Mood state and brain electric activity in Ecstasy users

Alex Gamma,[CA] Edi Frei, Dietrich Lehmann,[1] Roberto D. Pascual-Marqui,[1] Daniel Hell and Franz X. Vollenweider

Research Unit and [1]The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich, Lenggstr. 31, 8029 Zurich, Switzerland

[CA]Corresponding Author

Received 1 September 1999; accepted 3 November 1999
Published online by xx xxxx 2000

Acknowledgements: This work was supported by the Swiss National Science Foundation, Grant Nr. 31-52989.97) and the Swiss Federal Health Office (Grant Nr. 316.98.0724).

Resting EEG during open and closed eyes and subsequent mood ratings were obtained from 15 Ecstasy users and 14 Ecstasy-naive controls. Absolute spectral power on the scalp, and the three-dimensional, intracerebral distribution of neuroelectric activity using low resolution brain electromagnetic tomography (LORETA) were computed. LORETA revealed global increases of theta, alpha1 and beta2/3 power during eyes open in Ecstasy users, and spectral analyses revealed a right-posterior increase of alpha2 power (confirmed by LORETA) and increased beta band activity during open eyes. Ecstasy users had higher levels of state depressiveness, emotional excitability and a trend-level increase in state anxiety. The observed differences may be related to regular exposure to Ecstasy or other illicit drugs, or may be pre-existing. *NeuroReport* 11:1–6 © 2000 Lippincott Williams & Wilkins.

Key words: Drug abuse; Ecstasy; EEG; LORETA; MDMA; Mood

INTRODUCTION

The serotonin (5-HT) releaser 3,4-methylenedioxymethamphetamine (MDMA) is a widespread recreational drug contained in Ecstasy tablets frequently consumed by young adults at raves. The use of Ecstasy has been associated with memory [1] and attentional [2] deficits, mood impairment and other psychiatric complications [3], as well as alterations in sleep architecture [4]. Animal data indicate that these alterations may be due to MDMA-induced serotonergic neurotoxicity. Recent human evidence suggests that Ecstasy users may exhibit a reduction of 5-HT levels [2] and of the density of 5-HT nerve terminals [5], similar to that seen after high or repeated doses of MDMA in animals [6]. Potential electrophysiological alterations in Ecstasy users, however, have remained largely unexplored. One study found a positive correlation of MDMA use with absolute alpha and beta band power in the EEG [7]. Although no control group was included in that study, these findings indicate that regular Ecstasy use may have a lasting effect upon brain electric activity.

One drawback of spectral power analysis is that it cannot provide non-ambiguous information on the location and strength of the intracerebral, neuroelectric sources responsible for the observed distribution of scalp potentials [8]. This problem is addressed by a new method, low resolution brain electromagnetic tomography (LORETA), which yields the three-dimensional distribution of the intracerebral electric generators, based on multichannel surface EEG recordings [9–11]. Using LORETA, we have recently found marked region- and frequency-specific changes in neuroelectric activity after acute administration of MDMA in healthy volunteers (Frei *et al.*, unpublished data). The present study was designed to address the hypothesis that chronic exposure to MDMA might also be associated with changes in intracerebral brain electric activity as assessed by LORETA, or in the strength and scalp distributions of EEG frequency band power as assessed by spectral analysis. The present study also investigated whether possible electrophysiological differences in Ecstasy users were paralleled by differences in state variables of mood.

SUBJECTS AND METHODS

Subjects: Sixteen regular Ecstasy users were recruited at local raves and through postings at the university. Except for two subjects, all had used Ecstasy at least 100 times. The control group consisted of 16 Ecstasy-naive subjects recruited from university students by postings and word of mouth. The use of Ecstasy and other illicit drugs (cannabis, amphetamine, cocaine, LSD and magic mushrooms, which contain the hallucinogen psilocybin) in both groups was documented in telephone and personal inter-

views. Age, educational level and drug use characteristics for both groups are provided in Table 1. Prior to admission to the study, all subjects were screened by psychiatric interview, physical examination, electrocardiogram and blood analysis. No pathologies were revealed in the semi-structured psychiatric interview and none of the subjects had ever been in treatment for a psychiatric disorder. No somatic disease was present in any subject. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Psychiatric University Hospital.

