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Considerations Toward an Epigenetic and Common Pathways Theory of Mental Disorder

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Psychopathology emerges from the dynamic interplay of physiological and mental processes and ecological context. It can be seen as a failure of recursive, homeostatic processes to achieve adaptive re-equilibrium. This general statement can be actualized with consideration of polygenic liability, early exposures, and multiunit (multi-"level") analysis of the psychological action and the associated physiological and neural operations, all in the context of the developmental exposome. This article begins by identifying key principles and clarifying key terms necessary to mental disorder theory. It then ventures a sketch of a model that highlights epigenetic dynamics and proposes a *common pathways* hypothesis toward psychopathology. An epigenetic perspective elevates the importance of developmental context and adaptive systems, particularly in early life, while opening the door to new mechanistic discovery. The key proposal is that a finite number of homeostatic biological and psychological mechanisms are shared across most risky environments (and possibly many genetic liabilities) for psychopathology. Perturbation of these mediating mechanisms leads to development of psychopathology. A focus on dynamic changes in these homeostatic mechanisms across multiple units of analysis and time points can render the problem of explaining psychopathology tractable. Key questions include the mapping of recursive processes over time, at adequate density, as mental disorders unfold across development.

General Scientific Summary
Mental disorders develop in the midst of complex processes. A focus on causal mechanism can benefit from a focus on regulatory processes and on common pathways of effect across multiple risks and conditions.

Keywords: epigenetics, theory, common pathways, developmental psychopathology

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Static models of psychopathology are as a set of fixed entities are outdated. Instead, psychopathology must be understood dynamically. In that context, an epigenetic lens can open powerful avenues toward mechanistic discovery. That lens also harmonizes with the developmental reality. The onset of psychopathology disproportionately targets developing children, adolescents, and young adults (Homberg et al., 2016; Kessler et al., 2005). In turn, the dynamic, asynchronous process of human development is exquisitely sensitive to ecological context. Thus, like development itself, although some elements are static/stable, the entire syndrome is not; psychopathology emerges from dynamic cybernetic and transactional processes (Bronfenbrenner & Ceci, 1994; Cicchetti, 1984, 2016; Cicchetti & Natsuaki, 2014; Cicchetti & Toth, 2009; Hyman, 2018; Kendler, 2008; Miller, 1996; Thomas & Sharp, 2019).

Part 1 sets the stage. The first subsection, The Phenomena, provides a crucial context not only for this but for any theory in psychopathology, addressing the realities that characterize the phenomena of interest: its complexity, development-in-context, genotype-environment interplay, the importance of the exposome, and the nonignorable element of individual construal of experience. My intent is to orient the reader to the conceptual layers necessary to any theory of psychopathology. In the second subsection, Conceptual Clarifications, I define key multivalent concepts for present purposes. The third and final subsection of Part 1, Etiology and Epigenetics, provides context for the epigenetics element.

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Part 2 provides a theoretical sketch or schema of an epigenetic-centered model, then introduces and explains a multilevel, *common pathways* hypothesis that can render the complexity of the problem tractable.[1] I include example hypotheses and highlight epigenetic process, self-regulation, and the importance of integrating different units of analysis.[2]

Part 1: Setting the Conceptual Context

The Phenomena

The problem is compelling: Mental health disorders, addiction, and neurodevelopmental conditions collectively constitute the largest single source of health burden in the world in terms of years lived with disability (Whiteford et al., 2013). Any theory of mental disorder must account for the multiple known features of the phenomenon: complexity, development, environmental/social context, and self-regulating mental evaluations of experience.

Complexity

First, the conditions described in the *DSM* are not discrete diseases with discrete causes but are partially related, both phenotypically and biologically (Anttila et al., 2018; Borsboom et al., 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; de Jonge et al., 2018; Kotov et al., 2017; Plana-Ripoll et al., 2019; Radonjić et al., 2021). At least for descriptive purposes, they may be organized hierarchically (Achenbach, 2020; Kotov et al., 2017; Kotov et al., 2021), or alternatively, in a small-world network perspective (Borsboom et al., 2011). However, beyond stipulating the phenotypic and biological relatedness of the many conditions, my argument does not depend on a particular nosological architecture.

Yet, second, heterogeneity is also the rule. Even within putative disorders, etiological and phenotypic variability require characterization, to maximize mechanism discovery and clinical value. Indeed, as required by polygenic theory (Wray et al., 2018), even specific genetic etiology is heterogeneous, despite the partial genetic overlaps among conditions. Likewise, the clinical phenomena are protean: for any syndrome or dimension, features and expression can vary noticeably by age or social or incentive context.

Third, much psychopathology is on a continuum with normal function (Burns et al., 2019; Haslam et al., 2012; Hyman, 2010; Shankman et al., 2009; Waszczuk et al., 2020). However, properly describing its dimensional (or perhaps nonlinear) structure remains a methodological challenge (Borsboom et al., 2016). Further, the dimension model is incomplete, because some psychopathology reflects noncontinuous causality, such as early neural injury or rare gene mutation of strong effect.

Fourth, aside from such rare structural DNA variants or major teratogenic exposures, biological signals are weak: associations of individual genes or neural findings with clinical conditions are very small. Although mapping at the group level of biological and neural correlates remains important, and may be aided decisively by phenotype refinement (Nigg, Karalunas, et al., 2020) so as to support clinical care, the long search for definitive single biomarkers of individual disorders appears ill conceived for the vast majority (Harrington, 2019; Kapur et al., 2012; Miller, 1996). No isomorphism exists between the main population of psychopathology phenotypes and biology. This is not to devalue the role of the biological lens (see below), but to highlight the necessity of a multiunit perspective (Cicchetti, 2016).[3]

Development in Relation to Expectable and Expected Environment

Liability may be present before or at birth (Gustafsson et al., 2020; Neumann et al., 2020), but psychopathology itself is not—it emerges in stages, with recognizable homo- and heterotypic continuities. Some conditions emerge early in development (attention-deficit/hyperactivity disorder [ADHD], autism spectrum disorder, oppositional defiant disorder, learning disorders) and are seen as neurodevelopmental. Others have peak onset from the pubertal transition through the adolescent-young adult transition (mood disorders, psychoses, addictions, eating disorders; Martel, 2013)—although they may also have early neurodevelopmental roots (Corsi-Zuelli & Deakin, 2021; Eyles, 2021; Kloiber et al., 2020; Mansur et al., 2020; Schmidt & Mirnics, 2015). Intervention and prevention differ across developmental periods (preschool, adolescent transition, early adult transition; e.g., Nigg, Sibley, et al., 2020).

Development proceeds in the context of a species-wide *expectable environment*, or range of environments, within which normative programmed processes unfold. For example, humans "expect" speech from which they can learn language; they "expect" certain nutrients and are ready to utilize them. They do not expect extreme emotional neglect, or measurable levels of lead and organophosphate pesticides. The contemporary environment includes rare as well as *common* nonexpectable exposures (see Exposome section later).

