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# Smoking, psychiatric illness and the brain

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Tobacco smoking remains a leading cause of mortality and morbidity despite recent declines in prevalence. In 2012, global prevalence rates for tobacco smoking were estimated to be 31% for men and 6% for women.<sup>1</sup> Rates of smoking are markedly higher among people with psychiatric illness than in the general population, estimated at being 2–5 times higher in patients with several disorders, including schizophrenia, mood disorders, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), binge eating disorder, bulimia and substance use disorders.<sup>2–5</sup>

The aim of this editorial is to emphasize the importance of smoking as a factor that should regularly be considered as a potential confound in neurobiological studies of psychiatric illnesses. Smoking can be regarded as playing at least several roles in relation to psychiatric illness — as a causal factor contributing to psychiatric disorders, as an agent causing brain changes on its own that may interact with psychiatric pathophysiology, or as a modulator of effects of psychotropic medications. In each of these roles, smoking may impact the course of psychiatric illness and brain function.

## Smoking as a causal factor for psychiatric disorders

There is strong evidence for an association between smoking and the development or progression of psychiatric disorders at the 2 ends of the developmental timeline — namely, ADHD and Alzheimer disease/dementia. In the case of ADHD, a large body of evidence supports an association between maternal smoking during pregnancy and increased risk for ADHD.<sup>5</sup> However, whether maternal smoking is actually a causal factor for ADHD remains open to question, with recent research suggesting that the association may be due to a shared familial/genetic susceptibility for both smoking and ADHD.<sup>5</sup> Nonetheless, children with ADHD born from mothers who smoked during pregnancy have been reported to have more severe behavioural problems than children with ADHD born from nonsmoking mothers, with a dose–response relationship between the amount smoked and several cognitive and clinical variables in the children.<sup>6</sup> At a neurobiological level maternal smoking during pregnancy has been shown to be associated

with grey matter loss and cortical thinning<sup>7</sup> as well as functional alteration in neural circuitry involved in inhibitory control and reward<sup>8,9</sup> in children.

There is also strong epidemiological evidence that smoking is associated with increased risk for dementia and the development of Alzheimer disease.<sup>10</sup> In a 2-year longitudinal study of 186 healthy elderly individuals, Durazzo and colleagues<sup>11</sup> found that the rate of atrophy in several brain regions known to be affected by Alzheimer disease was greater in those with a history of smoking than in never smokers.<sup>11</sup> In a similar vein, in a study including elderly individuals with mild cognitive impairment or Alzheimer dementia and controls, Tiepel and colleagues<sup>12</sup> recently reported that smoking was associated with smaller basal forebrain volume in elderly patients with mild cognitive impairment as well as in healthy elderly individuals, suggesting that smoking may increase risk for Alzheimer disease by compromising cholinergic reserve capacity.<sup>12</sup> Although the precise mechanism by which smoking produces central nervous system (CNS) atrophy has not been pinpointed, it is plausible that these effects may be mediated through the burden of cardiovascular impairment caused by smoking and by the cumulative direct cytotoxic effects of some of the thousands of compounds present in cigarette smoke.<sup>11</sup>

Although much more highly speculative at this point, a contributory role for smoking in the pathogenesis of other psychiatric disorders has been postulated. For example, it has been suggested that smoking may contribute to the development and maintenance of anxiety disorders through nicotine's modulation of fear memory and emotion processing.<sup>13</sup> Effects of smoking on monoaminergic and glutamatergic systems, oxidative stress, and inflammatory and neurotrophic processes have also been hypothesized to contribute to the neuropathological mechanisms involved in the progression of bipolar disorder.<sup>14</sup>

## Smoking causes brain changes on its own that may affect psychiatric symptoms

With regards to neuropsychological function, short-term administration of nicotine has positive effects on aspects of cognition, including learning, memory and attention in healthy

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individuals,<sup>15–17</sup> as well as in patients with schizophrenia, Alzheimer disease or ADHD.<sup>15,16</sup> In contrast, chronic tobacco smoking has been shown to be associated with deficits in cognitive function, prominently verbal memory and processing speed, in middle-aged to elderly adults.<sup>16,17</sup>

Structural neuroimaging studies indicate that chronic tobacco smoking is associated with cortical thinning and size decreases in various brain structures. Karama and colleagues<sup>18</sup> analyzed MRI data from 504 individuals at 73 years of age and reported diffuse accelerated cortical thinning, especially in prefrontal areas, in smokers compared with nonsmokers, and dose-dependent correlations between the amount smoked and the extent of cortical thinning in some regions. In a recent meta-analysis of structural MRI data, Sutherland and colleagues<sup>19</sup> reported smoking to be associated with structural decreases in the insula, cerebellum, parahippocampus, prefrontal cortex and thalamus. Structural alterations, including decreases in grey matter volume of various brain structures and increased fractional anisotropy in diffusion tensor imaging studies, have been found not only in older smokers, but also in smokers younger than 30 years of age.<sup>20,21</sup>

