3

A Developmentally Informed Approach to Characterizing, Staging, and Intervening in Youth Mental Health Problems

From the Population to the Clinic

Jai L. Shah, Nicholas B. Allen, Shelli Avenevoli,
Christoph U. Correll, Helen L. Fisher, Ian B. Hickie,
Beatriz Luna, Dost Öngür, and Alison R. Yung

Abstract

This chapter articulates a framework for bringing together developmentally contextu-alized mental and physiological processes to guide the characterization, staging, and interventions necessary in treating mental health disorders in youth. This framework spans from population-level risk identification to individual-level clinical care, draw-ing on knowledge about developmentally informed trajectories and clinical systems. At a fundamental level, it necessitates appreciating the influence of both inherited and acquired factors on brain specialization and the setting of trajectories during periods of plasticity and risk, all of which delineate adult trajectories in multiple dimensions. More pragmatically, it requires us to track a range of salient mental/physiological systems during a dynamic developmental period that includes both vulnerability and risk, to contemplate their utility in identifying enriched groups that might benefit from further individual-level assessment in clinical or community settings, and to translate findings into planning prevention and intervention programs and to informing clinical decision making.

Group photos (top left to bottom right)   Jai Shah, Nick Allen, Beatriz Luna, Shelli Avenevoli, Christoph Correll, Dost Öngür, Alison Yung, Ian Hickie, Nick Allen, Helen Fisher, Jai Shah, Alison Yung, Shelli Avenevoli, Christoph Correll, Beatriz Luna, Dost Öngür, Helen Fisher, Nick Allen, Shelli Avenevoli, Ian Hickie, Jai Shah

Introduction: The Need

Clinical and epidemiologic research over the past two decades has shown that approximately 75% of mental disorders emerge in youth (Kim-Cohen et al. 2003) and that one in five young people is affected by mental illness. Yet while prompt treatment of initial phases could improve outcomes, existing services often struggle to detect and manage them: there are substantial delays in identifying and intervening in these conditions, long waits to access care, and poor utilization of ineffective or inappropriate interventions (Kessler et al. 2005; Rubio and Correll 2017a, b). Paradoxically, when services are eventually accessed, current interventions are designed predominantly around end-stage, categorically defined mental disorders as they stereotypically appear during adulthood (McGorry et al. 2018a).

These treatment gaps are even more startling because the period during which early-phase mental health problems emerge plays a critical role in setting the trajectory of biological, psychological, and social milestones as well as achievements. Thus our mental health system organized around traditional categorical diagnoses in adults, instead of fundamental mental and/or physiological systems during youth, means that current approaches to classification have lacked a developmentally informed, longitudinal perspective that takes into account underlying pathophysiology and associated intraindividual variability (Fisher et al. 2018). Treatment and prevention would be far more effective if classification better reflected the naturalistic emergence and onset of mental health difficulties and disorders in youth. In other words, the design and deployment of prevention and early intervention approaches should be tied to relevant knowledge about the etiology, risk, onset, and course of early-stage mental illness (Vos et al. 2012; WHO 2014).

Fortunately, recent attention to early and distressing mental experiences in youth, aged 12–25 yr, offers opportunity for diverse forms of intervention to occur during windows as "close" as possible to the age of onset (McGorry et al. 2003). These developmentally aware approaches should ideally be informed by fundamental mental or physiological processes that increase vulnerability (or protection) for trajectories leading to youth-onset disorders in large populations or identified subgroups. This gap is not filled by alternative organizational systems, such as the research domain criteria (RDoC) from the U.S. National Institute of Mental Health's (Insel et al. 2010). Although RDoC acknowledges the role of development and environmental exposures as orthogonal assessments (Cuthbert and Insel 2010), it was explicitly developed as a research tool and is not intended to guide clinical diagnoses or decision making in its current form (Cuthbert and Insel 2013).

