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Interaction of Meth Abuse, Tobacco Abuse, and Gender in the Brain

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The brain imaging research report by Sung et al. (1) in this issue interlaces multiple recent recurring strands in the clinical neuroscience of substance abuse. These include possible brain interactions between drugs in polysubstance abuse, alleged beneficial effects of tobacco that may promote its use as self-medication, and differential effects of substances on the male and the female brain. Investigations such as Sung et al. are salutary in that they encourage the field to engage rather than to avoid the complexities and controversies inherent in such topics.

On the street and in the clinic, polysubstance abuse is more the rule than the exception. Smoking and drinking go hand and hand. Both commonly accompany illicit substance abuse. Co-abuse of cannabis is frequent in users of so-called hard drugs. One could add further examples. Though far from the scientific ideal of examining a single drug in isolation, these realities can render it more practical (and at times unavoidable) to investigate populations who imbibe multiple substances. These populations furthermore pose particular relevant clinical and scientific questions. Notably, do deleterious chronic effects of multiple substances simply sum linearly or is there *toxic synergy* (amplification of harmful effects) between substances? Sung et al. embrace this issue by examining the effects of tobacco use on regional brain energetic metabolism in a sample of 57 chronic methamphetamine-dependent subjects, with plentiful lifetime history of consumption of other agents. Whilst controlling statistically for those other agents, Sung et al.'s principal finding offers a third response to the question of drug interaction: tobacco use may *protect* against at least one negative effect of methamphetamine, at least in females. Thus, explicit examination of the usual, but understudied, case of polysubstance abuse has produced an unusual and potentially meaningful result.

The particular finding concerns levels of the neurometabolite *phosphocreatine* (PCr) in the pregenual anterior cingulate cortex (pACC). In female but not male methamphetamine-dependent subjects, pACC PCr levels correlated *positively* (with high significance) with lifetime tobacco use. In prior work, the same laboratory (2) had found significantly lower levels of pACC PCr in (male and female) methamphetamine-dependent subjects than in

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healthy controls. Thus, the present paper finds that, among women who used meth, those who smoked more tobacco had higher PCr than those who smoked less. Rather than magnifying neurometabolic dysfunction, it seems tobacco use impeded progression of at least one methamphetamine-associated brain abnormality (low PCr) in these women. The second major finding of Sung et al. was that the positive relationship between smoking and PCr was stronger for heavy than for moderate or light female meth users. Thus, heavy users obtained the most putative tobacco-mediated protection against depressed PCr levels.

Recalling basic biochemistry, PCr is the substrate reservoir for ATP energy exchange in the creatine kinase reaction, a mainstay of cellular energetics. PCr serves as a buffer to maintain constant ATP levels in highly active cells, including neurons. The authors contend, reasonably, that high (or at least normal) cortical levels of PCr are “good”, i.e., healthy; low levels are “bad”. That fortifies the authors’ interpretation that smoking exerts a neuroprotective effect. The authors indicate that this is not the first time that apparent beneficial effects of tobacco or nicotine on the brain have been observed in clinical neuroscience. They cite well-known findings of reduced risk of Alzheimer’s (3) and Parkinson’s (4–5) diseases in smokers vs. non-smokers, as well as preclinical studies of neuroprotective effects of nicotine. These early epidemiological results appear to be holding-up for Parkinson’s (6), if not for Alzheimer’s (7). The authors postulate concrete candidate mechanisms by which smoking could lead to neuroprotection and elevation of cortical PCr. Moreover, they cite possible cognitive-enhancing and anti-depressant properties of tobacco that may lead meth-dependent subjects to self-medicate with tobacco. The latter properties are especially germane in women, who may be more prone to depressogenic effects of methamphetamine. To be fair, the authors also cite other work showing diminished cognitive capacities in chronic tobacco smokers. On the whole, Sung et al. adds incremental empirical support to a prior model of smoking as self-medication and unwitting prophylaxis against neurotoxicity in meth abuse (8–9). The brain site of the findings in pACC (no PCr effects were not observed in two other regions sampled, occipital and temporoparietal cortices) is relevant to the theme of depression. ¹⁸FDG-PET and other neuroimaging studies have associated the pACC and adjacent cingulate subregions with mood regulation (10) and with response to treatment for depression (11–12). Thus, low PCr may be one of multiple imaging signals characterizing low mood and pACC dysfunction; high PCr may signal pACC response to tobacco as a coarse, self-administered anti-depressive therapy. To their credit, *ab initio* and again just before the conclusion, Sung et al. underscore the well-documented deleterious effects of smoking on general health, lest anyone get the idea that habitual smoking is recommended to temper long-term consequences of meth abuse. Yet the conclusion remains plausibly argued that nicotine and/or some other agent(s) in tobacco smoke may partially shield against one metabolic consequence of methamphetamine abuse.

