SHORT REPORT

Increased visual cortical excitability in ecstasy users: a transcranial magnetic stimulation study

M Oliveri, G Calvo

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Objectives: To test the presence of abnormalities of visual cortical excitability in people using ecstasy as a recreational drug.
Methods: Ecstasy users and control subjects underwent single pulse transcranial magnetic stimulation (TMS) of the occipital cortex. The phosphene threshold was analysed and compared in the two groups.
Results: Phosphene thresholds were significantly lower in ecstasy users compared with control subjects, and were correlated negatively with frequency of ecstasy use. Frequency of use was positively correlated with the presence of visual hallucinations. The phosphene threshold of subjects with hallucinations was significantly lower than that of subjects without hallucinations.
Conclusions: The use of ecstasy as a recreational drug is associated with an increased excitability of the visual cortex, possibly linked with massive serotonin release, followed by serotonin depletion, in this cortical area.

Ecstasy (3–4 methylenedioxymethamphetamine (MDMA)) has gained increasing popularity as a recreational drug. Despite its perceived safety, a number of studies in experimental animals[1] and in humans[2–5] have reported that the drug is associated with toxic effects on the brain, especially on serotonergic axon terminals. This has increased the need of ecstasy users, general public, and governmental agencies involved in drug use policy to obtain accurate information on the risks of this drug for specific brain functions in humans.

In this connection, testing of visual cortex functionality in ecstasy users represents an interesting target for research, as many studies reported neurotoxic effects at the level of the occipital cortex[2–6] and as visual symptoms are one of the most relevant clinical manifestations associated with drug ingestion.

Here, we hypothesised that ecstasy use could specifically result in increased excitability of the visual cortex, a mechanism that could be directly involved in the production of visual hallucinations. This hypothesis was evaluated by directly stimulating human occipital cortex using transcranial magnetic stimulation (TMS) in a group of ecstasy users compared with normal controls. When applied to the occipital cortex, TMS can elicit conscious subjective light sensations (phosphenes) in the absence of visual stimuli.[7] The minimum TMS intensity that evokes phosphenes (phosphene threshold) represents a useful parameter of cortical excitability: phosphene threshold increase reflecting reduced visual cortex excitability and vice versa.

METHODS

Subjects

We studied 10 heavy ecstasy users (nine men/one women; mean (SD) age 22.7 (3.3) years) and 10 age matched control subjects (eight men/two women) with no self reported use of ecstasy or other psychoactive drugs (table 1). Heavy ecstasy use was defined as the use of 50 or more tablets containing MDMA as the active ingredient, at a dose of 100 mg per tablet, before the study. Participants were tested within three days after last assumption of ecstasy (one tablet during the weekend). Ecstasy users claimed to have not used psychoactive drugs other than ecstasy, with the exception of alcohol and, more sporadically, psilocybin mushrooms.

Table 1 Demographic characteristics of ecstasy users

Subject	Age	Sex	Frequency of use	Duration of use (y)	Phosphene threshold
1	23	M	3	5	40
2	22	M	1	3	72
3	28	M	1	6	90
4	18	M	2	2	75
5	21	M	3	3	65
6	19	M	1	5	70
7	24	F	2	4	62
8	23	M	3	2	35
9	21	M	3	1	60
10	28	M	1	1	70

Frequency of use refers to the number of tablets per week (see text for details).

All subjects gave written informed consent for participation to the study, and the protocol was approved by the institutional ethical committee.

TMS

Participants were seated in a semi-darkened room, blindfolded, and instructed to keep their eyes closed. They wore a plastic cap with a grid of 3×3 points, based on lines running parallel to lines connecting the inion and the two preauricolar points and the inion and the nasion. The points were spaced 2 cm apart and centred over Oz point of the 10–20 EEG system (10% of the nasion-inion distance above the inion).

Subjects were instructed to report any potential subjective sensations (visual, tactile, auditory) evoked by TMS.

TMS was performed using a 70 mm figure of eight coil (coil orientation parallel to the midline and current flowing in the cranio-caudal direction in the coil) connected to a single pulse biphasic stimulator, with maximum stimulator strength of 1.5 Tesla (Esaote, Florence, Italy).

Single pulse TMS was given to all grid points (five stimulations for each position), starting with an intensity of 30% of the stimulator output and increasing in steps no greater than 5% until phosphenes were reported or maximum stimulator output was reached. As soon as phosphenes were reported, the area surrounding the stimulation point was scanned by moving the coil in each direction along the axes of the grid in search of a site with an even lower phosphene threshold. Phosphene threshold was calculated in the optimal site and defined as the minimum stimulus intensity able to induce phosphenes in three out of five trials.