Experimental procedure: All subjects agreed to abstain from psychoactive drugs (except alcohol and nicotine) for the week prior to the experiment. After arrival at the laboratory, 31 scalp electrodes were applied according to the international 10/20 system (FP1/2, FPZ, F3/4, F7/8, FZ, FT9/10, FC5/6, T3/4, T5/6, TP9/TP10, C3/4, CZ, CP5/6, P3/4, PZ, PO9/10, O1/2, OZ). Both F3 and F4 served as common reference electrodes. An additional electrode was applied below the left eye, measuring eye movements for later artifact recognition. Subjects' resting EEG was recorded during open and closed eyes for ~3 min each, using a Nihon-Koden 32-channel Neurofile system with 1–50 Hz bandpass and 256 samples/s digitizing rate.

Mood during EEG was assessed by self-ratings immediately after the EEG session using the EWL mood questionnaire [12]. The EWL includes scales measuring efficiency/activity, inactivation, extroversion/introversion, well-being, emotional excitability, anxiety and depressiveness.

EEG data processing: The EEG data were carefully screened for eye, muscle, movement and technical artifacts. From each 3 min EEG recording, as many 2 s epochs of artifact-free EEG as possible were selected for further analysis. If no artifact-free epochs could be obtained, the record was omitted. EEG channels containing artifacts were interpolated, but epochs with more than four unusable channels were omitted. Spatial DC offset was removed (average reference recomputation), and the data were filtered into the seven statistically independent frequency bands [13]: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha1 (8.5–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz) and beta3 (21.5–30 Hz). After artifact editing, the EEG of 14 controls recorded during eyes closed, of 12 controls during eyes open, and of 15 Ecstasy users during both eyes open and closed were available for analysis.

Table 1. Means (s.d.) of demographic data and drug use

	Controls	Ecstasy users
Demographic data		
No. females	6	7
No. males	8	8
Age	26.0 (2.7)	22.5 (2.7)
Educational level[a]	3.7 (0.5)	2.5 (1.0)
Estimated lifetime illicit drug use		
Ecstasy (tablets)	0 (0.0)	222 (358.4)
Cannabis (joints)	46 (137.0)	320 (357.6)
Amphetamine (mg)	0 (0.0)	320 (782.3)
Cocaine (mg)	198 (692.0)	506 (586.6)
LSD ('trips')	0 (0.0)	6 (7.7)
Magic mushrooms (occasions)	1 (2.2)	3 (5.4)

[a] 1, junior high; 2, high school; 3, undergraduate school; 4, graduate school.

Intracortical neuroelectric activity: LORETA was used to compute intracerebral electric sources from the surface recorded EEG data. LORETA computes current density at each voxel in the brain as the linear, weighted sum of the scalp electric potentials [9,11]. It solves the inverse problem assuming that the smoothest of all possible activity distributions is most plausible. This means that neighboring voxels have maximally similar activity, a fact known from electrophysiology, where neighboring neuronal populations show highly correlated activity [14]. LORETA is capable of correct 3-D localization, although with blurring (low resolution) [11].

A three-shell spherical head model registered to the Talairach human brain atlas [15] was used, and the LORETA solution space was restricted to the cortical gray matter and hippocampus of the Talairach probability atlas (both atlases are available as digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute). The reported EEG electrode coordinates [16] were used for registration between spherical and realistic head geometry. A total of 2394 voxels at 7 mm spatial resolution were thus produced.

Because of the employed EEG sampling rate, there were 256 three-dimensional LORETA images for each second. As a first step in data reduction, for each subject a time-averaged LORETA image was used for analysis. Since EEG spectral frequency bands are known to reflect different functions and behave statistically independently [13], the available high temporal resolution was exploited to analyze the LORETA images of spectral power for the different frequency bands.

Data analysis: To correct for global variance in brain electric activity, LORETA 3-D images were first normalized by scaling all voxel values of a given subject so that their sum was equal to 1. The LORETA images were then statistically compared by voxel-by-voxel paired *t*-tests (based on log-transformed activities) for assessment of differences in localization of activity between Ecstasy users and controls (using one LORETA image for each subject, frequency band and condition). The resulting t-statistic images were examined to locate regions showing statistically significant effects using a non-parametric approach [17] for the t-statistic images with exact corrections for multiple testing. While this test concentrated on maximum signal amplitude for single voxels (single voxel statistics), a second non-parametric analysis assessed the significance of possible differences by their spatial extent, obtaining clusters of supra-threshold voxels (cluster statistics) [11,17].

