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The Contributions of the RDoC Research Framework on Understanding the Neurodevelopmental Origins, Progression and Treatment of Mental Illnesses

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Abstract

The National Institute of Mental Health proposed the Research Domain Criteria (RDoC) initiative as an alternate way to organize research of mental illnesses, by looking at dimensions of functioning rather than being tied to categorical diagnoses. This paper briefly discusses the motivation for and organization of RDoC, and then explores the NIMH portfolio and recent work to monitor the utility and progress that RDoC has afforded developmental research. To examine how RDoC has influenced the NIMH developmental research portfolio over the last decade, we employed a natural language processing algorithm to identify the number of developmental science grants classified as incorporating an RDoC approach. Additional portfolio analyses examine temporal trends in funded RDoC-relevant grants, publications and citations, and research training opportunities. Reflecting on how RDoC has influenced the focus of grant applications, we highlight examples from research on Attention-Deficit Hyperactivity Disorder (ADHD), childhood irritability, and Autism Spectrum Disorder (ASD). Lastly, we consider how the dimensional and transdiagnostic approaches emphasized in RDoC have facilitated research on personalized intervention for heterogeneous disorders and preventive/early interventions targeting emergent or subthreshold psychopathology.

Introduction

Over a decade ago, in 2009, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) initiative, with the strategic purpose to facilitate novel research approaches to the classification of psychiatric disorders. This was motivated by the need to address the scientific concern that the field had equated psychiatric illness with syndromes based on clinically observed diagnostic criteria, which were not well connected with neural and psychological mechanisms. RDoC represents an inherently translational approach, considering psychopathology in terms of dysregulation and dysfunction in

fundamental aspects of behavior as established through basic neuroscience and behavioral science research. The initiative is designed to integrate many levels of information, including genomics, circuits, physiology, and behavior, to better understand the basic dimensions of functioning underlying the full range of human behavior. RDoC is a focused research initiative, with an ultimate goal of informing an updated classification system, such that new categories are more homogenous and have a more personalized intervention strategy. We will ultimately achieve these goals through a rigorous and iterative process that first works to achieve a deeper understanding of psychological and biological systems related to mental illness, identify new biomarkers and bio-signatures, create more homogenous groupings for psychopathology and pathophysiology, and develop new interventions. As highlighted in Figure 1, RDoC can have direct influence as the field moves towards personalized interventions and refined diagnosis categories.

The RDoC framework as whole, depicted in Figure 2, encapsulates overall theories for approaching mental health research in new ways. To provide guidance to the field a matrix took shape, now containing six domains grouping relevant constructs in the rows of the matrix, and 'Units of Analysis' forming the columns. The matrix is intended to provide a conceptual structure to organize and communicate our understanding of fundamental behavioral-neural systems. Initially, expert groups for each of the domains were convened and, using current data and empirical evidence, offered suggestions for delineating each domain into useful constructs (and occasionally, sub-constructs) based upon joint evidence for a functional dimension of behavior and for an implementing neural circuit or system. They also provided elements that were relevant for each 'Unit of Analysis'. This provided an informative place to start, as the field adjusted to thinking within the RDoC framework. From its inception, the matrix was intended to evolve over time with new data and evidence. As such, all the elements listed within the matrix are there as exemplars; researchers are not bound to use these and only these in their RDoC-based research. Instead, the specific elements of the matrix may provide a rational place for investigators to start when designing a new study. Researchers are encouraged to use constructs and elements not listed, but to select them in a rigorous manner consistent with the rest of the RDoC matrix (Cuthbert & Insel, 2013; Cuthbert & Kozak, 2013; Sanislow et al., 2010). Ultimately, the matrix is seen as a resource to help the field formulate initial scientific questions and design, and not intended to constrain the scope of scientific exploration.

While the matrix does not specifically include development as a domain or construct, understanding developmental trajectories across various phases of the lifespan represents a critical consideration that is inherent in the RDoC framework. A foundational RDoC chapter stated, "One very salient aspect concerns developmental processes, seen as critical for multiple reasons" (Cuthbert & Insel, 2013, p. 1078). As elaborated in another early article, "The RDoC conceptualization includes developmental processes and interactions with the environment as orthogonal dimensions that should inform hypotheses and conclusions derived from the RDoC organizational structure. Their absence from the matrix is due only to the limitations of two-dimensional representation and should not be misinterpreted as indicating that these important considerations are not relevant to the RDoC research framework" (Morris & Cuthbert, 2012, p. 33).

Approaches using dimensional and functional assessments have long been integrated into clinical research of child and adolescent psychopathology and have proven to contribute to the understanding of heterogeneity within disorders, as well as identifying the commonalities across disorders that were once thought to be quite different (Garvey et al., 2016). One contribution of RDoC may have been to allow researchers some freedom from being bound to diagnostic categories within their research, which proves particularly important when considering child and adolescent populations. Development itself poses many discontinuities that may be more amenable to dimensional research; certain behaviors are considered normal during some developmental stages but can be a sign of mental illness at others. Relatedly, the concept of sensitive periods, when the effects of particular experiences have a strong influence on brain and behavior, may be more accessible when using a dimensional outlook. Studying these periods are key to understanding how the timing of events can impact risk for atypical development. Ultimately, understanding the interaction between constructs as they appear, mature, and differentiate is critical to RDoC-influenced developmental research.

Here, we look at the influence that RDoC has had on the portfolio of funded grants at NIMH, and the impact on the field at large – in terms of research impact, treatment development, trial design, and training focus for the next generation of scientists.

Influence of RDoC on the NIMH Developmental Portfolio

Defining the Developmental and RDoC portfolios

In order to define the set of funded grants that comprise the RDoC portfolio and the developmental portfolio, we first used a snapshot of grants funded between 2008 to 2019. The developmental portfolio is defined by grants that focus on populations ranging from ages 0-18, as well as those using a participant pool of adults focused on understanding childhood and developmental concerns (e.g., a study of adults with childhood ADHD to understand the longer-term trajectory of ADHD would be considered developmental). The developmental portfolio is relatively easy to delineate from the entire NIMH portfolio, as each project is assigned to a Program Class Code (PCC), and typically projects that focus on development fall into specific PCCs within the Institute. The developmental portfolio contains 844 grants that were funded between the years 2008 and 2019 as identified by selecting the grants within the appropriate PCCs.

Consistent with the intent of RDoC principles and approaches being applicable to NIMH's entire scientific mission, RDoC-related grants are not focused on any one scientific program or PCC within NIMH and, save for grant applications submitted to RDoC-specific funding opportunity announcements (FOA), information about the use of RDoC in each grant is not systematically captured. In addition, grants can adopt any number of principles from the overall RDoC initiative, creating, if you will, a dimensional "spirit of RDoC" across grants. For these analyses, the RDoC portfolio has been defined using a natural language processing algorithm to identify grants that have a high similarity score to a set of 83 hand classified, "gold standard" RDoC grants submitted to RDoC-specific FOAs. We used a machine learning approach called word2vec (Mikolov et al., 2013) which learns word relationships based on the title, abstract and specific aims of the grant. These relationships

are embedded into a high-dimensional vector space which is used to calculate a similarity score between each of the gold standard awards and all other NIMH awards. Grants with a score of 0.75 or higher had a 66% agreement rate with previously curated RDoC grants and were considered part of the RDoC portfolio for this analysis. These methods revealed 664 RDoC grants (among research project grants, on any topic, not limited to Developmental grants) that were funded between the years 2008 and 2019.

Overlap of RDoC and Developmental Portfolios

Using these portfolio sets, we can examine the overlap between the developmental portfolio and the RDoC portfolio and begin to highlight empirically the ways that the two have changed over time. RDoC-focused aims and methodology are represented in a fair portion of the developmental-themed research funded by NIMH. During this time window there were 293 new and competing grants that fall within the overlap of RDoC and Development, giving 34.7% of the developmental portfolio an RDoC focus (conversely, 44.1% of the RDoC portfolio focuses on development). A Venn diagram of this overlap is shown in Figure 3.

Examining the change in developmental portfolio year-by-year, we can see the impact that the introduction of the RDoC initiative has had on the composition of the portfolio. Figure 4 shows the percentage of the developmental portfolio that includes RDoC, broken into three time periods. The first time period, from 2008-2011, is considered Pre-RDoC, and constitutes the time before NIMH had published any specific calls for RDoC-informed research. Even before RDoC was officially announced, there was a steady 25% of the portfolio that seemed to be addressing research using RDoC themes. Developmental research is ripe for transdiagnostic and dimensional approaches, and this figure suggests that those approaches were already prominently utilized prior to the issue of RDoC FOAs.

The second time frame depicted in Figure 4, from 2012-2015, represents Early RDoC, the initial implementation of the RDoC initiative, with publication of RDoC-related notices and FOAs annotated on the graph. The adaptation to RDoC in developmental research can be seen as the percentage of RDoC grants climb steadily in these years, reaching a height of nearly 75% by 2017. The third timeframe, from 2016-2019, is considered Recent RDoC. As noted, the percentage of RDoC grants reaches a peak in 2017, and then begins to decline. This pattern coincides with the decline of specific RDoC-related funding opportunities. In 2018 and 2019, the percentage of RDoC grants plateaus at approximately 35%. While it is interesting to see that the introduction of RDoC and associated announcements elicited a large spike in RDoC grants in the developmental portfolio, it is of even more import that as a result the field seems to have responded positively to the idea of RDoC, as baseline level of RDoC in the portfolio has seen a rise of 10%. Programmatically, it is encouraging to see developmentally focused researchers leveraging dimensional, transdiagnostic, and multimethodological approaches to conduct research consistent with NIMH's efforts to bridge basic and applied science.

Bibliometric Analysis of the Developmental-RDoC Portfolio

Bibliometric assessments of grants that comprise the Developmental-RDoC Portfolio attest to the influence of these studies on the field; these grants have produced numerous publications, which have been well-cited. As shown in Figure 5, the number of publications produced from these grants has increased steadily over time, from 100 in 2008 to over 600 in 2020. The Relative Citation Ratio (RCR) is a metric developed by NIH representing a citation-based measure of influence (Hutchins et al., 2016). It is normalized to other papers in the same field and year, with a score of 1 representing a publication with average influence and publications with an RCR greater than 1 suggesting higher quality research. The weighted RCR is the sum of RCRs for all publications within an analysis group and is a measure of both the quantity and quality of a set of publications. This metric has also increased steadily over time. However, the average RCR over time – ignoring the quantity of publications – has been decreasing slightly, suggesting that the weighted RCR is being driven by the overall number of publications, and not their citation ratios. For these analyses, publications that cited the specific Developmental-RDoC portfolio grants as their funding source were used, but we did not verify that each of those papers was inherently RDoC. As such, the content of the resulting papers may not be completely RDoC-focused. Given that RDoC is a framework to help design and implement scientific studies, there is also a spectrum to the degree to which RDoC principles are included and adopted and not every finding or aspect of an RDoC project is expected to be wholly RDoC, but we do think that findings that arise from studies set up in any degree of RDoC-informed manner will be useful for pushing the field forward.

These portfolio analyses serve as an overview of the state of the Developmental-RDoC portfolio at NIMH. It highlights that allocation of funding towards RDoC-focused work has not only had a large impact on the focus of the portfolio, but a lasting effect on how the portfolio grows over time. While there were some projects that adopted RDoC themes before RDoC was officially launched, the level of RDoC-focused work has increased even after the specific funding dedicated to RDoC has lapsed. The bibliometric analyses show that RDoC work resulting from these grants continues to be a growing focus of the literary pool, and that they represent high-quality research, with an RCR greater than 2 throughout the timeframe, despite a slight decrease over time.

