Thinking of ecstasy: neuropsychological aspects of ecstasy use
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Citation for published version (APA):

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Chapter 1

General Introduction
The origin of ecstasy

“Ecstasy” is a widely used recreational illicit drug. Other names for ecstasy are: E, Adam, Roll, Bean, XTC, X, Go, Clarity, Essence, Stacy, Lover’s Speed, and Eve, all street names for +/-3,4-methylenedioxymethamphetamine (MDMA). MDMA was first synthesized by the German pharmaceutical company Merck in 1912. In the literature on ecstasy, it has been claimed repeatedly that MDMA was developed as an appetite suppressor. However, a systematic analysis of the original documents in Merck’s historical archive in Darmstadt, Germany, revealed that it only was an unimportant precursor in a new synthesis for haemostatic substances 71. The process for making MDMA was patented, but it was never developed for medicinal purposes. In the 1970s, psychotherapists started to use MDMA or “Adam” to support psychotherapy. A first description of its psychotropic effects in humans was provided by Dr. Shulgin in 1978 229. In the 1980s, MDMA became popular among teenagers and adolescents in the dance and rave scene. Because of its increasing popularity and because first publications appeared on potential neurotoxicity of the drug 196, therapeutic use of MDMA was dissuaded 13. Despite its illicit status (in the US since 1985 and in The Netherlands since 1988), the recreational use of MDMA kept growing. Moreover, pill-testing services in The Netherlands show that most of the tablets sold as ecstasy contain MDMA as the major component. In the period of recruitment and assessments of the subjects for the main study of this thesis, 95% of the tablets mainly contained MDMA with a mean of 78mg per tablet 54,55,164. Other substances that could be found in ecstasy tablets are MDEA (3,4-methylenedioxyn-ethylamphetamine), MDA (3,4-methylenedioxymphetamine, amphetamines, MBDB (N-methyl-1-(3,4-methylene-dioxyphenyl), PMA (paramethoxymethamphetamine), DOB (2,5-dimethyl oxy-4-bromoamphetamine), 2C-B (5-dimethoxyphenethylamine), caffeine, ephedrine. In this thesis, the term ‘MDMA’ is used when +/- 3,4 methylenedioxymethamphetamine (MDMA) is meant (for example in animal research), and the term ‘ecstasy’ is used in case it is uncertain whether the substance is MDMA or a MDMA-derivative (in the majority of human studies).

Effects of ecstasy on the brain

In the first hours after the intake of an ecstasy tablet, a feeling of openness, happiness, and friendship arises. In addition, users get a boost of energy which allows them to dance all night. The positive feelings are the result of an extensive depletion of serotonin in the brain, and to a lesser extent also of dopamine. Increased levels of extracellular noradrenalin lead to increased activity including accelerated heart rate and high blood pressure. Many week-end users report a mid-week mood dip. This mid-week low is due to an acute fall in serotonin, which is a rebound effect of an overcharged serotonergic system. Most studies regarding the negative effects of MDMA have focussed on the effects of MDMA on the serotonergic system. For example, animal studies have clearly shown long-lasting damage to the serotonin system caused by MDMA (see for review 206). Research on the neurotoxic effects of ecstasy on the human brain is much less conclusive and more complicated, because it is not ethical to carry out randomized experiments by administering a potentially harmful drug in different dosages to human beings and execute pathological investigation on their brain tissue. In this last decade,
brain imaging techniques have been used to investigate the toxic effect of ecstasy on the human brain. The main finding of those imaging studies is a decrease in serotonin transporter densities in heavy ecstasy users, although it is not sure whether these findings represent the cause or the consequence of ecstasy use and although these effects may be (partly) reversible. The exact mechanisms underlying MDMA-toxicity are not fully known, but it seems that dopamine plays a role in MDMA-toxicity. First, when the serotonergic system gets exhausted, dopamine enters into the serotonergic cells, where it is deaminated by monoamine oxidase-B. This oxidation results in free-radical formation and selective serotonin toxicity. Second, higher levels of extracellular dopamine are related to hyperthermia, which in turn creates serotonergic damage. An important issue in the research on ecstasy’s neurotoxic potential is the question whether ecstasy can cause functional deficits. Since serotonin plays a major role in cognition and mood, numerous human studies concentrated on the effects of ecstasy on these functions. The most consistent finding of studies in frequent ecstasy users is a decrease in verbal memory, but also decrements in visual memory, attention, and executive functions, and an increase of depressive symptoms, impulsivity, and sensation-seeking have been reported.

