

Localization of MDMA-Induced Brain Activity in Healthy Volunteers Using Low Resolution Brain Electromagnetic Tomography (LORETA)

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Abstract: 3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy') is a psychostimulant drug producing heightened mood and facilitated social communication. In animal studies, MDMA effects are primarily mediated by serotonin (5-HT), but also by dopamine (DA) and possibly noradrenaline (NA). In humans, however, the neurochemical and neurophysiological basis of acute MDMA effects remains unknown. The distribution of active neuronal populations after administration of a single dose of MDMA (1.7 mg/kg) or placebo was studied in 16 healthy, MDMA-naïve volunteers. Thirty-one-channel scalp EEGs during resting with open and closed eyes was analyzed in the different EEG frequency bands. Scalp maps of power showed significant, global differences between MDMA and placebo in both eye conditions and all frequency bands. Low resolution brain electromagnetic tomography (LORETA) was used to compute 3D, functional images of electric neuronal activity from the scalp EEG data. MDMA produced a widespread decrease of slow and medium frequency activity and an increase of fast frequency activity in the anterior temporal and posterior orbital cortex, concomitant with a marked enhancement of mood, emotional arousal and increased extraversion. This activation of frontotemporal areas indicates that the observed enhancement of mood and possibly the increased extroversion rely on modulation of limbic orbitofrontal and anterotemporal structures known to be involved in emotional processes. Comparison of the MDMA-specific EEG pattern with that of various 5-HT, DA, and NA agonists indicates that serotonin, noradrenaline, and, to a lesser degree, dopamine, contribute to the effects of MDMA on EEG, and possibly also on mood and behavior. *Hum. Brain Mapping* 14:152–165, 2001. © 2001 Wiley-Liss, Inc.

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INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA) is a recreational drug frequently used by young adults. Its subjective effects are characterized by a marked enhancement of mood and social interaction and an increase in sensory awareness [Greer and Tolbert, 1986; Vollenweider et al., 1998]. MDMA is also reported to increase psychomotor drive [Solowij et al., 1992], as it is known from stimulant drugs of the amphetamine type. In animals, its main

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neurochemical mechanism of action is the enhanced release and inhibited uptake of central serotonin (5-HT) [Green et al., 1996], but dopamine (DA) and noradrenaline (NA) were found or implicated in the mediation of MDMA effects [Battaglia et al., 1988]. It is unclear, however, to what extent the 5-HT, DA and NA systems contribute to the effects of MDMA and how MDMA affects neurophysiological, particularly electrophysiological brain processes in humans. The aim of this study was to characterize acute MDMA effects in terms of regional cerebral changes in brain electric (EEG) activity compared to placebo. Furthermore, by comparing the MDMA-specific EEG pattern with that of various 5-HT, DA and NA agonists reported in the literature, we attempted to clarify the relative contributions of these transmitter systems to the effects of MDMA.

Conventional analysis of surface EEG recordings by dipole modeling provides only limited information on the neural generators because it disregards their intracerebral distribution. The spatial distribution is particularly important in the case of higher brain functions that are commonly assumed to engage widely distributed regions [Mesulam, 1990]. Low resolution electromagnetic tomography (LORETA) [Pascual-Marqui et al., 1994; Pascual-Marqui, 1999], permits direct, true 3D functional imaging of brain electric activity based on the constraint of maximal smoothness of the solution. LORETA, unlike dipole modeling, does not need a priori knowledge about the putative number of discernible source regions. With this method, the high time resolution of the brain electric data can be fully exploited for functional imaging of brain activities of different qualities, because brain electric activity can be analyzed separately for the different EEG frequency bands that have different functional significances. This property has been exploited successfully in applications that validated LORETA with MRI and PET findings [Anderer et al., 2000; Pascual-Marqui et al., 1999; Pizzagalli et al., 2001; Worrell et al., 2000].