Influence of RDoC on Research Training

The RDoC initiative has also influenced the type of NIMH-funded institutional research training available to graduate and postgraduate students and fellows. Of twelve currently funded NIMH T32 Ruth L. Kirschstein Institutional National Research Service Award training programs focused on research of youth and early development, all include investigators who have been awarded RDoC-related grants as part of their faculty or leadership team. Another seven T32 awards include training activities explicitly focused on RDoC methodology and approaches. These include didactic lecture series, access to ongoing RDoC-related research activities, and initiation of projects that include human and animal experimental models; developmental psychiatric neuroimaging; psychiatric genetics and experimental therapeutics and biomarkers. While an RDoC focus is not explicitly noted as part of the T32 funding announcement, T32 training directors are starting to integrate

those approaches to prepare their students for RDoC-related studies and increase their competitiveness for future career success. Traditional graduate training programs may also begin to embrace changes to coursework, research methods, and practicum experiences to prepare their students to conduct RDoC-centric studies (Levenson, 2014; Levenson, 2017), although the extent to which RDoC-informed approaches have been and will continue to be incorporated into the larger community of child and adolescent research training programs remains to be seen.

The NIH Research Portfolio Online Reporting Tools

The data used in the above portfolio analysis is all available publicly, for the field to make their own queries. The NIH exemplifies and promotes the highest level of public accountability, and to that end has provided the Research Portfolio Online Reporting Tools (RePORT) website, which provides access to reports, data, and analyses of NIH research activities. Included in this website is the RePORT Expenditures and Results (RePORTER) module (https://reporter.nih.gov/), which allows users to search for NIH-funded projects, both intramural and extramural, and access publications that result from NIH funding. Many other tools are available on the RePORT website, that allow access to reports and summary statistics, common questions about NIH budget, and listing of awards by fiscal year, location, and organization. Throughout the paper below, we use some links to RePORTER to highlight grants that are good examples of how RDoC is being used in developmental research, but these are not indicative of preferential funding for certain institutions.

Reception of RDoC outside of NIMH

RDoC was introduced as a research priority at NIMH and has become more prominently featured throughout the portfolio, particularly as we have allocated funds to support RDoC-specific initiatives. We have also been encouraged by the introduction and adoption of RDoC principles outside of NIMH. Within the National Institutes of Health, both the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Drug Abuse (NIDA) have proposed similar concepts (NIAAA, 2016; NIDA, 2015). The NIAAA's Addictions Neuroclinical Assessment (ANA) aims to facilitate understanding of the origin of addictions at a biological level, with the hopes to lead to more individualized treatment (Kwako et al., 2017). At present, the classification of addictive disorders is based on the substance of abuse, however current science indicates that differences and similarities between addictions are not constrained by the substance of abuse. Much like RDoC, the ANA is a dimensional framework that incorporates behavioral measures, brain imaging, and genetic data. Similarly, NIDA has implemented a Strategic Planning Workgroup that's has highlighted a need to "Explore, evaluate, and implement novel approaches for characterizing the complex phenotypes of people with SUDs and substance use problems" (NIDA, 2015). Many of the goals of this workgroup are based in principles shared by both RDoC and the ANA.

The European psychiatric research community has also adopted approaches that mirror RDoC. The large-scale PRISM (Psychiatric Ratings using Intermediate Stratified Markers) project, funded through the EU-Innovative Medicine Initiative, aims to develop a quantitative biological approach to the understanding and classification of neuropsychiatric

diseases to accelerate the discovery and development of better treatments for patients (Kas et al., 2019). Similar to RDoC, PRISM study participants with a range of neuropsychiatric symptoms will be assessed using multiple methods in an attempt to parse current heterogeneous syndromes into homogeneous clusters. Additional European agency funded efforts consistent with an RDoC focus (Bong et al., 2020; Destoop et al., 2019; Hengartner & Lehmann, 2017; Hirjak et al., 2019; Holroyd & Umemoto, 2016; Kleinman et al., 2015; Luyten & Fonagy, 2018), include efforts focused on intervention development (Pasion et al., 2019), and drug discovery (Andersen et al., 2014; Fibiger, 2012; O'Tuathaigh et al., 2017; Tricklebank et al., 2021), and autism biomarker identification (Loth et al., 2017).

Influence of RDoC on Developmental Research

Similar to the influence that RDoC had on the focus of grant applications being funded, the introduction of the RDOC initiative has influenced the variety of scientific questions that have been pursued. One of the main problems that arise when conducting research based on diagnostic categories concern the issues of heterogeneity and non-specificity due to overlap of symptoms. Due to the varied ways that people can qualify for a symptom-based diagnosis, there can be people with the same disorder who share relatively few overlapping symptoms. Similarly, patients who share a common single symptom might have different diagnoses and underlying pathologies since different mental illnesses may have overlapping symptomatology. Research focusing on a single disorder suffers from the issue of grouping all patients together, despite known differences in symptomatology, and excluding cases where there might be more than one disorder. However, when we re-classify our participant groups based on dimensions of functioning, per RDoC, we are more likely to be looking at more homogenous attributes and can more easily understand the mechanisms and relationships among them.

RDoC was introduced to influence research design, to address shortcomings and provide some freedom to the field that was being overly confined by diagnostic categories. In addition to impacting the way participant groups are defined, RDoC can offer some new insight into methods and domains of study. The RDoC framework is structured with examples of domains of function, as well as units of analysis, and encourages the field to use multiple units of analysis (e.g., physiological measure, behavioral assessment, and neural circuitry) and measure one or more domain (e.g., negative valence, cognition and sensorimotor systems). In order to gain a more complete understanding of these complex disorders and deficits, it will be important for the field to find connections between different systems, how they work together, when they are independent, and how they change over time. Thus, the development of reliable, valid, and rigorous tools for measuring each domain is critically important. Some domains, like Cognitive Systems or Positive Valence, have a long history of tasks and paradigms that have been well-used and well-studied, wheras other domains, like Social Processes, do not have the abundance of paradigms that can be implemented easily or across large samples. NIMH has spent some time looking into the tools we have for assessments, via a Council Workgroup in 2016 (NIMH, 2016), as well as specific funding announcements[1] calling for work to develop tools and methods to explore relationships among the domains of the RDoC matrix.

Below we highlight three areas that showcase how RDoC has impacted the field of research. In one case, with Attention-Deficit Hyperactivity Disorder (ADHD), using RDoC has allowed for better exploration of heterogeneity within the diagnosis and highlighted different trajectories that are important for understanding ADHD persistence and remittance. In another case, childhood irritability, RDoC has helped to elucidate research that may span multiple diagnoses and uncover mechanisms involved in the behavioral phenomenon. And, in a third case, we look the utility of RDoC in studying risk for mental illness at much younger ages using the example of early biomarker research in Autism Spectrum Disorder (ASD).

Attention-Deficit/Hyperactivity Disorder – an example of heterogeneity

One of the major tenets of RDoC is its utility for exploring heterogeneity with a single diagnostic category. Recent work with ADHD highlights this advantage. ADHD is a prevalent and persistent developmental disorder that emerges early in childhood, characterized by excessive inattention, hyperactivity, or impulsivity (APA, 2013). Although onset can be very early in childhood, diagnosis of ADHD is typically established in the school age years, making ADHD one of the most common diagnoses in educational settings (Matthews et al., 2014). Children with ADHD are more likely to have poor outcomes in school (Loe & Feldman, 2007), be at increased risk of substance abuse (Adisetiyo & Gray, 2017), and they are also at a greater risk for developing subsequent mental illnesses into adulthood (Hinshaw, 2018). While the disorder name implies that the problem is inherently a deficit in attention, there has been much work that shows that the deficits experienced in ADHD might actually affect more than just this one system (Nigg, Karalunas, Feczko, et al., 2020), and there is a great degree of inter-individual variation in the manifestation of these issues (Hinshaw, 2018; Kofler et al., 2013; Nigg et al., 2002; Nigg, Karalunas, Feczko, et al., 2020). Classically, attention-focused research had shown that individuals with ADHD show deficits in several different forms of attention (e.g., covert attention, selective attention, sustained attention, and attentional capacity) (Barkley, 1997); however evidence indicates that this may be better thought of as a deficit with attention regulation (Hinshaw, 2018). Behavioral evidence supports the notion that ADHD can actually be an inability to detach attention from compelling stimuli, or hyperfocus (Hinshaw, 2018) and neuroimaging work shows intrusions of resting-state and default-mode networks when attention-focused networks should be engaged (Raichle & Snyder, 2007).

Clinical presentation of ADHD is heterogenous, with extensive variability in phenotypes demonstrated. In fact, the diagnostic criteria divides ADHD into three subtypes, one where inattention is prevalent, one where hyperactivity is prevalent, and a combined subtype where both features are equally present (APA, 2013). These sub-type presentations are not expected to be stable, as children diagnosed with ADHD can change their presentation over time (Braaten, 1997; Lahey et al., 2005; Nigg et al., 2002). This inherent heterogeneity supports the notion that ADHD might be best examined as a more dimensional disorder,

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[1]PAR-18-930: Development and Optimization of Task and Measures for Functional Domains of Behavior (R01)
RFA-MH-19-242: Computational Approaches for Validating Dimensional Constructs of Relevance to Psychopathology (R01)
RFA-MH-19-240: Computationally-Defined Behaviors in Psychiatry (R21)

falling along a continuum, and not treated as one homogenous group (Haslam et al., 2006; Martel, 2009; Matthews et al., 2014; Nigg et al., 2002).

More recently, work has been done to try and classify the heterogeneity within the ADHD population, trying to identify sub-types and profiles that are helpful to exemplify individuals at greater risk for persistent ADHD, those who may respond well to certain treatments, and those whose symptoms may remit during adolescence. An exploration of dimensional measures of executive functioning like working memory has uncovered multiple trajectory classes in both the ADHD and typically developing populations, as well as distinct relationships between cognitive processes and ADHD symptom change (Karalunas et al., 2017). Specifically, the rate of working memory improvement was shown to predict symptom remission in ADHD (Karalunas et al., 2017). In this case, working memory deficits that fail to return to age-appropriate norms before adolescence are correlated with persistence of ADHD symptoms through adulthood, whereas if working memory deficits do return to age-appropriate norms, subjects typically experienced a remittance of symptoms. A similar exploration using emotion trait profiles revealed three subtypes within a large sample of children with ADHD, "mild" (normative emotional functioning), "surgent" (high surgency), and "irritable" (high negative affect). The irritable group showed the highest stability over time, and the best prospective predictor of clinical outcomes, exhibiting a more severe and persistent set of ADHD symptoms (Karalunas et al., 2019). When combined with cognitive profiles, the surgent and irritable groups were easily split into a group with and without cognitive deficits. Those children who displayed an irritable emotional profile and cognitive deficits had the most severe ADHD symptoms (Goh et al., 2020). Further exploration with these subtypes and polygenic risk scores for both ADHD and Major Depressive Disorder (MDD) showed a much higher connection to ADHD than a mood disorder genetic profile (Nigg, Karalunas, Gustafsson, et al., 2020). This line of research demonstrates that using RDoC approaches has helped to identify subtypes of the disorder, which can be more informative to treatment and intervention practices.

Classically, research into the mechanisms of ADHD have focused on aspects of Cognitive Systems, mainly areas of attention as well as executive function, which are thought to be primary areas of deficits. However, the emergence of the RDoC Matrix has also opened up new avenues of research that focus on domains outside of cognition to look at the effects of ADHD. In recent years new work has begun to explore aspects of ADHD and the relevant aspects of positive valence (Cohen, 2019), negative valence (Stevens, 2020), and motor systems (Schweitzer, 2020). Taken together, this work hopes to paint a more complete picture of a complex psychiatric disorder.

