Deciding which of these causal pathways explains the relationships between cannabis and other illicit drug use will depend upon a convergence of evidence from a variety of sources, such as: animal studies of the plausibility of pharmacological mechanisms (e.g. [7]); studies of twins discordant for cannabis use (e.g. [8]); studies of the impact of the Netherlands cannabis policy on the 'gateway pattern'; and evaluations of drug education interventions to see whether delaying cannabis use reduces rates of other illicit drug use [2]. Whatever future research reveals about the causal explanations of the relationship between cannabis and other illicit drug use, it is no longer possible to regard the relationship as an artefact of residual confounding with little or no policy significance.

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COMPETING ACCOUNTS OF THE GATEWAY EFFECT: THE FIELD THINS, BUT STILL NO CLEAR WINNER

Less than a decade ago, there were seven competing interpretations of the existing evidence for the gateway link between cannabis and hard drug use [1]. On my scorecard, four candidates are still in the running: (1) a spurious association due to a common propensity for drug use, (2) a biochemical influence of cannabis on the propensity to use other drugs, (3) contact with hard drug-using subcultures or (4) contact with hard drug sellers. The important new analysis of the Christchurch longitudinal database by Fergusson *et al.* [2] does not eliminate the common propensity account, but it shows that any simple version is unlikely to be correct.

In domains where it is possible to compare random assignment experiments with econometric analyses of observational data, the latter sometimes produce biased estimates due to unobserved confounders [3]. As Fergusson *et al.* [2] note, their random- and fixed-effects controls probably rule out any unobserved factors that have a fixed shared influence on both cannabis and hard drug use in their data, but the analysis cannot rule out age-variant effects, or effects that interact with the observed variables.

More complex influences of this sort are conceivable. For example, genetic influences on some traits increase with age [4]. It is becoming increasingly clear that genetic and neuropsychological deficits interact with environmental factors in promoting antisocial behavior [5]. More generally, environmental constraints and opportunities often amplify the effects of personal traits and histories. Morral *et al.* [6] demonstrate how a spurious gateway effect can be produced by a propensity to use drugs that is correlated with opportunities to use drugs. Wagner & Anthony [7] present empirical evidence that exposure opportunities do differ as a function of student characteristics and histories.

Twin studies and animal studies compensate potentially for the lack of true experiments on this topic, but they are not yet persuasive. Lynskey and colleagues [8] report that marijuana use increases the risk of hard drug use in identical twins in the Australian Twin Register, but Tsuang *et al.* [9] supported a common vulnerability model over a causal marijuana gateway using the Vietnam Era Twin Registry. Lynskey *et al.* [8] note that their model cannot rule out unshared environmental influences, but surely the most important contribution of behavioral genetics has been the discovery that unshared environmental influences tend to swamp any effects of a shared environment [4].

Animal findings to date are also ambiguous. Cadoni *et al.* [10] have demonstrated cross-sensitization in rats between delta9-THC and morphine, but their behavioral sensitization measures (sniffing, gnawing, licking, locomotion) are exceedingly indirect proxies for actual consumption behaviors. Vela *et al.* [11] demonstrate actual changes in morphine self-administration in female rats, but as a function of perinatal exposure to delta9-THC, i.e. maternal consumption rather than self consumption. The professional reward for demonstrating a direct effect of TCH exposure on self-administration of opiates is presumably great, yet to date no one has claimed that prize.

MacCoun's reply:

Fergusson and colleagues dispute the plausibility of any "complex interactive relationships between confounders, use of cannabis and use of illicit drugs" and reject the notion on grounds of parsimony.