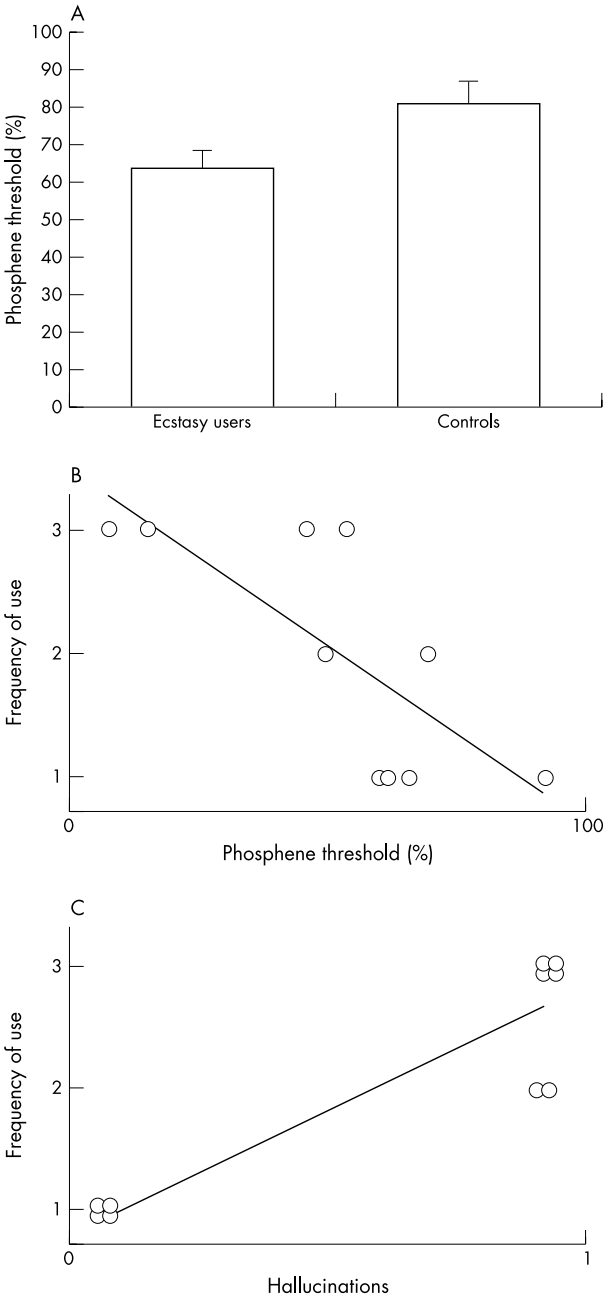

Figure 1 (A) Phosphene threshold (percentage of the maximum stimulator output) in ecstasy users compared with normal controls. Values indicate mean (1 SE). (B) Correlation between frequency of ecstasy use and phosphene threshold. (C) Correlation between frequency of ecstasy use and presence of hallucinations.

Only phosphenes reported in the visual field contralateral to the site of the stimulation were considered accurate.

To control for the reliability of the reported phosphenes, sham TMS trials were randomly intermingled with actual stimulations. During sham TMS trials, the coil was held at the same location as previously stimulated with the same intensity, but it was rotated at 90° (edge on to the scalp) so as to produce the same click noise without inducing any effective magnetic field in the underlying cortex.

Phosphene thresholds were compared in ecstasy users compared with controls by means of Student's *t* test. Spearmann's correlation coefficient test was used to correlate phosphene thresholds with frequency and duration of ecstasy use, and frequency of ecstasy use with presence of hallucinations. Phosphene thresholds of subjects with subjective reports of hallucinations and without hallucinations were compared with unpaired *t* test.

Six of the subjects reported the presence of complex visual hallucinations, mostly related to the acute ingestion of ecstasy.

Frequency of ecstasy assumption was evaluated with an arbitrary score ranging from 1 to 3:

1:<1 tablet per week (four subjects); 2: 1 tablet per week (two subjects); 3:>1 tablet per week (four subjects). Duration of ecstasy use (in years) was evaluated on the basis of the subjects' reports, and it ranged from one to six years.

RESULTS

All subjects reported accurate and consistent phosphenes that tended to extend from foveal parts of the visual field into the contralateral visual hemifield (percentage of ipsilateral phosphenes less than 2%). Optimal grid positions for eliciting phosphenes were always located in the upper third of the grid (2 cm above Oz and 2 cm right or left to the midline). None of the subjects reported phosphenes after sham stimulation.

Phosphene threshold was significantly reduced in ecstasy users as compared with controls ($t=-2.2$; $p<0.05$; fig 1). Phosphene threshold of subjects with hallucinations (56.2%) was lower than that of subjects without subjective hallucinations (75.5%; $t=-1.9$; $p=0.05$).