Absolute global EEG power per frequency band was computed as the mean power over all 31 electrode locations (channels) on the scalp. Additionally, channel-wise power values went into statistical analysis. All power data were log-transformed to make them conform to the normal distribution. Considering the statistical independence of the chosen frequency bands, analysis of variance (ANOVA) was performed separately for each frequency band. For the analysis of global power, condition (eyes closed/open) was

entered as within-subject factor. For the analysis of channel-wise power, condition and electrode were entered as within-subject factors.

Multivariate analysis of variance (MANOVA) was used to analyze EWL mood rating scores. Specific effects were tested for by HSD *post-hoc* analysis.

Probability levels of ≤ 0.05 were considered statistically significant.

RESULTS

Demographic data: Demographic data and lifetime drug use are reported only for those subjects whose EEG data were eventually available for statistical analysis (Table 1). Controls were older than Ecstasy users (26.0 *vs* 22.6 years, respectively) and had a higher level of education, since most of them were university students. Ecstasy users had generally used more other illicit drugs than controls.

EWL mood scores: EWL scores were significantly different in Ecstasy users and controls (Rao R $(7,24) = 2.38$; $p < 0.05$). Ecstasy users had significantly higher scores for depressiveness ($p < 0.02$), inactivation ($p < 0.05$) and emotional excitability ($p < 0.004$), while the increase in anxiety just missed statistical significance ($p < 0.06$; Fig. 1).

LORETA: Neither single-voxel statistics nor cluster-statistics yielded significant between-group differences in the distribution of intracerebral electric activity in the normalized LORETA results. In non-normalized LORETA results, no difference was found in single-voxel statistics, while cluster-statistics revealed brain-wide significant increases in theta, alpha1, beta2 and beta3 activity in Ecstasy users, but only for the eyes open condition.

Global EEG power: For all frequency bands, absolute global power was higher during eyes closed than during eyes open (all main effects of condition $F(1,25) > 15.0$; $p < 0.01$). There was no significant main effect of group for any frequency band, although Ecstasy users tended to have generally higher power than control subjects. There was a significant group × condition interaction for beta2 ($F(1,25) = 5.58$; $p < 0.03$). *Post-hoc* testing revealed that Ecstasy users had significantly higher global beta2 power than controls during eyes open ($p < 0.003$), while there was no difference between the two groups during eyes closed. For the beta1 band, we found a trend-level group × condition interaction ($F(1,25) = 3.7$; $p < 0.07$). In this band, Ecstasy users compared to controls had higher power during eyes open, but lower power during eyes closed.

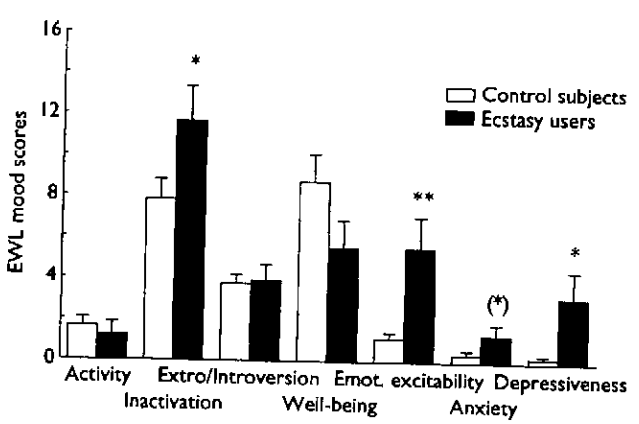

Fig. 1. EWL Mood scores for Ecstasy users ($n = 15$) and controls ($n = 14$). Whiskers represent s.e. Ecstasy users had higher scores for inactivation (being tired, dazed etc.), emotional excitability (being nervous, tense, irritable etc) and depressiveness. Elevated anxiety scores just missed statistical significance. * $p < 0.05$, ** $p < 0.01$.

Channel-wise EEG power: Three-way ANOVA revealed no significant main effect of group for any frequency band, although for the eyes open condition, Ecstasy users showed a tendency to have higher power across all electrodes in the theta, alpha1, alpha2, beta2 and beta3 bands. This tendency reflects the cluster-statistical increases in the theta, alpha1, beta2 and beta3 bands found in the non-normalized LORETA results during eyes open.

There was a significant group × condition interaction for beta1 ($F(1,25) = 5.46$; $p < 0.03$). During the closed eyes condition power was higher in controls, whereas with open eyes it was higher in Ecstasy users. This interaction parallels the trend-level group × condition interaction for beta1 found in the analysis of global power.

