Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2020 June ; 5(6): 560–561. doi:10.1016/j.bpsc.2020.04.010.

Heart Rate Variability as a Link Between Brain-Elicited Substance Cues and Substance Use Severity

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Heart rate variability (HRV) has been studied as a predictor or potential modifiable risk factor for various physiological and psychological conditions, including excess substance use and related disorders. Previous functional magnetic resonance imaging research has established a neuroanatomical overlap between the activity in areas associated with HRV modulation and structures associated with reward and addiction. Taken together, this literature suggests that there are hemodynamic alterations that are associated with each substance of abuse. Most of this research reports a decrease in HRV immediately after ingestion of the substance. This decrease may vary among substances, as inhaled substances (marijuana, cigarettes) may have a more direct route to influence the autonomic nervous system compared with swallowed substances (alcohol, pills). However, this postingestion temporal connection does not represent the anticipation of using the substance experienced by the individual.

Individuals may psychophysiologically prime themselves before using a substance, a phenomenon referred to as “craving” or “urge.” Priming may happen with simple substance cues, to which persons with substance use disorders are more sensitive, leaving the person to experience greater subjective craving. This sensitivity is expressed via attential biases to substance-related cues and psychological distress relating to the substance. Ultimately, the substance-related cues may have a deleterious impact on the normal or typical activity in the prefrontal and frontal corticial circuits. Previous research suggests that psychophysiological alterations from cues are not limited to the central nervous system, as the alterations also include peripheral determinants, such as HRV modulation (1). The substance cues may engage particular frontal and temporal structures that are tasked with regulating the balance between parasympathetic and sympathetic nervous systems. These neural structures are a part of the central autonomic network or the central autonomic nervous system. Once these cortical autonomic structures are taken offline or engaged by another task (i.e., substance use cues), the tonic inhibitory control of the central autonomic network or the central autonomic

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Disclosures

FGM has received grant support from Indivior Pharmaceuticals and Nektar Therapeutics and is a consultant for Astellas Pharmaceuticals for research unrelated to this commentary. LK, AAr, and AAb report no biomedical financial interests or potential conflicts of interest.

nervous system structure(s) are removed. Subsequently, sympathoexcitatory neural circuits activate and dysregulate the balance between parasympathetic and sympathetic activities, leading to a reduction in HRV levels. The results presented by Wang *et al.* (2) in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* are consistent with this framework, as alcohol drinkers (vs. healthy control subjects) experienced a decrease in HRV when presented with substance (alcohol)-related cues. Further, they were able to present differences within medial prefrontal activity and their association with alcohol use disorder (AUD) severity scores as a function of HRV.

To date, few studies have directly determined the intersection of substance use cues and autonomic activity via functional brain imaging or functional magnetic resonance imaging, but doing so could help disentangle causal components of the autonomic response and balance in substance users. The study by Wang *et al.* (2) is unique in that the direct observation of changes in brain activity using functional magnetic resonance imaging during a cue-elicited craving task, and simultaneous monitoring of HRV, allows for mediation analysis of the relationship between disease severity (in this case via the Alcohol Use Disorders Identification Test score), HRV (via root mean square of successive differences levels), and brain activity. Their finding that HRV mediates the association of cue-induced decreased ventromedial prefrontal cortex activity and a measure of disease severity (the Alcohol Use Disorders Identification Test score) is novel and important because it supports the hypothesis that changes in cue-induced brain activity exert control over the central autonomic network or the central autonomic nervous system and that the strength of this association either accrues over time with worsening of AUD or is directly related to AUD symptom severity. Thus, their findings are an important step forward not only in psychophysiological research but potentially in any translational research that includes autonomic activity. Moreover, the findings reported by Wang *et al.* (2) suggest that cue-elicited changes in HRV may develop over time. The data from drinkers with a spectrum of alcohol intake and AUD severity further suggests that AUD disorder may exacerbate these changes. The fact that subjective craving and change in HRV were not significantly correlated may speak to the potential usefulness of this biomarker beyond what is available with a simple rating scale.

