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RESEARCH ARTICLE

Long-term effects of MDMA (Ecstasy) on the human central nervous system revealed by visual evoked potentials

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Abstract

Several studies indicate long-term cognitive impairment of MDMA (ecstasy) users. In the present study we attempted to establish whether electrophysiological correlates of low-level cognitive processes present a long-term alteration, dependent on the level of use of ecstasy. We addressed this issue by investigating amplitude and latency of VEPs related to a very simple discrimination task involving sustained attention (arousal). Eight heavy-MDMA users, eight moderate-MDMA users and 18 drug-free control subjects were asked to discriminate whether the digit at the centre of the screen was 1 or 2. None of the subjects (except one) had used MDMA in the 6 months previous testing. We measured psychophysical performance and EEG, recorded in Oz and Fz during task execution. The heavy-MDMA users made significantly more errors than the other two groups ($p < .05$). Moreover, they presented reduced amplitude but not latency of VEPs in both Oz and Fz. The effect in Oz is present in P200 (for heavy users only, $p < .05$) and in P300 components (for both MDMA groups; heavy users: $p < .001$, moderate users: $p < .0.5$). In Fz, the amplitude effect is present in N250 (for heavy users only, $p < .05$) and in P300 components (for both MDMA groups; heavy users: $p < .05$, moderate users: $p < .05$). The three groups do not differ in early components, reflecting low-level processing. These results provide evidence of long-term electrophysiological abnormality displayed by ecstasy users and agree with the suggestion that even typical recreational doses of ecstasy are sufficient to cause long-term altered cortical activity in humans.

Introduction

The use of (±) 3,4-methylenedioxymethanphetamine (MDMA, "ecstasy") is common among young people in Western countries. MDMA is a potent and selective serotonin (5-HT) neurotoxin in a variety of animal species, including non-human primates (Commins et al., 1987; Green et al., 1995; O'Hearn et al., 1988; Ricaurte et al., 1988a; Ricaurte et al., 1988b; Schmidt and Lovenberg, 1986; Stone et al., 1986). Animal models of MDMA toxicity suggest a degeneration of serotoninergic (Colado et al., 2004; Green et al., 1995; Green and Goodwin, 1996; Ricaurte and McCann, 1992; Schmidt and Kehne, 1990) and dopaminergic neurons (Crespi et al., 1997; Ricaurte et al, 2002), although contradictory results are also found (Colado et al, 2004; Fone et al., 2003). Several studies, investigating how ecstasy exposure correlates with serotonin (5-HT) and dopamine system impairment, suggest a comparable neurotoxic effect in humans (Gerra et al., 2000, 2002; McCann et al., 1994, 1998, 1999, 2000; Semple et al., 1999), which has been suggested to be long-lasting (Cowan et al., 2003; Croft et al., 2001; Gerra et al., 2000; Parrot, 2002; Semple et al., 1999).

However, despite some biological evidence for brain serotonin injury in animals, there is mixed evidence relatively to consequences in neuronal substrate (Gamma et al., 2001; Buchert et al., 2004; Mithoefer et al., 2003; Ricaurte et al., 2003; Sumnall et al., 2003) as well as in cognitive processes (Gamma et al., 2001) of MDMA use in humans. The most common suggestion is that individual may have memory impairments as a consequence of MDMA use such as verbal memory (Bhattachary and Powell, 2001; Krystal et al., 1992; Parrot et al., 1998; McGuire, 2000), visuospatial memory (Verkes et al., 2001), visuospatial (Wareing et al., 2004a) as well as verbal (Curran and Travill, 1997; Wareing et al., 2004b) working memory impairment. The extent of cognitive impairment seems to correlate with the degree of MDMA exposure and the reduction in brain 5-HT (Bolla et al., 1998; Verkes et al., 2001).

