Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2008 December 12; 32(8): 1778–1781. doi:10.1016/j.pnpbp.2008.09.004.

Tobacco Smoking and MRI/MRS Brain Abnormalities Compared to Nonsmokers

E.F. Domino, M.D.*
Department of Pharmacology, University of Michigan, Ann Arbor MI 48109-0632

Abstract

This mini review emphasizes the fact that tobacco smoking causes small but real biologic brain changes that need to be studied in depth. A crucial question is whether these anatomical/chemical changes reverse toward normal when smokers quit. This review is presented to stimulate further research to answer this question.

Keywords

Tobacco smoking; brain abnormalities; brain changes; magnetic resonance imaging (MRI); magnetic resonance spectroscopy (MRS)

1. Tobacco smoking/nicotine

Basic science studies indicate that fetal and adolescent rats given chronic nicotine show persistent neurochemical and pathological brain changes (Trauth et al. 1999, 2000; Xu et al. 2001; Chen et al. 2003). Furthermore, it is well known that tobacco smoking during pregnancy increases spontaneous miscarriages, retards fetal growth, induces premature birth, and increases the risk of sudden infant deaths. The recent review by Shea and Steiner (2008) stresses the pathophysiological mechanisms by which nicotine, as one of the major substances in tobacco smoke, is involved. Less appreciated is the fact that chronic tobacco smoking induces subtle anatomical and chemical brain changes in normal adults. In view of the chronic cardiovascular effects of nicotine/tobacco smoking, it is no surprise that both silent and symptomatic strokes are more prevalent in smokers than nonsmokers (Howard et al. 1998; Longstreth et al. 1998). In addition, there are greater periventricular white matter hyperintensities in tobacco smokers reported in some studies (Fukuda and Kitani 1996; Kobayashi et al. 1997; Liao et al. 1997; Longstreth et al. 2000; Tsushima et al. 2002), but not in all (Yetkin et al. 1993; Yamashita et al. 1996). The greater the pack-year smoking history, the greater sulcal and ventricular size and brain atrophy in elderly smokers (Longstreth et al. 2000, 2001).

The availability of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) has stimulated further brain anatomical and chemical studies in younger tobacco smokers to detect subtle brain differences of possible pathological significance. Brody et al. (2004), using MRI, found that tobacco smokers compared to nonsmokers had smaller brain

Corresponding Author: E.F. Domino M.D., Department of Pharmacology, University of Michigan, Ann Arbor MI 48109-0632, Telephone: 734 764-9115, Fax: 734 763-4450, Email: efdabcde@umich.edu.

gray matter volumes and/or densities in bilateral prefrontal cortex, left dorsal anterior cingulate cortex, and right cerebellum. Greater pack-year smoking histories were found to be related to reduced prefrontal gray matter densities. Brody et al. (2004) commented that it was unknown whether predisposing factors that lead to smoking, the effects of chronic smoking, or a combination of factors were involved. Gallinat et al. (2006) also used MRI in a similar smoker/nonsmoker study. Smokers compared to nonsmokers had decreased anterior cingulate prefrontal and orbital frontal cortex gray matter volume and less gray matter density. Either gray matter volume or density was also decreased in the thalamus, cerebellum, and substantia nigra. Lifetime exposure to tobacco smoke correlated with decreased frontal, temporal, and cerebellar volumes. Recently, Paul et al. (2008) used diffusion tensor imaging (DTI) to study the microstructural integrity of white matter in a small group of healthy adult smokers and nonsmokers. Fractional anisotropy (FA) was used to measure directional water diffusion and "trace" as a measure of non-directional water diffusion. Higher FA and lower "trace" values indicate greater axonal integrity. The Fagerström test for nicotine dependence was used to assess the level of nicotine dependence. Higher scores represent a greater degree of dependence. Smokers with a high Fagerström dependence score had significantly lower FA in the body of the corpus callosum compared to smokers with a low Fagerström dependence score, and nonsmokers. It appears that high dose, very dependent smokers have decreased microstructural integrity of the body of white matter connecting the two brain hemispheres. It should be noted that the Brody et al. (2004), Gallinet et al. (2006), and Paul et al. (2008) studies mentioned above all used subjects with no history of stroke or brain lesion.

MRS is a useful methodology to determine brain neurochemical changes in vivo. Gallinat et al. (2007) used MRS to compare 13 smokers and nonsmokers matched for age, gender, and education. N-acetylaspartate (a neuronal and glial cellular marker that may reflect synaptic density) concentrations in the left hippocampus, but not in the anterior cingulate gyrus, were reduced in tobacco smokers. Total choline and creatine concentrations were similar in both groups. Choline concentrations were used to indicate cellular membrane turnover, and creatinine levels were used as an indicator of brain energy metabolism. Anterior cingulate total choline (primarily phosphatidylcholine) was positively correlated with peak years of smoking. The fact that greater lifetime smoking in the Brody et al. (2004) and the Gallinat et al. (2006, 2007) studies correlate with evidence of structural brain changes suggests chronic tobacco smoking as the etiologic factor.

