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Distinguishing withdrawal relief and direct effects of smoking

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In the prototypic procedure for studying the effects of smoking, smokers are deprived overnight and some measure is taken before and after smoking. For example, suppose self-reported anxiety was less after smoking than before smoking. Most authors would interpret this difference to indicate a direct anxiolytic effect of smoking. However, an alternate interpretation is that the pre-smoking anxiety level is elevated due to tobacco withdrawal and that the reduction in anxiety occurs because smoking relieves tobacco withdrawal. The argument against this interpretation is that overnight deprivation does not induce withdrawal. This assumption has not been directly tested; however, several studies suggest withdrawal effects can occur after only 6–12 h of deprivation (Hughes et al. 1990).

The distinction between direct effects and relief of withdrawal has not been generally recognized. For example, among the 43 studies on smoking in *Psychopharmacology* in the last 5 years, only 4 (9.3%) used non-smoker control groups.

One solution to resolve direct versus withdrawal effects has been to add a control group of nonsmokers. For example, assume smokers have less anxiety after smoking than when they were deprived and *less* anxiety than never-smokers (Fig. 1. lower panel). With this outcome, the effect is attributed to a direct effect from smoking (i.e., independent of withdrawal). On the other hand, assume smokers have less anxiety after smoking and the *same* anxiety as nonsmokers (Fig. 1. upper panel). The effect is attributed to relief of withdrawal.

The use of a nonsmoker control group does not completely solve the problem. Most studies that use a nonsmoker control imply but do not clearly state that the group includes never-smokers but not ex-smokers. Use of a never-smoker control group implicitly makes the assumption that the anxiety scores for never-smokers are equivalent to those that would have been obtained in smokers before they started smoking. Family, laboratory and longitudinal studies suggest this assumption is false; i.e., individuals who become smokers differ *a priori* from individuals who do not become smokers (Cherry and Kiernan 1976; Eysenck 1980; Seltzer and Oechsli 1985; Hughes 1986; Hartsough 1987) on many of the same constructs attributed to smoking (e.g., ability to concentrate, anger and socialization). Thus, in the example above (Fig. 1. lower panel), smoking smokers may differ from never-smokers, not due to the effects of smoking, but rather due to a priori differences.

Another possibility is to use ex-smokers as a control group, as both ex-smokers and smokers come from the same subject population. However, ex-smokers also appear to differ from current smokers on relevant baseline characteristics (e.g., anxiety) (Cherry and Kiernan 1976;

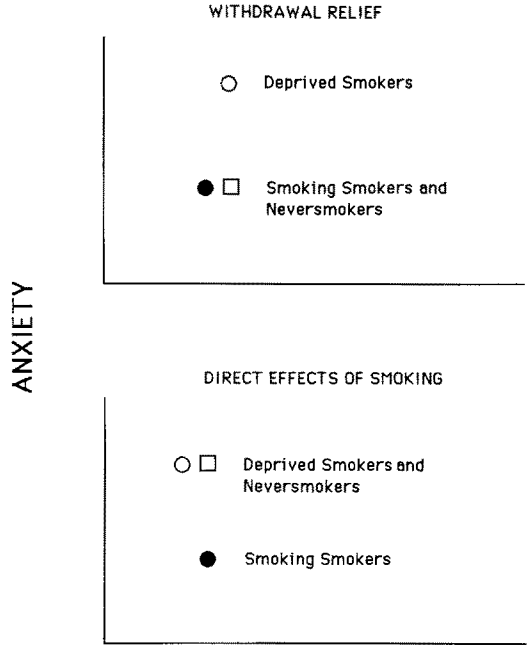

Fig. 1. Possible outcomes of studies using nonsmoker control groups. *Upper panel* = results consistent with a withdrawal relief interpretation. *Lower panel* = results consistent with a direct effects interpretation

Eysenck 1980) and on response to nicotine (Hughes et al. 1989). For example, a longitudinal study found that among smokers, those who quit were more extroverted prior to smoking than those who continued to smoke (Cherry and Kiernan 1976).

A third possible solution is to use minimally-deprived smokers (e.g., Fertig et al. 1986). For example, smokers could be asked to smoke 1–2 h prior to testing. This solution avoids problems of between-groups comparisons; however, it runs the risk of false negative results if some amount of deprivation is necessary to demonstrate a direct effect of smoking. In addition, although the procedure rules out the withdrawal interpretation, the interpretation that such effects improve mood or performance "above the norm" still requires a direct comparison between smokers and never-smokers. This is because smokers may differ a priori from non-smokers and the direct effects of smoking brings smokers to a level equivalent to never-smokers rather than above that of never-smokers.

A final solution would be to undertake studies comparing the morning performance, mood, etc. of smokers, never-smokers and ex-smokers. If these groups were similar, then one would conclude withdrawal does not occur after overnight deprivation, and thus control groups are unnecessary. However, such a study would need to have sensitive instruments, large well-matched groups and independent replications before results could be ruled out.

Until such studies are published, the best solution for demonstrating direct effects of smoking may be to use minimally-deprived subjects and include both never-smoker and ex-smoker control groups. For example, if one could demonstrate that the anxiety level among minimally-deprived smokers after smoking was less than their presmoking level and less than that of both never-smokers and ex-smokers, then one could more readily conclude that any differences were not due to preexisting differences or to withdrawal relief.

These comments about discerning direct versus withdrawal-relief effects and about the desirability of control groups are also relevant to studies of the effects of smoking cessation (Hughes et al. 1990) and, importantly, to other drugs of dependence.

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