Accordingly, in this chapter we articulate a framework for bringing together developmentally contextualized mental and physiological processes—one that can ultimately guide characterization, staging, and interventions in mental health difficulties or disorders in youth, from population-level risk
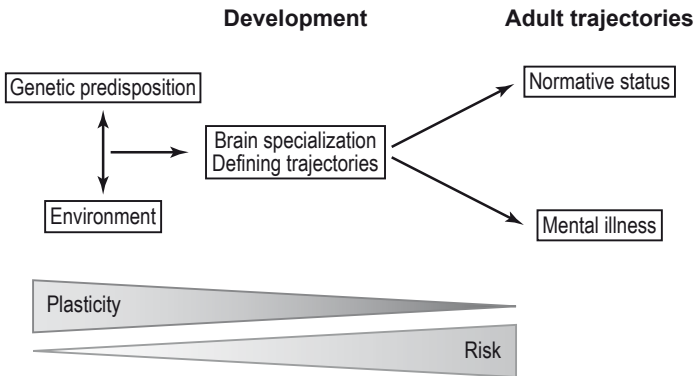
Figure 3.1 Conceptualization of a system to track developmentally salient, clinically meaningful mental/physiological systems and their translation from population-level risk to dimensions of mental ill-health. Any such schema must appreciate that there are complex relationships between these elements: etiologic factors, risk and plasticity, development, and their impact on adult trajectories.

identification to individual-level clinical care (Figure 3.1). Designing a framework and approach that draws on knowledge about developmentally informed trajectories and clinical systems to characterize and intervene in youth mental health problems involves a number of considerations. At a fundamental level, it necessitates appreciating the influence of both inherited and acquired factors (Figure 3.1, left) on brain specialization and the setting of trajectories (middle) during periods of plasticity and risk (bottom), all of which delineate adult trajectories in multiple dimensions (right). More pragmatically, it requires us to

- track a range of salient mental/physiological systems during a dynamic developmental period that includes both vulnerability and risk,
- contemplate their utility in identifying enriched groups that might benefit from further individual-level assessment in clinical or community settings, and
- translate such findings into planning prevention and intervention programs to inform clinical decision making.

Population-Level Differences in Mental and Physiological Maturation

The Framework: Identifying Vulnerable Youth

A developmentally informed approach must be embedded in appropriately contextualized population distributions as well as in knowledge regarding how an individual is progressing over time. As such, the tracking of trajectories in

individuals (especially perturbations from normative trajectories), and the subsequent identification of youth at earlier (ideally preclinical) stages of distress and impairment represent key features of this framework.

An additional consideration is the choice of mental physiological systems that are themselves under development and therefore dynamically changing during adolescence. These should be purposefully selected to capture the full spectrum of relevant phenomena across an appropriate range of time points, bearing in mind variability in a range of individual- and group-level factors such as neurological and psychological developmental stage, exposure to adversity, family environment, gender identification, genetic predisposition, and cultural context. The analogy is that of pediatric growth charts, a commonly used and clinically valuable tool rooted in normative development and reflecting both physiology and external influences (Gardosi et al. 2018). A youth mental health (age 12–25 yr) analogue to growth charts could provide insight within the margins of a normative template but, importantly, would also provide information on individual-level developmental trajectories over time (Figure 3.2).

The selection of specific systems to track requires careful consideration, and an exhaustive examination of all possibilities is neither feasible nor practical given our starting point. Instead, we have identified examples of developmentally relevant, fundamental mental/physiological systems that might serve as initial systems to be investigated: sensory processing, circadian rhythm/activation, threat arousal, emotional regulation, reward salience, neurocognition, social cognition, and metacognition (sense of self). Figure 3.3 shows how the first four could be tracked over time, compared to normative trajectories. We selected these systems based on their face validity and known involvement in healthy and unhealthy mental operations: each system shows significant developmental change and growth during adolescence and has strong putative and
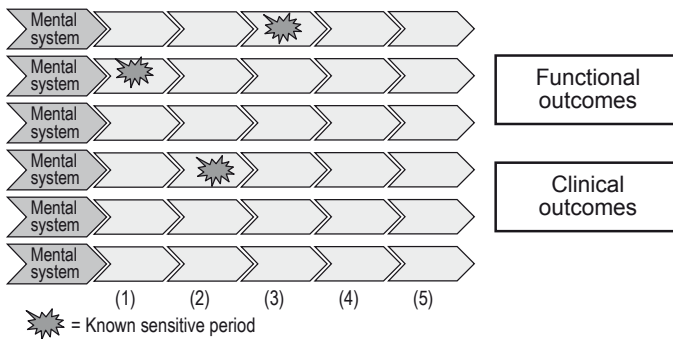