Childhood Irritability – an example of symptom non-specificity

Irritability is the most common reason that children are brought to the emergency room or outpatient evaluation (Brotman et al., 2006; Collishaw et al., 2010; Kelly et al., 2010; Leibenluft et al., 2003; Peterson et al., 1996; Stringaris et al., 2009). Early childhood irritability frequently persists as children age (Dougherty et al., 2013; Wiggins et al., 2014), predicts later mental illnesses (Brotman et al., 2006; Copeland et al., 2014; Stringaris et al., 2009) and poorer socioeconomic outcomes (Brotman et al., 2006). However, the presence

of irritable symptoms is correlated with multiple Diagnostic and Statistical Manual (DSM) diagnoses, including mania, bipolar disorder, major depressive episode, generalized anxiety disorder, ADHD, oppositional defiant disorder, and disruptive mood dysregulation disorder. The presence of irritability in multiple mental illnesses hinders its usefulness in serving as a diagnostic or predictive biomarker. The NIMH Workshop on Pediatric Irritability (February, 2014) and the First Congress on Pediatric Irritability (September, 2015) identified a need for transdiagnostic, dimensional research on irritability for better characterization of irritable phenotype(s) and deeper understanding of the underlying biological and psychosocial processes, in order to identify diagnostic and treatment-responsive biomarkers and targets for intervention (Avenevoli et al., 2015). In the years following these foundational meetings, many researchers have utilized the RDoC research framework to move from symptom-based, categorical assessments of irritability to dimensional measures aimed at uncovering biotypes useful for classification, clinical prediction, and experimental therapeutics.

The three domains that have been the focus of most RDoC approaches to irritability are Negative Valence, Positive Valence (Reward) and Cognitive Processes. Within the domain of Negative Valence, a key construct that has been extensively explored is frustrative non-reward. Irritable youth show lower thresholds for anger after failure to receive an expected reward (Brotman et al., 2017; Deveney et al., 2013; Meyers et al., 2017; Rich et al., 2011; Rich et al., 2007). Decreased thresholds for frustration are consistently associated with decreased amygdala activation when irritable youths fail to receive an expected reward, in comparison to typically developing youth (Deveney et al., 2013; Perlman et al., 2015; Rich et al., 2011). Some groups have reported decreased striatum, anterior and posterior cingulate, and middle frontal gyrus activation during frustration conditions for irritable youth vs. age-matched controls (Deveney et al., 2013; Perlman et al., 2015) ,while others have reported increases in anterior cingulate and medial frontal gyrus (Rich et al., 2011). In addition to the construct of frustrative non-reward in the Negative Valence domain, work on irritability has also focused on several reward-related constructs within the domain of Positive Valence including reward responsiveness (Kessel et al., 2016; Perlman et al., 2016) and probabilistic and reinforcement learning (Adleman et al., 2011; Dickstein et al., 2007). Within the Cognitive Processes domain, research on irritable youth has focused on cognitive control or response inhibition, the ability to withhold a dominant response in order to select a goal-consistent response. Irritable adolescents exhibit diminished selective attention and response inhibition compared to typically developing peers (Deveney et al., 2012; Pagliaccio et al., 2017; Rich et al., 2007; Tseng et al., 2019).

One challenging aspect of research on irritability, and its utility in identifying early risk for psychopathology, has been the fact that behavioral manifestations such as temper tantrums can be examples of age-appropriate typical development or can be a potential marker of clinical concern (Wakschlag et al., 2012). Longitudinal follow-up of a cohort of 3-year-olds with significant irritability was predictive of clinical diagnoses at age 6 (Dougherty et al., 2013) and age 9 (Dougherty et al., 2015). In order to develop measures that distinguish normative from clinically significant irritability, researchers have utilized dimensional measures of behaviors associated with irritability (e.g., easily frustrated or destructive tantrums) in participant groups with a full range of irritability severity. These studies have demonstrated that dimensional assessments have good sensitivity and specificity

for distinguishing normative development vs. clinically salient irritability predictive of longitudinal likelihood of diagnosis of a DSM disorder (Wakschlag et al., 2015; Wiggins et al., 2018). The RDoC emphasis on functional domains and constructs has been particularly helpful in identifying underlying processes that may confer developmental predisposition toward psychopathology (Wakschlag et al., 2014).

Just as work in older children and adolescents has focused on reward processes and cognitive control, so too, have these domains been explored in preschool children at baseline or subsequent follow-up visits. For example, Dougherty et al. (2018) found that children who had more severe levels of irritability in preschool had altered amygdala and ventral striatum connectivity with other cortical regions during the monetary incentive delay task than children with mild preschool irritability. High levels of frustration on non-reward trials have also been associated with higher levels of lateral prefrontal cortex activation measured by functional near-infrared spectroscopy (fNIRS) in children age 3-5 (Perlman et al., 2014). Similarly, higher temper loss scores have been associated with larger N2 amplitude in EEG and reduced no-go accuracy during frustration trials in children age 4-7 (Deveney et al., 2019). Some studies have focused on cognitive control and cognitive flexibility, measured with Go/No Go or Stroop tasks. The N2 negativity in EEG can distinguish preschoolers with high vs. low disruptive behavior (Grabell et al., 2017) and prefrontal cortex activity measured with fNIRS is correlated with irritability and cognitive flexibility in preschool age children (Li et al., 2017). The significance of these neurocognitive and neurophysiological findings in preschool age children is that symptoms of irritability can be mapped onto specific RDoC domains and brain circuits even before a child meets DSM diagnostic criteria. These biobehavioral markers can meaningfully distinguish between normative levels of irritability in young children and clinically significant levels of irritability that are correlated with neural and behavioral indicators of risk. The explosion of passive, remote sensors is currently enabling even earlier investigation of physiological correlates of irritability and vulnerability for psychopathology by facilitating collection of infant vocalizations, heartrate variability, sleep, and motor activity (Wakschlag et al., 2014).

Autism Spectrum Disorder – an example of early developmental research

One particular utility of the RDoC perspective may be in examining very early development as it relates to understanding later emergence of a clinical diagnosis. An illustrative example can be seen in the search for early biomarkers of autism spectrum disorder (ASD). While overt behavioral phenotypes of ASD typically begin to manifest around the second year after birth (Zwaigenbaum & Penner, 2018), the importance of early intervention in improving outcomes has made early identification of ASD markers a key area of research in this field. Many studies have shown deficits in neural connectivity in preschool-aged children diagnosed with ASD including atypical patterns of EEG (Coben et al., 2008; Cornew et al., 2012). In subsequent examination of infants, differential EEG patterns were seen in infants as young as 6 months at high familial risk for ASD relative to those at low familial risk (Tierney et al., 2012). Further, data driven modeling of EEG collected longitudinally from 3 months to 3 years was used to identify the frequency bands in the first or second year that most accurately differentiated later ASD risk and diagnosis (Gabard-Durnam et al., 2019). These measures identified potential risk biomarkers significantly earlier than behavioral

measures would have allowed; however, the use of a single diagnostic outcome limited their direct utility in terms of how to intervene at an individual level given the phenotypic heterogeneity of ASD.

In contrast, a longitudinal study of infant development in a prospective community sample used an RDoC perspective to examine the relationship between neonatal EEG power and developmental behavioral assessments at 24-36 months. The study found that while EEG power was not related to measures of children's cognitive development, play behaviors, or linguistic development, there was a relationship with social competence (Brito et al., 2019). While extremely preliminary, this type of finding represents a potentially important clarification about the relationship between a biomarker that may predict a diagnosis and what aspects of the broad ASD phenotype may be driving that particular biomarker. This, in turn, may inform which aspect of intervention might be emphasized in a more actionable way.

While this example of a biomarker signature is specific to a single modality of measurement (EEG), it serves as a microcosm of one of the central questions around early identification of biomarkers in ASD more broadly: does a biomarker need to be specifically related to the deficits seen in the disorder to have utility in informing early understanding of risk and potential intervention? Certainly, attempts have been made to use toddler ASD behavioral screeners in infants, but these have proven poorly reliable at these earlier ages (Parikh et al., 2021; Wetherby et al., 2008). However, given the heterogeneity and frequent comorbidities seen in ASD, it is fair to consider whether a focus on ASD-specific biomarkers is necessary. In a recent review and commentary, Talbott and Miller (2020) argue that moving the focus of early detection towards ASD-relevant transdiagnostic behavioral domains such as attention or self-regulation may allow for more effective targeted interventions based on individual needs as opposed to general developmental interventions that may not effectively treat core symptoms of ASD (and other disorders).

The current effort to develop an "NIH Infant and Toddler Toolbox" to provide just such a set of normed, domain-specific assessments for children between 1-42 months of age is an important step in this approach. By providing easily administered and easily scored assessments of domains including cognition, social functioning, language (receptive and expressive), numeracy, self-regulation, and executive function, researchers will be able to probe specific aspects of behaviors relevant to ASD or other disorders of interest without relying on general functioning measures or on disorder-specific screeners that are not age appropriate (Gershon, 2019).

The above three examples highlight specific lines of research that have been informed and expanded upon using RDoC approaches. Allowing research to break free from the confines of clinical diagnosis can open the field to uncover new relationships that weren't readily apparent when using diagnostic categories to define research groups.

Influence of RDoC in Developing Child and Adolescent Interventions

Although the RDoC initiative was not initially designed for use within the clinic, RDoC was conceived to ultimately reduce the burden of mental illness by providing research findings that can inform revisions of current diagnostic nosologies, lead to the development of new treatments targeted to underlying mechanisms of psychiatric disorders, and increase precision in treatment application through the identification of mechanistically similar subgroups (Garvey et al., 2016; Insel et al., 2010). For children and adolescents, the RDoC approach of integrating behavioral functions that cross current diagnostic categories may specifically help facilitate more precise interventions that target specific domains of functioning that contribute to disease heterogeneity commonly found in youth, identify early stages of psychopathology that may provide new targets for prevention or intervention, and preempt or alter the trajectory of illness across the lifespan. The translation of RDoC findings into clinical application will take time, but a number of reecntly funded studies demonstrate the potential for informing the development of new treatments.

Interventions and Disorder Heterogeneity

RDoC research can help tease apart heterogeneity within a single disorder, which serves to help focus interventions on particular deficits/symptoms experienced by an individual patient. In children and adolescents, heterogeneity in ADHD is an illustrative example. As is outlined above, ADHD attentional deficits are now known to include many dimensions, including deficits in working memory (WM). These are among the most consistently reported cognitive impairments in ADHD (Kasper et al., 2012). Performance on brief WM information-storage tasks predicts attention abilities, general aptitude, and academic achievement; moreover, performance on some WM tasks predicts ADHD-like behaviors in non-ADHD persons (e.g., multi-tasking, mind wandering, and difficulty following directions) (Fried et al., 2016; Kofler et al., 2017). Based on this evidence, numerous studies have used cognitive training approaches to improve working memory for ADHD (Cortese et al., 2015). These are operationalized through increasingly challenging training sessions over a period of weeks with the goal of reducing ADHD symptom severity and associated clinical dysfunction. Nearly all ADHD WM training research to date has focused on increasing WM storage capacity. These studies show that, while WM storage training reliably improves WM capacity, with gains that persist over time, scant evidence supports their consistent translation into improved ADHD symptom severity or better functioning (Cortese et al., 2015). Recent RDoC-inspired research has shown that executive working memory (EWM) skills can be conceptualized as promoting flexibility of selective attention measured by tasks that require attention shifting or updating (Bledowski et al., 2010) – lending stability to WM representations by filtering out extraneous distracting information or by suppressing interference of uninformative information. These EWM task behavioral deficits are by far the strongest WM deficits in ADHD, stronger than deficits in WM storage. This may be one reason why training of WM storage did not show clinical benefit. A small number of investigators have started to focus treatment development efforts on targeting these EWM skills to determine if they mediate improvement in clinical outcomes (Kofler et al., 2018; Kofler et al., 2020; Stevens et al., 2016).