Related to this, *developmental origins* theory posits that the fetus responds dynamically to physiological signals from the mother, which themselves are indices of her environment. The fetal physiological and epigenetic response constitutes *reprogramming* of development in anticipation of a *refined* expected postnatal environment. In this view, maladjustment occurs not only when the environment is outside of the species-general expectable environment, but also when the specific attempted predication and adaptation from the actual maternal cues is mismatched with the actual postnatal environment. For example, a baby "expecting" a violent environment (e.g., due to material emotional trauma) may develop with enhanced impulsivity and aggression but be born into a relatively stable and safe setting (e.g., the mother has relocated to a better setting or the child is adopted) for which those traits are

[1] Thomas and Sharp (2019) suggest that theory develops from *sketch*, to *schema*, to *testable model*. I propose a sketch that may be close to a schema. I bypass definitions of mental disorder, defining normal versus abnormal, and essentialism. See (McNally, 2011) and (Wakefield, 1992, 1999). The "illness" metaphor is fraught (Hudson, 1993) but may pertain for psychopathology as *complex* illness.

[2] With regard to distal causes, my argument is compatible with an evolutionary-adaptationist perspective (Ellis & Del Giudice, 2019) although not reducible to it. The focus herein is more proximal.

[3] The classic view in developmental psychopathology (paralleled in neuroscience) refers to *levels* of analysis, such as social, psychological, neural, and genetic. Recent thinking has moved away from this language (Thomas & Sharp, 2019). I use the term "units" to refer to these heretofore putative scales or levels of examination (see section on *Mechanism and reduction* later).

poorly suited.[4] Research on these early programming origins of psychopathology remains nascent, but promising data are emerging (Lester et al., 2018; Monk et al., 2019; Morgan et al., 2020; Ostlund et al., 2019). Developmental origins theory is amenable to a dynamic systems perspective (Kaliush et al., 2021) and to epigenetics (Conradt et al., 2018).

Critical developmental unknowns include (a) timing of exposure; (b) when and whether reprogramming changes *risk* versus *responsivity* to environment (Belsky & Pluess, 2009; Belsky et al., 2019); and (c) when and how the postnatal environment, in particular the infant–caregiver relationship in early life, moderates prenatal programming.

Genotype–Environment Interplay

That genotype is important in psychopathology is beyond dispute—but it generally confers *liability*, not psychopathology per se. While recognizing the role of rare gene variants of large effect in some cases, the field's focus is now on polygenic liability involving many genes of small effect, and on the form of genotype-environment interplay.

Genotype-environment interaction (GxE) can mean a specific physiological interplay of genotype and environment (e.g., genotypic regulation of how rapidly nutrients or toxicants are metabolized). In the polygenic context it means statistical dependency rather than biological process. In the decomposition of twin data, heritability can be inflated by GxE involving shared environments (Purcell, 2002). These shared-within-family effects may well involve population-wide exposures. Thus, to the extent GxE is involved, the typically robust heritability of major psychiatric conditions elevates the importance of *common* exposures, especially those that are outside the evolutionary expectable range. Important examples in contemporary societies known to be relevant to psychopathology include ubiquitous chemical toxicants and over- and undernutrition, as documented in Table S1. Necessary are contextually-informed rather than context-free biomarker, mechanism, and genetic studies. When GxE is mechanistic, one mechanism is epigenetic, that is regulation of gene expression (see Epigenetics section below).

Genotype-environment correlation (rGE) has two meanings. One is that environment can mediate genetic effects (called *genetic nurturance)* (Armstrong-Carter et al., 2020; Kong et al., 2018). For example, postnatal caregiving can transmit genetic effects even when alleles are not passed on (Armstrong-Carter et al., 2020; Kong et al., 2018), potentially reversing or amplifying genetic liability (Garg et al., 2018; Ribas-Fitó et al., 2003). In the offspring this is a purely environmental effect. The second meaning occurs when the environment is correlated with the transmitted alleles, that is, confounded with genotype. This correlation can be passive (parents pass on genes for high IQ and also read more to their child), evocative (child evokes certain response related to child personality), or active (child chooses certain activities, influenced by personality, itself genetically influenced). These effects may be more notable for proximal (e.g., caregiving) than distal (e.g., air pollution) exposures. Crucially, the unknown frequency, timing, and magnitude of rGE effects in psychopathology leaves unresolved the mechanism behind many genetic and exposure findings as well as some GxE findings.

Exposome

The preceding highlights the importance of the *exposome*—the diversity of exposures to "synthetic chemicals, dietary constituents, psychosocial stressors, and physical factors" (Vermeulen et al., 2020, p. 392; Wild, 2005) that influence human development. Examples of developmental variation in response to both social context (e.g., rearing environment) *and* genotype/biology are legion (Fenesy et al., 2019; Gottlieb, 2007; Henry et al., 2018; Hinshaw & Arnold, 2015; Meaney, 2010; O'Donnell & Meaney, 2020; Trentacosta et al., 2019; Tung & Lee, 2017). The importance of the exposome is underscored by the burgeoning literatures on social determinants of health (Alegría et al., 2018) and on cultural variation in development (Causadias & Cicchetti, 2018). To realize the potential in the industrious mapping of the genome and the neural connectome, then, the field also needs a proper account of the *exposome* (Rager et al., 2020; Vermeulen et al., 2020). Again, see Table S1 for selected examples.

Past efforts to establish a multiunit *developmental* account of the exposome for psychological development are foundational (Bronfenbrenner, 1977, 1979; Bronfenbrenner & Ceci, 1994; Fearon, 2018; Wachs, 1999). The work of Bronfenbrenner (1979) and its subsequent elaborations laid a crucial framework. Marking progress in the field, Wachs et al. (2014) provided a detailed overview of the importance of early environment, allostatic load, and different sensitive periods for development (e.g., early life may be salient for neural development, longer periods salient for psychosocial and cognitive development). They also gave examples of early biological (e.g., nutrients) and psychosocial influences. In the past decade, fruits of this line of work have enabled developmental scientists to document many early exposures and interventions that impair or facilitate development, and to guide prevention interventions (Britto et al., 2017; Britto & Pérez-Escamilla, 2013; Wachs et al., 2014). That progress dovetails with more recent work across a range of health outcomes applying newer computational tools (e.g., network analysis) to organize understanding of the exposome and associated, overlapping physiological responses (Vermeulen et al., 2020).

Yet the challenges remain daunting. Whereas some exposures are causal, for most substantial work remains to evaluate causal effects versus those that may be explained by genotype-environment correlation or other confound (Nigg et al., 2016; Riglin et al., 2020; Thapar & Rice, 2020). Further, environmental continually *moderates* development (e.g., school environment, neighborhoods, peer relations, and parenting style; Wachs et al., 2014). Here too, the degree of *causal* influence remains poorly described. Finally, effect sizes and success rates for prevention interventions remain unsatisfying. Additional theoretical elaboration may open the door to superior mechanistic intervention and prevention, motivating both this essay and others in this section.