We used LORETA to assess acute MDMA-induced changes of the cortical distribution of electric activity in the different spectral frequency bands in healthy, MDMA-naïve volunteers. We hypothesized that, due to its well established role in mood regulation, activity changes in the limbic system should be observed after MDMA-induced mood enhancement. Based on animal data, we further expected that MDMA would have some electrophysiological effects in common primarily with 5-HT, but also with DA and NA agonists.

MATERIALS AND METHODS

Subjects

Sixteen MDMA-naïve healthy subjects (6 women and 10 men; mean age = 26.0 years, SD = 2.5 years) without a history of drug abuse were recruited from university students and hospital staff. Before admission to the study all subjects were carefully screened by psychiatric interview to assure that they had neither personal nor family histories of major psychiatric disorders in first-degree relatives. Subjects were healthy according to physical examination, electrocardiogram and blood and urine analysis. Written informed consent was obtained from all subjects. The study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich, and the use of 3,4-methylenedioxymethamphetamine (MDMA) was approved by the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern.

Procedure and material

Thirty-one Grass electrodes were applied to the subjects' heads following 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). A further electrode below the left eye recorded eye movements for later artifact recognition. Both F3 and F4 served as common recording reference electrodes. After electrode application, subjects received MDMA (1.7 mg/kg body weight) or placebo (double blind application). There were two recording sessions for each subject, one with MDMA and the other with placebo; the sequence was pseudo-randomly assigned. Two hours after ingestion of MDMA or placebo, respectively, subjects lay down. Their resting EEG was recorded during eyes closed and eyes open, each for at least 3 min (Neurofile System, Nihon Kohden 32-channel headbox, 256 samples/sec, 1–50 Hz bandpass filter).

Off-line, the EEG data were carefully reviewed for eye, muscle, movement, and technical artifacts. Two-second epochs of artifact free EEG were used for further analyses. If three or fewer EEG channels contained artifacts, they were interpolated, otherwise the epoch was rejected. If fewer than 10 sec of EEG within one recording session were acceptable, the subject was omitted from further analysis. The final sample consisted of EEG data, for placebo as well as the MDMA session, from 14 subjects recorded with eyes closed and from 12 subjects recorded with eyes open. For all these subjects, MDMA and placebo EEG data were

available. On the average across subjects, 36.3 ± 14.4 sec of data for EO/MDMA, 39.2 ± 19.6 sec of data for EO/placebo, 39.4 ± 8.2 sec of data for EC/MDMA, and 56.1 ± 12.7 sec of data for EC/placebo were available for analysis.

Spatial DC offset was removed (average reference recomputation). Because EEG spectral frequency bands are known to reflect different functions and behave statistically independent, the analysis was done separately in the following seven bands [Kubicki et al., 1979]: 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).

Scalp maps of spectral power

All available epochs were submitted to FFT. For each medication condition, recording condition, frequency band, and electrode position, mean power was computed, and averaged across subjects. These averages were composed into scalp surface maps of band power distributions of the EEG data, to be statistically tested for differences between medication conditions.

Functional images of neuronal electrical activity

To compute the intracortical distribution of the electric activity from the surface EEG data, we used LORETA [Pascual-Marqui et al., 1994; Pascual-Marqui, 1999] that computes current density at each voxel in the solution space as the linear, weighted sum of the scalp electric potentials. It solves the inverse problem based on the assumption that the smoothest of all possible activity distributions is the most plausible one. This assumption is supported by electrophysiology, where neighboring neuronal populations show highly correlated activity [Silva et al., 1991]. Thus, LORETA results in solutions where neighboring voxels have maximally similar activity. Regardless of the electrophysiological validity of the smoothness constraint, LORETA is capable of correct, although blurred (“low resolution”) 3D localization as demonstrated in simulation work as well as in empirical validations [Anderer et al., 1998, 2000; Pascual-Marqui, 1999; Pascual-Marqui et al., 1999; Pizzagalli et al., 2001; Seeck et al., 1998; Worrell et al., 2000].

