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RDoC and the developmental origins of psychiatric disorders: How did we get here and where are we going?

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About a decade ago, the National Institute of Mental Health (NIMH) proposed an innovative framework, the Research Domain Criteria (RDoC), to classify psychiatric disorders, which offered a complementary approach to use with existing diagnostic systems to identify transdiagnostic factors that inform early detection of mental health disturbances and critically provide novel targets for interventions, particularly those cutting across traditional diagnostic boundaries. Historically, the tendency in psychiatric research and biomedical research more generally is to initially develop adult-oriented models and then, after testing and refinement, downwardly extend these frameworks to youth populations (Rutter, 2008). Central to the RDoC initiative, however, is the goal of clarifying developmental processes and illness trajectories by operationalizing dimensional constructs during sensitive periods of neurofunctional development to capture the early emergence of behavioral alterations and impairment and, accordingly, to identify psychological, biological, molecular, and genomic markers associated with psychiatric disorders across the lifespan. As developmental factors are inherent to all RDoC systems and the units of analysis therein, NIMH shepherded developmental-oriented research with targeted funding opportunity announcements—with this resulting work highlighting promising phenotypes and biological markers related to psychiatric illness.

RDoC: How did we get here?

Recently, Pacheco et al. reflected on the NIMH developmental portfolio from 2008 through 2019, highlighting trends within this area of research as well as novel advancements related to etiology and treatment (Pacheco et al., 2022). During this span, there were 239 NIMH funded grants that focused on both developmental and RDoC initiatives, reflecting 44.1% of the RDoC portfolio. Broadly, this research aimed to: (i) enrich our understanding of heterogeneity within a single disorder (e.g., attention-deficit/hyperactivity disorder [ADHD]), (ii) operationalize symptom non-specificity—focusing on core symptoms that are present across a multitude of psychiatric disorders (e.g., irritability), (iii) reveal novel origins of neurodevelopmental disorders (e.g., autism spectrum disorders), and (iv) guide the development of innovative interventions (e.g., working memory training for patients diagnosed with ADHD). Pacheco et al. (2022) overview of developmentally focused RDoC research *takes the pulse* of recent work while at the same time *painting a vision* for future directions and goals over the next decade.

Inherent to an RDoC-ian approach is the focus on dimensionality both within and across psychiatric disorders, and Pacheco et al. (2022) expertly showcase the value of applying an RDoC approach. In ADHD, for example, there are three primary subtypes: inattention, hyperactivity, or a combined presentation. The challenge, however, is that these subtypes are not believed to be stable (Lahey, Pelham, Loney, Lee, & Willcutt, 2005) and, therefore, ADHD may be better understood as a dimensional disorder (Martel, 2009). The cognitive systems domain has given researchers a framework for generating predictions about which cognitive dimensions are implicated in the etiology and maintenance of ADHD. Studies aligned with this RDoC approach have shown that working memory influences the persistence of ADHD and further identifies youth who are more responsive to treatment (Karalunas, Gustafsson, Fair, Musser, & Nigg, 2019).

By contrast, it also is well understood that there are symptoms core to a wide range of psychiatric disorders. Herein, Pacheco et al. (2022) provide an instructive overview of irritability—highlighting recent research that has used RDoC systems, namely, the Negative Valence (e.g., frustrative nonreward), Positive Valence (e.g., reward responsiveness), and Cognitive Systems (e.g., response inhibition) to identify discrete biobehavioral processes that underlie irritability. A central aim of this approach is to distinguish normative and developmentally appropriate childhood behaviors (e.g., tantrums) from biobehavioral dimensions that may be an early indicator for differential onset of psychiatric disorders among youth. That is, clarifying which RDoC constructs related to irritability and then prospectively predict specific disorder outcomes (e.g., ADHD versus Major Depressive Disorder). Taken together, this work is illustrative of how RDoC-consistent

biobehavioral phenotyping provides complementary information to more traditional Diagnostic and Statistical Manual of Mental Disorder (DSM) assessments which, ideally, can lead to a more comprehensive understanding of mental health disturbances in youth.

Notably, Pacheco et al. also emphasize that each of these approaches—heterogeneity within a disorder and non-specificity of symptoms—opens the door for new, innovative treatments. Focusing on discrete dimensions within a disorder may provide more targeted interventions that may alleviate a core subset of symptoms (e.g., working memory deficits in ADHD). Conversely, improved characterization of promising phenotypes that are common across disorders (e.g., irritability, anhedonia) may then result in the development of transdiagnostic treatments that may benefit youth struggling with a wide range of psychiatric disorders. Insomuch as the effectiveness of some of our current gold standard treatments for certain psychiatric disorders has plateaued in recent years, over time, RDoC may offer a framework to begin developing more novel, far-reaching interventions that could complement our existing pharmacologic and psychotherapeutic approaches.

RDoC: Where are we going?

