How do genes influence marijuana use? The role of subjective effects

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Abstract
This study investigated determinants of the subjective effects of marijuana and the relationship of subjective effects to marijuana use. Subjects were 8169 twins drawn from the Vietnam Era Twin Registry. Subjects who used marijuana more than five times reported whether they experienced each of 23 subjective reactions. Factor analysis identified a positive (pleasant) reaction factor and a negative (unpleasant) reaction factor. Both factors were related to duration and frequency of use. Pairs in which both members used marijuana more than five times were examined to assess determinants of subjective effects. Approximately one-quarter of the variance in each factor was determined by additive genetic influences; the remaining variance was determined by environmental factors that are not shared by members of a twin pair. The shared or family environment had no detectable influence on either subjective reaction factor.

Introduction
Individuals vary substantially in their use of marijuana. Environmental factors, such as availability of marijuana and the influence of peer groups, clearly affect use. Genetic factors also influence use of marijuana. This leads to a question about the mechanism or mechanisms by which genes influence the probability that an individual will use marijuana. We hypothesize that genes determine the individual’s physiology in ways that determine how the individual will feel when he or she uses marijuana and that these genetically influenced mechanisms will be reflected in the individual’s subjective reaction to...
the drug. These subjective reactions in turn influence how likely the individual is to use marijuana again. That is, if the individual feels good after using marijuana, he or she will be more likely to use it again. Conversely, if the individual feels bad, he or she will be less likely to use marijuana again. There are likely to be factors other than subjective reactions, such as peer pressure, that also have important influences on drug usage.

Marijuana may produce many different effects, including euphoria, impaired coordination, anxiety, depression, apprehension, suspiciousness, confusion, memory impairment, depersonalization, delusions and hallucinations. However, two individuals who ingest the same amount of the same substance may have distinctly different reactions. Naditch suggested that drug reactions are a "complex function of individual differences, expectancies, situational influences, and exogenously and endogenously introduced chemical changes in the body" (p. 394). The subjective effects of a drug are correlated with its reinforcing effects, which presumably influence how much the drug is used. Fabian & Fishkin suggested that marijuana may be smoked to achieve a pleasant or valued experiential state. They found that subjects who tried marijuana but did not continue to use it characterized marijuana intoxication as less pleasant than subjects who continued use. Similar research on alcohol use has found evidence that individual differences in subjective reactions to alcohol are associated with amount of alcohol consumption. de Wit et al. found that subjects who consistently chose alcohol in an experimental setting reported increased elation and vigor scores when drinking alcohol, while subjects who consistently chose a placebo beverage reported decreased elation and vigor scores when drinking alcohol. The authors concluded that individual differences in the subjective effects of alcohol influence consumption.

Genetic factors may influence drug reactions through individual differences in pharmacodynamics and pharmacokinetics. For example, two individuals of the same size may have dramatically different concentrations of a substance available in their bloodstreams after receiving the same dose. Individuals may also differ in the concentration of neurotransmitters, the number and sensitivity of neurotransmitter receptors and the amount of enzyme available to metabolize a drug. There is a large body of evidence from animal research that supports the influence of genetic factors on reactions to drugs. Research using selective breeding of mice has produced different strains that sleep several hours versus several minutes following equivalent doses of ethanol. Different reactions to the same drug may be under the control of different genes. For example, different genes control responses of motor stimulation and analgesia to morphine in mice. This is not surprising given that many drugs have complex mechanisms of action; for example, sedation in response to alcohol is related to GABA-activated chloride channels, while alcohol preference is related to serotonergic mechanisms and alcohol withdrawal seizures are related to NMDA-activated channels.

Cognitive variables also influence the use of psychoactive substances. Some individual reactions to substances may be related to differences in expectations about how the drug will make one feel. There is substantial evidence that expectancies about the effects of alcohol can have a substantial influence on behavior exhibited after consumption. Expectancies about the effects of alcohol are present in children and in non-drinking adults indicating that at least some expectancies about the effects of alcohol are learned in ways other than direct experience. Schafer & Brown suggested that expectancies about the effects of other drugs are likely to develop in the same manner as alcohol expectancies and are also likely to affect decisions about drug use.

We address the issue of how self-reported subjective effects of marijuana relate to the quantity and duration of marijuana use. It is hypothesized that the experience of positive effects is associated with greater use of marijuana and the experience of negative effects is associated with less use of marijuana. We take advantage of the twin structure of our sample to distinguish between genetic and environmental determinants of the subjective reactions.