But at the time of my writing, it was already apparent that interactive effects of latent risk propensities and environmental stressors are common, and often more powerful than main effects of either type of variable (see my cites 4, 5, 6, and 7). Subsequent research has only strengthened this claim; see for example three articles in the 2009 *Current Directions in Psychological Science, 18(3)*:

"Genes in Context: Gene–Environment Interplay and the Origins of Individual Differences in Behavior" (p 127-131) by Frances A. Champagne and Rahia Mashoodh;

"Social Regulation of Human Gene Expression" (p 132-137) by Steve W. Cole;

"Measured Gene–Environment Interactions and Mechanisms Promoting Resilient Development" (p 138-142) by Julia Kim-Cohen and Andrea L. Gold

I applaud Fergusson and colleagues for clarifying why evidence against a common-factor account is not necessarily evidence for a neurochemical account. Interestingly, the legalization debate may hinge less on whether the gateway effect is spurious than on why it is causal. US officials believe it is causal, and they advocate toughness against marijuana possession and sales. Dutch officials have long contended that it is causal, and their response was to permit retail cannabis sales, which does appear to have separated the soft and hard drug markets [12]. To make further progress on this debate, more empirical work is needed on the potential moderating effects of policy and market factors on the gateway association.

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TESTING THE CANNABIS GATEWAY HYPOTHESIS: REPLIES TO HALL, KANDEL *ET AL.* AND MACCOUN (2006)

We would like to thank the contributors for their interesting and thoughtful comments on our research. These comments raise three major issues: model specification, the contributions of animal studies and the political context.

Model specification

Kandel and associates [1] raise three major points regarding the model specification. First, they note that the analysis does not strictly test the gateway hypothesis, but rather examines the more general issue of the effect of cannabis use on individual predisposition to use other illicit drugs. While this criticism is sound, we would note that the analysis does examine the major issue raised by the gateway hypothesis: does using cannabis increase the likelihood that one will use other illicit drugs?

Secondly, Kandel *et al.* raise two important issues about the model specification we used. In particular, they suggest that the use of a lagged endogenous measure of other illicit drug use may lead to inconsistent parameter estimates. Further, they suggest that the model specification does not ensure that the use of cannabis preceded the use of illicit drugs within any given year of observation. To address these comments we have re-analysed the data, changing both fixed and random effects model specification: (a) replacing the contemporaneous measure of cannabis use by a lagged measure of cannabis use in the preceding year, ensuring that the assessment of cannabis use was temporally prior to the assessment of illicit drug use and (b) by eliminating the lagged endogenous measure of previous illicit drug use. Eight model estimates resulted, ranging from our original model using a contemporaneous measure of cannabis exposure and a lagged measure of illicit drug use to a model using a lagged measure of cannabis use and excluding the lagged measure of previous illicit drug use.

Table 1 displays the estimates of the model parameters linking cannabis use to illicit drug use, the associated standard errors and the Wald tests of statistical significance. The principal finding of Table 1 is that within each general model (fixed effects, random effects), variations in model specification have no effect on the general conclusions drawn in the study. In all cases the analyses suggest that, following covariate control, the use of cannabis remains related to increasing risks of the use of illicit drugs within a given year. The robust nature of the findings over a series of model specifications suggests that the concerns raised by Kandel and her associates about the role of temporal sequencing and the use of lagged endog-

Table 1 Parameter estimates for models linking cannabis use to other illicit drug use.

	Model type					
	Fixed effects			*Random effects*		
Model	*B*	*SE*	*P*[1]	*B*	*SE*	*P*[1]
1. Contemporaneous cannabis use; lagged other illicit drug use (original model)	0.93	0.07	< 0.0001	1.12	0.07	< 0.0001
2. Lagged cannabis use; lagged other illicit drug use	1.27	0.15	< 0.0001	1.11	0.13	< 0.0001
3. Contemporaneous cannabis use; no lagged illicit drug use	0.97	0.08	< 0.0001	1.16	0.07	< 0.0001
4. Lagged cannabis use; no lagged illicit drug use	1.11	0.14	< 0.0001	1.16	0.14	< 0.0001

[1]Wald χ^2 test of significance.

enous variables do not pose a major threat to the validity of the conclusions drawn.

MacCoun [2] raises somewhat different issues about the model specification by suggesting that our results do not eliminate the common propensity account, but that we do show that any simple version is incorrect. In effect, MacCoun argues that there may be complex interactive relationships between confounders, use of cannabis and use of illicit drugs which are not represented adequately in our model. While these arguments are possible, they are not particularly plausible and there seem few, if any, reasons to postulate the models proposed by MacCoun. Further, the application of Occam's razor would imply that the simplest interpretation of the data (i.e. cannabis use increases risks of illicit drug use) is to be preferred to the untested and more complex counter models proposed by MacCoun.