Phosphene threshold was negatively correlated with frequency of ecstasy assumption ($r=-0.8$; $t=-3.5$; $p=0.007$), while there was not any correlation with duration of ecstasy use ($r=0.22$; $t=0.6$; $p>0.05$). The presence of hallucinations was in turn directly correlated with frequency of ecstasy use ($r=0.9$; $t=6.3$; $p=0.0002$).

DISCUSSION

The main results of this study report how recreational use of ecstasy is associated with changes in the human brain, leading to an increased excitability of the visual cortex. This phenomenon was observed within three days after last assumption of ecstasy and it seems to be more linked with frequency than with duration of ecstasy assumption, although the small sample examined limits the conclusions that can be drawn on this point.

Previous studies[8] reported in normal controls values of phosphene thresholds lower than those observed in this study. This discrepancy could be explained by technical and methodological differences, in particular by the use of single pulse instead of repetitive trains of TMS to determine phosphene threshold On the other hand, these data do not weigh down the difference in visual cortical excitability reported in the two subjects' groups.

There is increasing evidence suggesting that occipital region of the cortex may be especially affected by extensive exposure to ecstasy. Chang *et al* used SPECT to study cerebral blood flow and reported that within three weeks of administration of two oral doses of ecstasy cerebral blood flow was decreased in the visual cortex.[4] Two ecstasy users who were scanned two to three months later showed increased cerebral blood flow in the same region. From a molecular point of view, in a recent SPECT study, Reneman *et al* showed that 5HT2A receptor binding was significantly increased in the occipital cortex of heavy ecstasy users compared with controls.[9] In addition, ecstasy use is positively correlated with absolute power in the alpha and beta frequency bands of EEG at sites overlying the main visual association pathways.[10]

Our findings with TMS complement these observations, suggesting that hyperexcitability of the visual cortex could be a physiological counterpart of the neuroimaging abnormalities described in this brain area. This phenomenon could be correlated with some of the synaptic events after ecstasy administration in experimental animals. It has been observed that MDMA induces both an acute release and reuptake inhibition of serotonin (5-HT) and to a lesser extent dopamine,

followed by depletion of intraneuronal 5-HT stores. The initially released 5-HT activates post-synaptic 5-HT2A/2C receptors located on GABA interneurons resulting in a decrease in GABAegic transmission.[1 11]

Considering the short drug free interval before TMS, visual cortical hyperexcitability could be linked to this phenomenon. Ecstasy could thus act on the visual cortex with a mechanism similar to that described in migraine with aura—that is, a condition with abnormal serotonergic transmission and increased cortical excitability attributable to reduced GABAergic tone.[12] An implication of such hypothesis is that visual cortex excitability should be maximal in the initial phases after ecstasy ingestion, while different findings could be observed in later stages, associated with axonal serotonergic degeneration. Although plausible, this mechanism of action of MDMA needs to be confirmed by a series of studies, testing phosphene thresholds at different times from ecstasy assumption, to better correlate visual cortical excitability changes with the sequence of pharmacological events associated with long term use of the drug. Moreover, further research with former ecstasy users would help to gain more information on the time course of cortical changes and so to the neurophysiological mechanisms involved.

An alternative explanation could be that the ecstasy group is biased in such a way that these people are prone to experiencing phosphenes independent of ecstasy use. In this case, hyper-excitability of the visual cortex could rather depend on behavioural manifestations associated with drug use (for instance, impulsivity, sensation seeking, increased tendency to unconsciously respond to the demand characteristics of the experimental situation). Although this hypothesis cannot be completely excluded, the correlation of phosphene threshold with visual hallucinations of ecstasy users emphasises the link between ecstasy and visual cortical excitability. In this connection, a number of evidences suggest that visual hallucinations and visual cortex are strictly related. Convergent results from PET and rTMS[13] and from event related fMRI[14] in normal subjects show that visual imagery critically depends on neural activity in the primary visual cortex; moreover, data from normal subjects[15] and schizophrenic patients[16] indicate that hallucinations are associated with increased activity in the ventral occipital lobe.

In conclusion, our data indicate the presence of increased excitability of visual cortical areas after ecstasy ingestion in humans. This phenomenon confirms the neurotoxicity of this substance and could represent one physiological counterpart of visual hallucinations associated with drug ingestion.

Authors' affiliations
M Oliveri, G Calvo, Department of Psychology, University of Palermo, Italy
M Oliveri, Fondazione "Santa Lucia" IRCCS, Rome, Italy

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Correspondence to: Dr M Oliveri, Laboratorio di neurologia clinica e comportamentale, Fondazione Santa Lucia IRCCS, Via Ardeatina 306 00179 Roma, Italy; maxoliveri@tiscalinet.it

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