At the level of functional neuroimaging, resting-state functional MRI (fMRI) studies of relatively large samples of smokers versus nonsmoking controls have reported altered connectivity in default and executive networks in the smoking groups.<sup>22,23</sup> Task-related fMRI studies in smokers have often focused on neural circuitry thought to be involved in mediating addiction to nicotine. For example, such studies have shown alteration in function of neural circuitry involved in inhibitory control, attentional systems and risky decision-making in smokers compared with nonsmoking controls.<sup>24–26</sup>

Overall, there is now substantial evidence that tobacco smoking is associated with changes in brain structure and neural circuitry in brain regions and systems clearly implicated in many psychiatric disorders. These findings, together with the high prevalence of smoking in psychiatric populations, highlight the importance of including smoking as a potential confounding variable in studies examining neural mechanisms of psychiatric disorders.

### Smoking as a modulator of effects of psychotropic medications

In addition to effects on its own, smoking/nicotine may modulate the metabolism of other psychoactive agents. Smoking is known to induce hepatic cytochrome P450 drug-metabolizing enzymes, particularly CYP1A2, involved in the metabolism of psychotropic drugs, including the antipsychotics clozapine and olanzapine, and other agents, such as other antipsychotics and benzodiazepines.<sup>27</sup> Mean plasma levels of clozapine are lower in smokers than nonsmokers, and in a patient quitting smoking, clozapine levels are predicted to rise within 1–2 days after smoking cessation.<sup>27,28</sup> CYP P450 enzymes are known to be present not only in peripheral organs, but also in the brain, where they may modulate local levels of endogenous and exogenous psychoactive compounds in a region-specific manner.<sup>29</sup> For example, in various brain regions, smokers have higher levels of

CYP2B6, an enzyme capable of metabolizing endogenous compounds, such as serotonin and testosterone, as well as exogenous agents, such as nicotine, cocaine, amphetamines and bupropion.<sup>30</sup> Therefore, in a number of instances, the effects of smoking status on metabolism of psychoactive drugs may be an additional way in which smoking could influence measures of brain function in some psychiatric populations.

### Importance of smoking as a potential confound for neurobiological findings in psychiatric illnesses

The importance of controlling for smoking as a potential confound in studies examining neural mechanisms of psychiatric illness is well illustrated by 2 recent studies. In a study including 112 patients with schizophrenia and 77 nonsmoking healthy controls, Schneider and colleagues<sup>31</sup> showed lower hippocampal and dorsolateral prefrontal brain volumes on MRI in smoking patients compared with nonsmoking patients, and only in smoking patients (not in nonsmoking patients) versus the nonsmoking controls. Adding even more to the complexity is a recent study indicating that smoking may be associated with differential effects on brain structure in patients versus healthy controls. Jørgensen and colleagues<sup>32</sup> included smokers and nonsmokers both in their sample of 506 patients with severe mental illness (psychotic disorder or bipolar disorder) and in their sample of 237 controls. They found decreased cortical thickness in prefrontal and insular regions in smoking patients compared with nonsmoking patients, but not in healthy smokers compared with healthy nonsmokers. This raises the possibility that patients might be more vulnerable than healthy controls to effects of smoking on brain structure, although the authors were cautious in endorsing this interpretation, as other factors, such as smoking intensity and age, might have accounted in part for these differential effects. The notion that smoking could have significant effects on brain structure or function only in individuals with specific psychiatric disorders but not in healthy controls is an area requiring further investigation.

### Smoking cessation among individuals with psychiatric illnesses

It would be remiss to end an editorial on smoking and psychiatric illness without emphasizing the importance of promoting smoking cessation among individuals with psychiatric illness. It has been estimated that approximately 40% of premature deaths in the United States caused by smoking occur in individuals with a mental illness.<sup>2</sup> In addition to effects on general health, smoking cessation may positively impact psychiatric symptomatology. For example, a recent meta-analysis found reductions in measures of anxiety and depression after smoking cessation, with an effect size at least as great as that for antidepressant treatments and a similar effect size in both the general population and populations with psychiatric disorders.<sup>33</sup> Yet the steady decrease in prevalence of smoking among the general population in recent decades has not been observed in populations with psychiatric disorders.<sup>2</sup>

Although the reasons for this are undoubtedly complex, a recent systematic review and meta-analysis found that a large proportion of mental professionals hold a negative attitude toward smoking cessation among psychiatric patients, believing that “patients are not interested in quitting” or “quitting smoking is too much for patients to take on,” and indicating a lack of training and time to help patients with their smoking reduction efforts.<sup>34</sup> This is undoubtedly an area that would benefit from further attention.

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