Published in final edited form as:

Biol Psychiatry. 2018 November 15; 84(10): e71–e72. doi:10.1016/j.biopsych.2018.08.011.

The Importance of Drug and Sex Effects in Psychiatric Research

Ansel T. Hillmer, Ph.D.^{1,2,3}

¹Dept. of Psychiatry, Yale University School of Medicine

²Dept. of Radiology and Biomedical Imaging, Yale University School of Medicine

³Dept. of Yale PET Center, Yale University School of Medicine

Rates of tobacco smoking are disproportionately higher among people with major psychiatric diagnoses and other substance use disorders. This disparity is an important aspect to improving public health. It is therefore critical that we consider tobacco smoking in human research of psychiatric disorders. The manuscript by Hirvonen et al. in this issue of *Biological Psychiatry* addresses this consideration by measuring cannabinoid 1 (CB₁) receptor availability in healthy male tobacco smokers compared to healthy male nonsmokers(1). CB₁ availability was measured with positron emission tomography (PET) imaging using [¹⁸F]FMPEP-*d*₂, an inverse agonist radioligand for CB₁ receptors. The authors reported significantly lower CB₁ availability in healthy tobacco smokers compared to healthy nonsmokers. Then, to further investigate the role of concurrent tobacco smoking with use of other substances, the authors examined tobacco smoking status within groups of daily cannabis users and individuals with alcohol use disorder from previously reported studies. Tobacco smokers who smoked cannabis or had alcohol use disorder did not exhibit significantly different CB₁ availability compared to nonsmokers from the same respective groups. In contrast, a separate group reported significantly higher CB₁ availability in tobacco smokers with schizophrenia compared to nonsmokers with schizophrenia(2). As Hirvonen et al. state, these collective findings nicely demonstrate that tobacco smoking has diverse effects on the cannabinoid system in different neuropsychiatric populations.

The interpretation of lower CB₁ availability in tobacco smokers vs. nonsmokers is not straightforward. Group differences in PET outcome measurements can be attributed to a number of factors, including differences in receptor number, differences in receptor occupancy due to endogenous or exogenous drug, or differences in affinity of the radioligand for the target site. Lower numbers of CB₁ receptors in tobacco smokers is the most likely interpretation in this case, as a radioligand analog of [¹⁸F]FMPEP-*d*₂ was insensitive to roughly 3-fold increases in endogenous cannabinoid levels(3). Hirvonen and colleagues hypothesize that tobacco smoking downregulates CB₁ receptors due to chronic alterations in endocannabinoid levels from repeated nicotine exposure. This hypothesis is based on preclinical work indicating that nicotine interacts with the cannabinoid system by altering endocannabinoid levels and that nicotine does not directly act at CB₁ receptors. However, it remains to be determined if CB₁ availability changes during abstinence. If

differences in CB₁ availability do not return to baseline levels after smoking abstinence, it remains an open question whether the CB₁ differences result from chronic substance use, or alternatively, if CB₁ availability may be present prior to chronic use and potentially contribute to drug use behaviors. This question is particularly important since CB₁ availability normalizes after abstinence from chronic cannabis(4–6), but does not change during at least 4 weeks of abstinence from heavy alcohol drinking(7, 8). In addition, the study sample represents moderate cigarette smoking based on 12±7 cigarettes/day and moderate levels of nicotine dependence, with no evidence for relationships between CB₁ availability and cigarettes/day or level of dependence. Future research that determines the threshold of tobacco smoking needed to alter CB₁ availability, or indeed if tobacco smoking reduces CB₁ availability at all (i.e. availability is lower before one begins smoking), is critically important to inform future research in targeting the cannabinoid system to help reduce rates of tobacco smoking.

Sex plays a critical role in the neurobiology of tobacco smoking and treatment outcomes. Inclusion of only men in the study population is a stated limitation of this paper, yet sex as a biological variable is particularly relevant for the cannabinoid system given reported sex differences in CB₁ availability in healthy controls(9). Thus, while an important first step, future work is required to determine how CB₁ receptors may be affected by tobacco smoking (and cannabis use and heavy alcohol use) in women, who represent nearly 45% (and growing) of the tobacco smoking population.

While tobacco smoking prevalence is declining globally (although the number of smokers is still increasing), the prevalence of cannabis use and cannabis use disorder continues to rapidly proliferate. Similar to tobacco smoking, cannabis use rates may be disproportionately higher among individuals with major psychiatric diagnoses. Three independent groups previously demonstrated lower CB₁ receptor availability in men who smoke cannabis daily compared to healthy controls with minimal lifetime exposure to cannabis (4–6). This lower CB₁ availability rapidly increases within 2 days of abstinence, but may require up to 4 weeks to reach control levels. Given the extensive interactions of the cannabinoid system with other neurotransmitter systems, cannabis use may be an important consideration for future human psychiatric research in a manner similar tobacco smoking.

The implications of systematically characterizing the effects of different substance use and sex as a biological variable in different psychiatric disorders may seem a tall order. Yet amid calls for personalized medicine, these relatively basic factors of sex and concurrent drug use (basic relative to the complexities of genetic contributions) represent low hanging fruit to improve clinical research. The manuscript by Hirvonen et al. demonstrates the importance and feasibility of this approach in men who smoke tobacco. Ultimately, similar research in other areas can improve patient care by studying samples that are more representative of the target population, and potentially illuminate sub-group specific therapeutic approaches.

Acknowledgements:

This work was supported by K01AA024788. The author would like to thank Dr. Kelly Cosgrove for her excellent mentorship and thoughtful review of this commentary. Dr. Hillmer has no conflicts of interest to report.

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