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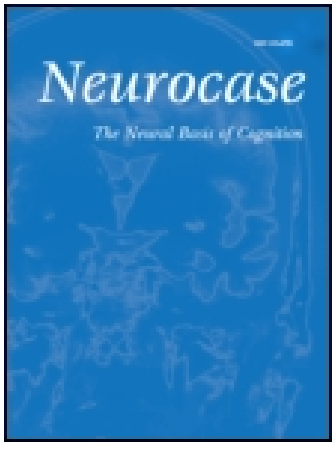

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Cognitive disorders after sporadic ecstasy use? A case report

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Cognitive disorders after sporadic ecstasy use? A case report

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Memory problems and changes in hippocampal structures after chronic ecstasy use are well described in the literature. Cognitive problems after incidental ecstasy use are rare, and the few patients described in case reports returned to their normal cognitive level after a relative short period. FV is a 39-year-old man who used an ecstasy tablet in 2005. This resulted in severe confusion for a few days. The confusion was followed by persistent memory complaints and difficulties orientating in new surroundings. An extensive neuropsychological examination 7 years after the ecstasy use revealed a severe memory disorder. Furthermore, his performance on a virtual reality test of navigation showed serious problems navigating in new surroundings. In comparison with matched control subjects (Bayesian approach for single case studies) his scores were significantly impaired on several subtasks of the navigation test. On a magnetic resonance imaging (MRI) scan of the brain bilateral hippocampal atrophy and sclerosis were visible, comparable to previous MRI studies describing hippocampal damage following ecstasy ingestion. This case report describes persistent memory and navigation disorders after sporadic ecstasy use, supported by structural brain abnormalities seen on the MRI scan. These findings revive the debate on whether sporadic ecstasy use can cause persistent cognitive deficits.

Keywords: ecstasy; cognition; memory; navigation; hippocampus

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Ecstasy or 3,4-methylenedioxymethamphetamine (MDMA) is frequently associated with changes in cognitive functioning. The effect of chronic use of this drug on cognition has been studied intensively and most studies reported a negative effect of ecstasy on cognitive functioning. For example, McCardle, Luebbers, Carter, Croft, and Stough (2004) investigated the effect of the drug on cognition and mood and concluded that chronic users had memory and attention problems. Furthermore, they had higher scores on depression scales compared to a control group. Cognitive impairments as a result of ecstasy use are also described in a review study of Parrott (2001) and a more recent review study of Chummun, Tilley, and Ibe (2010).

The cognitive impairments following ecstasy use seem to be the result of changes in serotonin and dopamine levels (Chummun et al., 2010). Cognitive deficits as memory problems may reflect the serotonergic changes in the hippocampus (Parrot, 2001), although not all studies report hippocampal changes (Obergriesser et al., 2001). The serotonin syndrome described by Parrot (2002) includes physical changes (e.g. behavioral hyperactivity, hyperreflexia, and tremor) as well as mental confusion. Chronic methamphetamine use is also related to severe gray-matter deficits in cingulate, limbic, and paralimbic cortices (Thompson et al., 2004).

As explained earlier, most studies involving ecstasy have focussed on the chronic use of this drug. The effect of recreational doses or low doses of ecstasy is less studied, and in most of the studies on low doses no clear relation between this drug and cognitive deficits has been found. A double-blind placebo-controlled study of Vollenweider, Gamma, Liechti, and Huber (1998) investigated the relation between a recreational dose of ecstasy and the acute effects on psychological and cardiovascular measures in participants without any history of drug use. Attention was measured by the Stroop color–word test and there were no differences found in performances of participants using ecstasy and participants using a placebo. In contrast, Gouzoulis-Mayfrank et al. (2000) reveal a worse performance of recreational ecstasy users on multiple cognitive tests in comparison to a control group. Although the authors of this study describe the use of ecstasy in their participants as "recreational", subjects used ecstasy 6 months or longer with a minimum frequency of twice a month or at least 25 occasions during the past 2 years. Jager et al. (2007) investigated the effect of incidental use of ecstasy on cognition. Participants in this study had used two tablets on average and were tested before and after the ecstasy use. No significant effects of these low doses of ecstasy on cognitive functioning were found. Another study of Stough et al. (2012) analyzed the acute effects of 100 mg of MDMA on cognitive functioning. They found negative effects on attention and working memory tests, but differences in performances were mostly diminished after 24 hr. All the participants in this study had a

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history of drug use, which makes a comparison with the study of Jager et al. difficult.

