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Review article

The research domain criteria framework: The case for anterior cingulate cortex

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ABSTRACT

The United States National Institute of Mental Health has recently promoted the Research Domain Criteria framework, which emphasizes the study of neurocognitive constructs that cut across different disorders. These constructs are said to express dimensionally across the population, giving rise to psychopathologies only in the extreme cases where that expression is maladaptive. Inspired by the RDoC framework, we propose that recent insights into the function of anterior cingulate cortex (ACC), a brain area said to be responsible for selecting and motivating extended behaviors, may elucidate the etiology of a diverse array of mental disorders. We argue that ACC function contributes to individual differences in personality traits related to reward sensitivity and persistence, and propose that the maladaptive expression of these traits contributes to multiple mental and neurological disorders. Our discussion is organized around a computational framework that relates the reward processing and control functions of ACC, as revealed by two electrophysiological phenomena called the reward positivity and frontal midline theta oscillations, to a distributed neural system underlying cognitive control.

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1. The challenge of diagnosing mental disorders

Recent years have seen a growing appreciation that differences between normal mental health and abnormal mental impairment are ones of degree rather than kind. In a striking example of this shift, the British Psychological Society has recently stated that, "One of the most important messages of this report is that there is no dividing line between 'psychosis' and 'normality'. There is no 'us' and 'them"' (British Psychological Society, 2014). The Society emphasizes that hearing voices when no one else is present – once seen as the hallmark of schizophrenia – is commonly experienced by people who do not otherwise exhibit pathology nor necessarily find the experiences to be disturbing. On this account, the symptoms of schizophrenia are expressed along a continuum, with many people exhibiting none of the symptoms and other people expressing more; the symptoms only become clinically relevant in extreme cases when that expression is maladaptive.

Despite this evolving perspective, most existing systems for diagnosing mental disorders are polythetic: Individuals are diagnosed with a disorder when they exhibit more than a threshold number of symptoms. This approach is heuristically convenient but problematic for a number of reasons. In particular, because polythetic classification systems are dichotomous, they coarsely group individuals at intermediate levels of vulnerability for a disorder with other people who exhibit either all or none of the symptoms of the disorder. The approach also categorizes individuals with non-overlapping subsets of symptoms into the same group, which can result in individuals with starkly different clinical profiles sharing the same disorder. For instance, the Diagnostic Statistical Manual (DSM)-IV defines depression according to a threshold criterion of four out of nine possible depression-related symptoms, which yields a total of 227 different combinations of symptoms that meet the diagnosis; when these symptoms are further subdivided into related sub-components of depression, the grand total balloons to 1497 combinations (Østergaard et al., 2011). The polythetic approach also permits different disorders to share particular symptoms in common, which raises questions about their nosological status. For example, anxiety and depression often co-occur, suggesting that comorbid anxiety and depression should be considered as a separate disorder distinct from pure anxiety and pure depression, and that the pure forms of the disorders may not even exist (Schwartz, 2011).

Rising to this challenge, the United States National Institute of Mental Health (NIMH) has advocated for the study of biologically-based intermediate functions that elucidate the causal factors underlying disorder symptomatology (Cuthbert and Insel, 2013; Cuthbert and Kozak, 2013; Insel et al., 2010; Sanislow et al., 2010). This Research Domain Criteria (RDoC) framework promises to "develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures" that "starts with basic mechanisms and studies dysfunctions in these systems as a way to understand homogeneous symptom sets that cut across multiple disorders, rather than starting with clinical symptoms and working backwards" (National Institute of Mental Health, 2015). This framework conceives of mental disorders according to an array of underlying, causative "constructs", as illustrated in Fig. 1. The top panel indicates the conventional approach, where each element in the top row indicates a potential disorder as specified by the current diagnostic systems (such as depression, schizophrenia, anorexia, and so on), and each arrow represents a potential symptom; on this view, a specific disorder (dashed red box) is characterized by a cluster of symptoms (dashed red arrows). By contrast, the RDoC approach (bottom panel) emphasizes the set of underlying functional constructs, each of which is understood to be mediated by a specific neural system that is vulnerable to disruption (for example, "fear processing" or "visual perception"). From this perspective, disruption to a particular construct (red dashed box) gives rise to symptomatology that can contribute to multiple different disorders (red dashed arrows). Crucially, the RDoC approach holds that each of these constructs are expressed dimensionally across the population, from typical levels of expression (solid black arrows) to clinically-elevated levels (dashed red arrows).

Furthermore, the RDoC framework conceives of these constructs in terms of a multi-level matrix that decomposes high-level "domains" into constructs and sub-constructs. In turn, these constructs can be interrogated using an array of empirical "units" of analysis that target different neurocognitive levels of processing (namely, "Molecules," "Cells," "Circuits," "Physiology," "Behavioral measures," and "Self-Reports"), together with specified "Task Paradigms" appropriate to the level of analysis. In order to provide a heuristic point of departure for further research into the issue, the contents of this matrix have been tentatively populated by a series of working groups convened by NIMH between 2010 and 2012. As of the time of this writing, five domains are proposed to comprise the top level of the matrix: "Negative Valence Systems," "Positive Valence Systems", "Cognitive Systems," "Social Process Systems," and "Arousal/Regulatory Systems," each of which are said to comprise a set of constructs. For example, the Cognitive System includes the constructs "attention," "perception," "working memory," "declarative memory," "language behavior," and "cognitive (effortful) control." The scientist is then tasked with relating neurobehavioral measures – such as single unit activity in prefrontal cortex, the functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent (BOLD) response in the hippocampus, performance on a particular task, and so on – to aspects of psychopathology, rather than to specific disorders as currently defined. This approach aligns well with previous efforts to identify endophenotypes, intermediate phenotypes, and biomarkers of psychopathology (Lenzenweger, 2013), as well as with formal computational approaches that illustrate how mental disorders can emerge from disruption to individual elements within complex neural networks (Adams et al., 2015; Maia and Frank, 2011; Montague et al., 2012).

Although we applaud this new emphasis on etiology over symptomatology, given that many of the proposed constructs are themselves poorly understood, we question whether populating the RDoC matrix in this manner has been premature. Anterior cingulate cortex (ACC) is a case in point. Table 1 lists all of the constructs and sub-constructs associated with units that have been attributed to ACC as of the time of this writing (National Institute of Mental Health, 2015). These constructs are said to support a wide variety of functions underlying all five high-level Domains, which range from "acute threat" in the Negative Valence Systems Domain to "self-knowledge" in the Social Processes Domain. Such diversity of function echos the panoply of theories and empirical phenomena for which ACC has become famous (Bush, 2009; Holroyd and Yeung, 2011). Taken at face value, this taxonomy would seem to suggest that serious disruption to ACC processing – say, as would result from an extensive lesion – would upset all of its associated constructs, inducing wholesale impairments across all five of the domains. We suggest that this multidimensional conceptualization of ACC function, which seems to point to a role for ACC in everything, is not useful for advancing research into psychopathology.

Here we offer a recent theory of ACC function as a new construct for understanding the role of ACC in mental disorders. Our argument is based on our previous proposal that ACC motivates the execution of extended behaviors according to principles of hierarchical reinforcement learning, which we call the HRL-ACC theory (Holroyd and Yeung, 2012). In keeping with the dimensional approach, we argue that this function is expressed along continua throughout the general population, manifesting as individual