The utilized version of LORETA employed a three-shell spherical head model registered to the Talairach human brain atlas [Talairach and Tournoux, 1988] available as digitized MRI from the Brain Imaging Center, Montreal Neurologic Institute. The registration between spherical and Talairach head geometry used the realistic EEG electrode coordinates reported

by Towle et al. [1993]. The LORETA solution space was restricted to the cortical gray matter and hippocampus in the Talairach atlas as defined by the corresponding digitized Probability Atlas available from the Brain Imaging Center, Montreal Neurologic Institute. A total of 2,394 voxels at 7 mm spatial resolution were produced under this neuroanatomical constraint.

LORETA images corresponding to the estimated neuronal generators of brain activity within a given frequency band are defined as follows. For a given subject, let $\Phi_{i,t}$ denote a vector comprised of the scalp electric potentials measured at each scalp electrode (any reference electrode is allowed), at time instant t ($t = 1 \dots N_\tau$), and for EEG epoch i ($i = 1 \dots N_\epsilon$). Let $\Phi_{i,t}^\Omega$ denote the band filtered EEG, where Ω denotes the frequency band of interest. The instantaneous current density estimate is computed as the linear transformation $J_{i,t}^\Omega = \mathbf{T}\Phi_{i,t}^\Omega$ where \mathbf{T} denotes the LORETA pseudo-inverse [Pascual-Marqui, 1999; Pascual-Marqui et al., 1999]. The LORETA image for the frequency band Ω is then defined as the spectral density of estimated current density signals:

$$\text{diag} \left[\frac{1}{N_\tau N_\epsilon} \sum_{\forall i,t} (J_{i,t}^\Omega)(J_{i,t}^\Omega)^T \right] = \text{diag}\{\mathbf{T}\mathbf{S}_\Phi^\Omega \mathbf{T}^T\}$$

where ‘diag’ denotes the diagonal of a matrix, the superscript ‘T’ denotes vector transposition, and \mathbf{S}_Φ^Ω denotes the filtered EEG variance-covariance matrix:

$$\mathbf{S}_\Phi^\Omega = \left[\frac{1}{N_\tau N_\epsilon} \sum_{\forall i,t} (\Phi_{i,t}^\Omega)(\Phi_{i,t}^\Omega)^T \right]$$

Owing to Parseval’s theorem on the equivalence of power expressed in the time and frequency domains [Cooley et al., 1977], the LORETA image can be computed more efficiently as:

$$\text{diag} \left[\frac{1}{N_\tau N_\epsilon} \sum_{\forall i,t} (J_{i,t}^\Omega)(J_{i,t}^\Omega)^T \right] = \text{diag}\{\mathbf{T}\mathcal{S}_\Phi^\Omega \mathbf{T}^T\}$$

where \mathcal{S}_Φ^Ω is, except for a scale factor, the Hermetian EEG cross-spectral matrix [Brillinger, 1981]:

$$\mathcal{S}_\Phi^\Omega = \left[\frac{1}{N_\epsilon} \sum_{\forall i,\omega \in \Omega} (\Phi_{i,\omega}^\Omega)(\Phi_{i,\omega}^\Omega)^* \right]$$

In the previous equation, $\Phi_{i,\omega}^\Omega$ denotes the discrete Fourier transform at frequency ω and the superscript

'*' denotes complex conjugate and vector transposition.

There was one 3D LORETA image for each subject in both eye-conditions, and in both medication conditions, and for each frequency band (total = $(12 + 14) \times 7 \times 2 = 364$).

Psychometric rating scales

Subjective state was assessed with two questionnaires.

The Adjective Mood (AM) rating scale [Janke and Debus, 1978; Lehrl et al., 1986] consists of 124 items yielding six factor-analytically derived main scales (adjective selections) that measure efficiency-activation, inactivation, extroversion/introversion, well-being, emotional excitability and anxiety. In addition, the well-being scale is composed of the two subscales 'self-confidence' and 'heightened mood,' and the anxiety scale consists of the three subscales 'apprehension-anxiety,' 'dejection,' and 'thoughtfulness-contemplativeness.'