Figure 3.2 Visualization of developmental trajectories, maturation, and sensitive periods for tracking mental/physiological systems, developmental context, and clinical and functional outcomes for young people. The depicted developmental stages are (1) childhood (9–12 yr), (2) early adolescence (12–15 yr), (3) late adolescence (15–18 yr), (4) transition to adulthood (18–21 yr), and (5) early adulthood (22–25 yr).
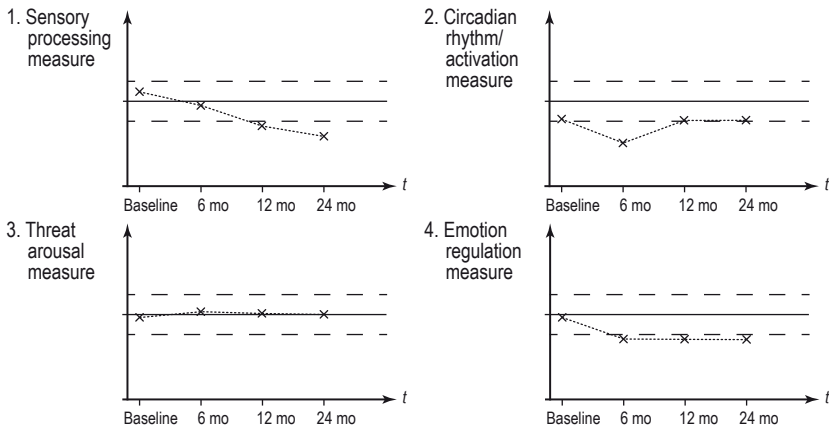
Figure 3.3 Graphical display of four proposed mental/physiological systems over time. The solid horizontal line represents the sex- and age-adjusted norm; dotted lines (above and below) represent its 95 percentile specific for each mental process domain. The line connecting each time point (e.g., baseline, 6 months, 12 months, 24 months) displays how an individual performs relative to the sex- and age-adjusted norm and relative to its own prior developmental state over time.

demonstrated links to the underlying psychopathology of emergent mental disorders in youth. Ideally, each system could be tracked in individuals over time, allowing early identification (and an offer of support) for persistent deviation from an expected trajectory.

For each of the proposed system domains, summary scores (and, possibly, subscores) on standardized measures (akin to weight percentile or BMI percentile) will need to be selected, tested, and agreed upon to enable the creation of such a multidimensional mental capacity growth chart. Ideally, all relevant dimensions would be tracked and visualized relative to each other to indicate (a) where an individual is located within normative development and (b) how any divergence tracked over time relates to the other dimensions. From a research perspective, this information would be useful to map individual and normative development across complex and interacting dimensions. For clinical decision making, it would help to identify areas of need for increased vigilance or monitoring in the context of emerging departures from normative development, low-risk preventive interventions when such departures begin to manifest clinically, or treatment of manifest abnormalities that are functionally relevant and/or lead to distress.

Contextualizing the Framework

Building on the notion of developmental trajectories, the framework presumes that there are critical or "sensitive" periods that serve as key time points at

which mental/physiological "milestones" should be attained in order for optimal development to occur at the subsequent life stage. Such sensitive periods are generally timed to when important information is available and most useful to the development of the organism (Fawcett and Frankenhuis 2015). For example, molecular mechanisms of critical period plasticity markers are active throughout adolescence in association cortices (such as prefrontal cortex), indicating active specialization of systems that define adult trajectories and are involved in all psychiatric illnesses (Hickie et al., this volume; Larsen and Luna 2018). Similarly, mean performance in cognitive tasks improves through the adolescent period, with trial-to-trial variability decreasing with age (Montez et al. 2017); this suggests that processes underlying cognitive abilities are present early, but that engaging these processes in a controlled, reliable fashion is a function of development. There are also compelling examples of such sensitive periods with respect to vision (Hensch 2005b) and language acquisition (Doupe and Kuhl 1999; Werker and Hensch 2015) in early life. Failure to attain milestones in these systems may critically impair the achievement of subsequent ones. In general, however, the nature and timing of sensitive periods in adolescence for human cognitive, affective, and social development are not as well understood, yet these may be critical to understanding the developmental windows for the emergence of specific forms of psychopathology as well as for their most effective treatment modalities (Dahl et al. 2018).