The field thus faces the extraordinary complexity of environmental inputs and their dynamic interplay with genotype and one another over time. High-level taxonomies of exposure (Wachs, 1999) are necessary, yet bely the deep granularity that a full accounting would require. For example, potentially hundreds of neuro-active chemicals are in commercial use and found in children's environments (Grandjean & Landrigan, 2014); only a handful have undergone serious scientific study for effects on child brain development. Studying all of them and interactions among

[4] In human research, pre- and postnatal risk environments often display some continuity, e.g., psychosocial adversity. Even so, fetal adaptation may be insufficient to what the child later encounters.

them and with genetic risk, diet, stress, and other factors is prohibitive. That foreshadows my subsequent emphasis on hypothesized common mechanistic pathways.

Mental Appraisal and Evaluation of Experience

It is not just the "objective" exposome that matters. How people interpret and *evaluate* their situation is also important. News headlines alone testify to the central role in psychopathology of existential issues (meaning, value) and mental evaluations. For example, in some demographic groups in the United States, life expectancy has declined due to opioid addiction, suicide, and poor health. These early deaths have been referred to as deaths of despair (Case & Deaton, 2020). Despair is existential. In another example, excessive expectations on children to achieve have been suggested as one factor in rising rates of ADHD identification in western societies (Scheffler & Hinshaw, 2014).

Mental processes like appraisal or evaluation, both automatized and deliberate, play an important role in depression (Hammen, 2018), anxiety (LeDoux & Pine, 2016; Newman et al., 2013), aggression (Allen et al., 2018; Benjamin et al., 2018), and drug use and addiction (Neighbors et al., 2019; Verdejo-Garcia et al., 2019). Likewise, mental construal is associated with successful treatment or recovery from depression or anxiety, as well as associated remodeling of brain function or even structure (Lissemore et al., 2018; Matsuda et al., 2019; Porto et al., 2009; Yoshino et al., 2018). The power of placebo or social bonds to enhance health is well-known (Ysseldyk et al., 2018).

In short, people ascribe meaning to their experience using narrative, symbol, schema, appraisal, or evaluation, and goal-referents. Doing so is part of self-regulation (below). Such appraisals support adaptive stability, adjusting cognition, emotion, and behavior in ways that (when successful) improve resilience (overcoming challenge) and overall adaptation (Yao & Hsieh, 2019; also see Table S2). Any account of mental disorder must address psychological self-regulation including mental evaluations (García-Mieres et al., 2019; Izard, 1993; Rachman, 2016; Salsman et al., 2020; Trope & Liberman, 2003).

Admittedly and crucially, the mental level is also idiographic and subjective. It stretches from cognitive evaluations (emphasized herein) to the human capacity for self-transcendence (art, music, religious ritual, symbol, experience) and the unassailable authority of subjective knowledge (knowing how I feel, who I love). The subjective experience is not directly accessible to scientific observation. Yet it cannot be simply dispensed with or theorized away. Rather, the interior aspect of mental disorder requires consideration in a scientific model to the extent possible. Its inclusion need not prevent a tractable theory (for discussion, see Schaffner, 2020).

Summary

A theory of mental illness has to address four domains: (a) systems *biology* (pathophysiology via neuroscience, genetics, and physiology); (b) the *exposome*, including the proximal social-relational environment, nutrition, and wider social and toxicant exposures; (c) *developmental timing and process* and *behavioral* analysis (early origins and programming, behavioral learning history, developmental trajectory); and (d) *mental/psychological* processes (attributions, evaluations, beliefs, meanings, and subjective phenomenology; herein I emphasize *evaluations*). I next clarify other key concepts before offering a theory sketch. To help navigate the next section, Table S2 provides a glossary of relevant, multivalent terms as I use them.

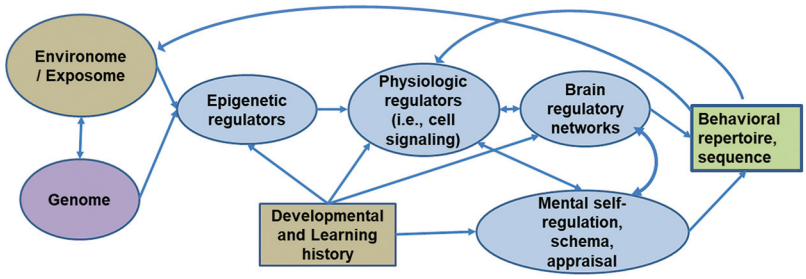
Conceptual Clarifications and Elements

Dynamic System

Full articulation of a specific dynamic systems model is beyond the scope of this article (see Kalisch et al., 2019; Nelson et al., 2017; Tay & Lim, 2020). Figure 1 points to a simplified model to describe, at different units of analysis, an epigenetic, common pathways framework of psychopathology. Dynamic system models

Figure 1

Schematic for a Mechanistic-Cybernetic Model of Psychopathology



Note. Each domain shown can be decomposed into component parts and relations (e.g., interacting elements of exposome, physiology, neural organization, or psychological self-regulation). The homeostatic system fails to adequately adapt to inputs from one or more of the perturbations (tan). Individual adaptation is supported or degraded by alterations in extrinsic (brown) risks and supports or intrinsic (blue) processes. Genetics can be a support or a risk so is in violet and is mediated and moderated as shown. Two-headed straight arrow = bidirectional influence; bidirectional curved arrow = correlated but not causal association (implementation); one-directional arrows = directional influences. See the online article for the color version of this figure.

are familiar in systems biology, neuroscience, clinical psychology, and developmental psychopathology (Cicchetti, 1984; Granic et al., 2016; Mascolo et al., 2016). Key axioms, drawing from developmental psychopathology and Craver's (2005, 2007) neuroscience-based view, include:

(a) Lower (smaller) units constrain but do not explain higher (larger or more complex) levels or units of analysis.

(b) *Emergent* properties are unique to the system as a whole and not reducible to its elements (see Table S2, for notation on issues with the idea of *emergence*). Thus, mental activity and behavior and their dysfunctions are not static elements of a person, but emerge from internal processes interacting with one another and with the functional context (Miller & Bartholomew, 2020). This view rejects *eliminative reductionism* (Table S2), which posits that smaller units of analysis will explain, and thus render superfluous, larger units. Craver (2005, 2007) points out that whereas eliminative reductionism (not his term) was highly productive in physics, chemistry, and molecular biology, it fails with dynamic systems (such as brain functioning or complex human behavior). At the same time, as noted in point (a), smaller units do still constrain the possibilities for larger units.

(c) Systems phenomena cannot be fully explained without including their own unit of analysis (for psychopathology, that unit is mental or psychological activity).

(d) The function of multiunit system components (whether ideations, emotions, behaviors, neurons, or genes) can be different in, and thus cannot be understood apart from, a particular *functional* context (Bertolaso & Ratti, 2018). The system is nondeterminative, as well, due to participation of stochastic processes (e.g., in neurodevelopment; White, 2019). In biology, "Cell-to-cell variability is an inherent and emergent property of populations of cells . . . no two genetically identical cells behave and look identical" (Xavier da Silveira dos Santos & Liberali, 2019, pp. 1495 & 1499). In relation to psychopathology, see (Miller, 1996; Miller & Bartholomew, 2020).

(e) Mutual regulation occurs among system components (component coaction). For example, top-down and bottom up processes mutually regulate one another.