The effects of incidental ecstasy use on brain structures have also been studied. De Win et al. (2007) analyzed the effects of low doses of ecstasy on the brain by comparing different brain areas with multiple imaging techniques. They did not find indications for structural neuronal damage in subjects who used ecstasy for the first time (De Win et al., 2007).

Taken together, the chronic use of ecstasy seems to have a negative effect on cognition, and hippocampal changes have been related to the chronic usage of this drug. Studies analyzing the effects of low doses of ecstasy on cognition and brain structures mostly did not find such effects.

In this case report, we describe a 39-year-old man, who reported severe memory and navigation problems after incidental ecstasy use. We examined the cognitive status of this patient 7 years after the ingestion. Standard neuropsychological tests were used to measure memory capacities. To analyze patients' navigation problems we made use of a more experimental virtual reality test. This case reopens the discussion whether a low dose of ecstasy can cause severe and persistent cognitive disorders.

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Methods

Case

FV is a 39-year-old, high-educated man. In 2005, FV had used one ecstasy tablet on a party, and directly afterwards he was confused, had trouble speaking correctly and he reported memory problems. After a day, the confusion and language problems disappeared, but the memory problems still remained. Two months after the ecstasy use FV visited the neurological outpatient clinic of the University Medical Center Utrecht. The neurological exam was normal and because the memory problems were in remission and further improvement was expected no imaging techniques were performed. In the years following this incident, the memory problems reduced somehow, but FV never came back to his old level of functioning. Therefore, in 2012, he visited the neurological outpatient clinic again. At that time FV reported problems in remembering appointments and information people told him. FV also reported difficulties orientating in new surroundings. He frequently made use of navigation equipment, both in his car and when biking (application on his smart phone). Just studying route information before leaving home was not sufficient. When parking his car he had to write down the location of this place, otherwise, he was not able to find his car back.

Medical history

FV reported he used ecstasy five to six times in the period 2002–2005. He states never to have used drugs after 2005. Friends of FV confirm that he was a sporadic user of ecstasy.

He suffered from hypertension but besides that there was no relevant medical history. He did not suffer from epilepsy. FV did not use any medication.

Before 2005, FV had no cognitive complaints. He graduated from university, worked several years at an academic level and started his own business, just before the ecstasy ingestion.

Neuropsychological assessment

To measure FV's cognitive status an extensive neuropsychological assessment was administrated. The most important cognitive domains (intelligence, language, visuoperception and construction, attention and executive functions, psychomotor speed) were measured and besides that a test for malingering and a depression scale were added to the assessment. In particular, the memory domain was measured in detail, and tests focussing on different memory processes were administrated. Working memory was assessed by the Digit Span of the Wechsler Adult Intelligence Scale–third edition (Wechsler, 1997) and the Corsi block-tapping test (Kessels, Van Zandvoort, Postma, Kappelle, & De Haan, 2000), verbal (long term) memory by the Rey Auditory Verbal Learning Test (RAVLT) (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005) and story recall of the Rivermead Behavioral Memory Test (RBMT) (Van Balen & Wimmers, 1993), and visual (long term) memory by the Location Learning Test (LLT) (Kessels, Bucks, Willison, & Byrne, 2012), Benton Visual Retention Test (BVRT) (Sivan, 1992) and the Modified Taylor Complex Figure (Hubley & Tremblay, 2002). To examine anterograde amnesia the Visual Association Test (VAT) (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002) was used and nonverbal recognition skills were assessed by the Doors Test (Baddeley, Emslie, & Nimmo-Smith, 1994) and the Continuous Visual Memory Test (CVMT) (Trahan & Larrabee, 1988).