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Other studies used tests sensitive to frontal cortical dysfunction. Parrott (2000) reviewed evidence of impaired higher executive processing in ecstasy users. More recently, Zakzanis and Young (2001) also found evidence of executive dysfunction using the Behavioural Assessment of the Dysexecutive Syndrome (BADS). Interestingly, this profile of high-level cognitive deficit has been related to a hypothetical integrative construct: namely reduced cortical inhibition (Parrott, 2000). More contradictory findings are those relative to a possible long-term attentional effect in MDMA users. Verkes et al. (2001) showed a stronger impairment in simultaneous than serial recognition of words and figures, a results which cannot simply be accounted for on the bases of memory deficit. Curran and Travill (1997) and McCann et al. (1999) found significant performance deficits on a sustained attention task requiring arithmetical calculations. Gouzoulis-Mayfrank et al. (2000) found that ecstasy users were unimpaired in simple tests of attention (alertness). However, they performed worse than control groups in the more complex tests of attention. On the other hand, Gamma et al. (2001) do not support the hypothesis of attentional deficits in MDMA users. They did not find evidence of a difference between MDMA users and controls in cognitive tasks requiring sustained attention, and statistical parametric mapping revealed that brain activity did not differ between the two groups during cognitive activation by an attentional task using Positron Emission Tomography (PET).

Overall, these findings provide mounting evidence that MDMA users may show impairments in several aspects of cognitive functioning. However, there are several problems with empirical research in this field. The evidence for impairments on several cognitive processes (i.e. long-term attentional deficit) is not conclusive and, in any case, in the literature there is a dissociation between behavioural and neuroscience investigation. To our knowledge, only few studies attempted to establish a correlation between cortical activity and cognitive variables (Dafters et al., 1999; Gamma et al., 2001; Reneman et al., 2001).

In the present paper we further tested the hypothesis that MDMA users present long-lasting alterations in neurophysiological substrate of cognitive processing, focusing on the cortical activity associated to a very simple cognitive task. This was done by measuring visual evoked potentials (VEPs), a method widely used to address the question of what physiological process is triggered by a given sensory stimulus (Regan, 1989). VEPs consist of an electrophysiological response (potential) time-locked to a sensory stimulus. Several components can be distinguished in VEPs and those occurring after about 50–75 ms from stimulus onset reflect cortical processing. It is widely assumed that the sequence of VEP's peaks correspond to an ordered sequence of information-processing stages, and indeed a major goal of so-called "cognitive psychobiology" is to identify particular VEP components as markers of different aspects or stages of information processing. Those components occurring within the range of 50–250 ms (exogenous) depend on the parameters of the physical stimulus and are little affected by cognitive factors with the exception of attention, which has been shown to affect very early positive and negative components. Latest components (P300, N400) are determined by cognitive events and by attention and may reflect recall from memory. In particular, there is evidence that P300 amplitude is proportional to the amount of attentional resources in terms of processing capacity that is employed in a given task (Kramer and Strayer, 1988; Regan, 1989) and reflects neural activity related to basic aspects of cognition (Polich and Kok, 1995).

Since long-term 5-HT dysfunction in MDMA users has been found to be related to total MDMA consumption we compared VEPs response elicited by a digit discrimination task in three groups of subjects: one group of polydrug users who had been heavy consumers of MDMA, one group of polydrug users who had made moderate use of MDMA, and one group of subjects who had never taken any illegal drugs.

Materials and method

Participants

Three groups of subjects participated in the study, two groups of MDMA users and one group of drug-naives. The first group comprised eight (7 males and 1 female) heavy-MDMA users, aged 25–32 years ($M \pm SD = 28 \pm 2.6$ years), with a history of at least 120 occasions of ecstasy use ($M \pm SD = 1054 \pm 720$, range from 120 to 3000). The second group was made by eight (7 males and 1 female) moderate-MDMA users, aged 20–26 years ($M \pm SD = 25 \pm 2.0$ years), with a history of no more than 100 occasions of ecstasy use ($M \pm SD = 52.4 \pm 3.3$, range from 25 to 100). One group of eighteen non-drug controls participated in the study. This drug-naive group consisted of a sub-group of relatively young individuals, (3 males and 6 females), aged 19–23 years ($M \pm SD = 22 \pm 1.4$ years), and a sub-group of relatively old individuals (5 males and 4 females), aged 24–32 years ($M \pm SD = 27 \pm 10.36$ years) (see Table 1). MDMA users were recruited either from the Drug Service in Padova (Az. USL) seeking treatment ($N = 8$), or were recruited through via a "snowball" effect ($N = 8$) (Callow, 1996) in which initial volunteers were asked to recruit additional volunteers among their friends. Control subjects were recruited amongst university students.