Method

Study subjects
Subjects were members of the Vietnam Era Twin (VET) Registry. The Registry, assembled from United States Department of Defense computerized military records and other sources,
comprises pairs of male–male twins born between 1939 and 1957 in which both members served in the US military during the Vietnam War era (1965–75). A questionnaire and blood group typing were used to determine zygosity; this method achieved 95% accuracy. For inclusion in the current study, both members of the pair must have been identified from Department of Defense files and at least one member must have responded to at least one of three previous surveys. Of the 10,300 eligible individuals (5150 pairs), 47 were deceased or incapacitated. Of the remaining cases, 8169 (79.6%) were successfully interviewed by telephone. The mean age of respondents was 44.6 years (SD ± 2.8, range 36–55 years); 90.4% were non-Hispanic white, 4.9% African-American, 2.7% Hispanic, 1.3% Native American/Alaskan Native and 0.7% “other”; 33.3% were high school graduates and 38.6% college graduates; 92.6% were employed full-time and 1.8% part-time.

Interviews were performed between 1992 and 1993 by telephone by the Institute for Survey Research at Temple University using experienced interviewers who recorded responses directly into a computer database. Interviewers were trained by one of the investigators (MJL) and their supervisor. Subjects were mailed a letter that explained the goals and procedures of the study. One to two weeks later an interviewer telephoned the subject, re-explained the study’s goals and procedures, detailed methods developed by the Registry for maintaining strict confidentiality and solicited consent for participation. Following the granting of consent, the interview was performed.

Assessment of subjective effects of marijuana
Registry members were asked, “Have you ever used marijuana (including hashish, bhang, ganja) more than five times?” Those who responded affirmatively were asked, “In the period shortly after you used marijuana, did it make you feel {subjective effect}?”, to which subjects answered yes or no. (The included subjective effects appear in Table 1.) Subjects who acknowledged using marijuana more than five times were also asked the following questions: “Have you ever used marijuana regularly, that is, once per week or more?”; “At what age did you begin to use marijuana regularly?”; “At what age did you last use marijuana regularly?”; “How many days per week did you use marijuana during your period of most frequent use?”; “How old were you when you started your period of most frequent use?”; “How old were you when you ended your period of most frequent use?”

Duration of regular use was defined as the age at which marijuana was last used regularly minus the age at which it was first used regularly. The same approach was used to calculate the duration of the period of most frequent use.

Statistical analysis
The 23 individual subjective reactions were subjected to factor analysis. Responses were assigned a value of one or zero for each item, depending on whether or not the subject reported experiencing the specific effect. A principal components extraction was used and the resulting factors were then rotated using a Varimax procedure. Factors were retained on the basis of an eigenvalue greater than one. Factor scores were computed by weighting each item by its factor loading and summing the item scores.

To determine if the subjective reaction factors were associated with patterns of use, Pearson product–moment correlations were calculated between each factor score and the duration of regular use, the duration of the period of most frequent use, and the number of days per week that marijuana was used during the period of most frequent use. Two-tailed probabilities were used for all analyses.

Scores on each of the subjective reaction factors were correlated between members of twin pairs separately for monozygotic (MZ) and dizygotic (DZ) twins using a Pearson product–moment correlation coefficient. The correlation coefficient for MZs was then compared to the correlation coefficient for DZs using Fisher’s Z-transformation. If the correlation was significantly greater (two-tailed test) for MZs than for DZs, it indicated that the score on the factor is genetically influenced.

In the next step, structural equation models that provided estimates of the proportion of phenotypic variance due to additive genetic effects (heritability or \( h^2 \)), common or shared environmental effects (\( c^2 \)), and unique or non-shared environmental effects (\( e^2 \)), were fitted to the twin correlations. The software package LISREL was used to estimate parameters by the method of weighted least squares, using the inverse of the
asymptotic variances of the correlations as the weights. The first model was a full model that includes the effects of additive genes \(h^2\), common or shared environment \(c^2\), and unique environment \(e^2\). The term \(e^2\) reflects influences that are specific to individuals rather than the pair and random error; these influences promote dissimilarity within pairs. The full model is compared with reduced models. Models without additive genetic effects \(h^2\) test whether the twin correlation is due solely to common environmental influences and models without common environmental effects \(c^2\) test whether familial aggregation is due only to additive genetic effects. To assess whether a submodel fitted the data worse than the full model, a \(\chi^2\) difference test was used. The difference in the \(\chi^2\) of the full versus the reduced model was distributed as \(\chi^2\) with degrees of freedom equal to \(df_{\text{reduced}} - df_{\text{full}}\). If this \(\chi^2\) is not significant, the reduced model is accepted as the more parsimonious explanation of the observed results. When the MZ correlation is greater than double the DZ correlation, it raises the possibility that “non-additive” genetic influences contribute to the family resemblance. Non-additive genetic influences may be produced by a single gene of major affect or by an interaction among a small number of genetic loci. This possibility is tested statistically by fitting a model in which the shared environmental parameter \(c^2\) is replaced with a “non-additive genetic” parameter \(d^2\). The significance of the parameter is determined by comparing the fit of the model that includes the parameter to the model in which it has been deleted.

