white matter growth than expected compared with both moderate drinking and abstinence [129]. In turn, early adolescent alcohol and drug use compromise neural connectivity and development of executive function into adulthood, with likely implications for further progression of externalizing behavior [130,131]. Taken together, these findings suggest that frontal brain regions that subserve executive functions, self-regulation, and emotion regulation are exquisitely sensitive to environmental insults, with almost certain implications for worsening externalizing behavior across development for already vulnerable individuals who are reared in contexts of cumulative risk. Although we restrict discussion here to externalizing outcomes, similar neurodevelopmental perspectives have been articulated for depression, anxiety, and obsessive-compulsive disorder [117,119].

5. Summary and Conclusions

Tremendous strides have been made in specifying etiologies of psychopathology using developmentally informed approaches, some of which were articulated initially in developmental psychopathology but now cut across disciplines. This is especially noteworthy given the relative youth of developmental psychopathology. In this closing

section, we offer some broad recommendations that might help guide future work, with recognition that subdisciplines have field-specific concerns.

Advances in our scientific understanding of mental illness will almost certainly require developmental *macrotheories* that integrate findings across disciplines and levels of analysis [26,32,87]. In some cases, such theories may be necessary to advance prevention and treatment efforts. For example, only with an integrated understanding of (1) predisposing temperamental and emotional vulnerabilities to delinquency, (2) the well-characterized developmental pathway of externalizing psychopathology depicted in Figure 3, and (3) relevant environmental risk mediators, were implementers of the NIMH Fast Track project able to reduce—as assessed via random assignment—substance use, violent crime convictions, drug convictions, and high-risk sexual behaviors among young adults who were enrolled in a targeted prevention program in elementary and middle school [132]. The theory of externalizing behavior described above represents but one among several examples of developmental macrotheories [26,133].

These macrotheories cannot be developed at single levels of analysis. In fact, no single level of analysis accounts for all or even most of the variance in any functional outcome. Additionally, given the complexity of psychopathology and the extensive expertise and resources required to conduct research across levels of analysis, few individual research laboratories can address even a fraction of relevant influences. Thus, progression of interdisciplinary and transdisciplinary science is a welcome and necessary development [35]. In fact, lingering arguments over which level of analysis (e.g., genetic, neural, environmental) deserves primacy in causal models of most mental disorders are anachronistic given complex, interactive determinants of human behavior [25,26,32,105].

Having said that, the transdisciplinary science that is so essential to modern psychiatry and developmental psychopathology will almost certainly benefit from more careful attention to issues of multimodal measurement across development. For example, studies of effects of stress on psychopathology can and likely should measure predictors and outcomes across levels of analysis including genetic vulnerability, immune responding and gene expression, neural responding, autonomic responding, subjective accounts of stress responding, and objective interview measures of life events to minimize recall bias. In fact, multimodal assessment was emphasized recently by the National Advisory Mental Health Council Workgroup on Tasks and Measures for RDoC [134], who called for more standardized, precise, and developmentally sensitive assessment methods.

Developmentally sensitive, multimodal assessment yields rich datasets and opportunities to map the etiology of psychopathology, yet deliberate planning is required to ensure adequate diagnostic and measurement precision [135]. As noted by the Council Workgroup [134], laboratory measurement paradigms sometimes become standard without being subjected to adequate validation. At other times, well-validated paradigms are avoided in favor of novel tasks of unknown validity [136]. To complicate matters further, tasks, questionnaires, and diagnostic assessment measures that are valid at one age may not be valid at another age, yet measurement invariance across development is rarely tested [137]. In such cases, claims

about group differences in behavior change across time are difficult if not impossible to interpret [138].

All of these issues limit the extent to which existing datasets can be compared and combined, yet interdisciplinary science requires effective collaboration, shared data, and common data collection methods. As described in the Council Workgroup report and elsewhere [134,139,140], although strides have been made toward construction and validation of common assessment methods, additional work is needed using developmentally informed designs. Furthermore, at least some measures that are considered standard in the field require further validation [141].

In closing, transdisciplinary research, including the growing partnership between psychiatry and developmental psychopathology, is a welcome development that has already enriched our understanding of emerging mental illness. We anticipate continued growth in years to come as new technologies increase our ability to specify etiopathophysiologies and elucidate the daunting complexity of psychiatric disorders across all relevant levels of analysis. As problems with measurement invariance and precision are addressed, we look forward to continued discoveries that improve our capacity to prevent and treat psychiatric disorders.

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Highlights

- Psychiatry and developmental psychopathology share common research agendas.
- Principles that bridge disciplines include emphasis on interdisciplinary research, elucidation of multicausal pathways to seemingly single disorders, description of multifinal outcomes from common etiological start points, and research conducted across levels of analysis spanning genes to environments.
- All of these principles address etiological complexity.
- To date, developmental psychopathology has placed greater emphasis than psychiatry on neuromaturational models, but this is changing rapidly.
- We discuss the complexity of emerging psychopathology across the lifespan by way of selected examples.

Fig. 1.

Progression from unidisciplinary to multidisciplinary to interdisciplinary to transdisciplinary science. At each step, disciplines become more integrated and interdependent. Psychiatry and developmental psychopathology have entered a transdisciplinary era [35,41].

Fig. 2.

Relations between numbers of syndrome-relevant GWAS single nucleotide polymorphisms (SNPs) and proportions of phenotypic variation explained for schizophrenia (SCZ), celiac disease, myocardial infarction (MI), rheumatoid arthritis (RA), and type II diabetes (T2D). Shaded regions represent posterior probability densities, derived from approximate Bayesian polygenic analysis (ABPA). Collectively, 8332 SNPs explain 50% of population based phenotypic variation in schizophrenia liability. Reproduced with permission from “Genome-wide association analysis identifies 13 new risk loci for schizophrenia”, by S. Ripke et al. [62], *Nature Genetics*, 45: 1150–9.

Fig. 3.

Etiological complexity of well characterized externalizing progression for many affected males. Low tonic striatal activity and blunted striatal reactivity while anticipating incentives arise from accrual of and complex interactions among genetic influences (heritable SNPs and CNVs, *de novo* mutations, epigenetic effects), impinging exogenous risk exposures (TBI, hypoxia), and neurohormone regulation. Any single research study can address very few of these influences. For simplicity of presentation, other neural systems that modulate striatal function are omitted [31]. Striatal dysfunction imbues an irritable, anhedonic mood state, which in turn elicits a temperamental/behavioral bias toward reward seeking to upregulate aversive mood. Genetic, neural, and temperamental vulnerabilities are expressed syndromally as ADHD, which predisposes to externalizing progression specifically in high risk environments [87].

Fig. 4.

A neurodevelopmental model of externalizing progression for many affected males. Early in life, impulsivity (ADHD) derives largely from subcortically-mediated neural vulnerability (top panel, left). Progression to more severe externalizing conduct occurs in conjunction with deficient in cortical neuromaturation, which gives rise to self- and emotion regulation deficits (top panel, right). Environmental risk factors potentiate this progression (see text). The bottom panel shows relative contributions of subcortical and cortical dysfunction to overall impairment across development.