History of drug use (Table 2) was obtained less than one week before testing. Participants were formally assessed by a personal detailed questionnaire and a general drug use questionnaire, which listed questions about a variety of different drugs. The use of MDMA, alcohol, tobacco, amphetamines, temazepam, cocaine, heroin, LSD, and magic mushrooms was assessed in this way. A specific drug use questionnaire requested information about the duration of the use of ecstasy, the last time of drug use, the amount (number of tablets) used in the previous month before stopping, the frequency of use, the average and maximum amount taken per session and an estimate of total life-time consumption. Exclusionary criteria for the four groups included: past or current history of head trauma, unconsciousness, hyperactivity disorder, psychiatric disorder, other diseases previously linked to EEG abnormalities such as cardiovascular disease or diabetes. All subjects were assessed for neurological and medical illness and psychopathology, as listed in Table 3. Subjects who were currently taking psychotropic medication or had ever received treatment for

Table 1. Participant's specifications. Mean age, gender and level of education for the four groups of subjects is shown. Note that the control group has been divided in two sub-groups (young and old).

	Control-young (n = 9)	Control-old (n = 9)	MODERATE-MDMA (n = 8)	HEAVY- MDMA (n = 8)
AGE	22 ± 1.4	27 ± 10.36	25 ± 2.0	28 ± 2.6
GENDER				
Male	3	5	7	7
Female	6	4	1	1
EDUCATION				
Lower	0	0	0	1
Intermediate	3	2	4	5
At least preuniversity	6	7	4	2

Table 2. History of drug assumption. History of drug assumption, assessed by a questionnaire, is reported for the three groups of subjects.

	Controls	MODERATE-MDMA	HEAVY- MDMA
ALCOHOL (litres x week)	2.1	2.6	3.7
Duration of use (years)	4.9	5.2	7.3
CIGARETTES (units x week)	68.6	66.6	105.8
Duration of use (years)	5.2	5.8	10.7
CANNABIS (joints x week)	2	24.6	38.7
Duration of use (years)	2	9	9.8
AMPHETAMINE			
(n. exposures x year)	0	1.8	1.2
Duration of use (years)	0	4.3	1.1
"MAGIC MUSHROOMS"			
(n. exposures x year)	0	1,8	0,5
Duration of use (years)	0	4,8	0,5
LSD ("trips" x year)	0	17	25,8
Duration of use (years)	0	4,5	3,7
COCAINE (g x year)	0	2,9	16,8
Duration of use (years)	0	4,1	6,4
OPIATES (HEROIN)			
(n. exposures in life)	0	1	0
METHADONE			
(n. exposures in life)	0	5	4.9
MDMA (n. exposures in life)	0	52,4	1054.1
Duration of use (years)	0	3,3	3,6
Duration of abstinence (years)	0	2,1	2.5

a psychiatric disorder or substance related disorders (except MDMA) were also excluded. All subjects had normal or corrected-to-normal vision and had abstained from the MDMA use for at least six months prior to VEP recording, except one moderate-MDMA subject who had a relapse of MDMA consumption one month before testing. The abstinence period, as well as history of drug use, was self-reported. All subjects provided informed consent prior to study participation.