Interventions Based on Early Manifestations of Disease

The study of RDoC constructs within a developmental framework may uncover early manifestations and differential pathways of disease progression that offer new targets to alter those trajectories at the earliest stages. Focusing on the fundamental components of behavior can allow for the detection, longitudinal monitoring, and targeting of emerging symptoms that do not meet criteria for a disorder, and ultimately may themselves be important targets for new therapies (Garvey et al., 2016). For example, studies in younger siblings of children with ASD charted the very early development of fundamental components of behavior (motor, language development, and social responsiveness) and found a decline in preferential attention to the eyes of others, an indicator of social attention between 2 and 6 months of age in those children who were later diagnosed with ASD (Bedford et al., 2012; Chawarska et al., 2014; Jones & Klin, 2013; Ozonoff et al., 2015). By understanding the natural progression of eye gaze and its relationship to social attention, investigators found a possible construct associated with ASD that may inform early detection and intervention. Building on this premise, Scherf et al. (2018) developed the Social Games for Adolescents with Autism (SAGA) to train children with ASD to attend and process eye gaze so as to increase understanding of gaze cues and attention to faces. SAGA is currently being evaluated as part of an NIMH-funded clinical trial (Scherf, 2016). Similarly, Lense and colleagues (2016) used observations of infant social behavior and eye entrainment, observable as early as two months of age, to posit the targeting of flexible rhythmic prediction by social musical activities to scaffold the rhythm and timing skills necessary for development of social rhythmic entrainment and more successful social interaction. This research team is currently evaluating this intervention to support the development of evidence-based music interventions to improve social communication for children with ASD (Lense & Jones, 2019).

Intervention and Disease Trajectory

RDoC-inspired mental health research allows investigators to recruit a homogeneous group of participants that do not meet criteria for a DSM disorder by selecting them based on their performance on behavioral tasks. Using individuals at clinical high risk for psychosis has allowed for the development of interventions that target sub-syndromal symptoms, with the goal of preventing the onset of psychosis. An example of this work includes processing speed training in teenagers and young adults at clinical high risk for psychosis. Impairments in processing speed are seen to emerge during early adolescence prior to the onset of psychotic symptoms that show a strong cross-sectional and longitudinal relationship to social function and eventual onset of psychosis (Carrion et al., 2011; Choi et al., 2017). Longitudinal studies have shown that deficits in processing speed are one of the best predictors of current and future social functioning impairments, social decline, and eventual conversion to psychosis (Carrion et al., 2011; Carrion et al., 2013). Preliminary evidence that processing speed can be altered and the strong rationale linking deficits in processing speed to poor social function can pave the way for development of novel interventions and can translate into improved outcomes for individuals at high risk for psychosis.

As an example, Cornblatt and colleagues (2021) are working to identify potential targets to prevent the onset of psychosis in young adults. Cognitive remediation strategies shown

to have positive effects in preventing the conversion of psychosis in adults have had mixed results in younger patients (Glenthoj et al., 2017). Hypothesizing that broad based approaches that attempt to address the full range of cognitive deficits seen in individuals with psychosis are insufficiently focused on the targets most likely to confer conversion, Cornblatt and colleagues have proposed an alternate approach that focuses on processing speed. Neurocognitive processing speed represents the rate at which an individual can perform a cognitive operation and is considered to be a core cognitive deficit in patients with schizophrenia (Ojeda et al., 2012). Processing speed has, in turn, been associated with downstream development of other behaviors such as social functioning; processing speed deficits have been shown to be strongly related to poor social functioning prior to the onset of psychosis, independent of positive symptoms (Cannon et al., 2008; Carrion et al., 2011; Carrion et al., 2013). These findings have led the Cornblatt team to propose a clinical trial (Cornblatt, 2021) to evaluate whether a specialized cognitive training package engages a neurocognitive processing speed target and, if so, determine whether those changes are associated with reductions in positive symptoms and improved social functioning.

Assessing Impact and Looking Forward

Since its introduction, the Research Domain Criteria has had an impact on the contents of the portfolio at NIMH, on the direction of research into specific mental illnesses as well as common transdiagnostic problems, and has even started to influence clinical treatment and interventions for patients as well as training for the next generation of scientists. With such a broad impact, it is important to understand that RDoC was implemented to address some shortcomings in a field that was driven entirely (funding, publication, and interventions) by symptom-based diagnoses that increasingly were dissociated from biological and psychological systems (Insel et al., 2010). RDoC was never intended to be a fix-all, but an additional tool for the field to use. Many misconceptions abound concerning RDoC, perhaps none more pervasive as to whether RDoC is required for NIMH funding. The portfolio analysis presented here showcases that the NIMH developmental portfolio is not exclusively limited to research using RDoC approaches, but RDoC has become a significant component of the portfolio. As RDoC was always intended to grow and evolve along with new discoveries and techniques, there is room for continued growth while using transdiagnostic and dimensional approaches in develpmental work. There is a general need for validation and optimization of measurement tools into younger ages, in order to assess constructs that may be useful in very early identification of risk for mental illnesses and strategies for prevention. The ability to explore constructs outisde of a strict diagnosis has given rise to biomarkers that are sensitive to dimensional differences and has identified mechanisms associated with heightened risk, sometimes when clinical symptoms are subthreshold, thus providing opportunities for modifiable, preclinical targets for selective and indicated preventive treatment. By shifting mental health research from symptom-based diagnostic categories to biotypes, RDoC has produced new constructs with less heterogeneity that in turn facilitate precision medicine approaches to optimize treatment selection by targeting the underlying processes that are relevant for an individual patient.

One notable challenge that lies ahead is the clinical translation of RDoC-driven findings into patient care. The development of evidence-based interventions can be a long process, and

agencies such as NIH and the FDA have implemented approaches to accelerate treatment development and reduce the time from bench to bedside (Insel, 2015; NIH, 2014). Although NIMH has funded a decade of RDoC focused research, those findings are only now translating to new treatment targets and approaches to manipulate those targets and impact the lives of children and their families. In addition, the RDoC approach is consistent with the FDA's more recent approach to consider specific symptoms (e.g., cognitive dysfunction in major depressive disorder) as suitable targets for drug development, rather than overall DSM diagnoses (FDA, 2016). Together, these approaches have the potential to more precisely target the underlying constructs that comprise disorders and speed the development of new interventions. Time will tell whether the RDoC initiative has been successful in driving the development of new treatments, but the initial signs are promising, as suggested by examples above.

The growing use of mobile sensors, passive monitoring, and ecological momentary assessments has made it possible to examine sleep and activity levels, social and family interactions, and neighborhood environment including noise and nightime light levels. The use of these types of measures also enables measurements in settings that are particularly meaningful in the lives of children and adolescents, such as in school settings, or during play and extracurricular activities, or at home. More work could be done to elucidate more culturally sensitive constructs, and identify domains of functioning that may be informative for exploration across different populations and/or in different contexts. The RDoC framework may also prove useful in understanding how social drivers of mental health "get under the skin" by acting on specific processes and brain circuits. Longitudinal studies enrolling individuals with a broad spectrum of dimensional behaviors can also enhance our undestanding of protective factors and resilience, elucidating capacities, resources and processes that are associated with better outcomes. The RDoC research framework is also conducive to the use of common data elements because assessment tools, behavioral tasks, physiological and neural measurements are increasingly shown to tap specific constructs and circuits as the community of researchers using RDoC approaches has grown. In concert with community-driven consensus on harmonized research tools, NIMH encouragement of data sharing through the NIMH Data Archive has resulted in a growing body of publically available datasets using similar measures, tasks, and data acquisition techniques; this resource provides a research ecosystem that can support the use of synthetic cohorts and bioinformatics approaches to explore larger datasets with power to understand complex interactions of multiple factors such as age, sex, socioeconomic status, race, and ethnicity. We look forward to new discoveries that will emerge as RDoC matures and follows its own trajectory of growth.

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References

Adisetiyo V, & Gray KM (2017). Neuroimaging the neural correlates of increased risk for substance use disorders in attention-deficit/hyperactivity disorder-A systematic review. Am J Addict, 26(2), 99–111. 10.1111/ajad.12500 [PubMed: 28106934]

Adleman NE, Kayser R, Dickstein D, Blair RJ, Pine D, & Leibenluft E (2011). Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry, 50(11), 1173–1185 e1172. 10.1016/j.jaac.2011.07.011 [PubMed: 22024005]

Andersen PH, Moscicki R, Sahakian B, Quirion R, Krishnan R, Race T, Phillips A, & Group CS (2014). Securing the future of drug discovery for central nervous system disorders. Nat Rev Drug Discov, 13(12), 871–872. 10.1038/nrd4489 [PubMed: 25435203]

APA. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).

Avenevoli S, Blader JC, & Leibenluft E (2015). Irritability in Youth: An Update. J Am Acad Child Adolesc Psychiatry, 54(11), 881–883. 10.1016/j.jaac.2015.08.012 [PubMed: 26506577]

Barkley RA (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull, 121(1), 65–94. 10.1037/0033-2909.121.1.65 [PubMed: 9000892]

Bedford R, Elsabbagh M, Gliga T, Pickles A, Senju A, Charman T, Johnson MH, & team B (2012). Precursors to social and communication difficulties in infants at-risk for autism: gaze following and attentional engagement. J Autism Dev Disord, 42(10), 2208–2218. 10.1007/s10803-012-1450-y [PubMed: 22278030]

Bledowski C, Kaiser J, & Rahm B (2010). Basic operations in working memory: contributions from functional imaging studies. Behav Brain Res, 214(2), 172–179. 10.1016/j.bbr.2010.05.041 [PubMed: 20678984]

Bong SH, Choi TY, Kim KM, Lee J, & Kim JW (2020). Correlation between executive function and quantitative EEG in patients with anxiety by the Research Domain Criteria (RDoC) framework. Scientific Reports, 10(1). https://doi.org/ARTN 18578 10.1038/s41598-020-75626-0

Braaten EBR, L. A (1997). Emotional reactions in adults with symptoms of attention deficit hyperactivity disorder. Personality and Individual Differences, 22(3). 10.1016/S0191-8869(96)00217-6

Brito NH, Elliott AJ, Isler JR, Rodriguez C, Friedrich C, Shuffrey LC, & Fifer WP (2019). Neonatal EEG linked to individual differences in socioemotional outcomes and autism risk in toddlers. Developmental Psychobiology, 61(8), 1110–1119. 10.1002/dev.21870 [PubMed: 31187485]

Brotman MA, Kircanski K, Stringaris A, Pine DS, & Leibenluft E (2017). Irritability in Youths: A Translational Model. Am J Psychiatry, 174(6), 520–532. 10.1176/appi.ajp.2016.16070839 [PubMed: 28103715]

Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, & Leibenluft E (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry, 60(9), 991–997. 10.1016/j.biopsych.2006.08.042 [PubMed: 17056393]

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, & Heinssen R (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry, 65(1), 28–37. 10.1001/archgenpsychiatry.2007.3 [PubMed: 18180426]

Carrion RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, & Cornblatt BA (2011). Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. Am J Psychiatry, 168(8), 806–813. 10.1176/appi.ajp.2011.10081209 [PubMed: 21536691]

Carrion RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, Correll CU, & Cornblatt BA (2013). Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry, 70(11), 1133–1142. 10.1001/jamapsychiatry.2013.1909 [PubMed: 24006090]

Chawarska K, Shic F, Macari S, Campbell DJ, Brian J, Landa R, Hutman T, Nelson CA, Ozonoff S, Tager-Flusberg H, Young GS, Zwaigenbaum L, Cohen IL, Charman T, Messinger DS, Klin A, Johnson S, & Bryson S (2014). 18-month predictors of later outcomes in younger siblings of children with autism spectrum disorder: a baby siblings research consortium study. J Am Acad Child Adolesc Psychiatry, 53(12), 1317–1327 e1311. 10.1016/j.jaac.2014.09.015 [PubMed: 25457930]

Choi J, Corcoran CM, Fiszdon JM, Stevens M, Javitt DC, Deasy M, Haber LC, Dewberry MJ, & Pearlson GD (2017). Pupillometer-based neurofeedback cognitive training to improve processing

speed and social functioning in individuals at clinical high risk for psychosis. Psychiatr Rehabil J, 40(1), 33–42. 10.1037/prj0000217 [PubMed: 27560455]

Coben R, Clarke AR, Hudspeth W, & Barry RJ (2008). EEG power and coherence in autistic spectrum disorder. Clinical Neurophysiology, 119(5), 1002–1009. 10.1016/j.clinph.2008.01.013 [PubMed: 18331812]

Cohen JR (2019). Cohen, J.R. (2019). Available from: https://reporter.nih.gov/project-details/9717605. [last accessed 27 December2021].