Tremendous progress has been made over the previous decade with regard to solidifying the value of RDoC. That said, there remains a notable tension between the DSM and RDoC, particularly with regards to charting a clear path forward for RDoC. Specifically, though the DSM is imperfect, it provides a tractable system for organizing information related to psychiatric illnesses. This information is accessible across patients and professionals and importantly, provides relatively clear benchmarks for knowing when clinical services might be beneficial (e.g., subthreshold versus threshold Major Depressive Disorder). During its near 7-decade history, the DSM has benefitted from iterative development, consistently refining our understanding of psychiatric disorders based on consensus agreement from leading experts in the field. The RDoC—established in 2009—remains in its nascency phase, and it is now just reaching its *early adolescent years*. Akin to most adolescents, it is in search of an identity, and doubtlessly, there are many growing pains ahead. The RDoC matrix was designed to be decidedly different from the DSM; however, the value of RDoC may rest with understanding how the diverse array of information gathered across units of analysis can be used to meaningfully advance our knowledge of psychiatric illness. Addressing this issue will determine whether the RDoC is a standalone organizing body, or rather, is a complementary tool that can be used to further refine the inevitable next version of the DSM. Neither path is *right* or *wrong*. Yet, at some point, perhaps in the near future, we will need to determine how to effectively use RDoC, particularly with regards to improving diagnosis as well as informing treatment that pushes us beyond what the DSM already provides.

In my view, a focus on neurodevelopmental markers related to psychiatric disorders provides this clear path forward for RDoC that is separable from DSM. For example, seminal research has charted normative cortical growth trajectories across childhood and adolescence (Gogtay et al., 2004). This has provided an opportunity to investigate whether deviations in cortical neurodevelopment reflect a true *deficit* (e.g., stable volumetric differences in a region of interest) or merely a *delay*. While a deficit represents a persistent alteration within a region throughout the life course, a delay, by contrast, suggests that the time course of cortical development differs within certain affected populations, which may account, in part, for the observed mental health disturbances. Research within ADHD, for instance, has exemplified this critical difference as both typically developing youth and children diagnosed with ADHD show similar cortical maturation over time, but there is a notable temporal delay in cortical development among patients with ADHD that may be related to the manifestation of behavioral an attentional symptoms (Shaw et al., 2011). This finding and many others underscore the importance of focusing on neurodevelopment trajectories, rather than cross-sectional observations, to understand the emergence of psychiatric symptoms.

Despite these findings, the more common approach within our field is to identify brain-related differences—viewed only through this cross-sectional snapshot—as deficits or abnormalities. To be clear, my own work has drawn similar tentative conclusions based on cross-sectional structural and functional MRI assessments among depressed and anxious adolescents (Auerbach et al., 2022). We, like many other researchers, passively acknowledge that there are developmentally sensitive periods, which may have profound effects on biobehavioral markers of interest, but our study designs are not necessarily equipped to characterize this effect. Part of the challenge in addressing the issue of *deficit* (or alteration) versus *delay* is born from a funding structure that is ill-suited to target fundamental questions about how developmental processes relate to the emergence of psychiatric disorders. Namely, the typical 5-year grant does not generally afford the time needed or sampling power to address core neurodevelopmental questions, particularly those most central to RDoC. Given these limitations, researchers have used savvy methodological approaches (e.g., accelerated longitudinal designs), and more recently, publicly available data sets (e.g., Adolescent Brain and Cognitive Development (ABCD) study) to tackle questions core to the neurodevelopmental origins of psychiatric disorders. Yet, as RDoC turns the corner into adolescence, NIMH-funding

initiatives supporting longer granting periods, particularly studying younger individuals during the transition from early childhood through adolescence, may provide a clear inroad for RDoC to further establish its value.

Another prominent factor core to the developmental origins of psychiatric disorders is puberty. Puberty, however, has a complicated relationship with RDoC. Most clinical research acknowledges that pubertal development has a profound influence on the timing and course of psychiatric illness (Vijayakumar, de Macks, Shirtcliff, & Pfeifer, 2018), but the integration of puberty within the RDoC is less clear. Puberty fundamentally affects various units of analysis across all RDoC systems, but there are challenges with how to optimally assess pubertal development. Many investigators rely on self- and/or parent-report instruments which capture physical changes corresponding to the 5 Tanner stages. This approach is not without limitations (e.g., reporting inaccuracies, ethnicity-related differences), but gold standard physical examinations can be overly intrusive within certain research contexts. Perhaps a more RDoC-ian consistent approach is to assess hormone levels to obtain an objective proxy for pubertal development. It is well-documented, however, that there is enormous variability in hormone levels both within and across pubertal stages (Dorn, Dahl, Woodward, & Biro, 2006). Moreover, there are important measurement issues that must be accounted for, which directly affects the reliability and reproducibility of findings (e.g., estradiol varies across the day and menstrual cycle; testosterone levels are influenced by circadian rhythm). Research using both subjective and objective approaches has broadly shown that puberty impacts cortical and subcortical development and function (Vijayakumar et al., 2018). A natural next step would then be to test whether the timing and tempo of puberty relates to RDoC systems in the service of capturing the early emergence of psychiatric symptoms. Returning to the example of ADHD highlighted by Pacheco et al. (2022), RDoC may guide novel directions of research that are less often examined—exploring, for instance, whether delayed pubertal development affects different constructs within the Social Processes System (e.g., perception of emotions) or the Sensorimotor System (e.g., neurofunctional alterations within the basal ganglia). Furthermore, if clear relationships emerge between discrete pubertal processes (e.g., delayed Tanner Stage, estradiol levels) and constructs within RDoC systems, pubertal processes could be more concretely integrated into the RDoC matrix, providing clearer guidelines for clinical researchers.

Summary

Now in the early adolescent years, RDoC will begin forging its identity. Much like all adolescents, there will be wrong turns, boundary testing, and strife. Yet, the adolescent years also are replete with self-discovery and growth. Moving forward through the next decade, planful integration of RDoC with developmentally focused research can be transformative—offering unique insights into the unfolding of psychiatric disorders as well as highlighting promising targets to improve clinical outcomes during a critical period of socioemotional and neural development.

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