Many questions remain about the relationship of HRV to AUD pathophysiology, and some new questions arise from Wang *et al.*'s study (2). Interestingly, they found that right anterior cingulate cortex and thalamus areas showed changes in activation with cues, though the relationship did not hold when introduced to the mediation analysis. Are other areas such as the right anterior cingulate involved in the cue-elicited HRV response? We have previously shown that drug cue–related attentional bias correlates with anterior cingulate cortex–hippocampus connectivity in cocaine users (3) and opioid users (4) using dynamic causal modeling. The use of dynamic causal modeling and effective connectivity may be a way to further study the relationship between these areas as they relate to cue-elicited HRV variation. Such methods may capture the circuitry activation in more detail. What is the role of HRV change in the maintenance of harmful drinking patterns, and can direct attenuation of the cue-induced HRV response reduce AUD symptoms? Does the change in cue-elicited HRV associated with AUD serve merely as an epiphenomenon and biomarker of illness? Even if so, HRV may still be useful for informing precision-guided treatments.

As we consider HRV as a vector for AUD symptomatology and potentially treatment, we must also consider the direct impact AUD has on HRV. AUD is associated with increased cardiovascular disease risk. Specifically, AUD is associated with cardiomyopathy, coronary heart disease, and myocardial infarction. Given that HRV is an important indicator for cardiovascular risk, including HRV in treatment-based cardiovascular risk prevention strategies for those with AUD or treatment programs designed to potentially limit AUD severity may be fruitful. Psychologically, studies have begun to identify HRV as a predictor of self-regulation, both physiologically and behaviorally. Further understanding or the phenomenology of HRV as it relates to AUD may help researchers and clinicians understand the pathophysiology of the disorder and work toward precision therapeutics. The implications of Wang *et al.*'s findings suggest that treatments disrupting cue-elicited HRV and reducing sympathetic activity (e.g., mindfulness or other forms of meditation or yoga) might be viable in treating AUD and perhaps also in reducing the cardiovascular disease–related mortality in those with AUD. The psychiatric sequelae of AUD, including anxiety and depressive disorders, are already being treated with forms of cognitive behavioral therapy programs infused with HRV as an indicator of self-regulation. Empirically informing and adapting similar programs may aid in mitigating cue response reaction time and ultimately in reducing the physiological response to alcohol-based cues in a person with AUD, thus reducing the AUD symptomatology behaviorally and physiologically. Some researchers and clinicians have initiated the biobehavioral path of treatment for substance use disorders, yielding some inconsistent results. Through mechanisms like HRV biofeedback-based treatments, some have seen reductions in substance cravings. However, there are remaining concerns with mood dysregulation posttreatment, where substance-using individuals have trouble maintaining learned mitigating behviors during episodes of relapse and emotional distress. Additional important concerns, such as the complex interplay or exacerbation brought on by polysubstance use and psychological disorders influencing cardiovascular health, also deserve elucidation.

Acknowledgments

This work was supported by National Center for Advancing Translational Sciences Diversity Supplement Grant No. 3UL1TR002649-02S1 (to LK). The contents herein are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

References

1. Ingjaldsson JT, Laberg JC, Thayer JF (2003): Reduced heart rate variability in chronic alcohol abuse: Relationship with negative mood, chronic thought suppression, and compulsive drinking. Biol Psychiatry 54:1427–1436. [PubMed: 14675808]
2. Wang W, Zhornitsky S, Le TM, Zhang S, Li C-SR (2020): Heart rate variability, cue-evoked ventromedial prefrontal cortical response, and problem alcohol use in adult drinkers. Biol Psychiatry Cogn Neurosci Neuroimaging 5:619–628. [PubMed: 32061544]
3. Ma L, Steinberg JL, Cunningham KA, Bjork JM, Lane SD, Schmitz JM, et al. (2018): Altered anterior cingulate cortex to hippocampus effective connectivity in response to drug cues in men with cocaine use disorder. Psychiatry Res Neuroimaging 271:59–66. [PubMed: 29108734]
4. Ma L, Steinberg JL, Bjork JM, Taylor BA, Arias AJ, Terplan M, et al. (2019): Cingulo-hippocampal effective connectivity positively correlates with drug-cue attentional bias in opioid use disorder. Psychiatry Res Neuroimaging 294:110977. [PubMed: 31439409]