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Clinical Advances From a Computational Approach to Anxiety

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Psychiatry faces a crossroads. In the United States, the field successfully navigated a transition in the mid-20th century, shifting from a focus on psychodynamic principles to the current emphasis on clinically observable phenomena. This transition improved reliability in assessment, facilitated clear communication about psychopathology, and brought much-needed attention to key issues in mental health research. However, the field arrived at the current crossroads when subsequent findings suggested that further advances will be difficult as long as assessment techniques remain solely focused on clinically observable phenomena (1).

To illustrate a path forward, this commentary describes research on anxiety, a concrete area for which studies may guide applications to other clinical problems. Work on anxiety capitalizes on cross-species conservation in brain-behavior relationships that manifest when mammals confront danger (2). Attempts to apply computational psychiatry to clinical problems benefit greatly from the availability of such cross-species research. The commentary defines a particular niche for computational psychiatry by describing how the tools it provides might bridge clinical and neuroscience research.

Needs Addressed by Computational Psychiatry

While computational psychiatry encompasses many methods, this commentary focuses on a subset of theory-driven techniques (3). Such techniques apply mathematics to describe, evaluate, and revise equations that relate variations in brain function to variations in behavior observed in the laboratory and in people's daily lives. By so doing, these equations effectively bridge multiple underlying constructs to address the need in psychiatry to clinically translate understandings of brain-behavior relationships. In the case of anxiety, relevant constructs appear in Figure 1, comprising activity in amygdala-related circuits, expressions of behaviors and associated changes in autonomic profiles that occur when individuals confront particular stimuli, and constructs indexed by clinical measures. Research can bridge these constructs and make neuroscience increasingly clinically relevant through the use of laboratory paradigms in humans that also are applied in research with animals. One such paradigm appears in Figure 1, for a child undergoing a fear-conditioning experiment.

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These aspects of computational psychiatry address two specific needs. One concerns the need for improved outcome prediction. Available data allow clinicians to provide patients with meaningful information on prognosis. However, in populations such as children or patients with mild symptoms, this information remains imprecise. For example, many children with severe anxiety mature to lead productive lives with few if any symptoms; others experience long-term impairment. Current methods do not satisfactorily differentiate between these groups and may never do so as long as they focus solely on clinical phenomena.

The other need is for improved treatment, in terms of both better tailoring of available treatments and the discovery of new ones. For example, some patients with anxiety disorders benefit from cognitive behavioral therapy, others benefit from medications, and still others require both modalities. Improved methods are needed for tailoring these treatments to patients. Still other patients fail to benefit from either treatment, which creates a need for novel therapies. Computational psychiatry provides tools for improving outcome prediction and treatment.

Precision in Thinking

More precise thinking represents one benefit of computational psychiatry. This follows when hypotheses about brain-behavior associations are expressed in equations.

Precision arises from a few aspects of the processes of generating equations. One aspect is the requirement to clearly focus research, which arises when scientists model particular behaviors in the laboratory to bridge neuroscience and clinical constructs. Figure 1 depicts a child completing a fear-conditioning paradigm. This paradigm uses an aversive scream as an unconditioned stimulus and faces as conditioned stimuli, including blends of faces incorporating features of the conditioned and nonconditioned stimuli (4). Such paradigms can be focused to quantify relationships among relatively narrow sets of behaviors, such as learned avoidance of stimuli in the laboratory and naturally occurring avoidance in patients' lives (5). With this approach, research attempts to understand particular sets of defensive behaviors. Such knowledge then can be used in later research to elucidate mechanisms of more complex clinical features, such as reported feeling states (2). By starting with a clear focus, computational approaches quantify factors that tightly link behaviors to brain function.

Precision also follows from the ways that computations are used to elucidate mechanisms of brain-behavior relationships. For example, in a conditioning experiment, such approaches can dissociate contributions to individual differences in avoidance from individual differences in learning, perception, or habituation. Although psychiatry infrequently applies equations in this manner, neuroscience regularly uses this approach. As described below, research on spatial navigation provides one particularly useful example (6), which could guide psychiatry as the field attempts to leverage advances in computational neuroscience to answer clinical questions.

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Linking Neuroscience Constructs to Clinical Questions

Corollary advantages arise from such precise thinking, which could broadly alter the current paradigm in psychiatry. Equations can be solved by using observational data to estimate underlying latent constructs, thereby providing a fulcrum on which to link brain functions to behaviors (3,6,7). Applied to clinical problems, this approach could elucidate mechanisms that generate individual differences in behavior, allowing psychiatry to address a fundamental challenge made difficult by the complex nature of brain-behavior relationships. The clinician cannot mechanistically understand many maladaptive behaviors fully without understanding the computations and associated brain functions that produce them. As such, focusing only on behavior leaves psychiatry with problematically incomplete understandings. The computational approach provides psychiatry with novel tools for meeting this daunting challenge.

Research on anxiety concretely illustrates the advantages that follow from computational approaches, applied to research on fear conditioning. Distinct equations use different parameters to quantify learning during a conditioning experiment, such as the one illustrated in Figure 1. Recent research mathematically compares these equations to elucidate mechanisms that allow healthy people to effectively adapt to aversive events encountered during a conditioning experiment (8). Extensions to patients could address clinically relevant questions. Specifically, Duits *et al.* (9) summarize current approaches to research on aversive learning in anxiety disorders, which compares groups on physiologic variables acquired during conditioning. Although this research already reveals relationships between clinical and physiologic variables, computational approaches could extend this knowledge. For example, the observed associations are attenuated by unreliability, and computational approaches reduce the impact of this problem. Moreover, the particular observed pattern of perturbed physiology in patients could arise from many problems in the brain, and a computational approach could adjudicate among the possibilities (8,10).