Problems in human research

Most human studies on the effects of ecstasy have used a cross-sectional design with retrospective assessments of ecstasy use. In a typical “ecstasy-study”, a group of ecstasy users (often frequent use) is compared with an ecstasy-naive control group, usually matched on age and gender. A complication in investigating the effects of ecstasy, however, is that most ecstasy users also use other substances. Therefore, observed deficits could be due to the use of psychotropic substances other than ecstasy or to a combination of other substances and ecstasy, rather than to the use of ecstasy alone. A second, significant problem inherent to the use of cross-sectional designs is that pre-existing differences cannot be excluded as an explanation for the reported differences between ecstasy users and controls, or even as a cause for ecstasy use. Therefore, no final causal statements can be made based on these cross-sectional studies. Although some studies showed a dose-response relationship between the cumulative ecstasy exposure and cognitive parameters (e.g.), others did not. A possible explanation for these inconsistent dose-response findings is that individuals vary in genetic vulnerability to the harmful effects of ecstasy. Since MDMA has major effects on brain serotonin pathways, hypothetically the serotonin transporter promoter region gene (5-HTTLPR) might modulate cognitive performance in ecstasy users. Two recent studies, however, failed to find such a moderating effect of 5-HTTLPR on memory function. Another potential candidate for the modulation of the effect of ecstasy on memory is the catechol-O-methyltransferase (COMT) gene. First, COMT is involved in the catabolism of ecstasy. Second, the COMT enzyme catalyzes the metabolism of extracellular dopamine, which seems to be involved in the process that leads to serotonin toxicity caused by MDMA. However, research on this topic is scarce and has only been carried out in animals.
The Netherlands XTC Toxicity Study (NeXT)

To get a better understanding of the causality of ecstasy neurotoxicity, the specific neurotoxic effects of ecstasy in relation to the use of other drugs, and the clinical relevance of ecstasy neurotoxicity, the Netherlands Research and Development Program on Substance Use and Addiction supplied a grant for the Netherlands XTC Toxicity (NeXT) study. The NeXT study is a concerted action of the Academic Medical Center of the University of Amsterdam, the Bonger Institute of Criminology of the University of Amsterdam, and the University Medical Center of the University of Utrecht. Multiple assessment techniques are used, including brain imaging, neuropsychological testing and self-report questionnaires. The NeXT-findings will result in four dissertations, each with a different focus: 1: SPECT and MRI imaging; 2: functional Magnetic Resonance Imaging; 3: Neuropsychology (present thesis); 4: Social factors (Vervaeke, in preparation). The current thesis focuses on the results of neuropsychological assessments. The overall outcome of this large project should contribute to the improvement of prevention messages, clinical decision-making, and the development of an (inter)national ecstasy policy.

Outline of the current thesis

Chapter 1 gives a general introduction on the history, effects and potential neurotoxicity of ecstasy, and highlights the limitations in scientific research into the consequences of ecstasy use.

In chapter 2 the outline and the objectives of the NeXT study are presented. The subsequent chapters aim to elucidate the specific sustained effects of ecstasy on neuropsychological functioning, relative to the confounding effects of other drugs and apart from 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. Because most ecstasy users tend to be polydrug users, it seems unjustified to ascribe neuropsychological deficits to ecstasy alone, while also other drugs have potential to exert a sustained negative effect on cognition. Therefore, we first investigated the specific sustained effects of ecstasy on cognition, relative to amphetamine, cocaine, cannabis, and alcohol, in a stratified sample of subjects with a broad variation in type and amount of drug use (chapter 3).

Although chapter 3 gives a better insight in the specific effects of ecstasy in relation to the impact of other substances, it is inherent to its retrospective design that pre-existing differences cannot be excluded to be responsible for the cognitive deficits found in ecstasy users. In the study described in chapter 4a we were able to rule out the confounding role of pre-existing differences in cognition by using a prospective design with baseline assessments of cognition, i.e. before the first use of ecstasy. Ecstasy-naive subjects with a high risk to start using ecstasy in the near future were tested before and after the first use of ecstasy, and compared with persistent ecstasy-naive controls. In addition to a better look at the causal role of ecstasy use, this study also provides knowledge about the effects of low dose ecstasy, whereas most other studies present effects of frequent or heavy ecstasy use. After the publication of this study, the editor of the publishing journal received a letter of two Norwegian researchers (see Appendix to
this thesis), who are involved in research on the positive effects of MDMA in psychotherapy. The letter raised several important questions concerning our prospective study. The response to this letter is enclosed in the thesis as chapter 4b.

In the same study, we determined the catechol-O-methyltransferase (COMT) polymorphism: a gene that may play a role in ecstasy-induced neurotoxicity, and could account for differences in susceptibility to the negative effects of ecstasy on cognition. Findings about a possibly moderating role of the COMT-gene in ecstasy-induced cognitive impairment are presented in chapter 5.

Although the literature, including our own studies from the NeXT project, provide considerable evidence for a sustained decrease in neuropsychological functioning in ecstasy users compared with ecstasy-naives, cognitive performance in these studies still remained within the normal range of a gender and age comparable general population. However, all studies up till now were performed in relatively young subjects between 18-35 years old, mostly in their twenties. Long term consequences of ecstasy use on the ageing brain are unknown. With increasing age, serotonin availability gradually reduces \cite{78,142,146,147}, which is associated with age-related memory decline and depression \cite{146}. Since ecstasy harms the serotonin system, we hypothesized that the negative effect of ecstasy on the serotonin system may add to the age-related decrease in serotonin, and that this should become visible in stronger verbal memory decrements and higher rates of depressive symptoms in older ecstasy users compared to older ecstasy-naive controls. The results of this study are presented in chapter 6.

Given the fact that all papers presented in this thesis provided evidence for a negative effect of ecstasy use on verbal memory, we thought it would be valuable to investigate whether future ecstasy use could be predicted by a neuropsychological measure of impulsivity. To explore this, we used the data of our prospective study cohort and reasoned that risky, impulsive decision-makers may be more likely to start using ecstasy in the near future than more conservative decision-makers (chapter 7).

Finally, we integrate and discuss all our results in chapter 8 of this thesis.