The Altered States of Consciousness questionnaire (ASC) is a visual-analog self-rating scale and a slightly modified version of the original APZ rating scale [Dittrich, 1998] (66 instead of 72 items). The ASC measures alterations in mood, thought processes, and experience of the self/ego and of the environment in drug- and nondrug-induced altered states of consciousness [Dittrich, 1996; Dittrich et al., 1985; Gouzoulis-Mayfrank et al., 1998, 1999; Vollenweider, 1998]. The questionnaire consists of three factor-analytically derived scales. The first scale, OB ('Oceanic Boundlessness'), measures derealization and depersonalization associated with a positive basic mood, and alterations in the sense of time. The second scale, VR ('Visionary Restructuralization'), refers to visual illusions, hallucinations, synesthesia and the altered experience of meaning. The third scale, AED ('Anxious Ego Dissolution'), measures thought disorder, ego disintegration, and loss of body and thought control associated with arousal and anxiety. These three scales have been shown to be dimensions independent of etiology, i.e., the condition that led to the altered state of consciousness [Dittrich et al., 1981].

Statistical analysis

The statistical non-parametric mapping (SnPM) method was used for the statistical analysis of LORETA images [Holmes et al., 1996]. First, the LORETA images were statistically compared by voxel-by-voxel paired *t*-tests (based on log-transformed ac-

tivities) for assessment of differences in localization of activity between MDMA and placebo (using one LORETA image for each subject, frequency band and condition), thus obtaining *t*-statistic images [the use of statistical parametric maps applied to LORETA images has been validated by Anderer et al., 1998, 2000; Kounios et al., 2001; Pascual-Marqui et al., 1999; Pizzagalli et al., 2001]. The *t*-statistic images were examined to locate regions showing statistically significant effects using a non-parametric approach [Holmes et al., 1996]. This approach, using a randomization strategy, determines the critical probability threshold *t*-values for the observed statistic with corrections for multiple testing. Although this test focused mainly on maximum signal amplitude for single voxels (referred to below as 'single voxel statistics'), a second non-parametric analysis assessed the significance of activity based on its spatial extent, obtaining clusters of supra-threshold voxels (referred to below as "cluster statistics") [Holmes et al., 1996]. The statistics of the power maps used the same strategy, but instead of voxels, electrode positions were entered.

For each of the two questionnaires, the psychological data were analyzed using two-way ANOVA with treatment conditions (MDMA vs. placebo) and psychometric scales (6 levels for the AM scale and 3 levels for the ACS scale, respectively) as repeated measures factors. The effects of MDMA on the AM subscales of the scales 'well-being' and 'anxiety' were analyzed by two-way ANOVA with treatment (MDMA vs. placebo) and subscales (2 or 3 levels, respectively) as repeated measures factors. Based on significant main effects or interactions, post-hoc comparisons for single scales were done using Tukey's tests. *P*-values < 0.05 were considered to be statistically significant.

Substance

Racemic MDMA (3,4-methylenedioxymethamphetamine) was obtained through the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics, Bern, from EPROVA AG, Schaffhausen, and prepared as capsules (10 mg and 50 mg) at the Pharmacy of the Kantonsspital, Luzern, Switzerland.

RESULTS

EEG

Power maps

Figure 1A,B illustrates the mean maps (across subjects) of the scalp distribution (landscape) of spectral

power in the seven frequency bands for the two medication conditions and the two recording conditions. Most of the maps are roughly bilateral symmetric. Comparing MDMA and placebo effects, the differ-

ences of the maps are less obvious, but close scrutiny will detect various local discrepancies. Using the non-parametric cluster statistics, the comparison of these power landscapes between medication conditions revealed significant differences in all seven frequency bands of both recording conditions (eyes open and close) at P -values ranging between $P < 0.033$ and $P < 0.0002$ (see Fig. 1).