Stimulus and task

The stimulus consisted in the cyclical alternation of a white digit (34.3 cd/m^2) with a red dot (19.5 cd/m^2) on a dark background (0.25 cd/m^2), displayed at the centre of the screen. The digit could be either 1 or 2, randomly. At a viewing distance of 57 cm the stimulus subtended an angle of 0.5 degrees. A two-alternative forced-choice (2AFC) task was used and the response had to be made, on average, every three trials[1] indicating, by pressing the appropriate key, whether the last presented digit was 1 or 2. No time pressure was imposed. Stimulus presentation timing was as follows: after subject's response a red dot was displayed for 2000 ms, and then the digit-dot alternation started with 800 ms of exposure interval for each stimulus. After 1 to 5 digit-dot alternation the screen become blank prompting for subject's response.

Before the experiment began, the experimenter gave the following instructions: "You will see a white digit (which can be 1 or 2) cyclically alternating with a red dot. When the sequence is interrupted and the screen goes blank, please respond which was the last presented digit by pressing either 1

[1]This was done for two reasons: first, to minimise EEG artefacts introduced by manual response, second, to engage a large amount of sustained attention in the task execution.

Table 3. Neurological and medical illness and psychopathology. Occurrence of neurological and medical illness and psychopathology, assessed by a questionnaire, is reported for the three groups of subjects.

	Controls	MODERATE-MDMA	HEAVY-MDMA
NEUROLOGICAL ILLNESS			
NEUROLOGICAL DISORDERS	0	0	0
HEAD INJURY	0	0	0
DISEASE LINKED TO EEG ABNORMALITIES (cardiovascular disease or diabetes)	0	0	0
UNCONSCIOUSNESS	0	0	0
SEIZURE	0	0	0
PSYCHOPATHOLOGY			
MOOD	0	0	0
ANXIETY	0	0	0
PSYCHOTIC DISORDERS	0	0	0
HYPERACTIVITY (YOUTH)	0	0	0
MEDICAL ILLNESS			
RENAL ILLNESS	0	0	0
ENDOCRIN ILLNESS	0	0	0
HEMATOLOGIC	0	0	0

or 2 on the keyboard. Try to keep your fixation on the stimulus (red dot or white digit) all the time. Try not to move your eyes, your head or your body during stimulus presentation. You can move your eyes/head/body and rest when the stimulus disappears, before making your response. Do not rush for responding, take your time."

Recording and analysis

Recording took place in a dedicated room with a constant low level of illumination and environmental noise. Subjects were seated in a comfortable upright chair with head movements minimised by means of a chin rest.

The electroencephalogram (EEG) was recorded from Ag/AgCl- coated cup electrodes placed at Oz, Fz, left (for reference) and right (for ground) earlobes. Electrodes placement followed the international 10/20 system. Electrode impedance was kept below 5 k. The EEG was amplified (BM 623, Biomedica Mangoni Pisa, Italy) and digitally converted (CED 1401, Cambridge Electronic Design, Cambridge, UK) under control of a second PC. Stimulation and recording onset were synchronised on the basis of the vertical retrace signal of the monitor that displaced the stimulus. The EEG was amplified 50000 times, bandpass filtered at 1–50 Hz, sampled at 1 KHz with a resolution of 12 bits, and stored on a hard disk. Artefact rejection was done off-line when the signal amplitude exceeded $\pm$ 100 μV.

The VEPs were obtained by averaging the signal and then were vertically aligned by taking as baseline their mean amplitude in the 0–50 range after stimulus onset.

Statistical analysis

Two-way ANOVAs with group type as between-subjects factor (moderate-MDMA users, heavy-MDMA users, Controls) and VEPs components with a latency of 100 (P100), 150 (N150), 200 (P200), 250 (N250), 300 (P300), and 400 (N400) ms as within-subjects factors were used to compare both the latency and amplitude of the three groups separately for Oz and Fz. In Oz, average peak latency for each of VEPs components in the three groups were: (P100: 113 - 121 ms; N150: 155 - 166 ms; P200: 212 – 224 ms; N250: 248 – 274; P300: 297 - 323; N400: 390 – 415 ms). In Fz, average peak latency for each of VEPs components in the three groups were: (P100: 121 – 139 ms; N150: 154 – 173 ms; P200: 213 – 222 ms; N250: 247 – 282; P300: 330 - 342; N400: 406 – 438 ms). Bonferroni-corrected t-tests were used for pairwise comparison. Age-effect (as well as sex effect) was assessed by comparing VEPs in the two sub-groups of the control group (young vs. old). Since no difference was found, the two sub-groups were merged. A separate ANOVA was used to compare the number of errors (behavioural data) in the three groups.