(f) Thus, *mechanism* here means causal explanation (Nicholson, 2012; Thomas & Sharp, 2019), not a machine-like linear process (see Table S2).

(g) Nonlinear change that includes phase transitions (organizational state changes) is incorporated across development.

(h) The system is self-organizing, and develops from lesser to greater complexity through cybernetic processes (feedback loops). The cybernetic principle is central to the present proposal. I highlight the importance of recursive adaptive processes as the system seeks to maintain homeostasis (equilibrium), thus providing both a ground of stability and canalization as well as dynamic development and change.

The idea of psychopathology emerging in the context of dynamic system properties is not new (Granic, 2005; Lichtwarck-Aschoff et al., 2009). However, empirical evidence that psychopathology actually behaves like a dynamic system has accrued only recently (Kendler et al., 2011; Kuranova et al., 2020; Lichtwarck-Aschoff et al., 2009; Nelson et al., 2017; Schiepek et al., 2016; Schiepek et al., 2014; Wichers et al., 2015). With those data in support, I stipulate that psychopathology is not a static entity responding to linear, unidirectional inputs. Rather it emerges from dynamic system interplay (Miller & Bartholomew, 2020). It is best understood at multiple units of analysis, with recursive dynamics over time (including processes of change and stabilizing/canalizing processes), and in relation to the ecological context.

Stressor and Perturbation

The exposome provides support and scaffolding for development, but also introduces stress, challenge, or perturbation. In theories of early development and in the concept of allostasis and allostatic load, "stressor" is broadly defined as any pressure strong enough to activate an adaptive compensation (Guidi et al., 2021; Monk et al., 2019; Palego et al., 2021; Wachs et al., 2014). To avoid confusion with psychological stress alone, I use p*erturbation* to reference the panoply of chemical and social challenges to development from the exposome that are strong enough to require an adaptive psychobiological response (see Table S2). Perturbation and adaptation are universal and continuous, rather than isolated to a subset of individuals in emotional distress. When the process diverts into maladaptation, it is psychopathology.

Self-Regulation

From a systems perspective, self-regulation means the adjustment of affect, thought, or action to maintain adaptation (Nigg, 2017; Table S2). It draws upon both extrinsic factors, such as social supports, and intrinsic factors, such as physiological responses and cognitive evaluations, operating in a mutually-regulating fashion. It depends on both (a) automatized bottom-up processes (typically anchored in physiological or subcortical-to-cortical response to perturbation) and (b) deliberate, top-down, goal-directed processes (explicit mental responses such as attribution, evaluation, planning, and problem solving, related to frontal cortical to subcortical neural projections). Top-down aspects of self-regulation (also referred to as *self-control*, Table S2) involve attentional control and executive function (Nigg, 2017).

I propose self-regulation as a common or shared *psychological* mechanism across most of psychopathology. For example, via either automatic or cognitive routes, anxiety and mood disorders are related to failure to regulate affect, ADHD to dysregulation of impulse, and schizophrenia to dysregulation of motivation. As a result, it is not surprising that partially overlapping neural circuitry also is involved in these disparate conditions (Table S3).

Regulatory mental and physiological processes (homeostatic/allostatic) are ubiquitous yet finite. Importantly, they can be mapped conceptually (McRae & Gross, 2020; Nigg, 2017; Sheppes et al., 2015), and computationally (Petzschner et al., 2021). Thus, a focus on self-regulation as a shared psychological or psychophysiological mechanism in psychopathology opens the door to modeling change as well as stability, creates a finite focus for mechanism study across

a range of environmental perturbations and behavioral outcomes, and is amendable to computational study.

Etiology and Behavioral Epigenetics

Epigenetics: Overview

A common biological pathway linking genetic and environmental influences is *gene regulation*. Sustained regulation of gene expression can result from *epigenetic* changes—heritable (across cell division, not necessarily human generations) changes to the genome that do not change the DNA sequence. Epigenetic changes can be caused by genes, by stochastic process, and crucially, by exposures. In the last case, they are a mechanism for implementation of GxE and a liability-exposure model. Indeed, at highly variable genetic sites, GxE or G + E appears to best explain many DNA methylation changes (Czamara et al., 2019; Czamara et al., 2021). I use epigenetics to mean *biological mechanisms that modulate or at least tag gene expression changes* (transcription modification; Table S2 provides further context).

Behavioral epigenetics (Moore, 2015) has emerged in the past decade following more established lines of work in cellular and tissue epigenetics. Interest in epigenetic influence on complex behavior was activated by fundamental discoveries in the 1970s (in animals) that epigenetic changes could be related to exposures and preserved over time, yet also reversed. It is now recognized that epigenetic effects, including in response to environments, play a major role in brain development (M. Li et al., 2018) and that genetic and exposome influences on behavior and psychopathology are in part mediated by altered gene expression (Barker et al., 2018; Smigielski et al., 2020; Wheater et al., 2020). The elucidation of a biological mechanism by which experience modifies gene action thus remains integrative and evocative for the field.

Epigenetics: Challenges and Cautions

Epigenetics are too often assumed, even by psychologists, to reflect mainly environmental input. While this assumption does have some support for psychopathology as noted above, genetic and stochastic processes also contribute (White, 2019). For example, newer studies that include genotype (MWAS+GWAS, Table S2) have indicated that peripheral DNA methylation in developmental psychopathologies like ADHD are also related to genes (Meijer et al., 2020; Mooney et al., 2020).

As with other biological signals, an epigenetic hypothesis faces the challenge of small associations for individual probes with psychopathology, at least in peripheral tissue. However, aggregated scores (e.g., MWAS principal components, region scores, or *polyepigenetic* scores targeting an exposure) may be more informative (O'Donnell & Meaney, 2020; Pries et al., 2017; Stevenson et al., 2020; Suarez et al., 2020). Note that like polygenic risk scores, they are not particularly informative about one particular mechanisms, but instead summarize various regulatory influences.

A further limitation is that the epigenetic demonstrations relevant to psychopathology and the exposome emphasized maternal emotional stress or childhood maltreatment (O'Donnell & Meaney, 2020). The logic in that fascinating work needs to be extended to inform a wider range of exposures and outcomes (Table S1 and S3). Further, most basic knowledge about environmentally triggered epigenetic remodeling influences on behavior is from animal and insect studies. These are powerful due to their experimental control, but generalizing to humans is problematic. The human environment does not resemble the environment of a laboratory animal, and human capacity to adapt to a wide range of environments substantially exceeds that of other animals.

Finally, studies in human behavior remain difficult for methodological reasons. DNA methylation varies across development (Mulder et al., 2021), with potential timing-specific effects (Cecil et al., 2016). Moreover, epigenetic signals vary by tissue and cell type. It is difficult to generalize from peripheral tissue to the brain (Bakulski et al., 2016; Conradt et al., 2018; Lappalainen & Greally, 2017; Mooney et al., 2020; Oldenburg et al., 2020). Yet the living human brain is relatively inaccessible, so scientists seeking systemic effects rely mainly on indirect methods, each with important limitations (postmortem brains, animal models, peripheral tissue assays).

