Thinking of ecstasy : neuropsychological aspects of ecstasy use

Schilt, T.

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Summary

This thesis aims to gain more insight in the specific (non-acute) effects of ecstasy on neuropsychological functioning. Methodological problems, that hinder most research in the field, have been minimized as far as possible.

Ecstasy or +/-3,4-methylenedioxymethamphetamine (MDMA) is a widely used recreational drug. Between 2001 and 2005, the percentage of the Dutch population (age 15-64) that ever used ecstasy increased from 3.2% to 4.3%, with more than 40,000 actual users in 2005. The scientific literature provides evidence for sustained harmful consequences of ecstasy use on the serotonin system in the brain, and its neuropsychological correlates.

However, studies on the effects of ecstasy on neuropsychological functions are hampered by methodological problems, such as insufficient matching of concomitant use of substances other than ecstasy. Therefore, it is not certain if effects can be ascribed to the use of ecstasy or to the use of other drugs. Moreover, due to the use of cross-sectional designs, potential pre-existent differences cannot be excluded. In addition, our understanding of dose-response characteristics and vulnerability factors that may predispose some individuals to experience more negative effects following ecstasy use is very limited. There are presumably important biological risk factors such as age, sex, and neurotransmitter polymorphism that are related to individual differences in vulnerability for the neurotoxic effects of ecstasy.

This thesis allowed for the potential confounding effects of other drugs, age, gender, neurotransmitter polymorphism, and pre-existing differences that might have impinged on previous ecstasy-studies with cross-sectional designs and a lack of control for the role of polydrug use. The studies described in this thesis were part of the Netherlands XTC Toxicity (NeXT) study. The overall objective of the NeXT research project was to become better scientifically informed about the neurotoxicity of ecstasy. The identification of specific health risks, such as cognitive impairment and brain damage, will provide a cogent argument for consumers to make informed decisions about recreational drug use, and can be used in prevention messages, clinical decision making, and the development of (inter)national ecstasy policy.

In **chapter 1** a general introduction is given about the history, the effects and the potential neurotoxicity of ecstasy. Methodological limitations of previous studies on the effects of ecstasy are described. The objective and outline of the current thesis is presented.

In **chapter 2**, the NeXT study is introduced, an extensive project studying the course, causality and clinical relevance of ecstasy-toxicity. The NeXT study investigates the toxicity of ecstasy with multiple assessment techniques in different substudies: (1) a cross-sectional sub-study among heavy ecstasy users and controls with variation in drug use, which should provide information about potential neurotoxic consequences of ecstasy in relation to other drugs, and (2) a prospective cohort sub-study in ecstasy-naive subjects with high risk for future ecstasy use, which should provide information on the causality and short-term course of ecstasy use and potential neurotoxicity. The assessment techniques included brain imaging, neuropsychological testing and self-report

questionnaires. So far, two dissertations on the NeXT study have been published: one on the fMRI data and one on the SPECT/MRI data. This thesis focussed on the neuropsychological assessments. A final thesis on the NeXT study will be published on the psychosocial aspects of ecstasy use in the near future.

There is ongoing discussion whether previously reported cognitive deficits are caused by ecstasy, by other drugs or by a combination of drugs. Therefore, we studied a population (n=67) with such a variation in type and amount of drug use that correlations between the use of ecstasy and other substances were relatively low allowing a valid interpretation of the results of multiple linear regression models (**chapter 3**). The results indicated that frequent ecstasy use specifically affects verbal memory, independently of the use of amphetamine, cocaine, cannabis, alcohol and tobacco.

In **chapter 4.1**, a prospective design was used to rule out the confounding role of pre-existent neuropsychological differences in the effect of ecstasy use on verbal memory and other neuropsychological parameters. A group of 188 ecstasy-naive subjects was assessed. During a follow-up period of two years, 58 subjects started to use ecstasy. These 58 incident ecstasy users were re-assessed and compared to 60 persistent ecstasy-naive subjects, selected from the original group of 188 subjects. The data showed that even incidental first ecstasy use (mean 3.2/ median 1.5 pills lifetime) had a negative sustained effect on verbal memory. After publication, these results were criticized by two Norwegian researchers in a letter to the editor of the journal that published our results. In **chapter 4.2** we addressed all the questions raised by the Norwegian researchers in an author reply in the same journal.