Collishaw S, Maughan B, Natarajan L, & Pickles A (2010). Trends in adolescent emotional problems in England: a comparison of two national cohorts twenty years apart. J Child Psychol Psychiatry, 51(8), 885–894. 10.1111/j.1469-7610.2010.02252.x [PubMed: 20497281]

Copeland WE, Shanahan L, Egger H, Angold A, & Costello EJ (2014). Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. Am J Psychiatry, 171(6), 668–674. 10.1176/appi.ajp.2014.13091213 [PubMed: 24781389]

Cornblatt BA (2021). Cornblatt, B.A. (2021). Available from: https://reporter.nih.gov/project-details/10193909. [last accessed 27 December 2021].

Cornew L, Roberts TPL, Blaskey L, & Edgar JC (2012). Resting-State Oscillatory Activity in Autism Spectrum Disorders. Journal of Autism and Developmental Disorders, 42(9), 1884–1894. 10.1007/s10803-011-1431-6 [PubMed: 22207057]

Cortese S, Ferrin M, Brandeis D, Buitelaar J, Daley D, Dittmann RW, Holtmann M, Santosh P, Stevenson J, Stringaris A, Zuddas A, Sonuga-Barke EJ, & European AGG (2015). Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. J Am Acad Child Adolesc Psychiatry, 54(3), 164–174. 10.1016/j.jaac.2014.12.010 [PubMed: 25721181]

Cuthbert BN, & Insel TR (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med, 11, 126. 10.1186/1741-7015-11-126 [PubMed: 23672542]

Cuthbert BN, & Kozak MJ (2013). Constructing constructs for psychopathology: the NIMH research domain criteria. J Abnorm Psychol, 122(3), 928–937. 10.1037/a0034028 [PubMed: 24016027]

Destoop M, Morrens M, Coppens V, & Dom G (2019). Addiction, Anhedonia, and Comorbid Mood Disorder. A Narrative Review. Frontiers in Psychiatry, 10. https://doi.org/ARTN 311 10.3389/fpsyt.2019.00311

Deveney CM, Briggs-Gowan MJ, Pagliaccio D, Estabrook CR, Zobel E, Burns JL, Norton ES, Pine DS, Brotman MA, Leibenluft E, & Wakschlag LS (2019). Temporally sensitive neural measures of inhibition in preschool children across a spectrum of irritability. Dev Psychobiol, 61(2), 216–227. 10.1002/dev.21792 [PubMed: 30328111]

Deveney CM, Connolly ME, Haring CT, Bones BL, Reynolds RC, Kim P, Pine DS, & Leibenluft E (2013). Neural mechanisms of frustration in chronically irritable children. Am J Psychiatry, 170(10), 1186–1194. 10.1176/appi.ajp.2013.12070917 [PubMed: 23732841]

Deveney CM, Connolly ME, Jenkins SE, Kim P, Fromm SJ, Pine DS, & Leibenluft E (2012). Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. Biol Psychol, 89(1), 148–155. 10.1016/j.biopsycho.2011.10.003 [PubMed: 22008364]

Dickstein DP, Nelson EE, Mc CE, Grimley ME, Knopf L, Brotman MA, Rich BA, Pine DS, & Leibenluft E (2007). Cognitive flexibility in phenotypes of pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry, 46(3), 341–355. 10.1097/chi.0b013e31802d0b3d [PubMed: 17314720]

Dougherty LR, Schwartz KTG, Kryza-Lacombe M, Weisberg J, Spechler PA, & Wiggins JL (2018). Preschool- and School-Age Irritability Predict Reward-Related Brain Function. J Am Acad Child Adolesc Psychiatry, 57(6), 407–417 e402. 10.1016/j.jaac.2018.03.012 [PubMed: 29859556]

Dougherty LR, Smith VC, Bufferd SJ, Kessel E, Carlson GA, & Klein DN (2015). Preschool irritability predicts child psychopathology, functional impairment, and service use at age nine. J Child Psychol Psychiatry, 56(9), 999–1007. 10.1111/jcpp.12403 [PubMed: 26259142]

Dougherty LR, Smith VC, Bufferd SJ, Stringaris A, Leibenluft E, Carlson GA, & Klein DN (2013). Preschool irritability: longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. J Am Acad Child Adolesc Psychiatry, 52(12), 1304–1313. 10.1016/j.jaac.2013.09.007 [PubMed: 24290463]

FDA. (2016). Psychopharmacologic Drugs Advisory Committee Meeting. Available from: https://www.fda.gov/media/95694/download. [last accessed 27 December2021].

Fibiger HC (2012). Psychiatry, the pharmaceutical industry, and the road to better therapeutics. Schizophr Bull, 38(4), 649–650. 10.1093/schbul/sbs073 [PubMed: 22837348]

Fried R, Chan J, Feinberg L, Pope A, Woodworth KY, Faraone SV, & Biederman J (2016). Clinical correlates of working memory deficits in youth with and without ADHD: A controlled study. J Clin Exp Neuropsychol, 38(5), 487–496. 10.1080/13803395.2015.1127896 [PubMed: 26902180]

Gabard-Durnam LJ, Wilkinson C, Kapur K, Tager-Flusberg H, Levin AR, & Nelson CA (2019). Longitudinal EEG power in the first postnatal year differentiates autism outcomes. Nature Communications, 10(1), 4188. 10.1038/s41467-019-12202-9

Garvey M, Avenevoli S, & Anderson K (2016). The National Institute of Mental Health Research Domain Criteria and Clinical Research in Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry, 55(2), 93–98. 10.1016/j.jaac.2015.11.002 [PubMed: 26802775]

Gershon R (2019). Available from: https://reporter.nih.gov/project-details/10045604. [last accessed 27 December 2021].

Glenthoj LB, Hjorthoj C, Kristensen TD, Davidson CA, & Nordentoft M (2017). The effect of cognitive remediation in individuals at ultra-high risk for psychosis: a systematic review. NPJ Schizophr, 3, 20. 10.1038/s41537-017-0021-9 [PubMed: 28560266]

Goh PK, Lee CA, Martel MM, Karalunas SL, & Nigg JT (2020). Subgroups of Childhood ADHD Based on Temperament Traits and Cognition: Concurrent and Predictive Validity. J Abnorm Child Psychol, 48(10), 1251–1264. 10.1007/s10802-020-00668-x [PubMed: 32666315]

Grabell AS, Olson SL, Tardif T, Thompson MC, & Gehring WJ (2017). Comparing Self-Regulation-Associated Event Related Potentials in Preschool Children with and without High Levels of Disruptive Behavior. J Abnorm Child Psychol, 45(6), 1119–1132. 10.1007/s10802-016-0228-7 [PubMed: 27891556]

Haslam N, Williams B, Prior M, Haslam R, Graetz B, & Sawyer M (2006). The latent structure of attention-deficit/hyperactivity disorder: a taxometric analysis. Aust N Z J Psychiatry, 40(8), 639–647. 10.1080/j.1440-1614.2006.01863.x [PubMed: 16866759]

Hengartner MP, & Lehmann SN (2017). Why Psychiatric Research Must Abandon Traditional Diagnostic Classification and Adopt a Fully Dimensional Scope: Two Solutions to a Persistent Problem. Front Psychiatry, 8, 101. 10.3389/fpsyt.2017.00101 [PubMed: 28638352]

Hinshaw SP (2018). Attention Deficit Hyperactivity Disorder (ADHD): Controversy, Developmental Mechanisms, and Multiple Levels of Analysis. Annu Rev Clin Psychol, 14, 291–316. 10.1146/annurev-clinpsy-050817-084917 [PubMed: 29220204]

Hirjak D, Wolf RC, & Northoff G (2019). GABA and Negative Affect-Catatonia as Model of RDoC-Based Investigation in Psychiatry. Schizophrenia Bulletin, 45(6), 1168–1169. 10.1093/schbul/sbz088 [PubMed: 31647566]

Holroyd CB, & Umemoto A (2016). The research domain criteria framework: The case for anterior cingulate cortex. Neuroscience and Biobehavioral Reviews, 71, 418–443. 10.1016/j.neubiorev.2016.09.021 [PubMed: 27693229]

Hutchins BI, Yuan X, Anderson JM, & Santangelo GM (2016). Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. PLoS Biol, 14(9), e1002541. 10.1371/journal.pbio.1002541 [PubMed: 27599104]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, & Wang P (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry, 167(7), 748–751. 10.1176/appi.ajp.2010.09091379 [PubMed: 20595427]

Insel TR (2015). The NIMH experimental medicine initiative. World Psychiatry, 14(2), 151–153. 10.1002/wps.20227 [PubMed: 26043323]

Jones W, & Klin A (2013). Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature, 504(7480), 427–431. 10.1038/nature12715 [PubMed: 24196715]

Karalunas SL, Gustafsson HC, Dieckmann NF, Tipsord J, Mitchell SH, & Nigg JT (2017). Heterogeneity in development of aspects of working memory predicts longitudinal attention

deficit hyperactivity disorder symptom change. J Abnorm Psychol, 126(6), 774–792. 10.1037/abn0000292 [PubMed: 28782975]

Karalunas SL, Gustafsson HC, Fair D, Musser ED, & Nigg JT (2019). Do we need an irritable subtype of ADHD? Replication and extension of a promising temperament profile approach to ADHD subtyping. Psychol Assess, 31(2), 236–247. 10.1037/pas0000664 [PubMed: 30359050]

Kas MJ, Penninx B, Sommer B, Serretti A, Arango C, & Marston H (2019). A quantitative approach to neuropsychiatry: The why and the how. Neurosci Biobehav Rev, 97, 3–9. 10.1016/j.neubiorev.2017.12.008 [PubMed: 29246661]

Kasper LJ, Alderson RM, & Hudec KL (2012). Moderators of working memory deficits in children with attention-deficit/hyperactivity disorder (ADHD): a meta-analytic review. Clin Psychol Rev, 32(7), 605–617. 10.1016/j.cpr.2012.07.001 [PubMed: 22917740]

Kelly C, Molcho M, Doyle P, & Gabhainn SN (2010). Psychosomatic symptoms among schoolchildren. Int J Adolesc Med Health, 22(2), 229–235. 10.1515/ijamh.2010.22.2.229 [PubMed: 21061923]

Kessel EM, Dougherty LR, Kujawa A, Hajcak G, Carlson GA, & Klein DN (2016). Longitudinal Associations Between Preschool Disruptive Mood Dysregulation Disorder Symptoms and Neural Reactivity to Monetary Reward During Preadolescence. J Child Adolesc Psychopharmacol, 26(2), 131–137. 10.1089/cap.2015.0071 [PubMed: 26771832]

Kleinman A, Caetano SC, Brentani H, Rocca CCD, dos Santos B, Andrade ER, Zeni CP, Tramontina S, Rohde LAP, & Lafer B (2015). Attention-based classification pattern, a research domain criteria framework, in youths with bipolar disorder and attention-deficit/hyperactivity disorder. Australian and New Zealand Journal of Psychiatry, 49(3), 255–265. 10.1177/0004867414557957