Other advantages of computational psychiatry arise from the framework around which research is structured. This framework forces the researcher to describe distinct computations that might each generate the particular observed patterns of perturbed physiology or behavior. The researcher then must create experiments that adjudicate among these possibilities, as clearly illustrated in the research on navigation (6). Applying the approach used to understand navigation illuminates a path for psychiatry. Individual differences in maze-learning ability, as indexed by path length during navigation, can be viewed as a construct analogous to individual differences in aversive learning, as indexed by physiology during conditioning. Much like perturbed physiology in anxiety, individual differences in maze-learning ability in rodents could reflect various computational capacities. For example, these differences could reflect differences in rodents' abilities to construct spatial maps or link particular stimuli to specific actions. Applications of a computational approach elucidate experiments that clarify the particular strategy used by an individual rodent. Similar applications in psychiatry could provide insights on the particular computations that generate perturbed physiology in conditioning experiments among patients with anxiety disorders.

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Figure 1 depicts brain-behavior relationships in a cross-sectional manner. Clinically relevant advances in psychiatry might require prospective research addressing questions for which available clinical data fail to produce answers. This research could attempt to predict specific aspects of prognosis or response to treatment alongside currently available clinical measures; for example, research might target clinically significant avoidance, a narrower construct than overall prognosis or treatment response. Progress would follow if constructs in Figure 1, concerning functioning in amygdala-related circuitry or responses to stimuli in laboratory paradigms, provide insights beyond those already provided by clinical measures concerning clinically significant avoidance. Work on mechanisms that enable rodents to navigate suggests that this approach provides psychiatry with important new tools and a systematic way to refine them. Computational tools use data from experiments to refine equations in ways that retain useful explanatory components while generating new equations to be evaluated in an iterative cycle.

Conclusions

In conclusion, the current crossroads confronting psychiatry arise from a need for tools that use neuroscience to augment clinical assessments to improve understanding of the mechanisms that generate behavior. Computational psychiatry provides such tools, which may address a fundamental challenge, given the complex multidetermined nature of brain-behavior relationships. By using computational psychiatry, principles can be applied to understand how variation in brain function generates particular behaviors. This provides a framework for using understandings of brain function to augment clinical tools in ways that improve outcome prediction and treatment.

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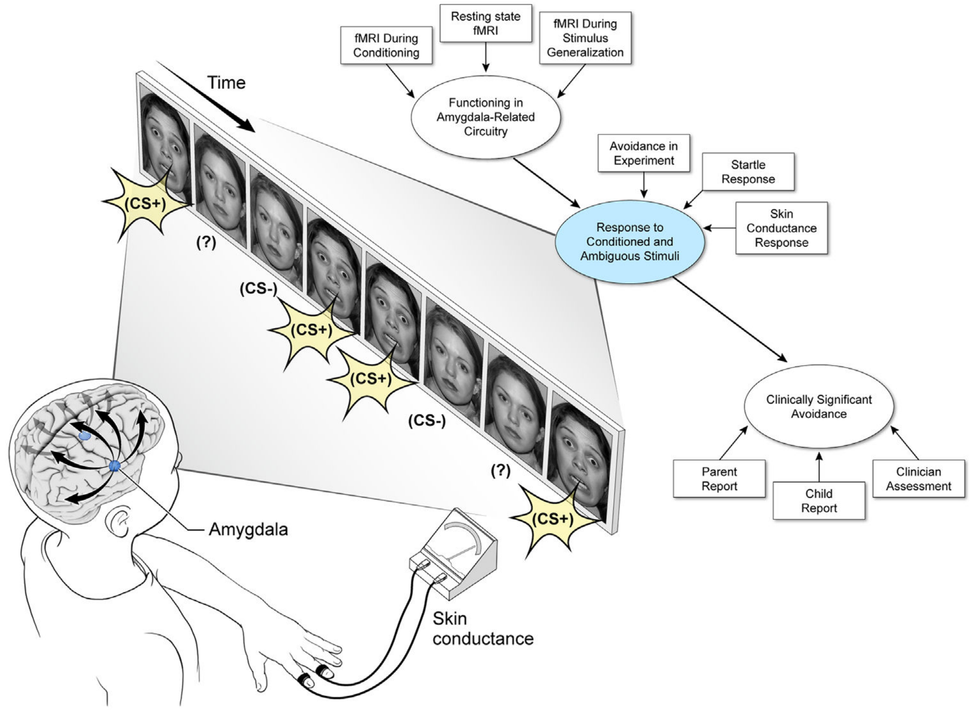

Figure 1.

The left side of the figure depicts an experimental paradigm for use in research on children's responses to danger. The paradigm provides a context for embedding equations that bridge constructs at three levels, depicted on the right side of the figure. These levels comprise activity in brain circuits, responses in the laboratory, and clinically relevant behavior. CS+, conditioned stimulus; CS−, nonconditioned stimulus; fMRI, functional magnetic resonance imaging.