Heritability of lifetime ecstasy use

Karin J.H. Verweij\textsuperscript{a,b,c,*}, Jorien L. Treur\textsuperscript{b}, Annabel Vreeker\textsuperscript{d,e}, Tibor M. Brunt\textsuperscript{d}, Gonneke Willemsen\textsuperscript{b}, Dorret I. Boomsma\textsuperscript{a}, Jacqueline M. Vink\textsuperscript{b}

\textsuperscript{a} Department of Biological Psychology/Netherlands Twin Register, Vrije Universiteit Amsterdam, van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands, The Netherlands
\textsuperscript{b} Behavioural Science Institute, Radboud University, Montessorilaan 3, 6525 HR Nijmegen, The Netherlands
\textsuperscript{c} Neuroscience Campus Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands
\textsuperscript{d} Trimbos Institute of Mental Health and Addiction, Utrecht, The Netherlands
\textsuperscript{e} Leiden University, Department of Psychology, section Health, Medical and Neuropsychology, Leiden, The Netherlands

\textbf{ARTICLE INFO}

Keywords:
Ecstasy
MDMA
Heritability
Genetics
Substance use
Twin study

\textbf{ABSTRACT}

\textit{Background:} Ecstasy is a widely used psychoactive drug that users often take because they experience positive effects such as increased euphoria, sociability, elevated mood, and heightened sensations. Ecstasy use is not harmless and several immediate and long term side effects have been identified. Lifetime ecstasy use is likely to be partly influenced by genetic factors, but no twin study has determined the heritability. Here, we apply a classical twin design to a large sample of twins and siblings to estimate the heritability of lifetime ecstasy use.

\textit{Methods:} The sample comprised 8500 twins and siblings aged between 18 and 45 years from 5402 families registered at the Netherlands Twin Registry. In 2013–2014 participants filled out a questionnaire including a question whether they had ever used ecstasy. We used the classical twin design to partition the individual differences in liability to ecstasy use into that due to genetic, shared environmental, and residual components.

\textit{Results:} Overall, 10.4\% of the sample had used ecstasy during their lifetime, with a somewhat higher prevalence in males than females. Twin modelling indicated that individual differences in liability to lifetime ecstasy use are for 74\% due to genetic differences between individuals, whereas shared environmental and residual factors explain a small proportion of its liability (5\% and 21\%, respectively). Although heritability estimates appeared to be higher for females than males, this difference was not significant.

\textit{Conclusions:} Lifetime ecstasy use is a highly heritable trait, which indicates that some people are genetically more vulnerable to start using ecstasy than others.

\textbf{1. Introduction}

Ecstasy is a widely used psychoactive drug that usually consists mainly of MDMA (3,4-methylenedioxymethamphetamine). MDMA is a strong central nervous system stimulant, which acts on the serotonin, dopamine, noradrenaline and other neurotransmitter systems (Cadet et al., 2007). The immediate effect of MDMA intake is that it reverses the normal process of serotonin, noradrenaline and dopamine reuptake and therefore leads to excess release of these neurotransmitters into the synaptic cleft (see Meyer, 2013 for a review on the effects of MDMA use).

Ecstasy intake has stimulant effects and users often take it because they experience positive effects such as increased euphoria, sociability and empathy, elevated mood, and heightened sensations (Meyer, 2013; Sumnall et al., 2006). In Europe, approximately 1.7\% of young adults (aged 15–34 years) have used MDMA/ecstasy in 2014, with estimates ranging from 0.3\% to 5.5\% between countries (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2016). The Netherlands is one of the main producing countries of ecstasy and the prevalence of last year use in the Netherlands is relatively high, with an estimate of 5.5\% in young adults (EMCDDA, 2016). In the US, the prevalence of lifetime ecstasy use has been estimated to be \sim 11.3\% (as measured in a national representative sample of more than 200,000 individuals aged 12–34 years, Falamar et al., 2015).

Ecstasy use is not harmless. Acute effects of ecstasy (MDMA) use include hyperthermia, hypertension, elevated heart rate, and hyponatraemia which could lead to an increased risk of seizures and coma (Devlin and Henry, 2008; Dumont and Verkes, 2006; Parrott, 2012). In rare instances MDMA/ecstasy use can also lead to death (Verschraegen et al., 2007). In addition, several studies have shown that users experience lethargy and lowered mood the days after use during the post-drug recovery period (Parrott, 2015). Other side effects of (regular)
ecstasy use include memory and cognitive problems (Morgan, 2000; Parrott et al., 2011), paranoia (Parrott et al., 2011), and disturbed sleep (McCann et al., 2009; McCann et al., 2008).