Results

Behavioural data

The one-way ANOVA with the group as between-subjects factor, showed that the number of errors did not significantly differ among the three groups ($F_{2,31} = 1.8$, $p > .05$). However, pairwise comparison (t-test) showed that the number of errors was significantly higher in the heavy-MDMA with respect to the control group ($t = 2.1$, $p < .05$). Behavioural data (Table 4) show very little difference between the groups in the digit-discrimination task. This is expected since it is generally found that MDMA-users impairment is present in tasks involving cognitive functions of higher level than the one we tested.

VEPs

Age and sex effects. In order to rule out the possibility that a VEP difference in either latency or amplitude between any of the two experimental groups and the control group could be due to a difference in age or sex, we first compared peak latencies and amplitudes within our control group by assessing the effect of age (sub-group of younger vs. older individuals) and sex. The two control sub-groups did not

Table 4. Behavioural data

	Controls	MODERATE-MDMA	HEAVY-MDMA
NUMBER OF ERRORS	0.9	1.5	2.5

Table 5. AMPLITUDE of Oz components of VEPs

	P100	N150	P200	N250	P300	N400
Heavy-MDMA	1.4 (1.4)	− .7 (1.2)	1.9 (1.2) a	1.1 (1.9)	2.2 (1.7) b	− .4 (1.3)
Moderate-MDMA	1.1 (1.3)	- 1.8 (1.7)	2.8 (1.1)	.4 (1.7)	3.6 (0.7) c	1.0 (1.7)
Controls	1.2 (1.2)	− 2.2 (2.2)	3.9 (2.0) a	.5 (3.0)	5.5 (1.9) b,c	− .5 (2.0)

a: controls vs. heavy-MDMA users $p < .05$.
b: controls vs. heavy-MDMA users $< .05$.
c: controls vs. moderate-MDMA users $< .05$.