Epigenetics: Prospects and Importance

The challenges are real. Yet prospects for epigenetic insight into psychopathology are sufficiently compelling as to commend integration in a dynamic model. The critical element is that epigenetic remodeling is dynamically responsive to the environment; it can exemplify experiential programming of gene expression (Meaney, 2010; O'Donnell & Meaney, 2020). As Table S3 documents, epigenetic involvement has begun to be identified in a range of psychopathologies. Likewise, several psychopathology-relevant exposures have epigenetic sequelae (albeit, often studied only in nonhuman animals).

Epigenetics elevates the importance of the exposome in development and anchors it back to biology. Epigenetic markers can index relevant exposures (in the context of genotype) as well as link to psychopathology (Richetto & Meyer, 2020; again, see Table S3). In theory, common exposures in early development can provoke systemic epigenetic response (e.g., DNA methylation of an immunological gene network). Such a response might then be common to many psychopathologies, and detected in peripheral tissue later, even though the *mechanistic* effect was in the central nervous system. It would thus serve as a *biomarker* of exposure and potentially of a mechanism. Such biomarker identification is promising for prior exposures (Noor et al., 2019; Richetto & Meyer, 2020), even in peripheral tissue (Aghagoli et al., 2019). It could even be an *exposome biomarker* for a causal (mechanistic) effect if system wide effects occurred and were known. More difficult but promising is that algorithmic epigenetic scores can be *phenotype biomarkers* (Stevenson et al., 2020; Suarez et al., 2020). In sharp contrast to these near term prospects, finding *mechanisms* of epigenetic influence on complex phenotypes is a more distal possibility.[5]

Part 2: Sketch of the Theory and Hypotheses

Theory Elements and Sketch: Overview and Recap of Perspective

The preceding discussion of exposome and mechanisms raises the level of complexity of to a potentially intractable degree. This state of affairs bedevils any nonsimplistic theory of psychopathology. However, if we stipulate that psychopathology emerges from

[5] Studies using bead-based arrays have provided tantalizing clues on both fronts (Smigielski et al., 2020). However, whole methylome and other sequencing may be necessary to describe mechanisms.

dynamic adaptation attempts or their failure within a dynamic system, it becomes possible to propose common mechanisms cutting across psychopathology. Doing so makes the problem tractable. Here then is a sketch of a theory following on that premise.

Process

Human development is dynamic and nonlinear, unfolding in an emergent manner via greater and greater complexity, differentiation, and organization from conception forward, during which new properties emerge as complexity increases. Dynamically, a partially definable genetic architecture (Cross-Disorder group of the Psychiatric Genomics Consortium, 2019) sets a liability for what we call psychopathology later. That genetic structure immediately encounters epigenetic changes in the germline from exposures to the parents, preconception, followed by the prenatal exposome. Then, throughout development, exposures continually serve to either stabilize or destabilize the dynamic processes of adaptation. Continually, the child and then the adult (the dynamic person-biology system), adapts more or less successfully in biological, physiological, and as the child matures, psychological (mental) spheres. This adaptive response includes alterations in neural development, mediated by chemical signaling (from mother-via-placenta-to fetus), and fetal and subsequent epigenetic change. Some of the epigenetic programming may be systemic and thus detectable as a biomarker in peripheral tissue later.

The adaptive process is recursive and continuous (i.e., cybernetic). Most perturbation is subtle enough that adaptation is easily attained or even strengthened. However, when the perturbation exceeds the capabilities of the system to adapt, then epigenetic, neural, and mental processes modify recursively in an attempt at adaptation that proves costly or becomes rigid or self-reinforcing, such that the individual is unable to adapt further. This sets the stage for or emerges as psychopathology, either relatively early (ADHD) or somewhat later and gradually (schizophrenia), perhaps only after further perturbation. Mental disorder thus emerges from a perturbation of a dynamic system that is unable to regain an adaptive equilibrium (or homeostasis) and instead canalizes into a maladaptive or unstable developmental course, culminating in frank psychopathology.

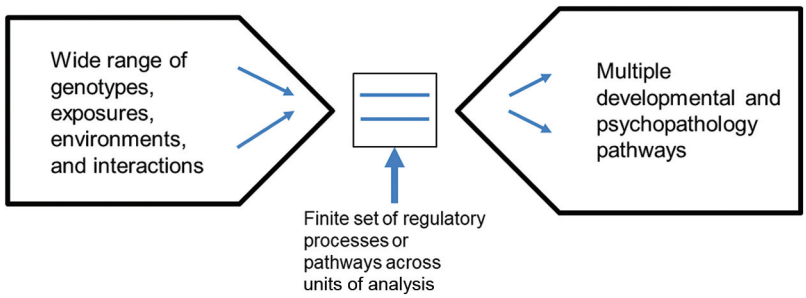
If genetic liability is high, then the perturbation may seem relatively minor (e.g., background toxicant exposure or suboptimal diet, maternal distress, losses that happen to everyone in life, temporary experimentation with drugs) such that perhaps most individuals would adapt without psychopathology. But an ill-timed or strong perturbation (frank physical abuse, moderately elevated lead exposure, perinatal complications, extreme maternal trauma, an unusual series of losses, or a rare genetic mutation of large effect) may disrupt adaptation and lead to psychopathology even when liability is only moderate. Figure 1 schematizes the model to this point.

Common Pathway Hypothesis

A major obstacle to explaining psychopathology is the vastness of etiological inputs to the extraordinarily complex recursive processes that govern human behavior and cognition and maintain functional adaptation. To address this, *a common pathways hypothesis* proposes that a circumscribed set of characteristic mechanisms can be identified within the relevant units of analysis, all in the regulatory domain. I hypothesize that the universe of mechanistic human self-regulatory processes is smaller than the universe of inputs or the complex combinations of behavioral and mental outputs. Figure 2 illustrates this logic. If correct, a finite and tractable set of homeostatic processes would emerge as shared across a wide range of exposures and psychopathologies, across multiple units of analysis: genetically (e.g., neurodevelopmental pathways), biologically (e.g., chemical signaling), neurally (e.g., control systems), and psychologically (e.g., self-regulation processes and mental evaluations; Table S3).

At the same time, the "funnel" content in Figure 2 is not singular (I do not propose to boil mental disorder down to a brain system, or a physiological system, or a mental process). It requires mechanistic description across multiple units, each of which can then become avenues for potential intervention. The most appropriate unit or explanatory perspective can vary across conditions or individuals, yet can be constrained. Key nodes of causal action may occur biologically (placental modification in response to infection, leading to alteration, or perhaps cost, in neural development); or cognitively (rumination in depression, sustained attribution-driven arousal in aggression or anxiety, body-perception in anorexia) and contribute to unfolding and sustained behavioral and biological change.

