Commentary

Toward Refinement of Our Understanding of the Fundamental Nature of Addiction

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In this issue, Kwako et al. (1) propose a heuristic framework and recommended a battery of measures for substance use disorders. This battery, named Addiction Neuroclinical Assessment (ANA), includes a wide range of measures that assess three domains: executive function, incentive salience, and negative emotionality. Kwako et al. (1) propose that this framework may improve our understanding of the mechanisms of addiction and provide prevention and treatment targets by focusing on a small number of functional domains alongside biologically informative assessments (e.g., genetics and neuroimaging) and other standard measures (e.g., substance use history and clinical life outcomes). This approach is conceptually consistent with the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health (2), which has yet to be adopted for substance use disorders (SUDs). This thought-provoking proposed ANA framework should serve as a springboard for a much-needed discussion on the scientific rationale, feasibility, and potential benefits of converging addiction research around a unified extensive assessment approach to propel progress in the field.

The proposed ANA is offered, in part, to address the challenges inherent in making clinical advances in the addiction field while solely relying upon outcome-based symptoms (i.e., negative impact upon life domains) for the diagnosis of SUD in the absence of biomarkers or other mechanism-informed measures. While significant progress has been made in the basic and clinical sciences of SUD, these advances have not yet fully translated to standard clinical care of addicted individuals. Most notably, the field lacks objective biological or neurocognitive markers with the sensitivity and specificity necessary for clinical application that uniquely distinguish individuals with SUDs from those who have been exposed to drugs or alcohol but do not develop SUDs. As a result, SUD continues to be clinically defined at the behavioral level, and the clinical conceptualization of its core features have remained relatively stagnant over the past 50 years (3,4). Kwako et al. outline several important challenges arising from the current diagnostic "outcome-based" approach that may be overcome with the adoption of a more "processed-based" or "mechanism-based" diagnostic approach.

To achieve this aim, ANA explicitly emphasizes greater linkage of SUD to cognitive and affective neuroscience, which we applaud, and underlines the importance of including methods (e.g., neuroimaging and genetics) for investigating important biological factors, when feasible. In addition to hypothesis-driven approaches, we agree with Kwako et al. that data-driven approaches in the absence of a clear a priori hypothesis (e.g., genome-wide association studies) may also play an important role in identifying novel underlying biological

mechanisms of addictive disorders. In a similar vein, the analysis of large data sets tapping the proposed functional domains may identify neurocognitive markers for initiation, maintenance, and treatment response across SUDs. Ultimately, the ability of any unifying framework, such as ANA, to facilitate clinical progress will depend not only on its foundations but also on its continued refinement and adaptation. An iterative process would be optimal, wherein SUD model–informed frameworks (such as ANA) guide data collection for both data- and hypothesis-driven investigations; these data would then be used to carefully and systematically refine conceptualization of the key functional domains and accordingly expand and contract the target lists of appropriate measures that will allow valid and reliable assessment of each domain. These refinements would then be incorporated into the SUD model–informed framework. Importantly—and for the field to avoid another lag in connecting SUD theory and clinical practice—any such research framework should be built with the expectation that it will be updated as new findings emerge. This process ensures that frameworks do not drift toward dogma over time and helps minimize lags in connecting SUD theory and clinical practice. In this light, the wide breadth of assessments recommended by ANA serves as a potential strength to enable such flexibility. As such, ANA could serve as an impactful jumping-off point. In the iterative process of applying and honing a framework such as ANA, the field can begin to address some important questions that were—perhaps deliberately—left open-ended.

Several existing limitations and challenges in the literature could guide the first applications of ANA. First, each of the proposed functional domains represents a rather broad construct. For example, executive function includes diverse functions, such as response inhibition, working memory, attention, problem solving, decision making, set shifting, and planning. Similarly, negative emotionality is also a broad and largely nonspecific construct. Negative affect may be difficult to operationalize, as shown by the large number of proposed tasks for this construct, ranging from tasks that may be sensitive to tolerance for negative emotionality (e.g., cold pressor task), to tasks that are not specifically designed to measure negative emotionality but may be disrupted by its induction (e.g., digit span), to self-report of indicators that have known associations with negative emotionality (e.g., Childhood Trauma Scale). As such, the recommended full ANA battery includes a range of tasks and questionnaires for each domain. Although in some clinical or research situations it will be feasible to administer the full 10-hour recommended ANA battery, many clinical situations or study designs will not allow for this approach. The inclusion of large numbers of

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assessments also brings issues about participant fatigue; particularly, addicted individuals who can tolerate 10 hours of assessment would likely lead to selection bias in the development of samples. We believe priority should be given to specification of key modifiable targets in these and other relevant domains (e.g., conscientiousness and cognitive control). If ANA were applied in this way, a helpful next step for the field would be the characterization of subcomponents of ANA according to optimal research or clinical questions/situations.

Second, the authors recommend ANA as a tool to develop diagnostic criteria for SUD. Therefore, it will be helpful to address the specificity and sensitivity of these measures to SUD. Comorbidity of other psychiatric conditions with SUD is rather common; much of the existing literature does not fully account for these comorbidities, and the three proposed functional domains have also been linked to multiple psychiatric disorders. In contrast to the executive deficits seen in patients with neuropsychiatric disorders, such as schizophrenia and dementia, the deficits seen in SUD are more subtle and have greater individual variability (5). It would be a valuable contribution to have ANA subcomponents classified based on whether they are expected to show shared or unique patterns of impairment within SUD and other psychiatric conditions. This information could improve specificity and sensitivity if diagnostic guidelines are developed from ANA, and in the interim could guide the choice of ANA tasks for studies of AD where comorbid conditions are not excluded (e.g., a study of AD that does not exclude for major depression may choose tasks that are typically impaired in addictive disorders [ADs] but not depression). A related challenge comes from the fact that most studies assessing cognitive functions in patients with SUDs have been cross-sectional and many have methodological shortcomings, such as comparison groups that were not matched for education, premorbid IQ, or other factors that could impact cognitive function (6). As the ANA is applied, it would be of value to distinguish which components of the battery are most robustly associated with ADs after accounting for these factors.

Another set of research questions that could be informed by the ANA (and then used to further refine the ANA) would be clarification of how domains or specific recommended ANA measures are differentially associated with the preexisting vulnerability to initiation of use, vulnerability to transitioning from use to addiction, acute effects of a drug, acute effects of withdrawal (short- or longer-term), responsiveness to treatment, and recovery with longer-term abstinence. Many of these effects are difficult to decouple within the existing AD cognitive literature, given the inconsistent consideration of recent substance/drug use or the potential influence of acute and chronic withdrawal states (6). This uneven consideration of such factors may contribute to the fact that cognitive deficits in ADs show substantial individual variability (5). If ANA is expanded and continually updated to place its recommended measures within the context of the current state of knowledge of this complex and ongoing line of research, it would facilitate further clarification of the process of the disease.

In addition to diagnostic value, it would be a valuable application of ANA to establish which domains or subdomains are most sensitive to change during or after specific treatments or across prolonged abstinence. These processes would be best measured longitudinally, and therefore it would be helpful to include within ANA the classification of which tasks are or are not recommended for repeated administration. There is still a paucity of assessments of these fundamental processes that are sensitive to change and that can be administered repeatedly. We believe future work should focus on filling these gaps, including new models of addiction that should incorporate the contribution of these functional domains. Kwako *et al.* have undertaken an important and difficult task to attempt to provide direction for the future of SUD research. The ANA provides a valuable framework; with iterative updates informed by the broader research community, it could facilitate the smoother integration of research with clinical practice.

Article Information

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