**Results**

There were 3884 twins (52.2%) who ever used marijuana and 2513 (33.8%) who used marijuana more than five times. All subjects who used marijuana more than five times were asked about their subjective reactions and were included in the determination of frequency of each reaction. Table 1 indicates that the rate for subjective reactions ranged from 93.4% for feeling relaxed or “mellow” to 6.7% for feeling irritable.

The results of factor analysis based on subjects who used marijuana more than five times are

<table>
<thead>
<tr>
<th>Subjective feeling</th>
<th>Prevalence (%)</th>
<th>Factor 1 (negative effects)</th>
<th>Factor 2 (positive effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confused</td>
<td>37.8</td>
<td>0.63</td>
<td>0.08</td>
</tr>
<tr>
<td>Unable to concentrate</td>
<td>55.6</td>
<td>0.56</td>
<td>-0.02</td>
</tr>
<tr>
<td>Paranoid</td>
<td>52.5</td>
<td>0.54</td>
<td>0.19</td>
</tr>
<tr>
<td>Jumpy</td>
<td>29.7</td>
<td>0.52</td>
<td>0.24</td>
</tr>
<tr>
<td>Anxious</td>
<td>40.1</td>
<td>0.48</td>
<td>0.30</td>
</tr>
<tr>
<td>Depressed</td>
<td>28.4</td>
<td>0.48</td>
<td>-0.01</td>
</tr>
<tr>
<td>Out of control</td>
<td>16.5</td>
<td>0.48</td>
<td>0.03</td>
</tr>
<tr>
<td>Lazy</td>
<td>64.7</td>
<td>0.44</td>
<td>-0.07</td>
</tr>
<tr>
<td>Dizzy</td>
<td>22.5</td>
<td>0.44</td>
<td>-0.01</td>
</tr>
<tr>
<td>Drowsy</td>
<td>62.0</td>
<td>0.42</td>
<td>-0.07</td>
</tr>
<tr>
<td>Keyed-up</td>
<td>17.4</td>
<td>0.36</td>
<td>0.24</td>
</tr>
<tr>
<td>Nauseous</td>
<td>9.0</td>
<td>0.33</td>
<td>-0.03</td>
</tr>
<tr>
<td>Guilty</td>
<td>42.6</td>
<td>0.32</td>
<td>0.14</td>
</tr>
<tr>
<td>Hear/see things that are not there</td>
<td>18.1</td>
<td>0.30</td>
<td>0.22</td>
</tr>
<tr>
<td>Laugh/cry</td>
<td>55.1</td>
<td>0.30</td>
<td>0.23</td>
</tr>
<tr>
<td>Irritable</td>
<td>6.7</td>
<td>0.27</td>
<td>0.11</td>
</tr>
<tr>
<td>Energetic</td>
<td>37.7</td>
<td>-0.06</td>
<td>0.59</td>
</tr>
<tr>
<td>Creative</td>
<td>56.3</td>
<td>0.06</td>
<td>0.52</td>
</tr>
<tr>
<td>Euphoric</td>
<td>60.9</td>
<td>0.14</td>
<td>0.48</td>
</tr>
<tr>
<td>Sociable</td>
<td>71.4</td>
<td>-0.08</td>
<td>0.45</td>
</tr>
<tr>
<td>Confident</td>
<td>23.5</td>
<td>0.21</td>
<td>0.40</td>
</tr>
<tr>
<td>Increased sex drive</td>
<td>48.4</td>
<td>0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>Relaxed or “mellow”</td>
<td>93.4</td>
<td>-0.02</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Table 2. Pearson product-moment correlations of factors with measures of marijuana use among subjects who were regular users (n = 1755)

<table>
<thead>
<tr>
<th>Subjective reaction factor</th>
<th>Length of regular use</th>
<th>Length of most frequent use</th>
<th>Days/week of most frequent use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor 1 (negative effects)</td>
<td>-0.13***</td>
<td>-0.14***</td>
<td>0.03</td>
</tr>
<tr>
<td>Factor 2 (positive effects)</td>
<td>0.11***</td>
<td>0.08***</td>
<td>0.07**</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001.