Again paralleling the results from the analysis of global power, there was a significant group × condition interaction for beta2 ($F(1,25) = 6.4$; $p < 0.02$); power was not different between groups during eyes closed, whereas during eyes open, Ecstasy users had significantly higher power ($p < 0.003$).

In the beta3 band there was a trend-level group × condition interaction ($F(1,25) = 3.9$; $p < 0.06$), i.e. for both open and closed eyes Ecstasy users had higher power than controls, but the difference was larger during eyes open than eyes closed.

There was a significant group × electrode interaction in the alpha2 band ($F(30,750) = 2.08$; $p < 0.001$). *Post-hoc* analysis revealed significantly higher power in Ecstasy users over right temporo-occipital regions (electrodes TP10, T6, P010, O2) and one left occiptal location (PO9; Fig. 2). This interaction indicates that the power landscape on the scalp was different between Ecstasy users and controls. Since different scalp landscapes of EEG power must have been produced by the activity of geometrically different neural generators, we examined normalized LORETA data for the alpha2 band to clarify the intracerebral localization of this difference. During eyes open, the maximal increase in alpha2 activity in Ecstasy users was located in the right temporo-occipital cortex, below the scalp area where the difference in power was found (Fig. 3, upper row). For the eyes closed condition, Ecstasy users had higher alpha2 activity maximally in the left medial occipital area, but the area of heightened activity extended to the right temporo-occipital region (Fig. 3, lower row).

DISCUSSION

The present study reports differences in brain electric activity measurements between chronic Ecstasy users and Ecstasy-naive controls. Ecstasy users had global increases in EEG spectral power during eyes open in the beta frequency bands, and local increases in right posterior areas in the alpha2 frequency band. Similarly, the results of non-normalized LORETA, in which global differences are