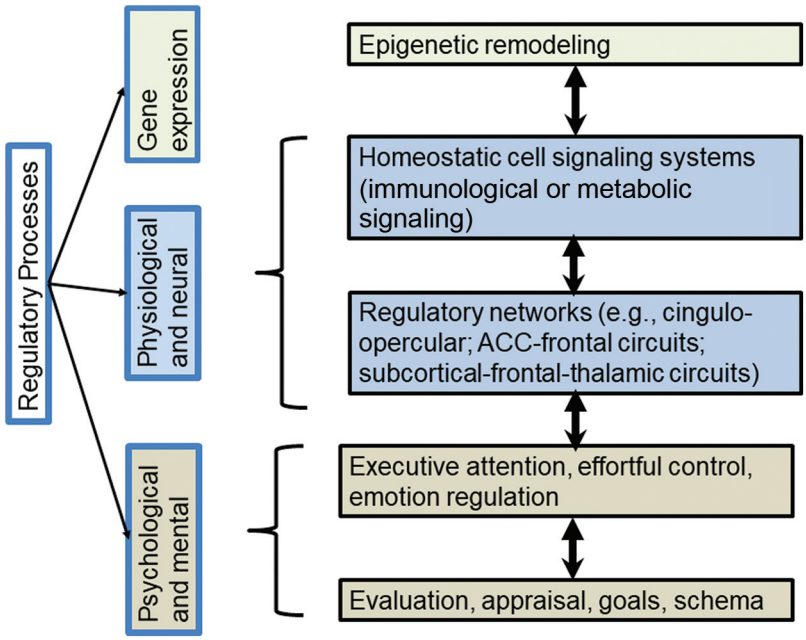
Figure 2
Funnel Visualization



Note. The available exposures, genotypes, and biochemical pathways potentially involved include the entire human biome and beyond (social context). However, it is hypothesized here that a small set of common regulatory or homeostatic mechanisms at the psychological and biological levels of analysis will participate in a disproportionate share of perturbations related to psychopathology. See the online article for the color version of this figure.

Figure 3

Proposed Contents of Common Pathway or Funnel Elements, Represented at Different Levels of Size, Abstraction, or Analysis



Note. Mechanisms to be described at each level are hypothesized to be finite and fewer than the extrinsic inputs or behavioral and psychological outputs involved in psychopathology. Within level increasing granularity is used to explain mechanism. See the online article for the color version of this figure.

As an analogy, consider the myriad bacteria and viruses that can cause illness—yet a single (multiunit) immune system responds to all of them. The response *product* (e.g., antibodies) is specific, but the *response process* is shared. Similarly, the cortical networks involved in higher order analytic thought and planning are activated for an infinite range of complex problems or goal conflicts. The *content solution* a person thinks of is particular, but the *supporting process* is shared across difficult problems. From an evolutionary perspective, this efficiency of process is the only way for an organism to meet a potentially unlimited array of challenges—to have an all-purpose regulatory response that can adapt itself to an unknown array of different challenges.

To flesh out this idea, Figure 3 illustrates four critical levels or units of analysis and offers exemplar hypotheses for common mechanisms at each level. These can be considered as example working hypotheses. Space limitations preclude their critical evaluation here but Table S3 provides selective empirical support for their reasonableness. In network terminology, the task is to differentiate (a) the most important spatial nodes (unit of analysis), and (b) the most sensitive temporal nodes (third trimester, pubertal transition, other; Jones et al., 2019).

Challenges and Considerations

I have noted that the most relevant level of analysis for a given subset of psychopathology may be at the mental/psychological level in some instances, but the biological or genetic level in others. This raises two important considerations.

First, I reiterate that although it may seem that the emphasis on environmental perturbation restricts this proposal to trauma or stress-related disorders like depression, anxiety, or posttraumatic stress disorder (PTSD), I propose that perturbations outside the evolutionary expected environment are common (see Exposome section).[6] These may represent nonshared environment in twin studies and contribute to heritability estimates if they are involved in GxE. I hypothesize that they in fact provoke epigenetic change and can lead to reorganization or, in dynamic systems language, *a phase change* toward atypical development. Because development is sequential and cumulative, with later skills relying on earlier ones to be in place, early negative[7] perturbations can lead to psychopathology at a later point (schizophrenia, bipolar disorder).

A second potential misunderstanding of my argument is that difficulties in adaptation may seem reminiscent of difficulties in coping, and most readily applicable to conditions like ADHD, oppositional defiant disorder, anxiety, or depression. They may seem too weak an explanation for the dramatic breakdowns in perception, motivation, and circadian processes in schizophrenia, bipolar disorder, or severe depression. I reemphasize that adaptation includes physiological and epigenetic change, not only psychological coping. For example,

[6] Beyond the scope of this article is whether they were just as common in ancient times, when many psychopathologies were already known and have only become a little more common.

[7] Of course, positive exposures also occur that enhance resilience, such as extra breastfeeding or exceptional parenting, which are side-stepped here in the interest of length limits.

schizophrenia likely has roots in early neurodevelopment, perhaps involving neuro-inflammatory inputs (Corsi-Zuelli & Deakin, 2021; Eyles, 2021; Schmidt & Mirnics, 2015). A similar story may emerge for bipolar disorder, perhaps involving metabolic pathways rather than inflammatory signaling systems (Kloiber et al., 2020; Mansur et al., 2020). These possibilities fit the current theory sketch.

Summary

A central hypothesis *is that multiple conditions will share specifiable biological, neural, and psychological mechanisms* (Figure 2, Figure 3). The corollary hypothesis is that these will be involved in maintaining homeostasis (regulatory). Thus, recursive processes are involved in change and can be mapped dynamically across time. If this hypothesis is correct, substantial explanatory power will accrue through a finite set of routes.

Hypotheses

Research Design Implications

In this section, I present hypotheses in schematic form. However, these come in the context of research design considerations. Many design recommendations from dynamic systems theorists are infeasible (e.g., requiring very dense time series data, which would be cost prohibitive for many multiunit studies). However, I note the following principles of design that follow from the present perspective:

(a) Emphasis on change over time (whether on very short time scales, as in dynamic regulation of heart rate or synchronization of neural networks), medium scales (e.g., changes across menstrual cycles), or long scales (development over several years).

(b) Emphasis on cybernetic processes as can be represented in multiple ways in graphical and other tools, such as network modeling (Jones et al., 2019; McNally, 2011).

(c) Designs that place biomarkers in ecological and interpersonal/psychosocial context, and environmental studies in genetic and physiological context and consider their interplay.

(d) Dynamic systems models offer a suite of graphical analysis tools (e.g., state-space grids) that may be helpful when sufficient data are available, as noted by Kaliush et al. (2021). For further design suggestions related to dynamic systems in developmental psychopathology, see Granic et al. (2016).

What follows extends from Figure 3 and is given partial support in Table S3. The hypotheses discussed in this section are also summarized in Table 1 for reference. Tests of each hypothesis would involve confirming their shared involvement in extended types of psychopathology and across extended ranges of exposome pressures and determining whether effect sizes are sufficient to be helpful in explanation. Their tests involve confirming or rejecting the relevance of the proposed recursive effects in onset and course of disorder.