Our conceptualization also assumes that an individual's departure from a normative trajectory can occur in more than one domain. Assessing such divergence across multiple domains is more likely to provide insight into the development of clinical distress, dysfunction, and disorders than if individual domains are considered in solitude. With appropriately large samples, processes may aggregate in combinations that have clinical relevance beyond that of current categorical diagnoses. For example, intraindividual variability in cognitive tasks has been commonly found to underlie schizophrenia, depression, borderline personality disorder (Kaiser et al. 2008; Millan et al. 2012), and ADHD (Munoz et al. 2003): neurocognition clearly does not define a specific disorder in its own right, but particular types of neurocognitive deficits may be found to cluster together in characteristic patterns with difficulties in other systems.

Based on the wealth of neurobiological and psychosocial evidence now available, the manifestation of non-normative trajectories in these systems during adolescence and young adulthood may be distinct from their manifestation during other periods. Specific exposures during or before youth may be especially salient in moderating risk or protective factors, particularly during the dynamic developmental period of adolescence. For example, the effects of socioeconomic factors on brain development are mitigated by exposure to positive parenting practices during early adolescence (Whittle et al. 2017). Similarly, during middle adolescence (typically 14–16 yr), developmentally relevant risk factors for a range of outcomes (e.g., peer stress, the breakup of

romantic relationships, and substance misuse) may be modifiable (Bagge et al. 2013; Mirsu-Paun and Oliver 2017). Thus, environmental exposures may have at least some degree of developmental specificity that is potentially modifiable at either the population or individual level.

Finally, research is greatly needed into normal developmental trajectories for each system, so that we can delineate a threshold of trajectory divergence (and persistence) at which point individuals or families could be offered the option of closer monitoring or clinical intervention. While non-normative trajectories in individual systems may not in and of themselves reflect clinical caseness, they may (in combination with knowledge regarding sensitive or critical periods) represent the earliest signs of what could develop into one or more clinical conditions. Changes in expected trajectories may then return to the original trajectory either spontaneously or as a result of interventions; alternatively, the new trajectory may persist, accelerate, or arrest. Further research is needed to delineate thresholds of trajectory divergence and/or persistence, again in the context of knowledge regarding sensitive periods and relevance for outcomes. Once a threshold is reached, individuals or families could be offered the option of closer tracking, a more comprehensive assessment, or escalation to lower- or higher-risk clinical interventions by health services. A template for this may be found in measures of reading achievement, in which a lack of attainment of this important milestone following a known critical period signals a time-sensitive need to intervene in different ways (Kamil et al. 2016).

Techniques and Technologies to Assist Identification

Although growth charting has been a fundamental part of other areas of medicine, most prominently pediatrics, much remains unknown regarding developmentally informed charting of mental and physiological systems that might underpin youth (and ultimately adult) mental ill-health. As mentioned, the tracking of mental/physiological systems would benefit from focusing on longitudinal trajectories rather than individual snapshots; the former would emerge based on repeated outcome measurements that can be compared to a dynamically changing "normative" trajectory. A major investment in measurement development is thus required to demonstrate analytic capacity, reliability, and validity for each relevant system. Moreover, before widespread implementation, foundational work would need to be done to determine norms for each system across gender, cultures, and relevant clinical subgroups as well as for temporal variation of norms, for example, within a culture or subgroup over time.

To that end, a qualitative leap forward in the ability to track trajectories would be enabled by feasible, user friendly, affordable, and scalable passive sensing technologies that allow for continuous high-frequency sampling of a

range of relevant behavioral and physiological systems (Mohr et al. 2017). Such approaches offer a unique opportunity to sample developmental changes with sufficient frequency to truly capture the dynamics of these phenomena. This high-frequency sampling may also be critical for revealing periods of greatest variability in behavioral and physiological functioning, which could correlate with plasticity during specific sensitive developmental periods. An exemplar approach increasingly used in research settings to obtain real-time fluctuations in mood and cognitive processes is the experience sampling method (ESM). This involves an individual systematically recording how they feel or what they are thinking about at multiple points across a day for several days in a row. Individuals receive a series of semi-random alerts via a beep from a mobile phone or wearable device during waking hours, and they are then tasked with completing a short questionnaire about their feelings, thoughts, social interactions, etc., at that precise moment in time. When taken together, these multiple recordings provide a more ecologically and time-sensitive assessment of a person's emotional and cognitive states and a picture of subtle fluctuations in these systems over time (e.g., 7 consecutive days) rather than a single cross-sectional snapshot (Reininghaus et al. 2016).