Navigation experiment

Besides general memory problems, FV also complained about problems navigation in new surroundings. Because a standardized neuropsychological assessment does not include tests to measure navigation skills properly, we added a virtual reality test of navigation to our assessment. This test, making use of the virtual Tübingen environment, was designed to measure navigation skills in a more complex and therefore realistic manner (see e.g. van der Ham et al., 2010). In this test, subjects are shown and asked to memorize a video of a route in virtual Tübingen. Afterwards different subtasks are

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administered; scene recognition, route continuation, route sequence, route order, route position, route distance, pointing, route drawing, and map recognition. *Scene recognition* concerns the recognition of 11 scenes shown in the movie, among 11 distractor scenes. *Route continuation* entails the indication of what turn was taken at 11 intersections. In the *route sequence task*, participants are asked to indicate the turns taken during the route by aligning arrows on small paper cards, accordingly. In the *route order task*, participants arrange 11 scenes in the order they appeared on the route. The route position, route distance, and pointing subtasks concern the geometrical features of the route. In *route position*, participants are asked to indicate the position of each of 11 scenes by drawing a vertical line on a horizontal line representing the total distance of the route. In the *route distance* subtask, they have to indicate the relative distance between two points on the route on a horizontal line, also representing the total distance of the route. In the *pointing task*, participants indicated the direction of their starting point and endpoint at each of the 11 scenes. A manual rotation device was used, on which the experimenter could read the responses in degrees. Finally, knowledge of the route layout was tested by means of *route drawing* and map recognition. First, the participant was asked to draw the route onto a map of the environment, in which only the starting point and starting direction was indicated. In the *map recognition* subtask, the participant was shown four possible maps of the route, and asked to point out the correct map.

Control subjects

To compare FV's performance of the task in the virtual environment, four matched control subjects were recruited. Mean age of the control subjects was 38.0 years (SD 3.7, range 34–42), all of them were similar to FV high educated (higher professional education or academic degree). The control subjects had no history of drug use.

Brain imaging

A routine clinical magnetic resonance imaging (MRI) scan was performed on a 1.5 Tesla scanner (Philips Medical Systems, Best, The Netherlands). The protocol included a transversal T2-weighted turbospin-echo (TSE) (repetition time [TR]/echo time [TE]/inversion time 2,200/10 and 2,200/100 ms), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time [TI] 6,158/100/2,000 ms), and diffusion weighted imaging (DWI) (TR/TE 2,258/81, b value 0/1,000) sequences (slice thickness 6 mm, slice gap1.2 mm, 19 slices), and a coronal T1-weighted inversion recovery (IR) (TR/TE/TI 2,892/22/410 ms) (slice thickness 4 mm, 38 contiguous slices).

Laboratory investigation

Laboratory investigations included a full blood count, serum creatine and electrolytes, liver function tests, thiamine, vitamin B12, and thyroid function. Furthermore, serologic testing for Lues and human immunodeficiency virus (HIV) was performed.

Statistical methods

FV's performances on the neuropsychological assessment were compared with normative data corrected for sex, age, and education level. Scores below the 16th percentile are called *below average*, scores below the 6th percentile are called *impaired*.

To compare FV with the matched control subjects we made use of the Bayesian approach for single case studies (Crawford & Gartwaite, 2007).

Results

Neuropsychological assessment

The neuropsychological assessment revealed no cognitive disorders in the language, visuoperception and construction, attention, and executive domain. All scores were average or above average (in comparison to normative data, corrected for sex, age, and education level). Psychomotor speed was above average. The premorbid verbal intelligence level was average; nonverbal intelligence level is high average. There were no signs of a depressed mood. The score on malinger test was optimal.

FV's performances on memory tests were striking. Working memory was on average level, but scores on all memory tests for long-term memory were below average or impaired. There were no differences in performances on verbal or nonverbal tests, except the more average scores on visual recognition tasks (Doors Test, CVMT). See Table 1 for a detailed description of FV's performance on the memory tests.

Navigation experiment

FV's performance on the subtests *route continuation*, *route sequence*, and *route distance* were significantly worse in comparison to matched control subjects (two-tailed tested, $p = .04$ to $.05$). His performance on the subtest *route position* was significantly worse on a one-tailed test ($p = .04$), and almost significant on a two-tailed test ($p = .08$). Furthermore, while all the control subjects were able to recognize the right map out of four, FV

Table 1. FV's performances on memory tasks of the neuropsychological assessment, compared with normative data corrected for sex, age, and education level.

Cognitive domain	Test	FV's score
Working memory	Digit span	15/30
	Corsi block tapping	16/30
Long-term memory	RAVLT	
	Immediate recall	7/8/8/8/7**
	Delayed recall	2/15**
	Recognition	25/30**
	LLT	
	Immediate recall (displacements)	22/15/13/16/9**
	Delayed recall	19**
	RBMT stories	
	Immediate recall	8**
	Delayed recall	0.5**
	Doors Test	17/24*
	Modified Taylor Complex Figure (delayed recall)	2.5**
	VAT	8/12**
	CVMT	80
	BVRT	Correct: 6* Error: 4*

Note: *Below average performance (≤16^e percentile), ** Impaired performance (≤6^e percentile).

selected one of the incorrect alternatives (see Table 2). FV's performance on the subtests *route recognition*, *route order*, *pointing*, and *map drawing* was not significantly different from the control subjects.