Although there is ample evidence for decreased verbal memory in heavy ecstasy users, findings regarding the presence of a dose-response relation between the amount of ecstasy use and cognitive functioning are inconsistent. These inconsistencies might be the result of individual differences in genetic vulnerability to the effects of ecstasy. In the prospective study cohort, we were able to determine the cathechol-O-methyltransferase (COMT) *val*^{158}*met* polymorphism, which gave us the opportunity to investigate if the harmful effects of ecstasy are moderated by the COMT gene. The results presented in **chapter 5** showed that subjects varied in their genetic susceptibility to the harmful effects of ecstasy on verbal memory, although also the use of other drugs seemed to play a role.

All studies up till now were performed in relative young subjects between 18-35 years old, mostly in their twenties. As a consequence, long term sequelae of ecstasy use on the ageing brain are unknown. With increasing age, serotonin availability is gradually reduced, which is associated with age-related memory decline and depression. Since ecstasy harms the serotonin system, we wanted to know if the negative effect of ecstasy on the serotonin system adds to the age-related decrease in serotonin, and if this would become visible in stronger verbal memory decrements and higher rates of depressive symptoms in older ecstasy users compared to older ecstasy-naive controls. Therefore, in **chapter 6** we compared neuropsychological functioning of 17 middle-aged ecstasy (polydrug) users with 16 ecstasy-naive polydrug users. This study confirmed that the harmful effect of ecstasy on verbal memory persists in middle-aged ecstasy users. This indicates that the effect of ecstasy adds to the age-related memory decline, but it does not seem to speed up the normal memory decline.

In **chapter 7** we investigated whether future first ecstasy use could be predicted by a neuropsychological measure of impulsivity. To explore this, we used the baseline data of a decision-making task (Iowa Gambling Task) that was assessed in our prospective cohort study and found that decision-making strategy was predictive for future ecstasy use in female participants, and that punishment sensitivity might be lower in future ecstasy users. However, the clinical relevance is questionable because differences were small.

The results are integrated and discussed in **chapter 8**. The final conclusion is that this thesis provides strong evidence for a negative sustained effect of ecstasy on verbal memory, based on studies with prospective and retrospective designs, both in poly-substance users and in ecstasy users with minimal exposure to other drugs, both in heavy users of ecstasy and in users of very low doses of ecstasy. Furthermore, we found indications for a genetic susceptibility to the effects of ecstasy. The clinical relevance of these findings is not immediately clear, because the mean of memory performances remained within the normal range of a sex- and age-comparable general population. However, in the ecstasy using groups, there were more individuals who performed below the normal range than in the ecstasy-naive groups. Moreover, the effect size of ecstasy use on verbal memory is in the order of half a standard deviation, which is not negligible. Finally, some of the effects seem to be long-lasting and maybe even permanent. Long term consequences like accelerated memory decline later in life, could not be excluded, although our first exploration (**chapter 6**) did not find indications in this direction. In summary, substantial but no dramatic effects of ecstasy use on neuropsychological functioning were observed in the current study, but negative effects were clinically relevant in some users and the effects tended to be long lasting. Moreover, these effects are supported by sustained neuroimaging abnormalities. Altogether, this is not the pattern of findings that is expected with an innocent and safe recreational drug that causes no problems as long as use is moderate and controlled. These data, therefore, leads us to a serious warning against the use of ecstasy as a recreational drug.

Some authors advocate the study of controlled use of MDMA as a therapeutic adjuvant to psychotherapy in the treatment of post-traumatic stress disorder or untreatable anxiety in terminal cancer patients. Possible positive effects of MDMA in otherwise untreatable patients may outweigh the potential negative effects of MDMA. For such applications of MDMA one should make a well-considered risk-benefit analysis, taking the negative effects on memory and other potential harmful side-effects into account.

Future research is needed, including replication of the study in low dose novice ecstasy users, taking genetic polymorphisms into account, and more extensive investigation on the interactive effects of ecstasy and concomitant drug use, and on the effects of ecstasy in the ageing brain.