LORETA

Even though these results would justify spatial post-hoc tests in all bands, we will report only those of the comparisons where the statistics applied to LORETA resulted in differences at $P < 0.10$ (of a total of 28 cases, 7 cases at $P < 0.01$, 5 cases at $0.01 \leq P < 0.05$, and 3 cases at $0.05 \leq P < 0.1$). The findings after MDMA ingestion will be described in terms of increase or decrease of activity in reference to the findings after placebo ingestion that was considered as control condition.

Table I reports the frequency bands and brain regions where the LORETA statistics detected differences between medication conditions. This table demonstrates that in the open eyes condition, for the slow and medium frequency bands of EEG delta, theta, alpha1, and alpha2, MDMA showed decreased activity; in the eyes closed condition, the same result was observed, except for alpha2. The opposite difference, increased activity after MDMA was observed for the fast frequency bands, EEG beta1, beta2 and beta3 in both recording conditions. In the eyes open condition, however, beta1 and beta2 showed, in addition, regions of decreased activity after MDMA.

Eyes open

Delta band activity was decreased mainly in the left premotor cortex (Table I and Fig. 2A). The decrease in theta band activity involved large, distributed regions, maximal in the posterior cingulate cortex. Decrease in

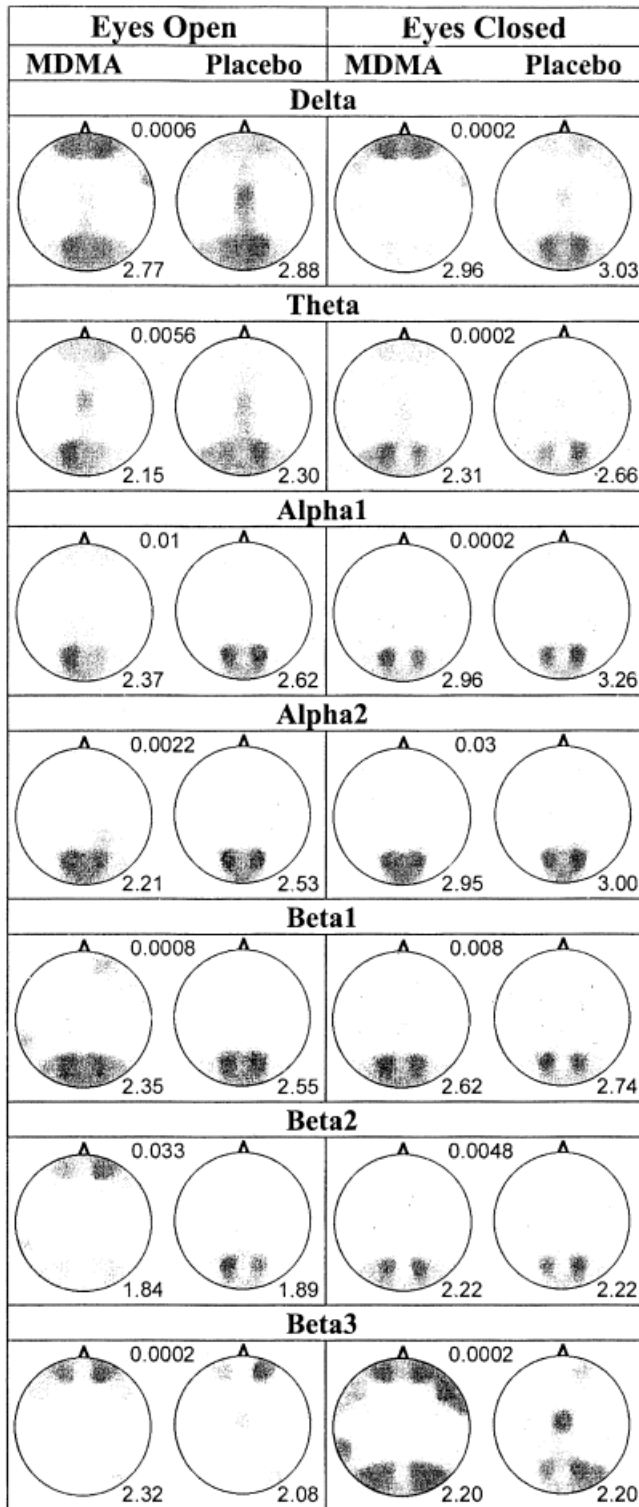


Figure 1.