Kofler MJ, Rapport MD, Sarver DE, Raiker JS, Orban SA, Friedman LM, & Kolomeyer EG (2013). Reaction time variability in ADHD: a meta-analytic review of 319 studies. Clin Psychol Rev, 33(6), 795–811. 10.1016/j.cpr.2013.06.001 [PubMed: 23872284]

Kofler MJ, Sarver DE, Austin KE, Schaefer HS, Holland E, Aduen PA, Wells EL, Soto EF, Irwin LN, Schatschneider C, & Lonigan CJ (2018). Can working memory training work for ADHD? Development of central executive training and comparison with behavioral parent training. J Consult Clin Psychol, 86(12), 964–979. 10.1037/ccp0000308 [PubMed: 30507223]

Kofler MJ, Sarver DE, Spiegel JA, Day TN, Harmon SL, & Wells EL (2017). Heterogeneity in ADHD: Neurocognitive predictors of peer, family, and academic functioning. Child Neuropsychol, 23(6), 733–759. 10.1080/09297049.2016.1205010 [PubMed: 27472007]

Kofler MJ, Wells EL, Singh LJ, Soto EF, Irwin LN, Groves NB, Chan ESM, Miller CE, Richmond KP, Schatschneider C, & Lonigan CJ (2020). A randomized controlled trial of central executive training (CET) versus inhibitory control training (ICT) for ADHD. J Consult Clin Psychol, 88(8), 738–756. 10.1037/ccp0000550 [PubMed: 32700955]

Kwako LE, Momenan R, Grodin EN, Litten RZ, Koob GF, & Goldman D (2017). Addictions Neuroclinical Assessment: A reverse translational approach. Neuropharmacology, 122, 254–264. 10.1016/j.neuropharm.2017.03.006 [PubMed: 28283392]

Lahey BB, Pelham WE, Loney J, Lee SS, & Willcutt E (2005). Instability of the DSM-IV Subtypes of ADHD from preschool through elementary school. Arch Gen Psychiatry, 62(8), 896–902. 10.1001/archpsyc.62.8.896 [PubMed: 16061767]

Leibenluft E, Blair RJ, Charney DS, & Pine DS (2003). Irritability in pediatric mania and other childhood psychopathology. Ann N Y Acad Sci, 1008, 201–218. 10.1196/annals.1301.022 [PubMed: 14998886]

Lense M & Jones W (2019). Available from: https://reporter.nih.gov/project-details/9883577. [last accessed 27 December2021].

Lense MD, & Dykens EM (2016). Beat Perception and Sociability: Evidence from Williams Syndrome. Front Psychol, 7, 886. 10.3389/fpsyg.2016.00886 [PubMed: 27378982]

Levenson RW (2014). The Future of Clinical Science Training: New Challenges and Opportunities. Clinical Psychological Science, 2(1), 35–45.

Levenson RW (2017). Clinical Psychology Training: Accreditation and Beyond. Annu Rev Clin Psychol, 13, 1–22. 10.1146/annurev-clinpsy-021815-093559 [PubMed: 28482690]

Li Y, Grabell AS, Wakschlag LS, Huppert TJ, & Perlman SB (2017). The neural substrates of cognitive flexibility are related to individual differences in preschool irritability: A fNIRS investigation. Dev Cogn Neurosci, 25, 138–144. 10.1016/j.dcn.2016.07.002 [PubMed: 27527736]

Loe IM, & Feldman HM (2007). Academic and educational outcomes of children with ADHD. J Pediatr Psychol, 32(6), 643–654. 10.1093/jpepsy/jsl054 [PubMed: 17569716]

Loth E, Charman T, Mason L, Tillmann J, Jones EJH, Wooldridge C, Ahmad J, Auyeung B, Brogna C, Ambrosino S, Banaschewski T, Baron-Cohen S, Baumeister S, Beckmann C, Brammer M, Brandeis D, Bolte S, Bourgeron T, Bours C, de Bruijn Y, Chakrabarti B, Crawley D, Cornelissen I, Acqua FD, Dumas G, Durston S, Ecker C, Faulkner J, Frouin V, Garces P, Goyard D, Hayward H, Ham LM, Hipp J, Holt RJ, Johnson MH, Isaksson J, Kundu P, Lai MC, D'ardhuy XL, Lombardo MV, Lythgoe DJ, Mandl R, Meyer-Lindenberg A, Moessnang C, Mueller N, O'Dwyer L, Oldehinkel M, Oranje B, Pandina G, Persico AM, Ruigrok ANV, Ruggeri B, Sabet J, Sacco R, Caceres ASJ, Simonoff E, Toro R, Tost H, Waldman J, Williams SCR, Zwiers MP, Spooren W, Murphy DGM, & Buitelaar JK (2017). The EU-AIMS Longitudinal European Autism Project (LEAP): design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. Molecular Autism, 8. https://doi.org/ARTN 24 10.1186/s13229-017-0146-8

Luyten P, & Fonagy P (2018). The stress-reward-mentalizing model of depression: An integrative developmental cascade approach to child and adolescent depressive disorder based on the Research Domain Criteria (RDoC) approach. Clinical Psychology Review, 64, 87–98. 10.1016/j.cpr.2017.09.008 [PubMed: 29107398]

Martel MM (2009). Research review: a new perspective on attention-deficit/hyperactivity disorder: emotion dysregulation and trait models. J Child Psychol Psychiatry, 50(9), 1042–1051. 10.1111/j.1469-7610.2009.02105.x [PubMed: 19508495]

Matthews M, Nigg JT, & Fair DA (2014). Attention deficit hyperactivity disorder. Curr Top Behav Neurosci, 16, 235–266. 10.1007/7854_2013_249 [PubMed: 24214656]

Meyers E, DeSerisy M, & Roy AK (2017). Disruptive Mood Dysregulation Disorder (DMDD): An RDoC perspective. J Affect Disord, 216, 117–122. 10.1016/j.jad.2016.08.007 [PubMed: 27554606]

Mikolov T, Chen K, Corrado G, & Dean J (2013). Efficient Estimation of Word Representations in Vector Space. arXiv preprint ArXiv, 1301.3781.

Morris SE, & Cuthbert BN (2012). Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. Dialogues Clin Neurosci, 14(1), 29–37. https://www.ncbi.nlm.nih.gov/pubmed/22577302 [PubMed: 22577302]

NIAAA. (2016). Scientists propose neuroscience framework for diagnosing addictions. Available from: https://www.niaaa.nih.gov/news-events/news-releases/scientists-proposeneuroscience-framework-diagnosing-addictions. [last accessed 27 December2021].

NIDA. (2015). Strategic planning workgroup on the complexity of substance use disorders and the continuum of substance use problems. Available from: https://www.drugabuse.gov/about-nida/strategic-plan/strategic-plan-workgroupreports-past-plans/strategic-planning-workgroupcomplexity-substance-use-disorders-continuumsubstance. [last accessed 27 December2021].

Nigg JT, John OP, Blaskey LG, Huang-Pollock CL, Willcutt EG, Hinshaw SP, & Pennington B (2002). Big five dimensions and ADHD symptoms: links between personality traits and clinical symptoms. J Pers Soc Psychol, 83(2), 451–469. 10.1037/0022-3514.83.2.451 [PubMed: 12150240]

Nigg JT, Karalunas SL, Feczko E, & Fair DA (2020). Toward a Revised Nosology for Attention-Deficit/Hyperactivity Disorder Heterogeneity. Biol Psychiatry Cogn Neurosci Neuroimaging, 5(8), 726–737. 10.1016/j.bpsc.2020.02.005 [PubMed: 32305325]

Nigg JT, Karalunas SL, Gustafsson HC, Bhatt P, Ryabinin P, Mooney MA, Faraone SV, Fair DA, & Wilmot B (2020). Evaluating chronic emotional dysregulation and irritability in relation to ADHD and depression genetic risk in children with ADHD. J Child Psychol Psychiatry, 61(2), 205–214. 10.1111/jcpp.13132 [PubMed: 31605387]

NIH (2014). A decade of discovery: The NIH roadmap and common fund. Available from: https://commonfund.nih.gov/sites/default/files/ADecadeofDiscoveryNIHRoadmapCF.pdf. [last accessed 27 December2021].

NIMH (2016). Behavioral assessment methods for RDoC constructs. Available from: https://www.nimh.nih.gov/sites/default/files/documents/about/advisory-boards-andgroups/namhc/reports/rdoc_council_workgroup_report.pdf. [last accessed 27 December2021].

O'Tuathaigh CMP, Moran PM, Zhen XC, & Waddington JL (2017). Translating advances in the molecular basis of schizophrenia into novel cognitive treatment strategies. Br J Pharmacol, 174(19), 3173–3190. 10.1111/bph.13938 [PubMed: 28667666]

Ojeda N, Pena J, Schretlen DJ, Sanchez P, Aretouli E, Elizagarate E, Ezcurra J, & Gutierrez M (2012). Hierarchical structure of the cognitive processes in schizophrenia: the fundamental role of processing speed. Schizophr Res, 135(1-3), 72–78. 10.1016/j.schres.2011.12.004 [PubMed: 22226902]

Ozonoff S, Young GS, Landa RJ, Brian J, Bryson S, Charman T, Chawarska K, Macari SL, Messinger D, Stone WL, Zwaigenbaum L, & Iosif AM (2015). Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. J Child Psychol Psychiatry, 56(9), 988–998. 10.1111/jcpp.12421 [PubMed: 25921776]

Pagliaccio D, Wiggins JL, Adleman NE, Harkins E, Curhan A, Towbin KE, Brotman MA, Pine DS, & Leibenluft E (2017). Behavioral and Neural Sustained Attention Deficits in Bipolar Disorder and Familial Risk of Bipolar Disorder. Biol Psychiatry, 82(9), 669–678. 10.1016/j.biopsych.2016.09.006 [PubMed: 27837919]

Parikh C, Iosif AM, & Ozonoff S (2021). Brief Report: Use of the Infant-Toddler Checklist in Infant Siblings of Children with Autism Spectrum Disorder. J Autism Dev Disord, 51(3), 1007–1012. 10.1007/s10803-020-04468-6 [PubMed: 32219636]

Pasion R, Martins EC, & Barbosa F (2019). Empirically supported interventions in psychology: contributions of Research Domain Criteria. Psicol Reflex Crit, 32(1), 15. 10.1186/s41155-019-0128-1 [PubMed: 32027006]

Perlman SB, Huppert TJ, & Luna B (2016). Functional Near-Infrared Spectroscopy Evidence for Development of Prefrontal Engagement in Working Memory in Early Through Middle Childhood. Cereb Cortex, 26(6), 2790–2799. 10.1093/cercor/bhv139 [PubMed: 26115660]

Perlman SB, Jones BM, Wakschlag LS, Axelson D, Birmaher B, & Phillips ML (2015). Neural substrates of child irritability in typically developing and psychiatric populations. Dev Cogn Neurosci, 14, 71–80. 10.1016/j.dcn.2015.07.003 [PubMed: 26218424]

Perlman SB, Luna B, Hein TC, & Huppert TJ (2014). fNIRS evidence of prefrontal regulation of frustration in early childhood. Neuroimage, 85 Pt 1, 326–334. 10.1016/j.neuroimage.2013.04.057 [PubMed: 23624495]

Peterson BS, Zhang H, Santa Lucia R, King RA, & Lewis M (1996). Risk factors for presenting problems in child psychiatric emergencies. J Am Acad Child Adolesc Psychiatry, 35(9), 1162–1173. 10.1097/00004583-199609000-00014 [PubMed: 8824060]