Plausibly argued, yes, but neither the isolated findings of this paper nor the putative neuroprotective effects of tobacco cited in prior literature are *definitive*, they are all merely *suggestive*. One cautions against exaggerated enthusiasm, especially in the light of the hazards of smoking. In any case, one commends the courage of the authors in advancing an interpretation that is in any sense pro-tobacco, given prevailing attitudes in the general

population and the research and treatment communities. It would have been easy and politically correct to suppress the findings or to formulate a tobacco-negative interpretation, but the authors chose not to. Instead they allude to the constructive possibility in future efforts of separating harmful from beneficial properties of nicotinic agents and applying them therapeutically.

The third intriguing aspect of the Sung et al. paper is that it adds to evidence of differential effects of methamphetamine on the brains of men and women. This is an important area that could impact clinical management. It implies the existence of subgroups of methamphetamine-dependent patients and points in the direction of individualized medicine. (Heavy vs. light methamphetamine-abusing women represents a possible finer subgrouping in this study.) A good deal of research supports the idea of meaningful differences between male and female methamphetamine-dependent subjects. Women appear more sensitive to the reinforcing effects of stimulants. Relatedly, women seem more susceptible to drug initiation, binge use, and relapse. They suffer more frequent and more severe depressive symptoms associated with methamphetamine abuse. They are also more prone to depression during cessation of tobacco smoking than men. These factors support the notion of Sung et al. that female meth-dependent subjects smoke as a way to offset depressive (they also mention anxious) symptoms. Since, in other work, PCr levels correlated negatively with severity of depression, the rise of PCr levels in female meth-dependent subjects with smoking may be concomitant with alleviation of depression. As estrogens apparently also exert neuroprotective effects, the authors suggest possible synergistic benefits between estrogen and tobacco contributing to increased PCr in females with greater lifetime tobacco smoking. Thus, the gender differences in tobacco smoking effects may be due to higher levels of estrogen in females. All in all, the contribution of Sung et al. is a good model neuroimaging paper for the skillful confrontation with and integration of multiple overlapping complexities (female vs. male, heavy vs. light users, co-morbid tobacco abuse, co-morbid depression,...) encountered in substance abuse research.

Limitations of Sung et al., which unfortunately partially impact on their interpretations, include absence of a tobacco-only control group (and of a non-smoking, non-meth group), failure to control for stage of the menstrual cycle in female subjects, and failure to assess depressive symptoms quantitatively (though depressive symptoms are highly prevalent in meth populations). These deficiencies are noted by the authors, who call for follow-up research. *In vivo* PCr levels were assayed non-invasively using ^{31}P magnetic resonance spectroscopy (MRS). Unlike widespread proton MRS, ^{31}P MRS of the brain cannot be performed on conventional clinical MRI scanners without adding a head coil tuned to the phosphorus nucleus and other special apparatus. Thus, ^{31}P MRS is available at relatively few centers. It is unlikely to evolve into a platform for any kind of routine clinical testing in the foreseeable future. Another limitation of ^{31}P MRS acknowledged by the authors is that—even with the advanced chemical shift imaging technique employed by Sung et al.—it requires relatively large sampling volumes (voxels). Thus, a PCr or other metabolite signal attributed to the pACC or other target brain structure may contain substantial contributions from other neighboring tissues (“partial-voluming problem”). Recognizing these limitations, Sung et al. adds to our understanding of the effects of meth and tobacco on the brain.

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