Table 3. Cross-twin Pearson product-moment correlations for MZ and DZ twins on the subjective effect factors among pairs in which both twins used marijuana more than five times

<table>
<thead>
<tr>
<th>Factor</th>
<th>( r_{MZ} ) (n = 353)</th>
<th>( r_{DZ} ) (n = 256)</th>
<th>Significance of MZ-DZ difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor 1</td>
<td>0.29***</td>
<td>0.06</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Factor 2</td>
<td>0.30***</td>
<td>0.08*</td>
<td>( p &lt; 0.01 )</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001.

presented in Table 1. Two factors with eigenvalues greater than one were retained. The first factor, which explained 13.9% of the variance, reflects negative or unpleasant effects such as feeling confused, paranoid, anxious and keyed-up. The internal consistency reliability of the first factor, as assessed by Kuder-Richardson formula 20, which is analogous to Cronbach's coefficient \( \alpha \) for dichotomous items, was 0.79. The second factor, which explained 7.9% of the variance, reflects pleasant or positive effects such as feeling energetic, creative, euphoric and sociable. The internal consistency reliability for the second factor was 0.63.

Table 2 contains correlations between factor scores and use characteristics among regular users (n = 1755). Only subjects who reported being regular users of marijuana could be included in these analyses because we did not collect information on quantity and frequency of use from non-regular users. The median duration of the period of regular use among all regular users was 9 years. The factors were correlated with the duration of period of regular use, duration of period of most frequent use and the number of days per week that marijuana was used during the period of most frequent use. The first factor, reflecting negative effects, was significantly negatively correlated with the length of regular and most frequent use. All correlations between the pleasant effects (factor 2) and the amount of use measures were significant and positive.

The correlations between members of twin pairs for the two factors are presented separately for MZ and DZ twins in Table 3. The table indicates that MZ twins were significantly correlated for both factors; DZ twins were significantly correlated for factor 2. The difference between the MZ and DZ correlation coefficients was significant for both factors, indicating a significant genetic influence.

We carried out univariate biometrical modeling on the two factor scores. A model that included no family resemblance (i.e. a model that included only \( e^2 \)) could be rejected for both factors (Factor 1: \( \chi^2 = 31.84, df = 5, p < 0.001 \); Factor 2: \( \chi^2 = 36.42, df = 5, p < 0.001 \)). A model that deleted the common environment (i.e. an \( h^2e^2 \) model) provided a good fit to the data for both factors (Factor 1: \( \chi^2 = 1.89, df = 4, p = 0.756 \); Factor 2: \( \chi^2 = 3.51, df = 4, p = 0.475 \)). A model that included a parameter for non-additive genetic influences as well as additive genetic influences did not provide a significantly better fit than a model with additive genetic influences alone. Therefore, the more parsimonious model (the \( h^2e^2 \)) was accepted. MZ correlations that are more than double the DZ correlations, as was the case for both factors, indicate that the common environment (\( c^2 \)) does not influence the trait. The best fitting model for factor 1 gave parameter values of \( h^2 = 26.6\% \) and \( e^2 = 73.4\% \). For factor 2, the values were \( h^2 = 28.8\% \) and \( e^2 = 71.2\% \).

Discussion
We investigated genetic and environmental
influences on subjective effects of marijuana and the relationship between subjective effects and patterns of use. Factor analysis identified two factors. The first factor described a negative reaction to marijuana characterized by feelings such as confusion, suspiciousness and agitation. The second factor included items that reflect pleasant effects such as feeling creative, euphoric, energetic and sociable. The factors we identified correlated with measures of use in the predicted direction; in general, positive effects were associated with more use and negative effects with less use. Schafer & Brown found a similar pattern regarding expectancies about the subjective effects of marijuana; non-users in their study reported stronger expectations of negative drug reactions and more frequent users expected more positive reactions.

Our data indicate that both factors are influenced by genes and the environment not shared by twins (also known as the unique environment). The environment shared by twins (also known as the common environment) includes their peer group, geographical region and age cohort, all of which could promote similar beliefs and attitudes about the effects of marijuana. However, the shared environment did not have a detectable influence on either positive or negative effects.

Research on another drug, cocaine, suggests one possible mechanism for how the nervous system may mediate the genetic influence on at least some of the reactions comprising factor 1. Satel & Edell found that subjects who had experienced paranoia in response to cocaine scored significantly more deviantly on the Perceptual Aberration Scale and the Magical Ideation Scale, two putative measures of proneness to psychosis. The experience of paranoia did not result from simply exceeding some threshold of use, but rather reflected a pre-existing disposition on which individual users differ. The authors speculated that subjects who respond to cocaine with the psychotic symptom of paranoia may have an intrinsic, subclinical vulnerability of the dopaminergic system. Dysregulation of the dopamine system is thought to occur in chronic cocaine users as well as in those with psychotic disorders.