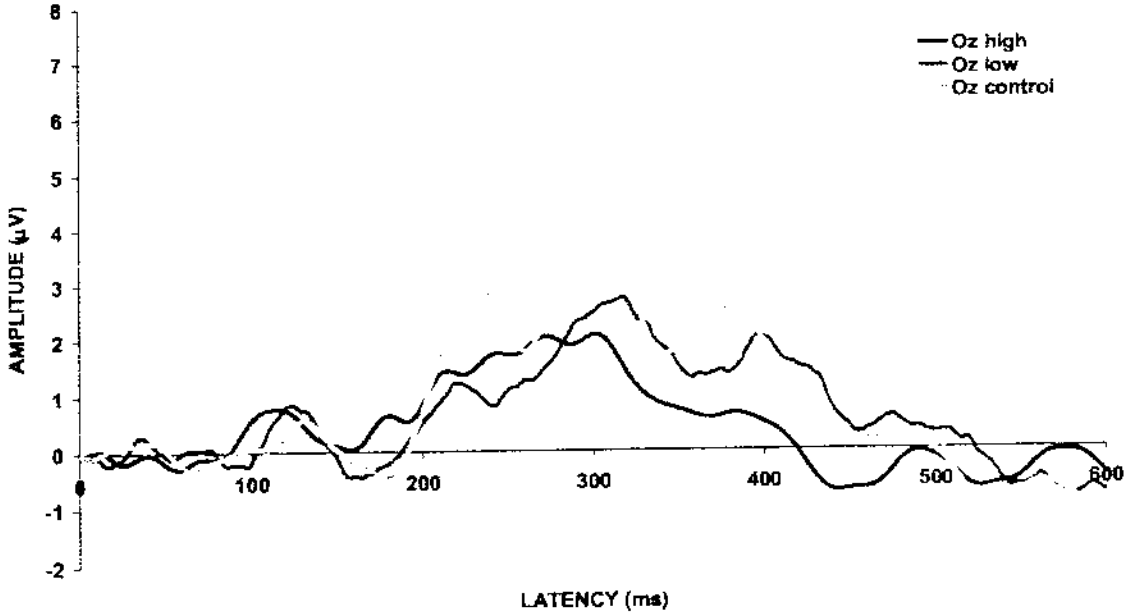

Figure 1. *VEPs recorded at Oz location, separately for the three groups.*

differ statistically in either latency or amplitude of VEPs, nor any difference due to sex was found. This result is methodologically important since it could not be excluded a priori that any difference found between the three groups of subjects may depend on subjects' age (Regan, 1989). On the bases of these results, the two groups were therefore pulled together in a large ($n = 18$) control group in the following ANOVAs.

MDMA effects. ***Oz***. The amplitude of VEPs components for the occipital (Oz) electrode are reported in Table 5 and Fig. 1.

The effect of component (peak) is significant ($F_{5,155} = 35.9$, $p < .0001$), as well as the interaction component x group ($F_{10,155} = 3.5$, $p < .0001$). The effect of the group factor is not significant. Bonferroni post-hoc tests show that, with respect to control group (no-drug), heavy-MDMA users present significantly reduced amplitude of P200 ($p < .05$) and P300 ($p < .0001$) components. P300 component was also reduced in moderate-MDMA users with respect to controls ($p < .05$). These results indicate that MDMA use reduces amplitude of intermediate (P200) and late (P300) VEP components and that P300 effect also occurs in individuals with moderate MDMA consumption.

The latencies of VEPs components for the occipital (Oz) electrode are reported in Table 6. The effect of the group factor is not significant. The effect of component (peak) is significant ($F_{5,155} = 700$, $p < .0001$), as well as the interaction group X component ($F_{10,155} = 2.5$, $p < .01$). However, Bonferroni post-hoc tests did not reveal any significant group difference within the selected components. This suggests that

Table 6. LATENCY of Oz components of VEPs

	P100	N150	P200	N250	P300	N400
Heavy-MDMA	121 (19)	155 (22)	206 (26)	248 (31)	310 (26)	389 (38)
Moderate-MDMA	120 (15)	166 (24)	224 (34)	271 (23)	323 (35)	393 (16)
Controls	113 (22)	160 (21)	214 (20)	249 (23)	297 (30)	415 (31)

Table 7. AMPLITUDE of Fz components of VEPs

	P100	N150	P200	N250	P300	N400
Heavy-MDMA	1.1 (1.5)	− .6 (1.4)	3.8 (2.6)	0 (1.9) a	3.3 (2.4) b	− 0.9 (1.7)
Moderate-MDMA	1.2 (0.9)	− .1 (1.0)	3.5 (1.9)	.1 (1.7)	2.8 (2.4) c	0 (3.3)
Controls	.8 (1.2)	− .8 (1.2)	3.8 (2.8)	2.3 (2.3) a	7.0 (4.0) b,c	1(4.4)

a: controls vs. heavy-MDMA users $p < .05$.
b: controls vs. heavy-MDMA users $< .05$.
c: controls vs. moderate-MDMA users $< .05$.

