Sex differences in dorsolateral prefrontal cortex dopamine release and the relationship to tobacco smoking treatment outcomes

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Sex differences exist in the behavioral and molecular mechanisms underlying tobacco smoking. For example, men tend to smoke for the reinforcing effects of nicotine whereas women tend to smoke for stress and mood regulation. While the mesolimbic dopamine (DA) system drives the reinforcing effects of tobacco smoking, the meso-cortical dopamine system—including dorsolateral prefrontal cortex (dlPFC)—is critical for inhibitory control and working memory function, which are both compromised by stress. Guanfacine, an α2-adrenergic agonist, enhances inhibitory control and reduces prefrontal cortical DA release. The goals of this study were to investigate sex differences in amphetamine-induced cortical DA release in tobacco smokers and to examine whether the magnitude of DA release predicted treatment outcomes. In this study, 25 tobacco smokers (12 females) participated in two same-day [11C]FLB-457 PET scans before and 3 hours after amphetamine administration (0.4–0.5 mg/kg, p.o.). After their PET scans, subjects participated in a 3-week guanfacine (3 mg, p.o., daily) trial. Toward the end of the guanfacine trial, in order to model the ability to resist smoking, subjects underwent a smoking-lapse paradigm following a psychological stressor. We measured time lapsed before the first cigarette. We compared percent change in binding potential (%ΔBP), an indirect measure of dopamine release, between males and females in dlPFC. Preliminary analyses suggested that female smokers have a smaller amphetamine-induced DA release in dlPFC (%ΔBP = 2.60 ± 3.19%) than male smokers (%ΔBP = 18.26 ± 5.91%; p = 0.03).

In female smokers, smaller amphetamine-induced DA changes were associated with shorter time to delay smoking following a stressor, p = 0.026, suggesting that the more blunted this response, the greater the inability to delay smoking. This relationship was not found in male smokers. This finding is consistent with previous literature showing that blunted DA responses predict poorer treatment outcomes.

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