The chance that someone tries ecstasy or becomes a regular user is likely to be influenced by various factors, including personality, peer substance use, the availability of the drug, and probably also by genetic factors. Previous twin studies have shown that (lifetime) use of various substances, including alcohol, nicotine, cannabis, and cocaine is moderately heritable (Kendler et al., 2003; van Beek et al., 2014; Verweij et al., 2010; Vink et al., 2005). There have also been published various twin studies on stimulant use. Findings of these studies differ substantially with heritability estimates in the range of twin studies on stimulant use. Findings of these studies differ (Kendler et al., 2003; van Beek et al., 2014; Verweij et al., 2010; Vink et al., 2005). There have also been published various twin studies on stimulant use. Findings of these studies differ (Kendler et al., 2003; van Beek et al., 2014; Verweij et al., 2010; Vink et al., 2005). There have also been published various twin studies on stimulant use. Findings of these studies differ (Kendler et al., 2003; van Beek et al., 2014; Verweij et al., 2010; Vink et al., 2005).

This non-specificity increases heterogeneity and makes it hard to draw conclusions about individual stimulant drugs. Here we use a large sample of twin-families to estimate for the first time the heritability of lifetime ecstasy use (ever versus never used ecstasy).

2. Material and methods

2.1. Participants and data

The study sample comprised twins and their family members registered at the Netherlands Twin Registry. In 2013–2014 adult participants filled out a survey. There were two versions of the survey, one for participants aged 60 years and older and one for participants under 60 years of age. The under 60 version included questions about sub-

ciparents that had ever used ecstasy, and — if they responded positively — age at first use, whether they had used in the last year, and how many times they had used ecstasy last year. Overall, 16,458 individuals filled out the question about ever use. In our analyses we included twins and up to one non-twin brother and one non-twin sister and we only included participants aged between 18 and 45 years. We chose this age-cut-off as the prevalence of ecstasy use among individuals older than 45 years was very low. The final sample comprised 8500 individuals (2778 males and 5722 females) from 5402 twin families with a mean age of 27.7 years (SD = 8.2). The sample included 876 complete MZ female, 320 MZ male, 385 DZ female, 159 DZ male, and 445 DZ opposite sex twin pairs, plus 2846 single twins (where the co-twin did not participate), and 1284 non-twin siblings. Zygosity of the same-sex twins was determined by DNA typing for 44% of the same-sex twins. For the remaining same-sex pairs zygosity was based on their response to standard survey questions about physical similarity between the twins. Agreement between zygosity based on survey data and DNA data in the Netherlands Twin Registry is 96% (Willemse et al., 2013).

2.2. Genetic modelling

We applied the classical twin model to partition the individual differences in liability to ecstasy use into that due to additive genetic (A), shared environmental (C), and residual influences (E). A denotes the variance resulting from additive allelic effects across all segregating genes. C refers to environmental influences shared by family members and may include shared home environment, parental style and the neighbourhood the twins and siblings grew up in. E includes environmental factors not shared between twins and siblings (e.g., individual-specific experiences), stochastic biological effects, and measurement error. The variance components can be estimated using twin data because identical (monozygotic; MZ) twins share nearly all their genes, while non-identical ( dizygotic; DZ) twins share on average half of their segregating genes. A, C, and E influences each predict different patterns of MZ and DZ twin correlations, and structural equation modelling is used to determine the combination of A, C, and E influences that best matches the observed data.

Twin analyses were performed using raw-data maximum-likelihood modelling procedures in the statistical package Mx (Neale et al., 2006). In maximum likelihood modelling, the goodness-of-fit statistic of a model to the observed data is distributed as chi-square ($\chi^2$). By testing the change in chi-square ($\Delta \chi^2$) against the change in degrees of freedom ($\Delta d$), we tested whether dropping or equating specific model parameters worsened the model fit. Data were analysed using a threshold model, assuming that a threshold delimiting the dichotomous categories overlays a normally distributed continuum of liability. Age, age$^2$ and sex effects were accounted for in the model by including them as covariates to adjust the thresholds. Further details of the twin design, and the threshold model can be found elsewhere (Derks et al., 2004; Falconer, 1989; Neale and Cardon, 1992; Posthuma et al., 2003).

3. Results

Overall, 10.4% ($N = 884$) of our final sample indicated they had used ecstasy during lifetime, with a higher lifetime prevalence in males (13.2%) than females (9.0%) ($p < 0.001$). We found a significant positive effect of age ($p = 0.02$) and a negative effect of age$^2$ ($p < 0.001$) on the prevalence of ecstasy use, with the highest prevalence among participants aged between early 20s and mid-30s.

Table 1 shows the twin and sibling correlations for lifetime ecstasy use. MZ twin pair correlations were higher than DZ twin pair correlations for both sexes, indicating genetic influences play a role in ecstasy use. The twin pair correlations were not significantly different between MZ males versus females or between DZ males, females, opposite sex twin pairs or sibling pairs, so we also provide the combined MZ and combined DZ/sibling twin pair correlations.