Magnetic Resonance Imaging

On brain MRI, bilateral hippocampal atrophy was observed on coronal T1 weighted images, corresponding with medial temporal lobe atrophy score 2. FLAIR- and T2-weighted TSE sequences showed increased signal of both hippocampi, without increased signal on DWI, which could indicate sclerosis (see Figure 1). Besides signs of hippocampal atrophy and sclerosis, the MRI scan was normal, and no other abnormalities (e.g. vascular lesions, tumors) were seen that could explain the cognitive impairments.

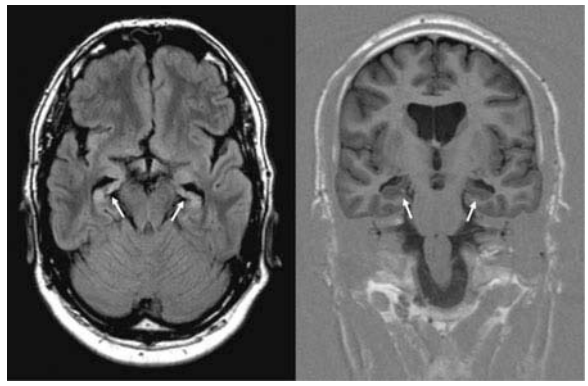

Figure 1. Bilateral atrophy and sclerosis of the hippocampi. Left: Fluid attenuation inversion recovery (FLAIR) sequence, showing increased signal of both hippocampi (arrows), which could indicate sclerosis. Right: T1-weighted inversion recovery (IR) coronal image, showing volume loss of the hippocampi on both sides (arrows), medial temporal lobe atrophy (MTA) score 2.

Laboratory investigation

Laboratory investigations were all normal, even as serologic testing for Lues and HIV.

Discussion

FV is a 39-year-old man who suffers from serious memory and navigation problems after sporadic ecstasy use. FV has great difficulties in daily life remembering appointments or things people told him. Furthermore, he is not able to navigate appropriately in new surroundings and gets lost when he is not using navigation tools.

In line with the complaints FV reported, the neuropsychological assessment revealed major memory disorders. On the virtual reality test of navigation, FV had significantly worse scores on different subtests in comparison to

Table 2. FV's performance on the navigation experiment.

Subtest	FV's score	Mean score and SD of control subjects	*t* and *p*
Scene recognition (% correct)	86	88 (16)	−.11 (n.s.)
Route continuation (% correct)	45	91 (13)	−3.17 (.05)
Route sequence (items correct)	0	5.75 (1.5)	−3.43 (.04)
Route order (score 0–22)	3	14.5 (7.1)	−1.45 (n.s.)
Route position (degrees deviation)	30	14 (5.4)	2.65 (.08)
Route distance (degrees deviation)	35	9.3 (7.4)	3.11 (.04)
Pointing starting point	73	51 (16)	1.23 (n.s.)
Pointing endpoint (degrees deviation)	79	61.8 (11)	1.40 (n.s.)
Map drawing (cm correct)	31	69.8 (34)	−1.02 (n.s.)
Map recognition	Incorrect	Correct	

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matched control subjects. He had trouble remembering what turns were made on the route and he had no "internal map" of the route. He also had difficulties remembering the geometrical features of the route (position of scenes on the route and relative distance between to scenes on the route). Finally, he was unable to select the correct map out of four potential maps. Strikingly, he was able to recognize scenes from the route, remembered their order, and the direction of the start and end of the route. Therefore, his impairment in navigation skills cannot simply be explained by a general memorization problem, as not all navigation aspects tested were impaired.

The findings of the neuropsychological assessment and the virtual reality test can explain the complaints of FV in daily life fully. Importantly, the cognitive problems appear to have arisen directly after the ecstasy ingestion in 2005 and therefore we related the cognitive problems to the use of this drug. The relation with ecstasy use is further supported by the structural changes in the hippocampus seen on the MRI scan of FV. The hippocampus plays a crucial role in memory processes (Eichenbaum, 2004) and also in the ability to navigate (Goodrich-Hunsaker, Livingstone, Skelton, & Hopkins, 2010; Maguire et al., 1998).

