Thinking of ecstasy : neuropsychological aspects of ecstasy use

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Chapter 2

The Netherlands XTC Toxicity (NeXT) study

This is an abridged and slightly adapted version of:

Neurotoxicity of Ecstasy
Objectives and Methods of a Study Investigating
Causality, Course, and Clinical Relevance

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Introduction

In the early 1990s a steep increase in ecstasy (3,4-methelenedioxymethamphetamine, MDMA*) use occurred when the substance became popular as a dance and party drug in many European countries. According to a general population survey among Dutch residents of 12 years and older in 2001, annual incidence was 0.5%, lifetime prevalence was 2.9%, and last month prevalence was 0.5% with higher prevalence among residents of Amsterdam (8.7% and 1.1%, respectively), and higher prevalence among young adults between 20 and 24 years old [1]. Among a population of 16 million inhabitants in The Netherlands approximately 70,000 people were monthly users of ecstasy. Prevalence rates were higher among males than females in the general population [1], as well as among students [150]. On a yearly basis 250-300 ecstasy users (0.4% of 70,000) were seeking advice or help for their ecstasy use at the addiction consultation and treatment centers in The Netherlands [54].

Despite the vastly growing scientific literature on the toxic effects of ecstasy on the human brain (e.g. [25,140,189,190,222]) and its functional sequelae (e.g. [49,74,190,255]), some crucial questions regarding the causality, course, and clinical relevance of the potential neurotoxicity of ecstasy have not been answered yet. Research in this area suffers from several methodological limitations.

First, most ecstasy users are also likely to consume other drugs like cannabis, amphetamine, cocaine, alcohol and tobacco [220]. Therefore, it is difficult to differentiate between the effects of ecstasy and the effects of other drugs.

Second, the lack of baseline data leads to interpretative difficulties concerning the causality between ecstasy use and potential toxicity. Because of ethical and legal issues, most research on ecstasy-induced neurotoxicity in humans has been performed with cross-sectional study designs including retrospective assessment of ecstasy use. This leaves the possibility that observed differences between ecstasy users and controls were pre-existent [57,112,126,155].

Third, little is known about the clinical relevance of observed serotonergic changes in humans. Functional abnormalities seen in ecstasy users include memory disturbance, depression, impulsivity, and other neuropsychiatric disorders in which brain serotonin has been implicated [19,49,156,158,170,190,255]. It is important to study both the effects of ecstasy on serotonergic axons, and also the potential clinical consequences related to damage of these axons.

Finally, our understanding of dose-response characteristics and vulnerability factors which may predispose some individuals to experience more negative effects following ecstasy use is very limited. For example, it is important to find out whether brain pathology observed in heavy ecstasy users also occurs in less frequent users. Some researchers have argued that even a single moderate oral dose of MDMA might be neurotoxic in humans [77,138], while others advocate the controlled use of MDMA as a therapeutic adjuvant for psychotherapy (e.g. [53]). Furthermore, it has been suggested that environmental circumstances during ecstasy use (e.g. temperature, noise, dehydration, exhaustion, stress) [172], and the combination with other substances (e.g. alcohol, cannabis,

* In this paper, the term 'MDMA' is used for ecstasy known to contain pure MDMA (laboratory conditions), the term 'ecstasy' is used for tablets/powder thought to be ecstasy although containment of merely MDMA was not confirmed (general practice).

amphetamines) [28,44,207] could modify ecstasy-induced brain damage. Moreover, there are presumably important biological risk factors such as age, gender, and neurotransmitter polymorphism that are related to individual differences in vulnerability for the neurotoxic effects of ecstasy.

Because of limitations in current ecstasy research and the accompanying unanswered questions about its potential neurotoxicity, the Netherlands Research and Development Program on Substance Use and Addiction supplied a grant for the **Netherlands XTC Toxicity (NeXT)** study addressing this public health issue. The overall objective of the present research project is to come to better informed scientific knowledge regarding the neurotoxicity of ecstasy. The identification of specific health risks, such as cognitive impairment and brain damage, would 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 a (inter)national ecstasy policy.

