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Playing It Safe: A Video Game Probing the Relationship Between Addiction, Gender, and Avoidance

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Heroin addiction is a growing public health problem in the United States, driven by an epidemic of opioid painkiller misuse.[1] Individuals with opioid use disorders show a wide range of behavioral abnormalities that may have diagnostic and prognostic value.[2,3] Avoidance is a common behavior intended to prevent aversive experiences.[4] However, avoidance that exceeds the level of impending threat[5] is maladaptive and could be symptomatic of psychopathology.[2,6,7]

In an innovative and thought-provoking study that appears in this issue of *JCP*, Sheynin et al[8] used a video game to study avoidance behavior in heroin-dependent patients. In this paradigm, inspired by Molet et al,[9] players control a spaceship and gain points by shooting enemy spaceships and avoiding being shot down.[9,10] Warnings about an impending attack by enemy craft were displayed periodically on the screen. Players could avoid being shot down and losing points by "hiding" their virtual spaceship. However, a hiding spaceship could not shoot down enemy craft, preventing the player from accruing game points. During the acquisition phase of the task, warnings were followed by an attack from enemy craft. During the extinction phase, warnings were no longer followed by an attack. Authors found that while male patients and controls showed comparable avoidance during a virtual attack, male patients hid their spaceships more during the warning periods and were slower to stop hiding during the extinction trials. In contrast, there was no difference between female patients and controls.

Sheynin et al previously reported using this task to capture individual differences in vulnerability to anxiety,[10] supporting its potential clinical relevance. Studies show that individuals with substance use disorders (SUD) tend to downplay the severity of their disease and are reluctant to actively cope with stressful real-life issues in general.[3,11–13] Given the association between maladaptive avoidance and poor SUD treatment outcomes,[14,15] reducing avoidance has become one of the key objectives in some addiction recovery programs.[11,16] The computerized video game paradigm reported by Sheynin et al[8] has the potential to provide a quantifiable index of maladaptive avoidance.

The male patients' excessive hiding during the warning periods of both the acquisition and extinction phases suggests greater maladaptive avoidance in this cohort. While these results are consistent with an earlier study in SUD patients showing greater harm avoidance[13] and more difficulty learning from prior mistakes,[2] they seem to contrast the well-established tendency toward greater than normal risk taking in SUD patients.[17] Such an apparent contradiction could be due to the multifaceted nature of avoidance behaviors that entail both cognitive and emotional components.[4] Effective avoidance of threats requires accurate cognitive representations of the association between stimuli, behavior, and outcome.[18,19] However, one's lower tolerance of negative emotion associated with threat is a key factor that determines the degree of avoidance.[6,20] Therefore, maladaptive avoidance in male heroin-dependent patients could result from either impaired cognitive processes, such as insufficient working memory and cognitive flexibility,[21] or excessive emotional reactivity to aversive events.[13,22]

Sheynin et al[8] found that while female patients and controls were equally good at avoiding being shot down during the video game task, male patients showed greater avoidance than the male controls. This important sex difference suggests that while the male patients' avoidance was maladaptive, female patients' avoidance was intact. All patients in the Sheynin et al[8] study had a history of heroin dependence; however, during the study, most were maintained on methadone and a few on buprenorphine. The sex differences in neuroendocrinology and neurochemistry[23–25] make agonist maintenance an important factor in the interpretation of the study findings. Some cognitive side effects of methadone are not sex-specific.[26] However, methadone lowers plasma testosterone,[27,28] a principal male sex hormone that not only controls male reproductive function, but also promotes aggressive behavior.[29,30] Buprenorphine has a much smaller effect on plasma testosterone.[31] Therefore, opioid agonist maintenance treatment could modulate the differences between the male and female patients, between the male patients receiving buprenorphine and methadone, and between all male patients and controls. It is possible that the exaggerated avoidance in the male patients was in part due to the effect of methadone on testosterone levels, which could have reduced aggressive behaviors in the video game and increased hiding behaviors. Future studies could test this hypothesis by comparing methadone-maintained patients with a control group maintained on buprenorphine or long-acting naltrexone or a group treated nonpharmacologically.

Seven of 27 patients in the Sheynin et al[8] study reported having a diagnosis of schizophrenia, while 7 more reported

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depression, panic disorder, bipolar disorder, or cluster B personality disorder. Schizophrenia coincides with a range of cognitive deficits from impaired language processing to poor working memory,[32,33] functions that may be required to perform the study video game task. Considering the gender differences in the prevalence of both schizophrenia[34] and depression,[35] it would be important to ensure that these disorders were balanced across genders in Sheynin et al.[8]

Sheynin and colleagues'[8] study highlights the rapidly growing use of video games, mobile phone apps, and virtual reality techniques as outcome measures and therapeutic interventions in clinical research and practice.[36–39] Such "gamification" increases ecological validity of the test and is especially relevant in the context of impaired motivation that hampers experimental assessments in SUD.[40] While Sheynin et al[8] are making an important contribution to our understanding of the mechanisms of avoidance in opioid addiction, its potential clinical applications would require additional research directly linking the video game performance to the real-life maladaptive avoidance in SUD patients. It would also be interesting to determine whether video game performance can predict treatment outcomes, similar to recent studies using neurophysiological biomarkers.[41,42] To disentangle the cognitive and emotional mechanisms of exaggerated avoidance, one could add standard measures to the video game paradigm. For instance, the Wechsler Adult Intelligence Scale[43] or the Wisconsin Card Sorting Test[44] would address cognitive performance, and the Affective Go/No-Go Task[45] would address emotional responses. Since real life almost invariably involves social interactions, it would be interesting to examine SUD patients' maladaptive avoidance in a social context. For example, a 2-player[46] rather than a solo video game could probe aspects of social cognition such as theory of mind, cooperation, and empathy, which are known to exhibit gender differences[47,48] that may be affected by SUD. Finally, it is yet to be determined whether the findings in Sheynin et al[8] can be generalized to other substances of abuse. Answering these questions will help to unravel the complex interactions between addiction, gender, and avoidance behavior and translate the approaches and results presented here to clinical practice.

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