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The value of clinical and translational neuroscience approaches to psychiatric illness

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Abstract

Borsboom and Kalis conflate biological approaches with extreme biological reductionism and common-cause models of psychopathology. In fusing these three distinct ideas, they use evidence against extreme reductionism and common causes to devalue biology. Here, we highlight recent work underscoring the value of clinical and translational neuroscience approaches for understanding the nature and origins of psychopathology and for developing improved interventions.

Keywords

affective neuroscience; biological psychiatry; clinical neuroscience; mental illness; translational neuroscience

MAIN TEXT

Borsboom & Kalis (B&K) conflate biological approaches with extreme biological reductionism and common-cause models of psychiatric illness. In fusing these three distinct ideas, B&K use evidence against extreme reductionism and common causes to devalue clinical and translational neuroscience approaches—effectively throwing the baby out with the bathwater. But, like the paper-and-pencil approaches favored by B&K, biological approaches do not necessitate either extreme reductionism or singular causes. Although mental illness is undeniably based in brains and genes (Geschwind & Flint, 2015; Turkheimer, 1998), we agree with B&K that biological interventions are not necessarily the only or even the best way of tackling every mental illness (Kendler, 2012; Lilienfeld, 2014; Miller, 2010). Likewise, we agree that psychopathology reflects the interaction of multiple

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contexts and causes—from molecular pathways to culture—with their importance varying across individuals, development, sexes, and disorders (Birnbaum & Weinberger, 2017; Kendler, 2012; Shackman & Fox, *in press*).

The network framework championed by B&K describes patterns among symptoms, but it fails to provide a deeper explanation—biological, cognitive, or computational—of where those patterns come from. With respect to risk and etiology, it focuses on symptoms, environmental factors (e.g., stress), and the connection strengths (covariance) among them. Although this framework can describe variation in risk and resilience, it cannot explain why some individuals and their biological relatives are predisposed to experience specific symptoms in maladaptive ways or how environmental factors interact with particular symptoms to produce psychopathology. In contrast, biological approaches are beginning to do just that:

- Anxiety patients and individuals at risk for developing anxiety disorders show increased amygdala activity (Etkin & Wager, 2007; Fox et al., 2015; Fox & Shackman, *in press*) and aberrant amygdala connectivity (Birn et al., 2014)
- Extended amygdala activity is heritable (Fox et al., 2015), associated with specific molecular pathways (Fox et al., 2012; Roseboom et al., 2014), and amplified by stress (Shackman, Kaplan, et al., 2016)
- Heightened amygdala reactivity confers risk for the development of future internalizing symptoms, particularly among individuals exposed to stress (Shackman, Kaplan, et al., 2016)
- Anxiolytics dampen amygdala reactivity (e.g., Del-Ben et al., 2012)
- Amygdala damage markedly reduces signs and symptoms of anxiety in humans and monkeys (Feinstein, Adolphs, Damasio, & Tranel, 2011; Oler, Fox, Shackman, & Kalin, 2016)

These findings suggest that circuits encompassing the extended amygdala causally contribute to the development of maladaptive anxiety (Shackman, Tromp, et al., 2016). Such observations are hardly limited to the amygdala and anxiety. Other work highlights the importance of ventral striatal circuits to anhedonia (Bewernick, Kayser, Sturm, & Schlaepfer, 2012; Greer, Trujillo, Glover, & Knutson, 2014; Nugent et al., 2014; Pizzagalli, 2014; Schlaepfer et al., 2008; Stringaris et al., 2015).

In rejecting common-cause models, B&K neglect evidence that uncorrelated and dissimilar disease phenotypes can reflect common substrates (Kotov et al., 2017; Zhu, Need, Petrovski, & Goldstein, 2014), a pattern not readily explained by symptom-network models. Individual differences in amygdala metabolism, for example, are associated with both neuroendocrine and behavioral signs of anxiety—two phenotypes that are only weakly correlated with one another (Shackman et al., 2013). Likewise, lesions and other perturbations of the amygdala produce coherent changes in a range of disease-relevant phenotypes—neuroendocrine activity, passive avoidance, vigilance, and anxious feelings—suggesting that the amygdala-centered circuits represent a (but likely not the only) common cause for some (but not all)

key features of pathological anxiety (Fox & Shackman, *in press*; Inman et al., *in press*; Oler et al., 2016).

Mental illness imposes a staggering burden on global public health and there is an urgent need to develop better treatments (Global Burden of Disease Collaborators, 2016). Symptom-network approaches to treatment represent, at best, incremental improvements over current clinical practice. Most clinicians already focus more on symptoms and their interconnections than on DSM diagnoses and their myriad specifiers (Waszczuk et al., 2017). In contrast to symptom-network approaches, recent biological research highlights the possibility of developing completely new interventions and more efficiently matching patients to treatments (‘stratified medicine;’ Drysdale et al., 2017; Woo, Chang, Lindquist, & Wager, 2017). On-going genomics research represents one of the few feasible paths to identifying and prioritizing new molecular targets, a prerequisite for developing improved drugs (Gandal, Leppa, Won, Parikshak, & Geschwind, 2016; Pankevich, Altevogt, Dunlop, Gage, & Hyman, 2014). In short, biological approaches afford opportunities for improving the lives of patients that go far beyond those afforded by symptom-centric frameworks.

So where do we go from here? B&K remind us that clinical and translational neuroscience has historically been oversold and under-delivered (for a related perspective, see Gordon & Redish, 2016). Billions of dollars have, as yet, failed to uncover new assays or cures (Shackman & Fox, *in press*). Although B&K tell us that this reflects the futility of biological reductionism, a growing number of clinicians and neuroscientists—including the architects of the National Institute of Mental Health Research Domain Criteria (RDoC)—have concluded that past underperformance reflects limitations of DSM diagnoses, rather than any intrinsic limitation of biological approaches (Gordon & Redish, 2016; Kozak & Cuthbert, 2016).

Categorical diagnoses pose several critical barriers to discovering the nature and origins of psychopathology, including rampant co-morbidity, low symptom specificity, marked symptom heterogeneity, and poor reliability (Fried & Nesse, 2015; Galatzer-Levy & Bryant, 2013; Hasin et al., 2015; Kessler, Chiu, Demler, & Walters, 2005; Krueger et al., *in press*; Olbert, Gala, & Tupler, 2014; Regier et al., 2013; Watson & Stasik, 2014). Addressing these problems requires that we focus on understanding the computational, cognitive, and biological bases of circumscribed symptoms or symptom clusters (e.g., anxiety, anhedonia). This ‘symptoms-not-syndromes’ approach (Fried, 2015) would also more naturally align with animal models (Fox & Shackman, *in press*).

In conclusion, there is a real intellectual danger to adopting B&K’s framework wholesale. Although symptom-network approaches are valuable, they steer us away from deeper explanations for why some individuals and their biological relatives are prone to particular symptoms. A more holistic approach, one that embraces both biological and non-biological approaches, is likely to yield greater dividends for understanding the nature and bases of psychopathology and accelerate the development of improved treatments.

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