Design

General design of the study

Only a long-term prospective study of serotonergic function in ecstasy-naive individuals randomly assigned to MDMA or placebo conditions could determine decisively whether recreational use is neurotoxic to human beings and whether these toxic effects are reversible or not. However, given the existing data on brain abnormalities in MDMA-treated animals and in human ecstasy users, such a study is ethically not acceptable. Therefore, we chose for the current project to study causality, course, and outcome of various indicators of brain pathology (e.g. neuroimaging) and possibly related clinically relevant symptoms (e.g. neuropsychological and psychopathological symptoms) of ecstasy neurotoxicity by means of two different study-designs. The project includes (1) a cross-sectional sub-study in heavy ecstasy users and controls with variation in amount and type of drug use that will provide information on potential neurotoxic consequences of ecstasy use in relation to the use of other drugs [**chapter 3** of this thesis] , and (2) a prospective cohort sub-study in ecstasy-naive subjects with a high risk for future first ecstasy use that will provide information on the causality and short-term course of ecstasy use and potential neurotoxicity, especially for low exposure levels [**chapters 4** and **5** of this thesis]. The combination of these sub-studies with the use of similar assessment procedures in all sub-studies will provide additional information regarding the neurotoxicity of ecstasy use in humans.†

† Besides the sub-studies described in this chapter, this thesis contains two extensions of the NeXT-project: (1) a study on the effects of ecstasy in the first generation ecstasy users, who are now middle-aged [**chapter 6** of this thesis], and (2) a study on the predictive value of a neuropsychological indicator of impulsivity for the initiation of ecstasy use [**chapter 7** of this thesis].

Design and study samples of the sub- studies

I. Cross-sectional sub-study among heavy ecstasy users

The two main objectives of the cross-sectional sub-study among heavy ecstasy users were (a) to specify potential neurotoxic consequences of heavy ecstasy use in relation to the use of other drugs, and (b) to validate the various assessments techniques. The potential neurotoxicity of heavy ecstasy use was investigated with a retrospective assessment of drug use history and by comparing neuroimaging and neuropsychological outcomes in a stratified sample of 67 subjects. Multiple regression analysis with ecstasy and other drugs as separate regressors was applied to investigate the specific effects of ecstasy and the relative contributions of cannabis, amphetamine, cocaine, alcohol, and tobacco on the outcome parameters. Overall, subjects could be classified according to five different profiles or 'groups' with variations in the amount and type of drug use: (1) heavy ecstasy polydrug users, including both poly-substance users and selective ecstasy users; (2) polydrug controls with a history of heavy amphetamine and/or cocaine and cannabis use but very limited ecstasy use; (3) ecstasy-naive cannabis users; and (4) drug-naive controls.

II. Prospective cohort sub-study

To study the causal nature of ecstasy use on neuroimaging and neuropsychological abnormalities observed in ecstasy users and to determine the effect of relatively low cumulative dosages of ecstasy, a sample of 188 ecstasy-naive young adults (18-35 yrs) with a relatively high probability to start using ecstasy in the near future was followed during a period of 12 to 24 months. Main criteria for inclusion were intention to probably or certainly use ecstasy for the first time in the near future and/or having one or more friends who already use ecstasy. After baseline examination subjects had to complete questionnaires sent to them by mail about their drug use every three months. The neuroimaging and neuropsychological outcome parameters were assessed directly following recruitment in the total cohort (N=188), i.e. before first ecstasy use, and several weeks to months after first ecstasy use in all incident ecstasy users (expected N=50-60), and in a control group of persistent ecstasy-naive subjects from the initial cohort of 188 subjects (matched on gender, age, IQ, and cannabis use). To study whether a low dose of ecstasy use was neurotoxic, follow-up outcome parameters were compared between first ecstasy users and persistent ecstasy-naives, taken baseline outcome into account.