To our knowledge, this is the first demonstration of persistent cognitive disorders after sporadic use of ecstasy. Gardner, Lawn, Fatovich, and Archer (2009) also described two cases with acute hippocampal changes on MRI after ecstasy ingestion. These patients reported cognitive problems, but those diminished after a relatively short period. The first patient used half a tablet ecstasy every few months (not further specified). After ecstasy ingestion, he had tonic–clonic seizures and on the MRI scan of the brain 2 days later high signal and swelling of the hippocampus was seen. A later scan showed hippocampal atrophy. After a few months, this patient was asymptomatic and had returned to work. The second case had also seizures after ecstasy use, followed by confusion and memory difficulties. She returned to work within a few days and the cognitive complaints disappeared in the following months. On her MRI scan a similar swelling of the hippocampus followed by atrophy was seen, as is also described in our patient.

This case report reopens the discussion whether sporadic ecstasy use is harmful or not. In previous years the risks of a recreational dose of ecstasy was discussed. In the study of Vollenweider et al. (1998), subjects received a dose of MDMA. Gijsman, Verkes, van Gerven, and Cohen (1999) discussed the administration of this dose to healthy subjects. They stated that, based on animal research, it cannot be excluded that the rapid decrease in concentration of serotonin after a single dose of ecstasy does not cause damage to the serotonergic neurons. Vollenweider Gamma, Liechti, and Huber (1999) responded to these statements by explaining that reductions in serotonin levels do not automatically results in serotonergic neurodegeneration (Colado, Williams, & Green, 1995; O'Shea, Granados, Esteban, Colado, & Green, 1998). A more recent study of Jager et al. (2007) did not find evidence for effects of a low dose of ecstasy on cognitive functioning.

In light of the currently available evidence, it is still not totally clear what the precise consequences are of a low dose of ecstasy. Our case report describes, in contrast to the other studies, persistent and severe cognitive deficits after sporadic ecstasy use.

A few aspects of this study may raise questions and need to be discussed.

Although FV stated that before 2005 he did not have any cognitive complaints, we have no previous neuropsychological assessment to compare the current test scores to. We cannot fully establish that there were no cognitive deficits before the ecstasy use. Nonetheless, FV obtained a Master's degree without any problems and there were no signs of any cognitive problems in daily or professional life.

Another issue of discussion involves the etiology of the cognitive disorders. Based on the story of FV we assume that the problems arose directly afterwards the ecstasy ingestion. The kind of cognitive disorders, even as the kind of hippocampal damage, have been associated to (chronic) ecstasy use in previous studies. Taken these facts together, we assume that the cognitive disorders and the hippocampal changes of FV are the result of his ecstasy use in 2005. This assumption is strengthened by the fact that the MRI scan did not reveal vascular lesions, tumors, or other causes that could explain the cognitive impairments. Laboratory investigations were also normal and gave no indications for alternative explanations. We did not find any indications for a depressed mood or for malingering. Finally, FV was not involved in litigation. Nevertheless, we cannot fully exclude all other possible causes (e.g. hypoxia during an epileptic attack) and it is regrettable that no imaging techniques were performed directly after the ecstasy ingestion.

One could doubt whether the ecstasy FV had taken was pure MDMA or also contained other substances. Right after the incident the other pills FV and his friends had bought were tested by Trimbos Instituut (center of expertise on mental health and addiction). Test results showed that the pills contained 150 mg pure MDMA.

As mentioned in the introduction cognitive disorders after chronic ecstasy use are frequently described in the literature. FV states that he only used ecstasy sporadically in the period 2002–2005. His friends confirm this low use of ecstasy. The marked alteration in functioning of FV is striking, and is not expected after chronic use.

Because this is a single case report we should be cautious in drawing conclusions. Nevertheless, the present findings may help in further understanding of the relation

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between ecstasy use and cognition. Taken together, this case report describes a man with severe and persistent cognitive disorders after incidental ecstasy use. On his MRI scan of the brain hippocampal atrophy was seen. These findings call for closer examination of individual cases on the effects of low doses of ecstasy on cognition and on brain structures. Is it possible that more cases such as these exist but that individual stories are neglected by studying large groups?

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Disclosure statement

The authors of this study confirm that they do not have any financial interests or benefits arising from this research.

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