Clinical Application and Implementation of the Proposed Framework

Our focus here is on the potential use of the proposed system in youth mental health clinical settings, including for the purpose of decision making. Table 3.1 provides an example of an assessment tool that begins to characterize clinical correlates of each of the eight exemplar core mental/physiological systems (rows) at a single timepoint. To complete the tool, information acquired would first need to be indexed to data from developmentally informed representative population-level sampling (e.g., obtained using wearable and other mobile health technologies), as well as individual-level data that can be gathered in a clinical setting. In other words, the framework captures underlying markers that may relate to core features across a range of mental conditions and disorders, both requiring and allowing for clinical context.

The rows represent various features relevant to the characterization of each fundamental system, such as the symptom/sign manifestation, severity, duration, and developmental context. These will require clinical correlation between the raw data collected regarding mental/physiological systems and their functional impact on individuals' lives. For certain rows (e.g., the symptoms/signs and modifiable factors), free text can be entered to ensure that as much relevant clinical detail as needed is being collected. For example, in the portion, "Manifestations," clinical observations or potentially relevant factors can be added that might affect an understanding of etiology, ongoing exposures, or protective factors. In an era of patient-centered outcomes, self-rated

Table 3.1 Clinical assessment tool for the proposed framework and application for autism spectrum disorder (*) and bipolar spectrum disorder (+). The number of each symbols represents the putative severity of deviation from normative development.

	Sensory processing	Circadian system/ activation	Threat arousal	Emotional regulation	Reward salience	Neuro-cognition	Social cognition	Metacognition (sense of self)
Manifestations								
Trajectory:								
Symptoms, Signs,	+	+++	++	+++	++	***	***	*
Dysfunction	+		+	**		+		
Duration		+++		+++		**	**	
Severity		+++		+++		**	**	
Appraisal				**		**	**	
Functioning		+		+	+			
Developmental Context								
Other specific clinically relevant factors: To be completed across each domain as needed								
Childhood trauma								
Argument with spouse/peer								
Family history of bipolar disorder								
Clinician to add examples								
Interventions	Antisocial personality disorder	Sleep hygiene, circadian structuring, social rhythm therapy	CBT, selective serotonin reuptake inhibitors	Dialectical behavioral therapy	Addiction treatment, behavioral activation	Cognitive remediation	Social skills training	CBT, interpersonal therapy

scales and instruments should be used to make such data collection feasible in busy clinical settings. For most of the columns, data should eventually be available from developmentally appropriate standardized instruments, such as rapid neurocognitive testing batteries or high-frequency sampled physiological probes, as in circadian rhythms or threat arousal, via wearable or other new technologies.

Although the intended effect of the tool is to track mental/physiological systems in at-risk or affected individuals, Table 3.1 has been filled out for two examples: individuals with a prototypical autism spectrum disorder (*) and bipolar spectrum disorder (+)—to demonstrate relevance. There is some overlap between the two individuals, but the overall message is that each may present with non-normative features in relatively distinct systems, which in turn points to the need for different forms of early intervention that target specific systems rather than diagnoses. This example also illustrates how the system-based framework and approach intersects with clinically relevant information, and how current DSM or ICD diagnoses can transition to the targeting of system-level abnormalities that are graded in terms of severity, developmental relevance, and time trajectory (see also Figure 3.2).

Ultimately, the framework's utility at the individual level will emerge only as data in each cell in the table can be gathered easily and tracked over multiple timepoints. Although intra- and inter-individual variations in developmental timing velocity and milestone achievement may have a surprisingly wide range, we assume that clinically relevant departures from developmental norms would be traceable with sufficient sensitivity and specificity within the proposed framework by means of e-health-based and clinical longitudinal tracking across relevant individual systems. As mentioned, individual data must also be placed within the context of appropriate population norms once the latter can be appropriately contextualized across dimensions of age, sex/gender, race/ethnicity, culture, etc.