Assessments

Exposure to ecstasy and other substances

We assessed various aspects of ecstasy use and other substances such as cannabis, alcohol, tobacco, amphetamines and cocaine, with validated drug-use questionnaires [248]. To exclude acute pharmacological effects of substance use on the main outcome parameters, subjects had to abstain from drug use for at least two weeks and from alcohol for at least one week prior to testing. This was checked through urine drug screening (enzyme-multiplied immunoassay for amphetamines, ecstasy, opiates, cocaine, benzodiazepines, cannabis, and alcohol). The absence or presence of prior ecstasy use and prior use of related substances such as amphetamines, MDA and MDEA was

checked in hair of all ecstasy users and of a random sample of 25% of the ecstasy-naive controls, using gas chromatography/mass spectroscopy analysis.

Outcome parameters (indicators of neurotoxicity)

In the current project indicators of neurotoxicity were studied using a combination of neuroimaging, neuropsychological, and psychopathological assessments with techniques that already proved to be effective in detecting different aspects of serotonin-related neurotoxicity. In addition, currently known potential confounders (e.g. age, substance use, personality, depression, cognitive functioning, serotonin and dopamine transporter genotype) were assessed.

Imaging parameters

Since the imaging parameters are not part of the current thesis, we refer to the dissertations of Jager (2006)[108] and De Win (2007)[51] for a detailed description of the Magnetic Resonance Imaging (MRI), Proton Magnetic Resonance Spectroscopy (^{1}H-MRS), Single Photon Emission Computed Tomography (SPECT), Diffusion Tensor Imaging (DTI), Perfusion Weighted Imaging (PWI), and functional Magnetic Resonance Imaging (fMRI).

Neuropsychological and psychopathological parameters

As serotonin modulates many neuropsychological processes, it can be expected that ecstasy-induced damage to serotonin axons leads to impairment of functions in which serotonin is involved, such as impulsivity, mood disorders, and memory function. Previous research on the functional consequences of serotonergic neurotoxicity induced by ecstasy showed converging evidence of impairment in memory [86,192,255]. However, studies on the effect of ecstasy use on mood, impulsivity, and sensation seeking are less conclusive because there are indications that symptoms of increased depression, impulsivity, or sensation seeking might be pre-existing or even predispose subjects to ecstasy use [3,49,126]. This could be thought of memory deficits as well. In the current project, subjects are assessed on a battery of tests on various aspects of cognitive functioning and with self-report questionnaires on depression and personality traits.

Neuropsychological tests

The neuropsychological test battery in the current project includes tests that have proven to be sensitive to ecstasy-related neurotoxicity and tests related to functions or brain areas that are thought to be affected by ecstasy use (e.g. prefrontal cortex, occipital cortex, hippocampus). Moreover, tests were selected by their sensitivity to detect subtle impairments in younger persons. The following cognitive domains are tested: working memory, verbal memory, visual memory, visuospatial ability, and verbal intelligence.

Working memory/executive functioning: Impaired function of working memory in ecstasy users was found in several studies (e.g. [137,266]). The PASAT (Paced Auditory Serial Addition Test)[94] is administered in the current study to measure working memory and information processing accuracy. Subjects have to add numbers presented by a recorded male voice to a preceding number. A Dutch adaptation of the Digit Span (subtest of Wechsler Adult Intelligence Scale- revised WAIS-R)[267] is used to measure attention and working memory [128]. The version of Lindeboom gives a more reliable difference score

between repeating digits in forward and in backward order by offering subjects one series of digits extra per length. Previous studies found decreased scores on the Digit Span in ecstasy users [86,141] while others did not [14]. Finally, we use the Iowa Gambling Task to measure decision-making and risk-taking behaviour [4]. It provides participants with choices from four decks of cards, each associated with a specific degree of reward or punishment.