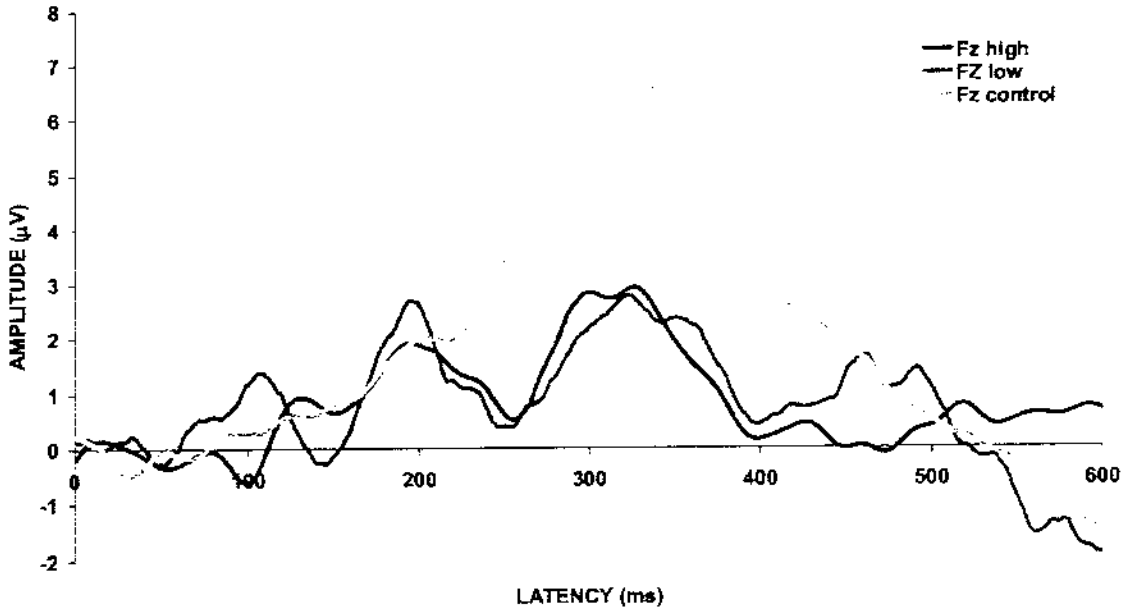

Figure 2. *VEPs recorded at Fz location, separately for the three groups.*

Table 8. LATENCY of Fz components of VEPs

	P100	N150	P200	N250	P300	N400
Heavy-MDMA	139 (32)	173 (36)	222 (32)	282 (31)	342 (42)	425 (47)
Moderate-MDMA	136 (21)	164 (26)	220 (41)	282 (45)	331 (49)	406 (58)
Controls	121 (33)	154 (35)	213 (39)	247 (39)	334 (65)	438 (55)

the latency of VEPs components of either heavy-MDMA or moderate-MDMA users never significantly differed from that of controls.

Fz. The amplitude of VEPs components relative to the frontal (Fz) electrode are reported in Table 7 and Fig. 2 respectively. The effect of component (peak) is significant ($F_{5,155} = 24.61$, $p < .0001$), as well as the interaction component x group ($F_{10,155} = 2.81$, $p < .005$). The effect of the group factor is not significant. Bonferroni post-hoc tests show that, with respect to control group (no-drug), N250 component was

significantly smaller in heavy-MDMA users ($p < .05$) and nearly significantly smaller in moderate-MDMA users ($p = .06$). P300 component was reduced in both moderate ($p < .05$) and heavy-MDMA users ($p < .05$) with respect to controls. These results indicate that both moderate-MDMA users and heavy-MDMA users present smaller amplitude in the exogenous late VEP components.

The latencies of VEP components for the frontal (Fz) electrode are reported in Table 8. The effect of component is significant ($F_{5,155\cdot364}$, $p < .0001$), whereas the effect of group and the interaction group X component is not. This indicates that the latency of VEPs components of either heavy-MDMA or moderate-MDMA users never significantly differed from that of controls.

Conclusion

The major finding is that there is a long-lasting effect of MDMA use, reflected in VEPs amplitude but not latency. In Oz, the amplitude of intermediate (P200) and late (P300) is smaller in heavy-MDMA users than controls. Moderate-MDMA users also present smaller amplitude of P300 with respect to controls. In Fz, the amplitude of P300 is reduced in both heavy- and moderate-MDMA users with respect to controls. Amplitude of N250 component is also reduced, in heavy-MDMA users only. The three groups do not differ in the amplitude of early components, reflecting early processing. To our knowledge this result provides one of the first (see also Reneman et al. (2001) for a related finding) direct evidence of a long-term effect of MDMA use on VEP responses associated to low-level cognitive tasks. It is accepted that a difference in latency in VEPs latency reflects differences either in conduction time or in timing processing (Regan, 1989). Since our subjects do not differ in latency of VEPs component we infer that processing speed is not affected in these individuals.