2. Tobacco smoking plus ethyl alcohol

There is considerable basic science and clinical evidence that chronic alcoholism produces structural brain abnormalities (Jernigan et al. 1991; Hommer et al. 2001; Fein et al. 2002; Cardenas et al. 2005 2007). Tobacco smoking and alcohol ingestion frequently occur together. Therefore, it is of interest that the two addictions together produce additive brain changes (Durazzo et al., 2004, 2006a,Durazzo et al., b, 2007a,Durazzo et al., b,c; Gazdzinski et al., 2005, 2006, 2008). Durrazzo et al. (2006a) studied MRS and cognitive effects after one month of alcohol abstinence. Recovering alcoholic nonsmokers showed significant increases in N-acetylaspartic acid and choline containing compounds in their frontal and parietal lobes. Chronic tobacco smoking had adverse effects on the recovery of N-acetylaspartic acid and choline concentrations. Subsequently, Durazzo and Meyerhoff (2007) reviewed the literature on additional adverse neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism, with suggestions of specific future studies, especially with females. Women appear more sensitive to alcohol-induced brain damage than men (Hommer et al. 2001).

3. Tobacco smoking and incipient Alzheimer disease

There is considerable evidence that the brain cholinergic system of Alzheimer's disease (AD) patients is severely compromised (see Giacobini and Pepeu 2006). Kihara et al. (1997) reported that nicotinic receptor stimulation protects neurons against β-amyloid toxicity. In contrast, Kukull (2001) found evidence from cohort studies suggesting that smoking either is unrelated to, or possibly increases the risk of, Alzheimer's disease. Recent brain imaging data suggest that chronic tobacco smoking worsens the disease in elderly smokers. Almeida et al. (2008) recruited 39 pairs of 70–83 year old Australian smokers and never smokers matched for age, sex education, and handedness. The subject volunteers were clinically similar and free of cognitive impairment, history of stroke, or other serious medical conditions. Gray matter brain density was measured by MRI. Compared to never smokers, the smokers had decreased gray matter density bilaterally in the frontal cortex, posterior cingulum precuneus, and right thalamus. In their discussion, the authors stated that their data confirm older adult smokers have decreased gray matter densities in brain areas previously found to be associated with chronic smoking and incipient or mild AD. The cross-sectional design of this study does not allow a causal relationship to be inferred. However, the authors do note that future longitudinal investigations could clarify the relationship between smoking, and the development of cognitive impairment and dementia. Vermeer et al. (2003) reported on the incidence and the risk factors associated with silent brain infarcts. Tobacco smoking, with its associated vascular complications, is certainly an important factor to consider. The silent infarcts would not be expected to be reversible upon quitting smoking.

4. Nonpharmacological factors

Chronic back pain and increased age are nonpharmacological factors associated with decreased neocortical gray matter volume (Apkarian et al. 2004). Patients with chronic back pain also have decreased right anterior thalamic gray matter density. The role of tobacco smoking in these patients was not determined. The fact that tobacco smokers with chronic fibromyalgia (Yunus et al., 2002) complain of more pain than similar nonsmoking patients, and that smokers are more likely to report back pain (Deyo and Bass 1989; O'Connor and Marlowe 1993; Lindal and Stefansson 1996; Andersson et al. 1998; Eriksen et al. 1999), and other pain (Palmer et al. 2003; Riley et al. 2004), implicates tobacco smoking as an additional factor to chronic pain itself. Male compared to female patients with higher blood pressure also have lower regional gray matter volumes and poorer cognitive function (Gianaros et al. 2006). All of these findings, suggestive of subtle brain pathology, indicate that many factors affect gray matter volume and/or density. It is important to note that back pain is not as well established as a risk factor for decreased gray matter volume as are other ailments. Many neurological diseases, such as Alzheimer's disease, Huntington's disease, and multiple sclerosis, are closely associated with decreased gray matter or brain volume. However, a discussion of these disorders and others are outside of the scope of this review. There is also some evidence of a relationship between genes and environmental interactions, which may differ in smokers vs nonsmokers, e.g., serum oxidant carotenoid levels and white matter lesions (den Heijer et al., 2001), stroke risk and white matter hyperintensity (Jeerakathil et al., 2004), and A185C/C406T kinesin light-chain 1 variants and white matter demyelinization (leukoaraiosis; Szolnoki et al., 2007). Another example of gene environmental interaction is T-786C polymorphism in endothelial NO synthase genes (Nasreen et al., 2002).

Finally, psychiatric/behavioral factors must be considered in view of the high incidence of tobacco smoking in mentally depressed and schizophrenic patients. An important percentage of average smokers show symptoms of depression. These behavioral/psychiatric issues will not be reviewed here but clearly must be considered in further studies in the future.

Conclusions

Current brain imaging techniques demonstrate that chronic tobacco smoking produces discrete and localized changes in brain cortical volume, density, and chemistry. Many of the brain areas involve executive functions of the prefrontal lobes and memory mechanisms in the hippocampus. The review by deBry and Tiffany (2008) proposes some of these brain areas in a model for the development of impulsivity involving tobacco-reduced adolescent cognitive development. Whether the induced anatomical and chemical changes are reversible toward those of nonsmokers is a major question that can only be answered in long term longitudinal studies. Such studies can easily begin with adult chronic smokers who wish to quit smoking and who could be followed over the months and years of abstinence in a smoking cessation clinic. During the elapsed time period from start to complete cessation, each smoking brain should be scanned using MRI, DTI, and MRS measurements of their brains to determine if the initial changes are reversible. Longitudinal studies must also be done to clarify the relationship between smoking and brain abnormalities. It is a possibility that preexisting brain abnormalities may increase the likelihood of smoking and addiction. To further investigate this relationship, longitudinal studies must examine brain morphology and chemistry before and after initiation of smoking.

Further research on this topic is a high priority for all tobacco smokers, ex-smokers, and nicotine replacement users.

Acknowledgements

Supported in part by NIDA grant 5RO1 DA-018974-02 and the Pharmacology Education and Research Development Fund 276157.

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