MacCoun also suggests that twin study data may be more informative and points to the conflicting results found by Lynskey *et al*. [3] and Tsuang *et al*. [4]. Here two points should be noted. First, the logic of the discordant twin design proves to be very similar to the logic of the fixed effects model. In the twin model we compare two individuals with the same genes and common environment but differing in exposure to cannabis. In the fixed effects model we compare the same individual with the same genes and common environment under differing exposure to cannabis. Both approaches control for the effects of common non-observed genes and environment. Furthermore, there is a good explanation of the inconsistent results reported by Lynskey *et al*. and Tsuang *et al*. In particular, both studies gathered only limited data on the use of cannabis and the use of illicit drugs in populations varying in age. Because the association depends on the extent of cannabis use and varies with age it is perhaps not surprising that the study findings were inconsistent. Our analysis highlights the importance of collecting comprehensive data on both cannabis use and illicit drug use over the period from adolescence to adulthood.

Contributions of animal studies

Kandel *et al*. [1] argue strongly for the use of animal studies to explore causation in this area, implying that the greater control available in animal studies makes them a better means of exploring causation than epidemiological studies where appropriate confounds cannot be controlled. While it is true that, all things being equal, laboratory research will provide firmer evidence than correlational research, in our view Kandel *et al*. overstate their case. It may indeed be possible to gain important insights into the ways in which cannabis may affect the brain and thence propensity to use drugs from animal studies; but the extent to which processes observed in rats, mice and flies in the laboratory are analagous to the processes involved with humans in the street is likely to be highly contentious. Rats, mice and flies do not and cannot have the complex matrix of social and cultural experience of humans, and to assume that laboratory findings based on animals can be generalized readily to human experience in choosing to use and abuse cannabis and other illicit drugs is drawing a very long bow indeed.

The political context

Both Hall [5] and MacCoun [2] discuss issues relating to the politics of cannabis use. In particular, in the past there has been a clear tendency to dismiss the gateway hypothesis as being a statistical artefact that can be explained away by postulating the presence of non-observed confounders. Our research makes such claims less plausible and as Hall points out: '. . . it is no longer possible to regard the relationship as an artefact with little or no policy significance'. The policy significance of these findings is, however, unclear. On one hand, it may

be argued that cannabis has a direct effect on the use of illicit drugs by altering individual susceptibility to use these drugs. Alternatively, the association may arise because the use of cannabis encourages differential association with drug dealers, drug users and a youth culture that encourages drug use. As we note, these explanations have opposite implications for drug policy, with the first tending to support a prohibitionist approach to cannabis, whereas the second suggests an approach of decriminalizing cannabis to break the linkages between cannabis use and illicit drug markets. As both MacCoun and Hall point out, these perspectives coincide with the ways in which US and Dutch policy making has regarded the evidence on gateway effects, with US policy using gateway effects to justify prohibition and Dutch policy using this evidence to support liberalization. The difficulty that arises is that neither approach (prohibition, liberalization) has been shown clearly to break the linkages between cannabis use and illicit drug use (see, for example, Reinaman *et al.* [6]).

Future directions

It is our view that to clarify further the mechanisms that underlie gateway effects, two types of research are needed. First, as noted by Kandel *et al.* there is a clear place for laboratory-based studies to clarify the underlying neurophysiological and related mechanisms by which the use of cannabis may increase individual susceptibility to other forms of illicit drug use. These studies offer the hope of establishing the extent to which cannabis use may change individual susceptibility to illicit drug use by altering neurophysiological functioning. Secondly, there is a need for sociological and social psychological research to examine the extent to which social climate (including legislation, youth culture and association with drug dealers) may create circumstances in which using cannabis leads to an increased risk of using other illicit drugs. This approach offers perhaps the best hope of determining the extent to which gateway effects arise from social processes that increase the likelihood that cannabis users will experiment with and use other illicit drugs.

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