Results of the univariate twin model can be found in Table 2. We first fitted a sex limitation model which allows for qualitative and quantitative sex differences in the A, C, and E influences on ecstasy use. We found no evidence for qualitative sex differences in the A estimate, indicating that the source of genetic variance does not differ between males and females. Although the A, and C point estimates are rather different between sexes, we also found no evidence for quantitative sex differences in the variance component estimates. Therefore, we equated the variance component estimates over sexes. In the general ACE model, individual differences in liability to lifetime ecstasy use could be mainly (for 74%, $p < 0.001$) explained by genetic differences between individuals, whereas shared environmental differences and residual factors explained a small proportion of its liability (5% and 21%, respectively). The shared environmental influences on lifetime ecstasy use were not significant ($p = 0.61$). The genetic model fitting results are provided in Supplementary Table S1.

Table 1

<table>
<thead>
<tr>
<th>Twin/twin-sibling correlation (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ females</td>
</tr>
<tr>
<td>0.78 (0.67–0.86)</td>
</tr>
<tr>
<td>MZ males</td>
</tr>
<tr>
<td>0.80 (0.65–0.89)</td>
</tr>
<tr>
<td>DZ females + F-F siblings</td>
</tr>
<tr>
<td>0.37 (0.21–0.52)</td>
</tr>
<tr>
<td>DZ males + M-M siblings</td>
</tr>
<tr>
<td>0.59 (0.39–0.75)</td>
</tr>
<tr>
<td>DZ opposite sex + M-F siblings</td>
</tr>
<tr>
<td>0.39 (0.24–0.52)</td>
</tr>
<tr>
<td>MZ males + females</td>
</tr>
<tr>
<td>0.79 (0.70–0.85)</td>
</tr>
<tr>
<td>DZ males + females + siblings</td>
</tr>
<tr>
<td>0.42 (0.32–0.51)</td>
</tr>
</tbody>
</table>

MZ = monozygotic; DZ = dizygotic; F = female; M = male.
4. Discussion

We applied a twin design to determine for the first time the genetic, shared environmental, and residual influences (including unique environmental effects) on vulnerability to lifetime ecstasy use. Overall, 10.4% of the sample had used ecstasy during lifetime, with a somewhat higher prevalence in males than females. Our findings from the twin modelling indicate that individual differences in liability to lifetime ecstasy use are mainly due to genetic differences between individuals; the heritability was estimated to be 74%. Shared environmental and residual factors explain only a small proportion of the liability to ecstasy use (5% and 21%, respectively). Although the heritability estimates were also higher for females (75%) than males (42%), this difference was not significant. The heritability estimate of lifetime ecstasy use appears to be somewhat higher (and the C estimates lower) than those of lifetime use of most other substances including stimulants, for which heritability estimates generally range between 20 and 60% (e.g., Kendler et al., 2000; Lynskey et al., 2007; Verweij et al., 2010; Vink et al., 2005). However, an overview article by Ducci and Goldman (2012) showed that heritability estimates of opiates and cocaine use were also higher than 60%. It is important to note, however, that the confidence intervals of the variance component estimates are wide, which is a general limitation of threshold models, in particular for dichotomous traits (Neale et al., 1994). This may also explain why the seemingly considerable differences in A and C estimates between males and females are not significant. The nature of the data and the relatively low prevalence of use in the general population also precluded us from performing genetic analyses on the other ecstasy variables, such as last year use or frequency of use. Another limitation of this study is that we relied on self-report data, which is subject to response-biases such as social desirable responding.

To summarise, lifetime ecstasy use is a highly heritable trait, which implies that some people are genetically more vulnerable to start using ecstasy than others. Future genetic studies could focus on more severe forms of ecstasy use such as frequency of use, and on the genetic overlap with use of other substances and other potential determinants of substance use, such as personality traits. Also, large gene-finding studies should aim at finding genetic variants underlying individual differences in genetic liability to ecstasy use and explore if these overlap with vulnerability to use of other substances.

Role of funding source

Nothing declared

Conflict of interest

No conflict declared

Acknowledgements

We warmly thank the Netherlands Twin Register participants whose data we analysed in this study. KJHV is supported in part by a 2014 NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation. JMV, JLT, and the data collection of the 2013–2014 survey of the NTR are supported by ERC Starting Grant ‘Beyond the Genetics of Addiction’, grant number 284167 (PI: JMV). DIB acknowledges the KNAW Academy Professor Award (PAH/66355). Data collection and zygosity typing was also supported by grants from the Netherlands Organization for Scientific Research [NWO-MagW 480-04-004; Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL)] and the Avera Institute, Sioux Falls, South Dakota (USA).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2017.05.007.

References