Epigenetic-Genetic Unit of Analysis

The smallest level is gene regulation. The theme is that DNA structure may set liability but the operative mechanism is regulation of gene expression (for an interesting perspective here see Turkheimer et al., 2014). Gene expression is genetically and epigenetically regulated. Epigenetic regulation serves a homeostatic function and should show dynamic associations with onset and course over time. Table 1 provides the very simple epigenetic hypotheses that follow here if the model is correct. The ideas in Table 1 have initial support, albeit mostly in studies of nonhuman animals (see Table S3). For research and clinical applicability, a dynamic model perspective would ask about change over time and recursive effects relative to risk and adaptation. For example, it would be useful to discover when and to what extent epigenetic remodeling follows versus precedes behavioral change after exposures. The *hypothesis* is that epigenetic alteration (or else gene expression itself) will show dynamic directional effects on behavior or on physiological or neural correlates of behavior, in a recursive manner (this would be refuted if directional change in epigenetic score or finding was not mirrored by change in the target behavioral outcome; though again, small effect sizes are still expected). If supported, then composite scores reflecting system-wide activity could function in clinical algorithms or in research models (Stevenson et al., 2020).

The Physiological Unit of Analysis

Systems biology identifies tens of thousands of potentially relevant molecules, proteins, and enzymes. However, it can be hypothesized that chemical signals critical to maintaining homeostasis are crucial (Dunn et al., 2020). A salient example is immunological signalers such as cytokines and chemokines (Dunn et al., 2020; Izvolskaia et al., 2020; Oppenheim, 2018). Table S3 illustrates the potential widespread involvement of immunological signaling molecules as common pathways in psychopathology. Of course, these interact in complex ways with related systems such as the microbiome, the aforementioned epigenetic signals, mitochondrial alterations, and brain glial cells, among other linkages. I hypothesize that, at the physiological level, this family or another like it will account for meaningful variance in early development and subsequently in relation to multiple psychopathologies (Na et al., 2014). Other key ligands include hormones regulating response to stress and energy balance. Clearly, the interplay of these examples with oxidative stress, HPA axis, and other systems invites a more extensive, yet still finite, mapping.

Specific hypotheses are again listed in Table 1. In those hypotheses, I use immunological/inflammatory signaling as the primary common pathway; this is a stand in for the clumsier statement that one or more common intercellular signaling systems should emerge as commonly affected across multiple kinds of exposures and psychopathologies. It may be that the particular signaling system affected varies across psychopathologies (e.g., immunological, HPA, metabolic). In this example, immunological functioning interacts closely with the microbiome (Tilg et al., 2020), so an associated hypothesis is included in Table 1. Dynamically, these hypotheses would expand to enable assessment of component change in relation to other units (e.g., neural reorganization, epigenetic remodeling, immunological signaling units).

The Neural Unit of Analysis

I do not attempt to propose a new neural framework for regulatory functioning or homeostatic maintenance of mental life. However, recall from early in the article that while it is possible to conceive at least heuristically of disorder-specific neural networks (for one attempt, see Kandel, 2018), recent neuroimaging data strongly qualify such distinctions (T. Li et al., 2020). Instead, overlap and nonspecificity seem to

Table 1
Example Hypotheses at Four Scales, Levels, or Units of Analysis

Analysis	Hypothesis
Genetic and epigenetic	Epigenetic measures (e.g., DNA methylation profiles, algorithms, or principal components) will be detectable in relation to exposures that are associated with psychopathology (Smigielski et al., 2020). They can introduce both stable markings of exposure (e.g., DNA methylation scores of lifetime smoking or in utero smoking exposure) and at the same time change dynamically in response to exposure over time, in which case change will in turn be associated with behavior or exposure change in recursive pattern until stability is reached.
	Epigenetic signals associated with a common adaptive system such as immunological function will be identified across multiple psychopathologies, as recently seen for schizophrenia (Smigielski et al., 2020) and ADHD (Neumann et al., 2020). However, these signals at the specific level will include both general (most psychopathologies) and specific (to particular kinds of psychopathology) signals.
	Epigenetic algorithms that index exposure will map to exposures related to psychopathology (Richetto & Meyer, 2020) using peripheral tissue measures and ultimately be verified in relation to neurodevelopment, indexing a biomarker of system-wide compensatory response. Similar approaches can be used to index treatment response or responsivity (Gardea-Resendez et al., 2020; Goud Alladi et al., 2018). For example, it will be possible to create epigenetic profiles related to stress, inflammatory activity, smoking, alcohol exposure, or other exposures (Stevenson et al., 2020) that will be combinable to map a risk or exposome profile for a given child and then related to brain or cognitive development.
	Change over time in epigenetic scores (using summary scores for systems) will recursively interact with physiological, cognitive, or behavioral change, thus predicting individual differences related to psychopathology.
Physiological/cellular	Higher systemic inflammation /immune response (or alternative signaling response system) will be seen in women whose offspring go on to develop psychopathology.
	The same common signals seen in women whose offspring develop psychopathology will also be seen elevated in individuals with psychopathology (Goldsmith & Rapaport, 2020).
	Anti-inflammatory intervention in early life will mitigate impacts of multiple known risk factors (e.g., dietary, metabolic, toxicant) for multiple conditions (Thompson et al., 2018).
	Such intervention may also reduce psychopathology symptoms across multiple disorders (Fond et al., 2020).
	Microbiome signals (perhaps related to dietary response; Bordeleau et al., 2020) will emerge as an influence in multiple psychopathologies (Tilg et al., 2020).
	Dynamic change in cell signaling summary scores or targeted mechanistic measures will interact with epigenetic or neural change in dynamic, recursive fashion. Individual variation in change of the dynamic direction or set point will relate to psychopathology risk or severity.
Neural (multiple levels exist within neural of course; here only two are noted)	Changes in brain regulatory structures or networks, either at the macro level (e.g., control networks) or micro level (e.g. microglia function) will change recursively with change in epigenetic or physiological signals and mediate behavioral change in dynamic, bidirectional fashion over time.
Psychological (also called mental, cognitive)	Self-regulation of cognition, affect, or behavior can be identified as a functional mechanism in multiple psychopathologies. The weak version of this hypothesis is that either bottom up or top down aspects of self-regulation are commonly identified. The strong or risky version of this hypothesis is that top-down self-regulation mechanisms are shared. Hence, the corollary risky hypothesis is:
	Cognitive evaluation (appraisal) of experience meanings can be identified as a functional mechanism within self-regulation across multiple psychopathologies.
	Cognitive evaluation mechanisms will respond dynamically to exposome challenge and parallel physiological change bi-directionally, until a stable pattern is reached over time. Individual differences in particular patterns of change will index response to clinical intervention or change in clinical course.

be the rule. The relevant higher-order regulatory neural systems can be conceived in terms of functional networks (e.g., the cingulo-opercular network, the default mode network, the executive control network; Petersen & Posner, 2012; Posner et al., 2016; Table S3 citations); as frontal-subcortical-thalamic loops (Bonelli & Cummings, 2007); or as key nodes within regulatory networks (e.g., the anterior cingulate cortex; Posner et al., 2016). The primary hypothesis is that they will reorganize in response to perturbation, with individual differences related to emergence or course of psychopathology over time.