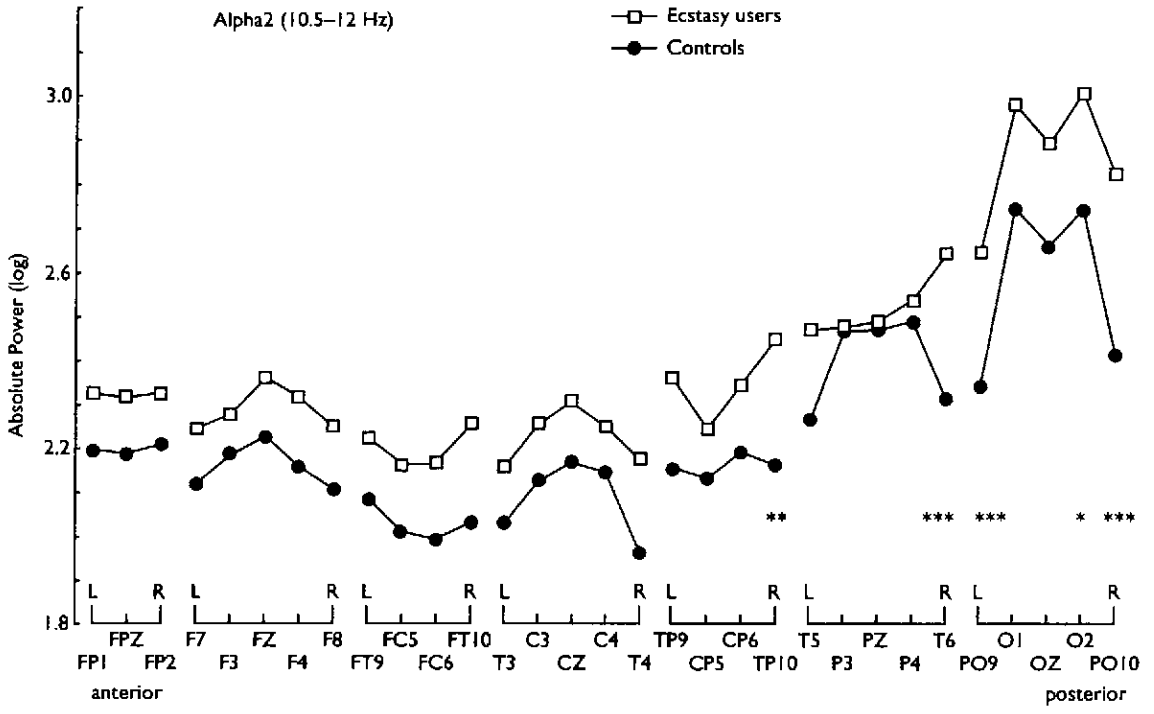

Fig. 2. The significant group × electrode interaction for the alpha2 (10.5–12 Hz) band indicates that the power landscape (the scalp distribution of channel-wise power) differs between Ecstasy users and controls. While all electrodes tended to have higher power in Ecstasy users, the strongest and statistically significant increases were found at right temporo-occipital electrodes. Vertical: log-transformed absolute power; horizontal: electrode locations (channels) connected by lines for the seven left-to-right transversal chains (brackets), from anterior (left) to posterior (right). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Tukey's test).

not factored out, revealed global increases in intracerebral neuroelectric activity during open eyes in the theta, alpha1, and beta2–3 bands. Power decrease in all frequency bands is generally seen after arousal stimuli, during orienting reactions. Thus, our findings of generally increased power in Ecstasy users might suggest disturbed alertness mechanisms. This view would be in line with reports that Ecstasy users show deficits in attention [2].

Brain electric differences between Ecstasy users and controls were more pronounced during eyes open. A possible explanation for this state-dependence may be that compared to eyes closed, the eyes open condition is a more activated state in which possible neurophysiological differences are enhanced.

To our knowldege there is only one other study using electroencephalography in Ecstasy users. Dafters *et al.* examined 23 recreational Ecstasy users and reported a positive correlation of Ecstasy use with absolute alpha (8–12 Hz) and beta (12–20 Hz) power [7]. Since their study design did not include a control group, it remains open whether spectral power in their subjects was abnormal compared to Ecstasy-naive controls. Still, their data indicate that frequent exposure to Ecstasy may alter spectral power in consistent ways, particularly leading to a rise in alpha and beta EEG activity. These results are in line with the increases in alpha and beta activity in the present cohort of Ecstasy users.

The functional significance of this increased alpha EEG activity is not clear, since a unique functional role is not attributable to alpha. Dafters *et al.* suggest that, since increased alpha might be a clinical marker for HIV brain pathology [18], its presence in Ecstasy users could indicate reduced cortical activity caused by neurotoxic MDMA effects. However, alpha alterations in Ecstasy users could certainly also arise simply by virtue of their being in a different functional state without necessarily involving an underlying neurobiological impairment. Nevertheless, it is noteworthy that stronger alpha2 activity in Ecstasy users was clearly localized in predominantly right temporo-occipital regions (Brodmann areas 37 and 19). It might be of future interest to search for region-specific behavioral changes in Ecstasy users. Since more alpha conventionally is viewed as a sign of local non-engagement (relaxation), a decrease of local functions (visual–auditory associations for area 37) could be hypothesized.

Heightened beta activity in our Ecstasy sample is interesting, since several clinical studies found increased beta power in depressive patients [19] and Ecstasy users in our study also had elevated scores for state depressiveness. Thus, increased beta activity may be a reflection of depressive symptomatology. However, clearly more research is needed to reliably link quantitative EEG measures to specific psychological or neurobiological conditions in Ecstasy users.

Ecstasy subjects had higher levels of state depressiveness and state anxiety during EEG measurements. These findings are consistent with case reports of anxiety and depressive disorders [3,20] in recreational Ecstasy users and with a recent study reporting that 27 of 41 Ecstasy users feel more susceptible to either depression or anxiety