Refinement of the specific systems to be studied, or addition of novel systems, should also be investigated. Additional rows and/or columns could be added for individualized and qualitatively different sets of systems or markers, (e.g., insight). The information from Table 3.1 can also be used as a standardized means of documenting, visualizing, and communicating the collected information in clinical settings. Thus, a clinician has multiple options once they have identified a departure from a normative trajectory: they can attempt (a) to lessen the degree and impact of departure from normative development, (b) to bring system-level departures back onto a developmental track, or (c) to obtain critical information and additional data that recontextualizes the departure. This could establish opportunities and indicators of need for intervention, along with devising and validating the capacity of specific interventions (ranging from watchful waiting to increasing monitoring, to preventive measures or more intensive interventions).

Translation to Clinical Systems, Staging, and Interventions

Ethical Implications

If this framework is used for population-level screening, a persistent non-normative trajectory (or one that continues to "fall off the curve") may signify an enriched group at heightened vulnerability for a clinically relevant outcome, rather than identifying individuals with the outcome itself. Thus, as with traditional screening approaches in medicine, tools to identify potential non-normative trajectories may need to be biased toward sensitivity rather than specificity in order to capture enriched populations that can then be offered more detailed assessment. However, the move from systems of data collection based on large population studies, which utilize clinical assessments and various technologies, to the realm of health systems is fraught with challenges. Although elements of this approach have been attempted in the past, a systematic effort to bridge the public health perspective with clinical interventions and service design—from offering low-intensity interventions to groups at relatively low risk, to higher-intensity interventions for those enriched in various dimensions (e.g., family history, symptomatology, pathophysiology)—requires input from a range of disciplines, from epidemiology to ethics.

Perhaps the foremost of these challenges involves the implications of labeling individuals or vulnerable groups as "deviant" from developmental norms, along with societal or actuarial inferences that might be drawn from this. In the clinical realm, the extent to which population-level measures of mental/physiological systems map (or not) onto currently defined clinical disorders remains to be tested. This issue is intricately linked to the risk of prematurely identifying individuals as (false positive) clinical cases, based simply on raw data from mental/physiological systems. Such risk should not be taken lightly. Determining whether an individual's non-normative trajectories, dysfunction, distress, or other features meet threshold levels for "caseness" would depend, in part, on available interventions and context (clinical, local, and cultural). A clinical team might therefore suggest additional longitudinal tracking with more specific metrics and evidence-informed tools to differentiate "false positives" from those who have indeed transitioned to at-risk or early-phase clinical trajectories, bearing in mind the risk–benefit ratio of whatever preventative or other intervention is under consideration. In a public health context, the task may require identifying cases for indicated prevention programs in the community or in primary care, where issues of specificity may be less relevant. Depending on the circumstances, tracking could take place through passive data collection (via monitoring naturalistic patterns in behavior and physiological functioning) and/or more active sampling (e.g., in laboratory-based measurement of response to stressors or perturbation of the process under consideration).

With the multidimensional framework, attention to a vulnerable subgroup (e.g., those with a family history of specific mental illness) could be analyzed

with regard to one or more mental/physiological systems. Specific individuals with non-normative trajectories on multiple processes could then be offered closer monitoring or even low risk–benefit interventions if they desired. A parallel example may be provided by the use of consumer smart watches to provide enhanced, continuous tracking of cardiac physiology in those at risk for cardiac disease (Koshy et al. 2018) . Similarly, relevant data and behavior could be collected via mobile, wearable technology to monitor risk of acute psychiatric crises. This could enable resources to be provided to those seeking immediate help as well as provide feedback to ameliorate symptoms, such as risk of suicide or relapse in psychosis, mania, or depression (Kennard et al. 2018; Torous et al. 2018).