Mediating neural mechanisms can also be identified at a more granular level. For example, staying with the immunological example, an important candidate is neuroinflammation (Dunn et al., 2020), with associated involvement of glial cells and astrocytes responsive to brain chemokine and cytokine signaling. Microglia play a homeostatic role in the brain (Cowan & Petri, 2018; Nayak et al., 2014; Wright-Jin & Gutmann, 2019), making them a promising common mechanism in a dynamic neural model of mental disorder. The dynamic question concerns how change over time and recursive modification occurs until

health—or decompensation—emerge in a new stabilization. I hypothesize that the process would correlate with behavioral and mental self-regulation (or breakdowns of regulation) over time.

The Psychological Unit of Analysis

In the funnel model, I do not suggest that mental *contents* are finite, but that the *processes* relevant to psychopathology are. Within a finite set of key processes, specific contents are unique to the individual (particular ways of making meaning, or interpreting their experience). An analogy might be the finding that the equation for reward discounting appears the same across many species, whereas parameter weights vary across species and incentive context. Two related processes, each able to be mechanistically decomposed (at least in principle), are salient.

The first, overarching process is *intrinsic self-regulatory processes*. I previously noted that self-regulation involves an interplay of automatic and intentional (goal directed) processes or mental activities (Nigg, 2017). *Top down* elements appear to be shared across a range of psychopathologies. For example, attentional control (Burgoyne & Engle, 2020) supports executive functioning, emotional regulation, and fluid intelligence; its breakdowns are observed in in ADHD, anxiety, depression, schizophrenia, bipolar disorder, and PTSD (Table S3).

The second, a component of the first, is *appraisal schema*, or *evaluations*. Evaluations are both implicit (nonconscious) and explicit. They serve to help regulate emotion, confer meaning, and thus guide behavior (Tamir, 2021). *Implicit* evaluative representations can occur in a wide range of psychopathologies (Teachman et al., 2019) both a mechanism and an outcome. Recent theories propose a continuous iterative process by which mental evaluations are continuously updated, with implicit processes followed up by explicit (conscious) revision (Cunningham & Zelazo, 2007; Ehret et al., 2015; Tamir, 2021). Implicit evaluations are difficult but not impossible to measure (Teachman et al., 2019). Mental evaluations can be thought of as a seamless element of the continuous dynamic of homeostatic stabilization that constitutes psychological regulation. They are a common pathway for much psychopathology (see Figure 3, Table S3, and Table 1).

Clinical and Prevention Relevance

Can a multilevel dynamic proposal inform applied problems? I noted early on the relevance of multilevel models to risk prevention efforts. All of the mechanisms noted in this essay are already recognized as potential mechanisms for intervention; proposed here is the potential to integrate them around epigenetic and dynamic processes. Mascolo et al. (2016) provide extensive elaboration on how their approach to dynamic systems should inform clinical practice; many of their suggestions hold here. A central one is a shift in conceptualization away from static conditions with linear inputs, and toward an emergent formulation (this is consistent with a developmental psychopathology perspective as well). It also highlights the value of sequential behavioral analysis in clinical evaluation. Kaliush et al. (2021) suggest that clearer identification of phase-state transition periods, particularly in early life, could enrich a prevention focus. As mathematical description of these processes rapidly improves, targeted intervention should improve as well.[8] Further, clinical algorithms could utilize composite scores reflecting system-wide activity in brain, such as a *polyvertex score* (Zhao et al., 2019) or related score for functional networks (Mooney et al., 2021), or epigenetic or physiological summary scores (Stevenson et al., 2020). These would target regulatory process and could become indices of clinical change (the complexity of interpreting poly-scores notwithstanding).

Conclusion

The goal of mental health intervention at a human level is to support, heal, and help a struggling person. Restating the goal in the dry language of a schematic theory, it is to reestablish homeostasis, perhaps at a new set point, for a faltering dynamic system. Doing so can include introducing new information (biologically or cognitively), adding supports (e.g., social), or providing opportunity for reorganization (e.g., new environmental niches).

Key gaps in knowledge include: (a) insufficient mapping of the exposome; (b) underemphasis on causally informative designs; (c) insufficient cross-fertilization of genetic, physiological, psychological, and exposure studies (i.e., the problem of decontextualized biomarker studies); (d) insufficient joining of prenatal and postnatal influences in the same cohorts (which is beginning to change); and (e) slow application to developmental studies of psychopathology of network and other system-modeling tools or to multiunit dynamics.

Developing the present sketch or theory schema would entail mapping the dynamics of a system seen at multiple units of analysis including genetic liability, exposures of varying significance, epigenetic response, and regulation of brain development, and psychological processes involved in self-regulation including mental evaluations. A key challenge concerns how to map patterns of recursive feedback (cybernetic processes) over time within and across units of analysis. Initial developmental trajectories may be reversible in many instances once these mechanisms are better understood. However, at present sensitive periods of development (where in dynamic systems terms, phase shifts are likely to occur), and mechanisms of stabilizing someone in a maladaptive state, are still only partially elucidated.

In terms of priorities for the field, the complexity of the bio-psychological system of the person can be focused for scientific purposes on (a) mapping of the exposome (as in the ECHO consortium effort); (b) testing of mechanistic hypotheses involved in the epigenome and in key chemical communication systems (inflammatory factors and stress hormones); (c) more use of longitudinal network and other models that can track recursive processes over time in relation to phenotypic expression. I have sketched the beginnings of testable hypotheses.

Overall, the core hypothesis is that neurobiological and psychological pathways of influence are finite and represent shared mechanisms across many psychopathologies. I hypothesized that this is because their function is regulatory, and that the human bio-psychological system has a finite number of multipurpose processes that adapt to varying pressures (immune response is an exemplar). Epigenetic regulation of gene expression in the face of environmental pressure is an essential mechanism to include, and not merely a metaphor for development, even though its central role

[8] Mathematical description of neural, cognitive, and behavioral dynamic processes is advancing rapidly. It will be increasingly tractable to quantify perturbations and the recursive process around them while considering individual variations in parameter weightings for finite (if extensive) process equations.

remains to be fully determined. The principle of common regulatory processes is reflected in different units of analysis such as the physiological (cell signaling), the psychological (evaluations and other intrinsic self-regulatory mental processes), and their corresponding implementing neural networks.

A finite (albeit complex) set of these processes respond to the array of inputs relevant to psychopathology and produce its specific forms as their content, as schematized in Figure 2 and Figure 3. In this dynamic context, while the vast complexity of neural and psychological processes is involved, and the potential inputs and outputs are vast, the critical mechanisms (defined in dynamic systems theory as controlling processes) shaping mental disorder are finite and isolated to regulatory systems.

Testing this logic requires a shift away from studies of single inputs (just the genome, or just a given environmental risk) or single domains of psychopathology, toward integrated study of multiple psychopathology and risk factors. It can be targeted on a-priori hypotheses of which the possibilities can be limited to adaptive processes. While multiple psychopathologies should be studied, units can be studied in subsets so long as they are subsequently connected to other units in an integrated explanation. Thus, the tools are already in place to undertake novel tests and to develop the approach outlined in this essay.

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