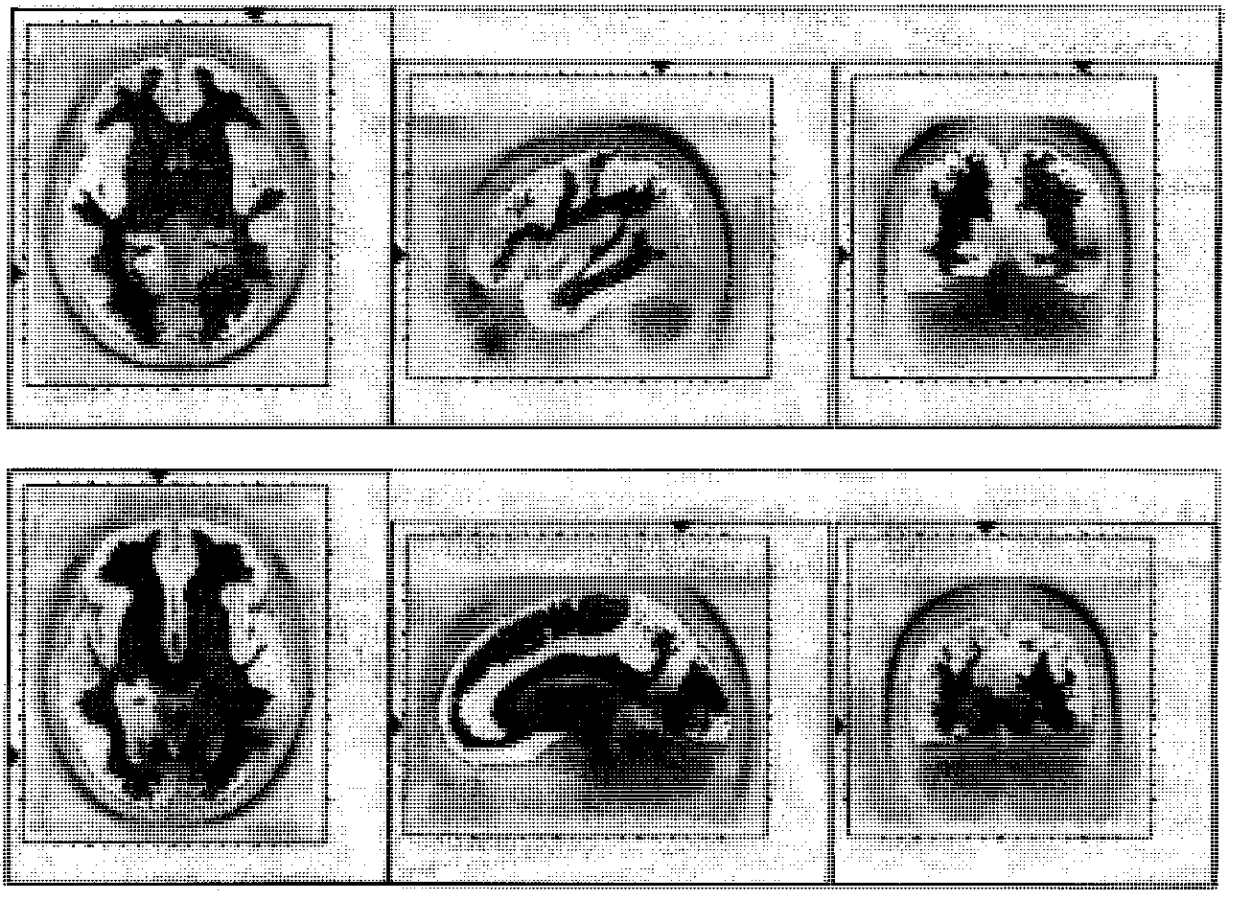

Fig. 3. Orthogonal (axial, sagittal and coronal) LORETA tomography slices showing the area (red) of increased alpha2 EEG activity in Ecstasy users. The voxel of maximal difference in the entire 3-D volume (triangular arrows) was located in the right posterior temporal cortex (Talairach coordinates 46, −60, 1) during eyes open (upper row), and in the left medial occipital cortex (Talairach coordinates −10, −74, −6) during eyes closed (lower row). The LORETA images assess the intracortical localization of the neuroelectric difference underlying the difference of the EEG power landscapes on the scalp (Fig. 2) between Ecstasy and control subjects. L = left, R = right, A = anterior, P = posterior.

as a long-term side effect of continued Ecstasy use [21]. In this context, heightened emotional excitability (including being nervous, irritable, tense, vulnerable etc), and inactivation (including being tired, exhausted and lacking in energy etc) in our Ecstasy group could be seen as psychovegetative concomitants of depressive or anxiety-related symptoms.

It has been suggested that such signs of mood impairment may be the result of a persistent serotonergic dysfunction caused by MDMA neurotoxicity, as evidence from the assessment of 5-HT transporter density in the brain of Ecstasy users suggests5. Alternatively, mood differences may be pre-existing and unrelated to Ecstasy use, possible associated with different personality profiles or life style. Indeed, the present Ecstasy subjects had higher levels of trait nervousness, aggressivity and depressiveness than did controls, as assessed by the Freiburg Personality Inventory [22]. Personality differences such as increased adventurousness and sensation-seeking, decreased hostility and increased or decreased impulsivity have also been described in Ecstasy users [21,23]. Moreover, the party-oriented life style of many recreational Ecstasy users, including the present sample, involves decreased rest and food intake, which may have a detrimental effect on mood and emotional well-being. Finally, there is the possibility that pre-existing mood impairment may be the cause for and not the consequence of Ecstasy use. Large prospective, longitudinal studies could possibly shed new light on the potential causal relationship between Ecstasy use and mood impairment.