Although the pharmacological effects of cocaine and marijuana differ, both drugs produce psychotic-like subjective experiences such as paranoia. Some negative reactions could be due to a common final pathway that reflects some pre-existing genetically influenced susceptibility in a system (e.g. dopaminergic system) that is perturbed by both marijuana and cocaine. Recent work on the pharmacology of marijuana supports this conjecture. Gardner et al. found that in Lewis rats, delta 9-tetrahydrocannabinol (THC), the most potent psychoactive component of marijuana, augments intracranial electrical self-stimulation in the median forebrain bundle (MFB) and presynaptic basal dopamine efflux in the nucleus accumbens and prefrontal cortex. This suggests that marijuana augments brain reward circuits through mesocorticolimbic dopamine pathways. Gardner & Lowinson reported that THC enhances MFB stimulation reward and increases dopamine release in reward relevant MFB projection loci. Linszen et al. suggested that the relationship of marijuana to the recurrence of psychotic symptoms in schizophrenics may be mediated by an effect on the dopaminergic system.

The correlations between subjective effects and duration and frequency of marijuana use were significant but not very large. There are several possible reasons for these results. Some power to demonstrate an association between subjective effects and other variables may have been lost because data were dichotomous. We did not get information about the frequency or strength of the reaction, which may have had an influence on frequency of use that we could not detect. The design of the study may also have missed some of the variability in the duration and frequency of marijuana use because these variables were only obtained from subjects who reported being regular users of marijuana. Of the 2513 subjects who reported using marijuana more than five times and were therefore asked about their subjective reactions, 758 never became regular users of marijuana.

Limitations of the present study include uncontrolled exposure to marijuana, the retrospective design and the reliance on self-report. Marijuana consumed by subjects undoubtedly varied considerably in potency, adulteration with other drugs and amounts used during individual sessions. Subjects were asked to accurately recall subjective reactions that may have been experienced years prior to the research interviews. In order to study subjective effects, however, there is no alternative to dependence on self-report measures; obtaining a sample of
twins as large as the one included in this study for a study with controlled laboratory administration of marijuana would be impractical and, most probably, impossible. Moreover, the naturalistic nature of marijuana consumption in the present study may enhance the generalizability of findings. The National Vietnam Veterans Readjustment Study found no differences between male veterans of the Vietnam era and their civilian counterparts for the life-time prevalence of drug abuse/dependence, which suggests that the present results are generalizable to non-veteran males. Because we obtained usable data only from subjects who used marijuana five times or more, our parameter estimates may not be generalizable to individuals who used marijuana fewer than five times.

Our analyses may have underestimated the influence of highly unpleasant subjective effects on patterns of use because some individuals who had extremely aversive initial reactions to marijuana might not have gone on to use marijuana more than five times. Twins were interviewed separately, so their reports were not influenced by sharing answers with one another. It is possible that MZ twins were more likely than DZ twins to use marijuana together, and to describe their subjective experiences to one another. However, analyses of our data indicated that frequency of contact between members of a pair did not contribute significantly to the degree of similarity of the twins for drug abuse. Therefore, we do not believe that contact between the twins is likely to be responsible for resemblances in subjective effects.

Genetic influence on subjective effects is probably one of several genetically influenced mechanisms that mediate the association between the genotype and the phenotype of drug-using behavior. For example, personality variables that are influenced by genetic factors, such as sensation seeking, are also likely to be related to drug usage. Environmental factors are also very likely to influence drug use via mechanisms in addition to learned beliefs and expectations.

As mentioned previously, there has been promising work using animal models to study the role of genetic factors on drug reactions. However, it would be quite difficult to establish meaningful models of "paranoid" and "creative" feelings in non-human species. Therefore, this study may represent a useful link between phenomenology and the biological laboratory. The finding that subjective feelings in response to marijuana are influenced by genetic factors suggests that these reactions might be amenable to appropriate biological research approaches.

Naditch reviewed the area of adverse reactions in response to psychoactive drugs and found suggestions that such adverse reactions indicate "poor adjustment," "rigid or brittle defensive structures," or "poorly organized personalities." The data reported here suggest the addition of "genetic vulnerability" to Naditch's list of putative causes for adverse reactions. Our findings indicate that subjective reactions to marijuana are significantly heritable and, at least partially, physiological in origin. The environment that is shared by twins did not exert a detectable influence on the subjective reactions to marijuana.

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