Verbal Memory: The most substantial evidence for cognitive deficits in ecstasy users is on impaired functioning of ecstasy users on verbal memory tasks [17,192,238,255]. Verbal memory can be measured using the Rey Auditory Verbal Learning Test (RAVLT)[195]. In the current study a Dutch version is administered [249]. Subjects have to memorize a series of 15 words in five learning trials. Immediate recall is tested after each trial. Delayed recall and recognition are measured after 20 minutes.

Visual Memory: Previous studies on non-verbal memory reported inconclusive results [2,171]. We use a computerized adaptation of the Memory for Designs test [89]. The original test with 14 figures was split in two separate tests to obtain a parallel version. After a slide show of seven figures, five seconds each, subjects have to draw the figures from memory. The show is repeated five times. Delayed reproduction is measured after 15 minutes.

Visuospatial functioning: Also studies on visuospatial functioning produced contradictive results [2,171], although there are indications that brain areas such as the parieto-occipital and occipital cortex, involved in visuospatial functioning, are affected by ecstasy use [189]. In the current study the first test to measure visuospatial functioning is the Mental Rotation Task [228]. Participants are presented with 20 pairs of block designs drawn from different points of view. Within 3 min they have to judge whether pairs of designs are identical or different. A computerized and adapted version of the Judgement of Line Orientation (JOLO) [12] is used to test visuospatial working memory. The JOLO requires subjects to identify which 2 of 11 lines presented in a semicircular array have the same orientation in two-dimensional space as two target lines. The target lines in our assessments are only shown for one second, directly followed by the 11 lines.

Verbal Intelligence: The Dutch Adult Reading Test (DART), the Dutch version of the National Adult Reading Test [166], is administered to estimate pre-morbid verbal intelligence (DART-IQ) as it is relatively insensitive to cognitive impairment caused by neurological disorders [217].

Psychopathological questionnaires

Current depression is assessed using the Beck Depression Inventory (BDI) [11]. The BDI is a 21-item self-report rating inventory which measures characteristic attitudes and symptoms of depression in the week prior to assessment. The BDI has proven to be a reliable and valid indicator of depression [10,22]. Increased BDI scores were reported in recent and former ecstasy users [49,238].

Also, increased impulsivity scores were reported in ecstasy users [19,156]. The Dutch version of the Barratt Impulsiveness Scale (BIS-11) is used in the current study to assess impulsivity [178]. The Dutch BIS-11 contains 31 self-report items that have to be scored from 1 to 4. Total scores and subscale scores on attentional impulsivity ('difficulty in concentrating'), motor impulsivity ('acting without thinking'), and non-planning impulsivity ('thinking about the present rather than the future') will be calculated.

The 'Spannings Behoefte Lijst' (SBL), a Dutch adaptation of the Sensation Seeking Scale [276], is used to measure sensation seeking [62,63]. The SBL contains 51 sensation seeking items, for which respondents have to indicate on a five-point scale to what extent they (dis)agree with the statements. Both total scores and scores for subscales on thrill and adventure seeking (TAS), experience seeking (ES), boredom susceptibility (BS), and disinhibition (DIS) will be calculated. Increased sensation/novelty seeking in ecstasy users was reported in various studies [57,73,214].

Potential confounders

Various potential confounders that have been identified in the literature are assessed in all or part of the subjects included in the sub-studies: use of other drugs than ecstasy; demographic variables such as age, gender, level of education; ethnicity; serotonin transporter genotype; catechol-O methyltransferase genotype.

Ethical considerations

The project was approved by the local medical ethics committee. To rule out any suggestion that we approve or stimulate the use of ecstasy (especially in ecstasy-naive subjects), all volunteers were informed about potential negative consequences of ecstasy use. In addition each participant had to sign informed consent, which states that participation was voluntary, that ecstasy is potential harmful and that the examiners do not have the intention to stimulate the use of ecstasy.

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