Interface with Clinical Staging

A framework that overlaps with our approach, particularly once individuals are at the point of help-seeking, is that of clinical staging. In recent years, staging has been applied across the spectrum of major mood and psychotic syndromes in young people (Cross et al. 2014; Purcell et al. 2015). However, the mental/physiological systems and phenomena our framework highlights likely cut across traditional diagnoses (Table 3.1), as do presentations of youth experiencing the first phases of mental health problems or illness. Thus, clinical stages need to be more than arbitrary cutoff points on a single dimension of illness severity or duration. For example, circadian disturbance is likely to be relevant not only to those with bipolar-type disorders but in other mood and psychotic syndromes as well. Similarly, neuro- and social-cognitive processes are not only relevant to those with psychotic syndromes but are also likely to be strong predictors of social and other functional outcomes for those experiencing anxiety and mood syndromes.

   In addition to its transdiagnostic parallels with our framework and approach, clinical staging can also help guide treatment selection on the basis of severity, characteristics, and personal choice rather than categorical diagnosis. Once individuals move from nonclinical to clinical settings, staging can be used to inform the entire range of decision making: from watchful waiting to invasive interventions, depending on combinations of stage, dysfunction, and distress as well as independent objective measures and other factors. In the arena of youth mental health, this implies greater use of less noxious (psychological and behavioral) approaches at early stages, reserving medications for those with more discrete syndromes or later stages of illness. It also implies that interventions are often being used for one or more purpose; that is, to treat the current syndrome and/or reduce the chance of progression to a later stage of illness.

   The multidimensional framework proposed here will hopefully over time capture and map core components of biologically or clinically relevant systems onto clinical stages. In this way, it should assist the development of clinical staging, by promoting the move away from a strong reliance on either symptomatology, illness severity or duration.

Implications for Interventions

Aside from clinical staging, particular life phases (e.g., early, middle, or late adolescence as well as high school and postsecondary education) could be used to identify settings where interventions might best be situated. For example, education regarding sexual and romantic experiences has often been delivered in schools with the tone, content, and detail of delivery varying in accordance to the year of study. Similarly, studies could evaluate the effectiveness of interventions across different developmental stages, since plasticity is variable across systems and sensitive periods. This would help identify the potential for endogenous adaptation to environmental circumstances, as well as periods of particular sensitivity or those when interventions will be less effective. This, in turn, creates variable opportunities and challenges for intervention modification efforts: the proportion of individuals in certain settings (e.g., exposure to higher education) is increasing dramatically in the developed world, and may provide a more cost-effective option for interventions with high start-up costs but lower incremental costs.

This framework can also help us evaluate the impact of modifiable as well as nonmodifiable factors at differential developmental stages. For example, exposure to certain factors may cause deviations from normative development in specific systems whereas particular interventions may attenuate the impact of such factors. These exposures and stages should also be viewed in the context of sensitive periods, when particular exposures or endogenous processes may have a particularly perturbing or protective effect on one or more components. For example, childhood trauma may perturb a number of domains, including both physiological components as well as clinical measures. Alternately, factors present during the prenatal period may not be causative of a specific disorder in and of themselves. They may, however, place individuals at risk for the impact of other subsequent factors that contribute to departures from normative trajectories and mental conditions as we currently know them. Alternatively, they could be refined or redefined by using the proposed developmentally sensitive systems approach. In future work, the focus should be on understanding how certain risk and protective factors might contribute to the time of onset and subsequent course of developmental abnormalities that can culminate in mental disorders, and eventually whether relevant interventions can mitigate or supplement those factors.

Opportunities and Challenges

Our proposed framework should be viewed as a work in progress. It offers both an opportunity and a challenge, and will hopefully stimulate further research needed to clarify whether the eight initially formulated systems (along with additional dimensions) are able to yield insight into mental/physiological growth

charting, and how this can best be achieved. Issues that need to be tackled to improve its impact include

- the identification and development of appropriate and scalable assessment tools for large cohorts seen and treated in real-world settings,
- the development of meaningful summary metrics, degree of integration of clinically and biologically relevant information, sufficient sensitivity, and specificity of clinically relevant thresholds for various levels of "caseness," and
- the utility for diagnostic formulation and treatment planning in clinical settings.

A further concern is that a research and implementation agenda organized around tracking mental/physiological systems over time could lead to stigmatization and discrimination of adolescents considered to be following "non-normative" trajectories. A clear imperative, then, is to identify those at risk of future mental health problems and to offer them preventative assistance without characterizing them as being "different" or "deviant." Table 3.2 summarizes arguments for and against the proposed framework.