Raichle ME, & Snyder AZ (2007). A default mode of brain function: a brief history of an evolving idea. Neuroimage, 37(4), 1083–1090; discussion 1097-1089. 10.1016/j.neuroimage.2007.02.041 [PubMed: 17719799]

Rich BA, Carver FW, Holroyd T, Rosen HR, Mendoza JK, Cornwell BR, Fox NA, Pine DS, Coppola R, & Leibenluft E (2011). Different neural pathways to negative affect in youth with pediatric bipolar disorder and severe mood dysregulation. J Psychiatr Res, 45(10), 1283–1294. 10.1016/j.jpsychires.2011.04.006 [PubMed: 21561628]

Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, & Leibenluft E (2007). Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. Am J Psychiatry, 164(2), 309–317. 10.1176/ajp.2007.164.2.309 [PubMed: 17267795]

Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, Wang PS, & Cuthbert BN (2010). Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol, 119(4), 631–639. 10.1037/a0020909 [PubMed: 20939653]

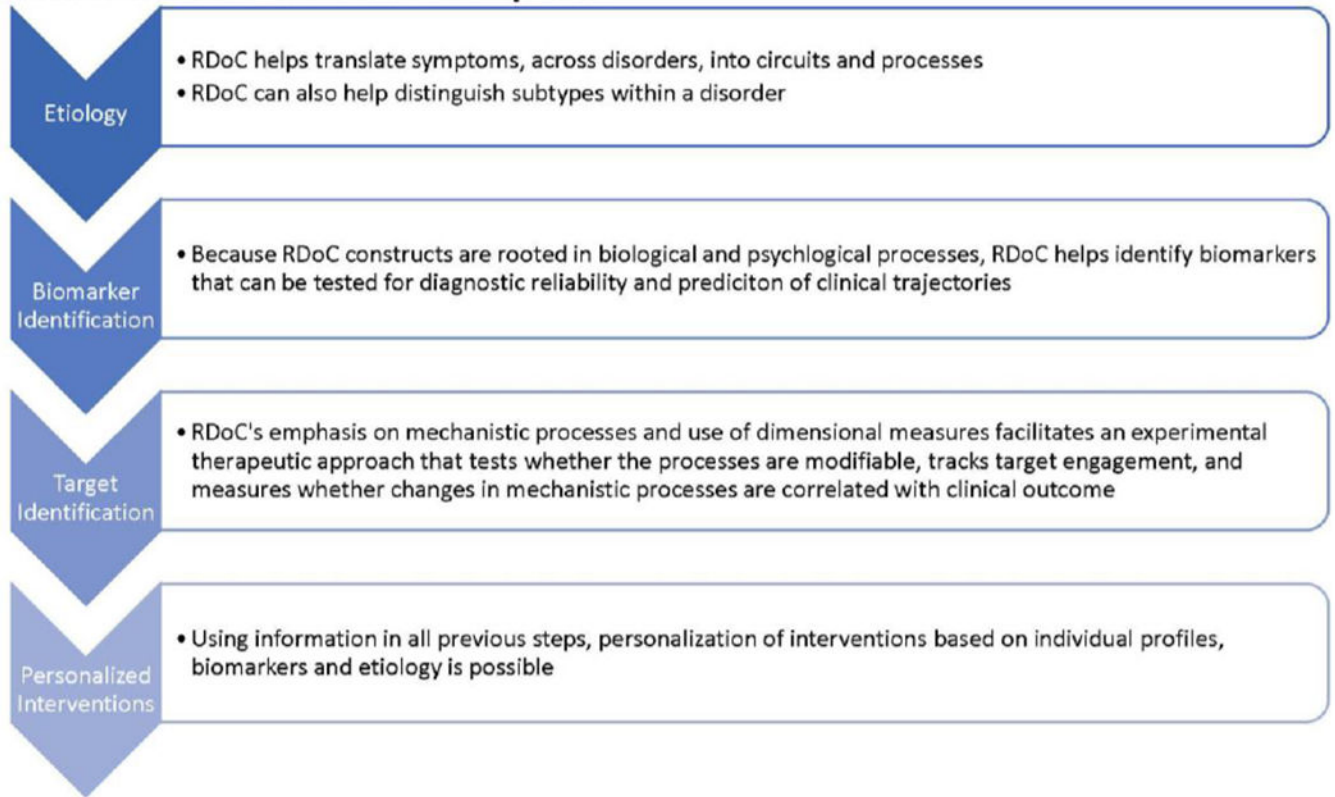Scherf KS (2016). Available from: https://reporter.nih.gov/project-details/9935161. [last accessed 27 December2021].

Scherf KS, Griffin JW, Judy B, Whyte EM, Geier CF, Elbich D, & Smyth JM (2018). Improving sensitivity to eye gaze cues in autism using serious game technology: study protocol for a phase I randomised controlled trial. BMJ Open, 8(9), e023682. 10.1136/bmjopen-2018-023682

Schweitzer JB (2020). Available from: https://reporter.nih.gov/project-details/10064501. [last accessed 27 December 2021].

Stevens MC (2020). https://reporter.nih.gov/search/07ktenG0HE6Jvv6STGutPA/project-details/9897171

Stevens MC, Gaynor A, Bessette KL, & Pearlson GD (2016). A preliminary study of the effects of working memory training on brain function. Brain Imaging Behav, 10(2), 387–407. 10.1007/s11682-015-9416-2 [PubMed: 26138580]

Stringaris A, Cohen P, Pine DS, & Leibenluft E (2009). Adult outcomes of youth irritability: a 20-year prospective community-based study. Am J Psychiatry, 166(9), 1048–1054. 10.1176/appi.ajp.2009.08121849 [PubMed: 19570932]

Talbott MR, & Miller MR (2020). Future Directions for Infant Identification and Intervention for Autism Spectrum Disorder from a Transdiagnostic Perspective. Journal of Clinical Child & Adolescent Psychology, 49(5), 688–700. 10.1080/15374416.2020.1790382 [PubMed: 32701034]

Tierney AL, Gabard-Durnam L, Vogel-Farley V, Tager-Flusberg H, & Nelson CA (2012). Developmental Trajectories of Resting EEG Power: An Endophenotype of Autism Spectrum Disorder. PLoS One, 7(6), e39127. 10.1371/journal.pone.0039127 [PubMed: 22745707]

Tricklebank MD, Robbins TW, Simmons C, & Wong EHF (2021). Time to re-engage psychiatric drug discovery by strengthening confidence in preclinical psychopharmacology. Psychopharmacology (Berl), 238(6), 1417–1436. 10.1007/s00213-021-05787-x [PubMed: 33694032]

Tseng WL, Deveney CM, Stoddard J, Kircanski K, Frackman AE, Yi JY, Hsu D, Moroney E, Machlin L, Donahue L, Roule A, Perhamus G, Reynolds RC, Roberson-Nay R, Hettema JM, Towbin KE, Stringaris A, Pine DS, Brotman MA, & Leibenluft E (2019). Brain Mechanisms of Attention Orienting Following Frustration: Associations With Irritability and Age in Youths. Am J Psychiatry, 176(1), 67–76. 10.1176/appi.ajp.2018.18040491 [PubMed: 30336704]

Wakschlag LS, Briggs-Gowan MJ, Choi SW, Nichols SR, Kestler J, Burns JL, Carter AS, & Henry D (2014). Advancing a multidimensional, developmental spectrum approach to preschool disruptive behavior. J Am Acad Child Adolesc Psychiatry, 53(1), 82–96 e83. 10.1016/j.jaac.2013.10.011 [PubMed: 24342388]

Wakschlag LS, Choi SW, Carter AS, Hullsiek H, Burns J, McCarthy K, Leibenluft E, & Briggs-Gowan MJ (2012). Defining the developmental parameters of temper loss in early childhood: implications for developmental psychopathology. J Child Psychol Psychiatry, 53(11), 1099–1108. 10.1111/j.1469-7610.2012.02595.x [PubMed: 22928674]

Wakschlag LS, Estabrook R, Petitclerc A, Henry D, Burns JL, Perlman SB, Voss JL, Pine DS, Leibenluft E, & Briggs-Gowan ML (2015). Clinical Implications of a Dimensional Approach: The Normal:Abnormal Spectrum of Early Irritability. J Am Acad Child Adolesc Psychiatry, 54(8), 626–634. 10.1016/j.jaac.2015.05.016 [PubMed: 26210331]

Wetherby AM, Brosnan-Maddox S, Peace V, & Newton L (2008). Validation of the Infant-Toddler Checklist as a broadband screener for autism spectrum disorders from 9 to 24 months of age. Autism : the international journal of research and practice, 12(5), 487–511. 10.1177/1362361308094501 [PubMed: 18805944]

Wiggins JL, Briggs-Gowan MJ, Estabrook R, Brotman MA, Pine DS, Leibenluft E, & Wakschlag LS (2018). Identifying Clinically Significant Irritability in Early Childhood. J Am Acad Child Adolesc Psychiatry, 57(3), 191–199 e192. 10.1016/j.jaac.2017.12.008 [PubMed: 29496128]

Wiggins JL, Mitchell C, Stringaris A, & Leibenluft E (2014). Developmental trajectories of irritability and bidirectional associations with maternal depression. J Am Acad Child Adolesc Psychiatry, 53(11), 1191–1205, 1205 e1191-1194. 10.1016/j.jaac.2014.08.005 [PubMed: 25440309]

Zwaigenbaum L, & Penner M (2018). Autism spectrum disorder: advances in diagnosis and evaluation. BMJ, 361, k1674. 10.1136/bmj.k1674 [PubMed: 29784657]

Key points

- This review contains the results of an initial portfolio analysis to look at the impact of RDoC on the NIMH developmental portfolio.

- This review also discusses how RDoC has influenced the research focus of the field, both in understanding the mechanisms and interventions/treatments of psychopathology.

RDoC and the Translational Pipeline

Etiology
- RDoC helps translate symptoms, across disorders, into circuits and processes
- RDoC can also help distinguish subtypes within a disorder

Biomarker Identification
- Because RDoC constructs are rooted in biological and psyclogical processes, RDoC helps identify biomarkers that can be tested for diagnostic reliability and prediciton of clinical trajectories

Target Identification
- RDoC's emphasis on mechanistic processes and use of dimensional measures facilitates an experimental therapeutic approach that tests whether the processes are modifiable, tracks target engagement, and measures whether changes in mechanistic processes are correlated with clinical outcome

Personalized Interventions
- Using information in all previous steps, personalization of interventions based on individual profiles, biomarkers and etiology is possible