A limitation of our study is that our subject groups were imperfectly matched with regard to the use of illicit drugs other than Ecstasy. Since our Ecstasy subjects had taken considerably more other illicit drugs, one or several of these compounds may have contributed to the observed differences in quantitative EEG measurers and mood state. A further unavoidable problem pertinent to this type of study is that there was no control over the purity and doses of ingested substances. These data rely on subjects' retrospective estimates of their past drug consumption, which will necessarily involve a considerable measure of uncertainty. Furthermore, it has been pointed out that such estimates may be particularly inaccurate in Ecstasy users, since they potentially suffer from memory deficits [24].

CONCLUSION

Our data provide evidence for both global and localized increases of EEG alpha and beta frequency activity in

regular Ecstasy users compared with Ecstasy-naive control subjects. These differences were state dependent, i.e. present predominantly during eyes open but not eyes closed. Ecstasy users also reported a higher occurrence of depressiveness, anxiety and psychovegetative symptoms during EEG measurements. It is unclear whether the observed electrophysiological alterations and symptoms of impaired mood are linked and whether they are related to MDMA-induced serotonergic neurotoxicity, to the use of other drugs or to pre-existing differences.

REFERENCES

1. Parrott AC, Lees A, Garnham NJ *et al. J Psychopharmacol* **12**, 79–83 (1998).
2. McCann UD, Mertl M, Eligulashvili V *et al. Psychopharmacology* **143**, 417–425 (1999).
3. Schifano F and Magni G. *Biol Psychiatry* **36**, 763–767 (1994).
4. Allen RP, McCann UD and Ricaurte GA. *Sleep* **16**, 560–564 (1993).
5. McCann UD, Szabo Z, Scheffel U *et al. Lancet* **352**, 1433–1437 (1998).
6. Ricaurte GA, Martello AL, Katz JL *et al. J Pharmacol Exp Ther* **261**, 616–622 (1992).
7. Dafters RI, Duffy F, O'Donnell PJ *et al. Psychopharmacology* **145**, 82–90 (1999).
8. Lehmann D and Michel CM. *Electroencephalogr Clin Neurophysiol* **76**, 271–276 (1990).
9. Pascual-Marqui RD, Michel CM and Lehmann D. *Int J Psychophysiol* **18**, 49–65 (1994).
10. Pascual-Marqui RD, Lehmann D, Koenig T *et al. Psychiatry Res Neuroimaging* **90**, 169–179 (1999).
11. Pascual-Marqui RD. *Int J Bioelectromagnetism* **1**, 75–86 (1999).
12. Janke W and Debus G. Die Eigenschaftswörterliste (EWL-K)–Ein Verfahren zur Erfassung der Befindlichkeit. Göttingen: Hogrefe, 1978.
13. Kubicki S, Herrmann WM, Fichte K *et al. Pharmakopsychiatr Neuropsychopharmakol* **12**, 237–245 (1979).
14. Silva LR, Amitai Y and Connors BW. *Science* **251**, 432–435 (1991).
15. Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. Stuttgart: Thieme 1988.
16. Towle VL, Bolanos J, Suarez D *et al. Electroencephalogr Clin Neurophysiol* **86**, 1–6 (1993).
17. Holmes AP, Blair RC, Watson JDG *et al. J Cerebr Blood Flow Metab* **16**, 7–22 (1996).
18. Baldeweg T and Gruzelier JH. *Int J Psychophysiol* **26**, 431–442 (1997).
19. Pollock VE and Schneier LS. *Biol Psychiatry* **27**, 757–780 (1990).
20. McCann UD and Ricaurte GA. *Biol Psychiatry* **32**, 950–953 (1992).
21. Morgan MJ. *Neuropsychopharmacology* **19**, 252–264 (1998).
22. Gamma A, Buck A, Berthold T *et al. Eur Neuropsychopharmacol* **9 (Suppl 5)**, 237–238 (1999).
23. McCann UD, Ridenour A, Shahain Y *et al. Neuropsychopharmacology* **10**, 129–138 (1994).
24. Morgan MJ. *Psychopharmacology* **141**, 30–36 (1999).