The VEPs amplitude results indicate that MDMA consumption affects cortical activity reflected in both exogenous (P200 and N250) and endogenous (P300) aspects of information processing. There is consisting evidence that P200 and N250 amplitude depend on physical parameters of stimulation. For example, Bach and Meigen (1992) and Caputo and Casco (1999) showed that N250 is modulated by global figure-ground segmentation. Oka et al. (2001) reported evidence that P200 amplitude is affected by figure symmetry. On the other hand, it is widely accepted that P300 is an endogenous component (Regan, 1989). A general feature of the effects here reported of MDMA use on VEPs is that they seem to be present in those components of cortical activity, which are affected by attentional demands (Coull, 1998).

However, the precise relationship between attentional demands set by a very simple digit discrimination task as the one used in the present study and the strong VEPs amplitude effect in MDMA users is not evident. A possible link is suggested by the view that a substantial portion of P300 variation appears to be caused by factors not only related to alterations of the task structure but also to fluctuation in the arousal state of the subject. Indeed, parameters contributing to P300 and N250-P300 complex production are shown to be sensitive to the "energetical" or "intensive" factors that are induced by the activation state rather than by the task (Kok, 1990; Kulikowski et al., 1984). Since the task we used seems to be very easy for all groups, the effect of MDMA consumption on P300 amplitude could indeed be interpreted as a result of a non-specific reduction of the whole organism's activity level, resulting from variations of reticular system activation (Lindsley, 1961).

However, the finding of an amplitude effect on specific stimulus-dependent components (P200, N250) but not other components (P 100 and N150) does not support the suggestion that MDMA affects in general mode cortical activity in human brain. Indeed, a general arousing effect is expected to facilitate the alerting effect of sensory processes and therefore to be reflected in earlier as well late VEPs components (Kulikowski et al., 1984). The reduced arousal is also very difficult to conciliate with the very interesting hypothesis that reduced cortical inhibition may be a general explanation of behavioural and cognitive impairment in these individuals (Parrott, 2000). On the bases of these considerations it cannot be excluded that a specific attenuation of late VEPs components may be possibly related to cognition in a more focused way (Polich and Kok, 1995). Indeed, McKetin and Solowij (1999) suggested that late processing negativity (increased negativity of ERPs in the interval of 270–700s) represents the active maintenance of the attentional race corresponding to the relevant stimulus in preparedness for further processing. Naatanen (1990) proposes that late processing negativity to the relevant stimulus reflect the activity of a limited-capacity executive processor and that it is generated by a subcortical structure in the frontal lobe (Giard et al., 1988).

Although a specific explanation has to be considered, the alternative explanation of our findings in terms of a general reduction of the arousal level seems to us more appealing for several reasons. First, laboratory animals are shown to develop serotonergic(5-HT) neurotoxicity after repeated doses of MDMA. Anatomical studies show that serotonergic neurons originating from Rafe nuclei project extensively to all levels of the central nervous system. Moreover, in favour of the hypothesis of a general effect is the results of McCann et al. (1998) which reported that serotonin transporters at the synapses were reduced in ecstasy users in every brain region studied, and the study of Gamma et al. (2000) that provided evidence from PET studies of a distributed cluster of brain areas underlying the various effects of MDMA in humans.

To conclude, these results provide new evidence that cortical activity associated with low levels of cognitive processing is altered after prolonged exposure to ecstasy. They confirm the evidence of long-term EEG deficits (Dafters et al., 1999) displayed by drug-free ecstasy users and are consistent with the evidence that even typical recreational doses of ecstasy are sufficient to cause neurotoxicity in humans and that this neurotoxicity is associated with a subtle, but significant, low-level cognitive deficit.

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