Figure 1.
This figure provides a basic overview of the translational pipeline, along with the ways that RDoC-focused research can influence each step.
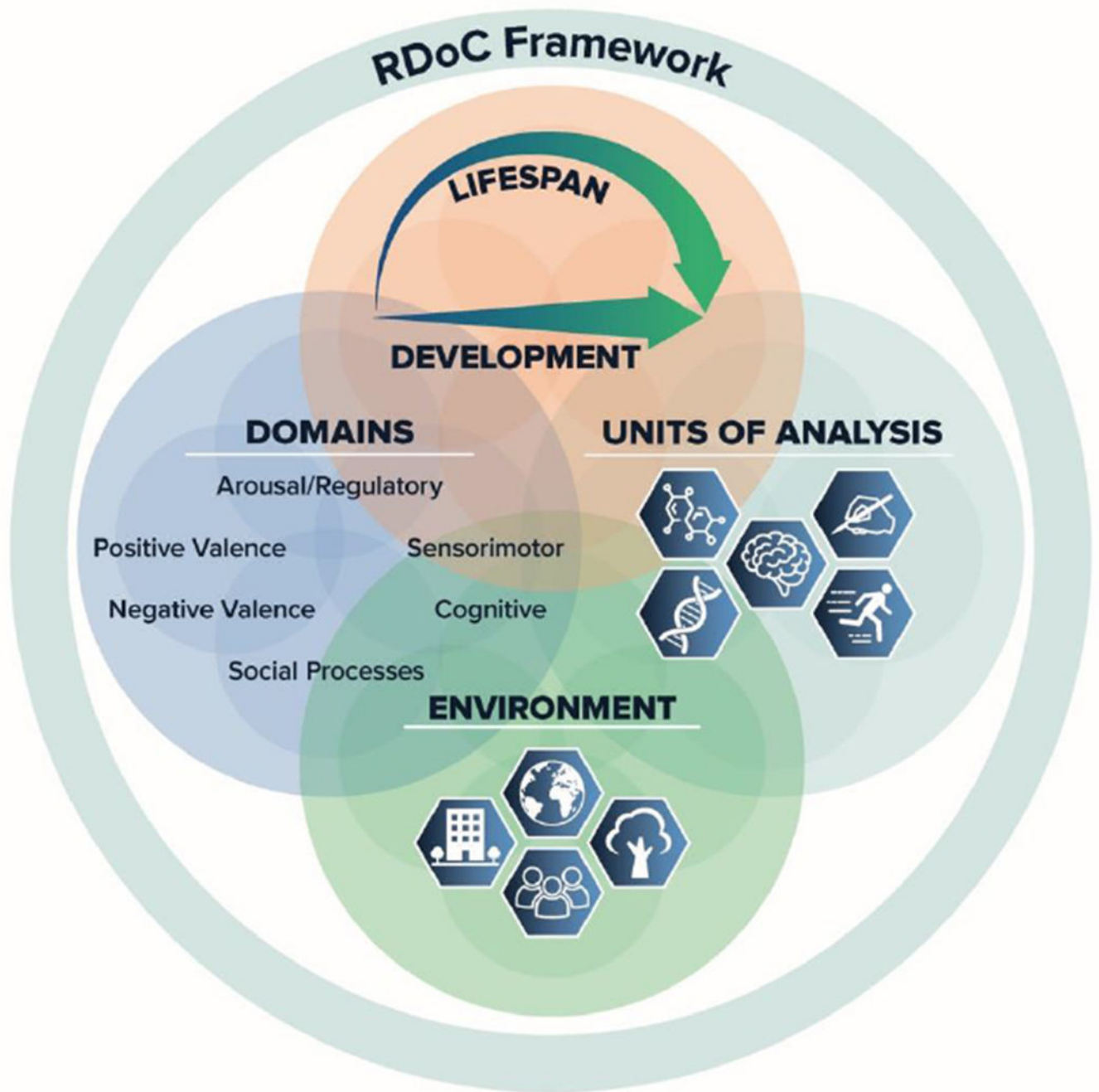
Figure 2.

This figure is a visual representation of the RDoC framework. The framework is a dynamic structure that currently focuses on six major domains of human functioning (e.g., Negative Valence Systems, Cognitive Systems). Contained within each domain are several behavioral elements, or *constructs*, that comprise different aspects of its overall range of functions. Constructs are studied along a span of functioning from normal to abnormal with the understanding that each is situated in, and affected by, environmental and neurodevelopmental contexts. Measurements of constructs can be made using several

different classes of variables, or *units of analysis*, which include genetic, physiological, behavioral, and self-report assessments. The RDoC framework is designed to evolve based on new findings from the research community and thus will be modified to include new and/or revised constructs and domains.
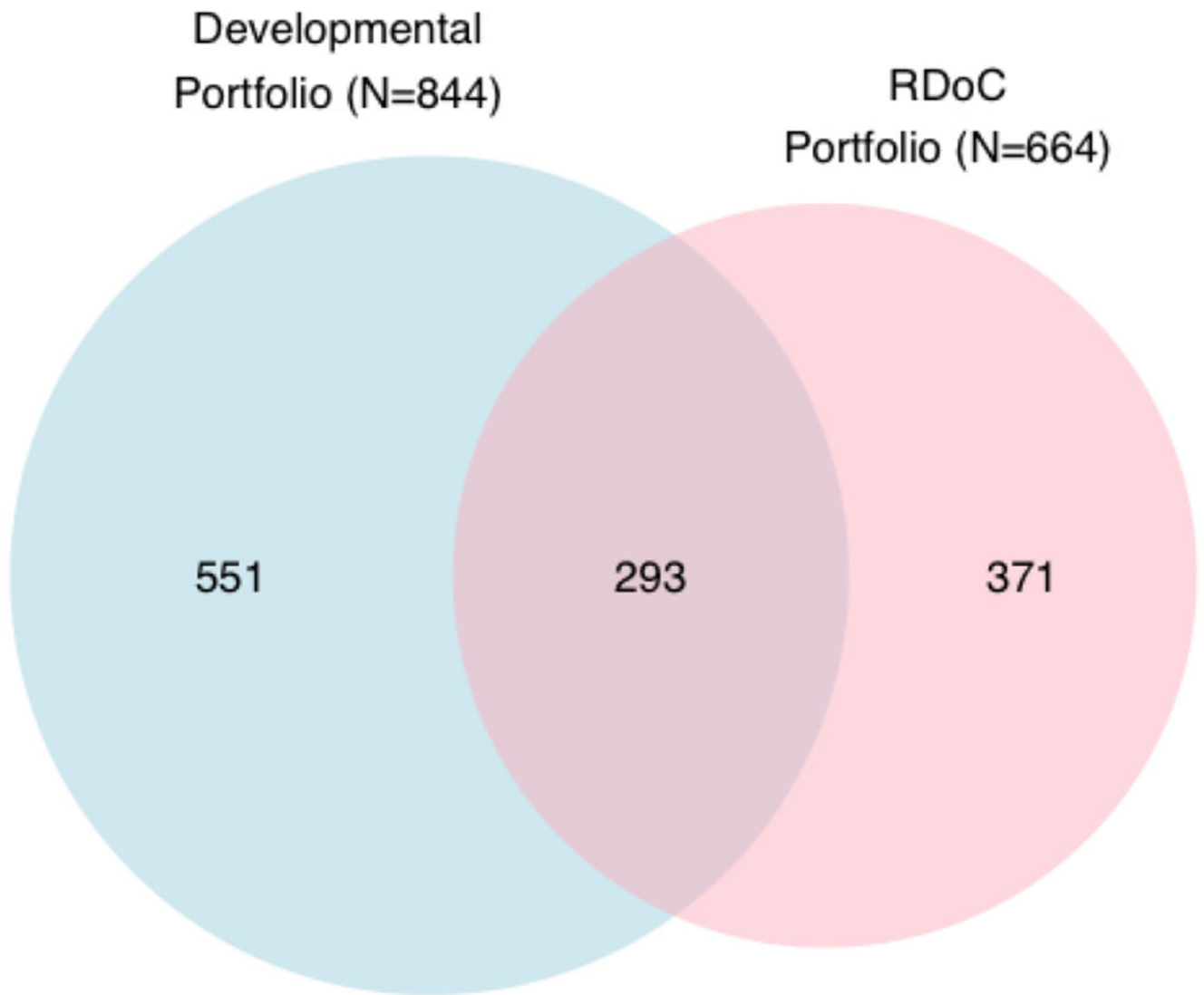
Figure 3.
A Venn diagram depicting the overlap between the NIMH Developmental Portfolio (n=844) and the NIMH RDoC Portfolio (n=664) between 2008 and 2019. There were 293 funded grants that fall in both portfolios.
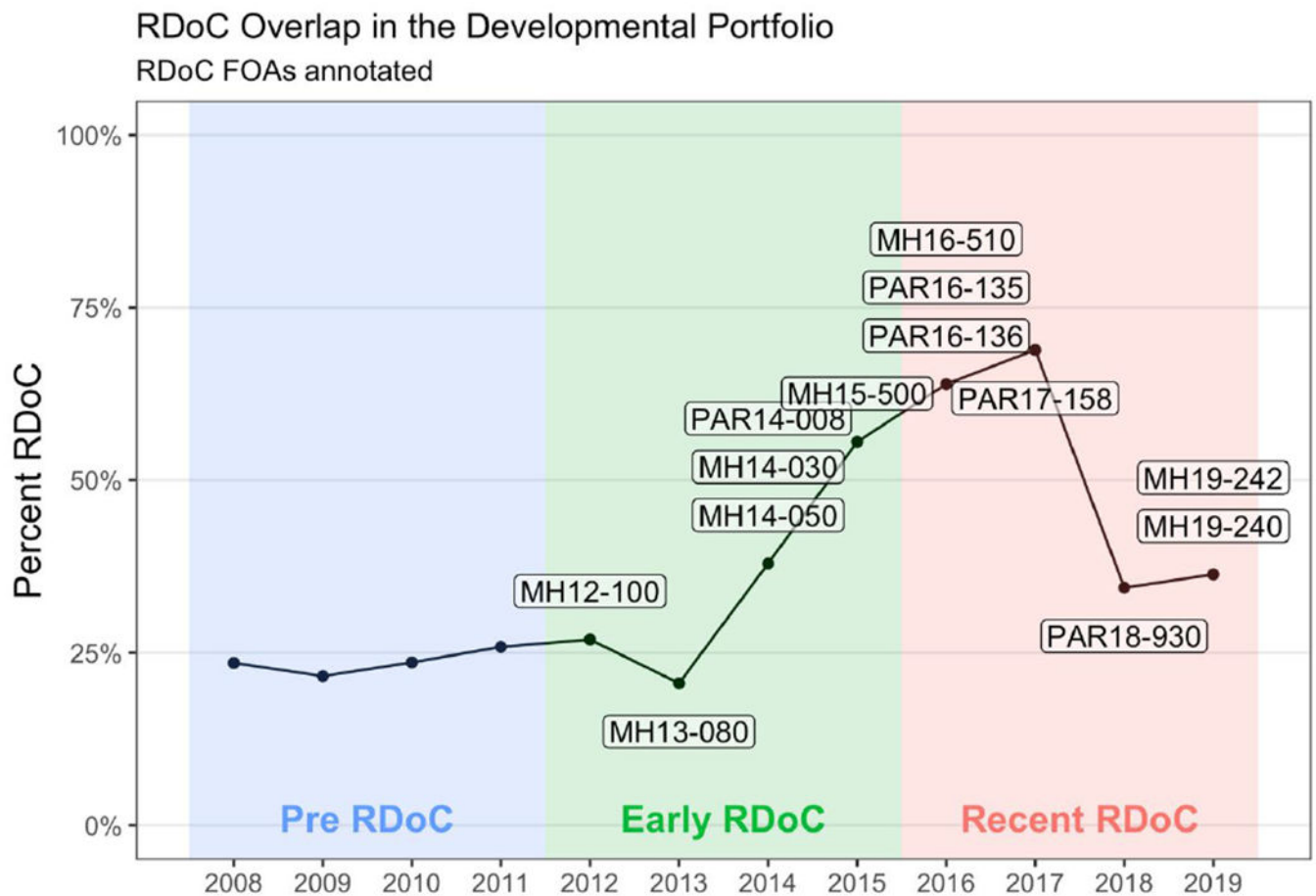
Figure 4.
A line graph showing the percent of the Developmental Portfolio that is also in the RDoC Portfolio by year, from 2008 to 2019. Timeframes of "Pre RDoC", "Early RDoC", and "Recent RDoC" are shaded in blue, green and red (respectively), to identify the timeframes relationship to the initiation of the RDoC framework at NIMH. Relevant Funding Announcements are overlaid to depict the allocation of funds specific to RDoC research.[2]

Figure 5.
The bar graph on the left shows the number of publications that came from the RDoC-developmental portfolio per year from 2008-2019. The bar graph on the right shows the weighted RCR, representing a citation-based measure of influence, of the publications per year. The weighted RCR is normalized to other papers in the same field and year, with a score of 1 representing a publication with average influence. The red line shows the average RCR by year.