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The importance of standardization of stimuli for functional MRI tasks to evaluate substance use disorder pathology

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Despite over 2 decades of work using functional magnetic resonance imaging (fMRI) to characterize the neural circuitry underlying substance use disorder (SUD), our field is still unable to definitively state which neural circuitry alterations are most consistently associated with the presence of an SUD, or which are the most clinically relevant (e.g., able to predict outcome or treatment response). The absence, thus far, of a replicated neural biomarker may be due, in part, to the lack of standardized stimuli and tasks across studies. The article by Stauffer et al. (1) in this issue of the *American Journal of Drug and Alcohol Abuse*, entitled “American Alcohol Photo Stimuli (AAPS): A standardized set of alcohol and matched nonalcohol images,” is aimed at making available a standardized, matched set of photographic alcohol and nonalcohol beverage stimuli, and at establishing their face and construct validity by comparing appetitiveness and task performance in heavy versus light drinkers. Stauffer et al. is important and unique from previous similar work by Pronk et al. (2), which measured drinking urges to alcohol cues in heavy versus light drinkers, because it used North American culture-relevant stimuli, and from work by Pulido et al. (3) which assessed affective (arousal, valence) and perceptual (familiarity, complexity) features of alcohol stimuli in young nondrinkers only. Increased standardization of fMRI tasks across laboratories may help mitigate the absence of consistent replication from study to study.

There are three main categories of imaging tasks typically used in fMRI SUD research: those engaging circuits involved in (2) cognitive control, (3) processing emotional stimuli and emotion regulation (emotional tasks), and (4) processing drug cues. It is believed that vulnerabilities in any of these three domains could predispose an individual to suffer from loss of control over alcohol and drug use, and that these vulnerabilities have an underlying neurobiological basis measureable with fMRI. Indeed, brain activation during these tasks holds promise as being more sensitive than self-report or behavioral performance on neuropsychological tests, as fMRI more directly measures the underlying neurobiology rather than symptoms or signs of dysfunction and is more objective than self-report.

A wide variety of tasks have been utilized during fMRI within each of the three aforementioned categories [see (4,5) for a summary of the cognitive control and emotional

tasks utilized in SUD and (6–9) for details on the types of alcohol cue tasks]. Results from these studies in SUDs show that there are some consistencies within categories, but also some major inconsistencies that are often difficult to explain. During tasks of cognitive control in SUDs, hypoactivation is often observed during response inhibition, whereas hyperactivation is generally observed during selective attention (4,10–12) relative to controls. This highlights that different task designs can produce different neural patterns, even when the underlying constructs being measured are presumed to be similar. Similarly, there are some unifying themes regarding the brain responses during emotional tasks [e.g., individuals with SUD mount a less robust ventromedial prefrontal cortical response than controls (5)] but inconsistencies in the direction of the effect of an SUD diagnosis on insular and amygdalar activation (5). Finally, in the area of cue reactivity, although there is some consistency across studies investigating the overall differences between the presentation of alcohol and control cues, the relation to clinically relevant metrics such as AUD severity or effects of treatment on cue-related response is less consistent [see (13) for review].

Many of the explanations for nonreplication relevant to all (nonimaging) clinical SUD studies also apply to fMRI SUD studies. These reasons have to do with variability in the population assessed, including inpatient or outpatient status, length of abstinence, drug of choice, illness severity, treatment seeking vs. not, gender, comorbid psychiatric conditions, and/or age. However, fMRI research presents other challenges that contribute to difficulty replicating results, including different analysis software packages (FSL, SPM, AFNI, Brainvoyager), different thresholding levels/methods (e.g., familywise error, false discovery rate, cluster-based thresholding), regions of interest vs. whole brain analyses, and different volumes used within which to correct for multiple comparisons. Establishing standard stimuli will move us in the direction of keeping one of the many possible variables constant.

Using standardized stimuli across laboratories would increase confidence in the results and provide a better understanding of the networks involved in processing these particular cues. The effects of subsequent of task (e.g., stress induction) or treatment (e.g., specific pharmacotherapy) manipulations to an identified neural network could be more clearly isolated. Rather than having to explain away idiosyncratic findings that potentially result from a given stimulus set, studies would be able to more confidently assert which cognitive or clinical mechanisms are contributing to an observed brain response. Prior studies, for example, have found that brain responses to visual alcohol cues (i.e., pictures) in the striatum are positively associated with worse treatment outcome (14), are reduced in response to treatment with naltrexone (15), and are predictive of clinical response to naltrexone (16); replication of these findings using a standard stimulus set would move the field toward establishing these responses as useful biomarkers. On the other hand, self-report measures of cue reactivity or peripheral physiological markers (e.g., salivary response, galvanic skin response) have largely used similar methods across studies and nevertheless have found mixed evidence that these measures can predict relapse (17,18); whether similar efforts to predict outcome with fMRI-based predictors can reliably improve relapse prediction remains to be seen.

Another related benefit of articles such as Stauffer et al. to our field is the importance of establishing construct validity [the degree to which a test measures what it claims, or

purports, to be measuring (20)]. Brain activation during working memory tasks has been found to be both elevated and reduced in AUD compared to controls, depending on the type of task used (4). This could be due to a construct validity problem; it is unwise to assume that just because a working memory-like task is run during fMRI, it is actually measuring the same underlying construct as validated working memory tasks, and activating working-memory brain networks.

Although we strongly support attempts at standardization, there are limitations that must also be considered with this work. First, a total of 18 alcohol stimuli and 18 nonalcohol stimuli were matched by Stauffer et al. While this number is adequate for a single fMRI session, repeated scanning sessions would require more stimuli to prevent habituation responses. In addition, certain designs (e.g., oddball tasks) require additional stimuli to produce an adequate number of trials. Future efforts generating a more comprehensive library of standardized stimuli with hundreds of pictures would be extremely valuable to the field. Second, although Stauffer et al. mention that specific brands were not included, inclusion of branded as well as unbranded stimuli would be important for those investigations exploring the frequency of consumption of a particular branded beverage. For example, brain responses to stimuli of an individual's favorite brand may elicit much larger brain responses. Relatedly, there may be considerable regional variation that may not lend itself well to a single standardized set of images; participants in Albuquerque report beers from local microbrews as their most frequently consumed beverage, which is unlikely to be captured in a standardized picture set from another region within the United States. Finally, including ratings of the pictures in this larger picture set would be essential. For example, in the International Affective Pictures Series (21), ratings of arousal, valence, and dominance are included in the normative picture series; this is useful when designing tasks and matching pictures across categories.

Despite these challenges and limitations to standardization, it is imperative to continue toward this goal. To establish the utility of fMRI formapping the brain circuitry changes underlying addiction, to measure biomarkers predictive of treatment response, or to identify neural circuitry-based treatment targets, we need to be more rigorous about replicating our methods and findings across laboratories and populations. Although a proposal to develop a standardized database may not be well-received by review boards because of relatively low innovation, this work is critical for moving the field toward clinically useful neural markers of SUD pathology and treatment effects.

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