Setting the Course for a Future Research Agenda

This initial description of a developmentally informed approach to understanding mental/physiological systems that are indicative of emerging psychopathology during adolescence spans from populations to enriched (vulnerable) groups and to clinical or other service settings. Far from being finalized, it is a conceptual framework to be iteratively refined over time: improved knowledge regarding mental/physiological systems at the population-level will inform clinical decision making, which in turn can be utilized to further develop knowledge regarding systems at both individual and population levels. The framework also aims to contribute explicitly to the identification and validation of clinic-pathologic cutoff points, which could assist in defining both clinical stages and determining where and what kinds of interventions are required between cutoff points. The ultimate goal is to derive earlier, more specific, and personalized treatments.

Critical questions for future research of this paradigm are as follows:

- What are the most relevant, fundamental mental/physiological systems that need to be charted to best understand mental health and ill-health as it develops during childhood, adolescence, and young adulthood—the time frame when the majority of major mental disorders start to emerge?
- What are the normative trajectories of these fundamental maturational systems underlying mental disorders during adolescence?

Table 3.2   Arguments in favor and against the proposed framework and its application**.**

Pros	Cons
• Alternative to binary diagnostic labels, which integrates knowledge regarding normative developmental trajectories, phenomenology, and clinical staging. In doing so, it arguably promotes a more comprehensive and holistic view of the person at the center of care	• Based on assumptions about core underlying systems related to mental illness and their developmental anchoring, not all of which might be associated with clinically relevant phenomena and not all of which may be proven true by further research into the proposed mental/physiological systems
• Promotes a multidimensional understanding of individuals and their contexts that has an additional temporal quality	• Risk of being too complex and unwieldy and therefore not clinically useful
• Encourages thinking in developmental terms, with measurement of dynamic, high-frequency mental and physiological systems that might over time be found to aggregate	• Although one might see the framework's multidimensional nature as a strength, others might see this as overly dimensional, including clinicians who are trained in/used to binary classification and decision making
• Prompts health system planners, clinicians, and researchers to think jointly about the intersection of development with clinical staging for the purpose of prevention and early intervention	• Potential for providing a false sense of security for clinicians, whereby asking a larger number of questions ends up superseding the overall perspective of the patient and their social, familial, and vocational spheres
• Has the potential to evolve into precision medicine that is individualized and thus more effective	• In identifying individual systems/components, whether mental or physiological, the framework may be perceived to be reductionist
• Is sensitive to early markers of risk for mental illness or inability to thrive and could thus prevent a trajectory from veering into mental illness.	• Risk of overdiagnosing abnormal development given the large variations in normative development

- What combinations of mental/physiological systems during adolescence lead to risk for persistent distress and impairments, and in which contexts?
- How can normative and non-normative trajectories in the identified fundamental mental/physiological systems best be measured?
- To what extent could current or evolving technologies measure the systems identified in a mobile, unobtrusive manner with relatively high-frequency sampling?
- To what extent do mental/physiological systems vary depending on sampling frame (e.g., across time windows, cultures)?

- What meaningful summary metrics have clinical face validity and utility?
- How would one define "caseness" within the proposed framework? To what extent does this vary across settings and for specific purposes?
- Are the analytic methods currently available to analyze such data (from intraindividual to vulnerable groups to youth populations) sufficient, or are further developments required?
- In individuals presenting for care, where are they in relation to their age, stage, and culturally normative trajectories, with regard to the mental/physiological systems identified?
- Do interventions that may improve mental/physiological systems lead to actual benefits in terms of reduced distress or functional impairment?
- What are the processes that best determine individual variability in impaired trajectories that would inform interventions (e.g., sex, genetics, trauma)?

Finally, it is critical to note that the success of our proposed approach and framework will not be measured by improvements in intermediate effects, such as population-level mental and physiological phenomena or systems. At its apex, the complex package of systems, methods, enrichment of vulnerable groups, clinical staging, and treatments that might be set in motion through this agenda would need to be seen through the lens of early intervention principles and implementation science. In other words, success down this path will only be realized through public campaigns to enhance mental health literacy, larger numbers of young people seeking low-threshold care voluntarily, substantial reductions in delays to care, improved delivery of stage-appropriate and developmentally sensitive interventions, reduced incidence of illness, and of course improved clinical and functional outcomes.