Mean scalp maps (over subjects) of spectral power in the seven EEG frequency bands during eyes open and closed, after MDMA and placebo. The global statistical difference (P -value of non-parametric cluster statistics) for each comparison between MDMA and placebo maps is stated between the compared maps. Map gray scale from zero power (white) to maximal power (black), individually scaled for each map (maximal value in right lower corner, in log of square root of power). Note that all comparisons were significant at $P < 0.033$, but that the significance is not always obvious in visual examination.

TABLE I. LORETA results of MDMA-induced regional changes in brain electrical activity

Condition	Frequency band		Brain region (Brodmann area)			Local maximum		
	Name	Range (Hz)	Left	Bilateral	Right	Brain area	x, y, z ^b	
Eyes open	Delta	1.5-6	↓ ^a				Prefrontal (6)	-24, -11, 50
	Theta	6.5-8	↓				Posterior cingulate (23)	-3, -32, 29
	Alpha1	8.5-10	↓	Global Posterior cingulate (23, 31) Parietal (7)		Occipital (19)	Posterior cingulate (23)	-3, -46, 22
	Alpha2	10.5-12	↓	Posterior cingulate (23, 31)		Parietal (7) Occipital (19) Cingulate gyrus (30) Temporal (20, 21, 22, 38) Inferior frontal (44)	Posterior cingulate (23)	-3, -39, 22
	Beta1	12.5-18	↑	Insula		Insula Orbitofrontal (47)	Insula	39, 10, -6
	Beta2	18.5-21	↓	Parietal (7)	Orbitofrontal (11) Frontal (25) Temporal (38) Occipital (19) Temporal (21, 38) Orbitofrontal (11) Frontal (25, 45) Insula		Parietal (7) Temporal (38)	-10, -74, 50 46, 10, -20
Eyes closed	Beta3	21.5-30	↑				Occipital (19) Temporal (21)	-10, -81, 43 -52, 3, -41
	Delta	1.5-6	↓	Posterior cingulate (23) Prefrontal (6)			Posterior cingulate (23)	-3, -11, 29
	Theta	6.5-8	↓	Anterior cingulate (32) Posterior cingulate (23) Temporal (22) Parietal (40) Occipital (17) Prefrontal (6, 8, 9) Posterior cingulate (31) Anterior cingulate (24)		Occipital (19) Parietal (40) Fusiform (20) Parahippocampus (30)	Posterior cingulate (23)	-3, -39, 22
	Alpha1	8.5-10	↓	Prefrontal (8)			Prefrontal (8)	-3, 38, 36
	Beta1	12.5-18	↑				Temporal (38)	46, 10, -13
	Beta2	18.5-21	↑	Temporal (38) Orbitofrontal (47)		Temporal (21, 38) Orbitofrontal (47) Temporal (20, 21) Insula Orbitofrontal (47) Subcallosal gyrus (25)	Temporal (38) Temporal (38)	46, 10, -27
Beta3	21.5-30	↑	Temporal (20, 37, 38) Parahippocampus (36)			Temporal (37)	-59, -60, -13	

^a Downward arrows indicate decreases, upward arrows increases of electrical activity for MDMA compared to placebo.

^b Coordinates are defined in the standard stereotaxic space of Talairach.

^c Cluster statistics.

^d Single voxel statistics.

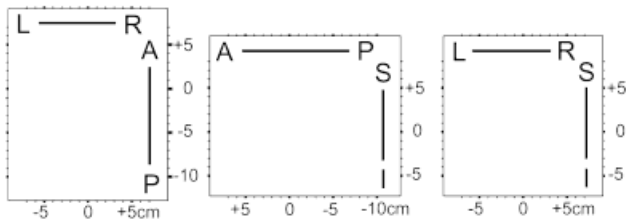
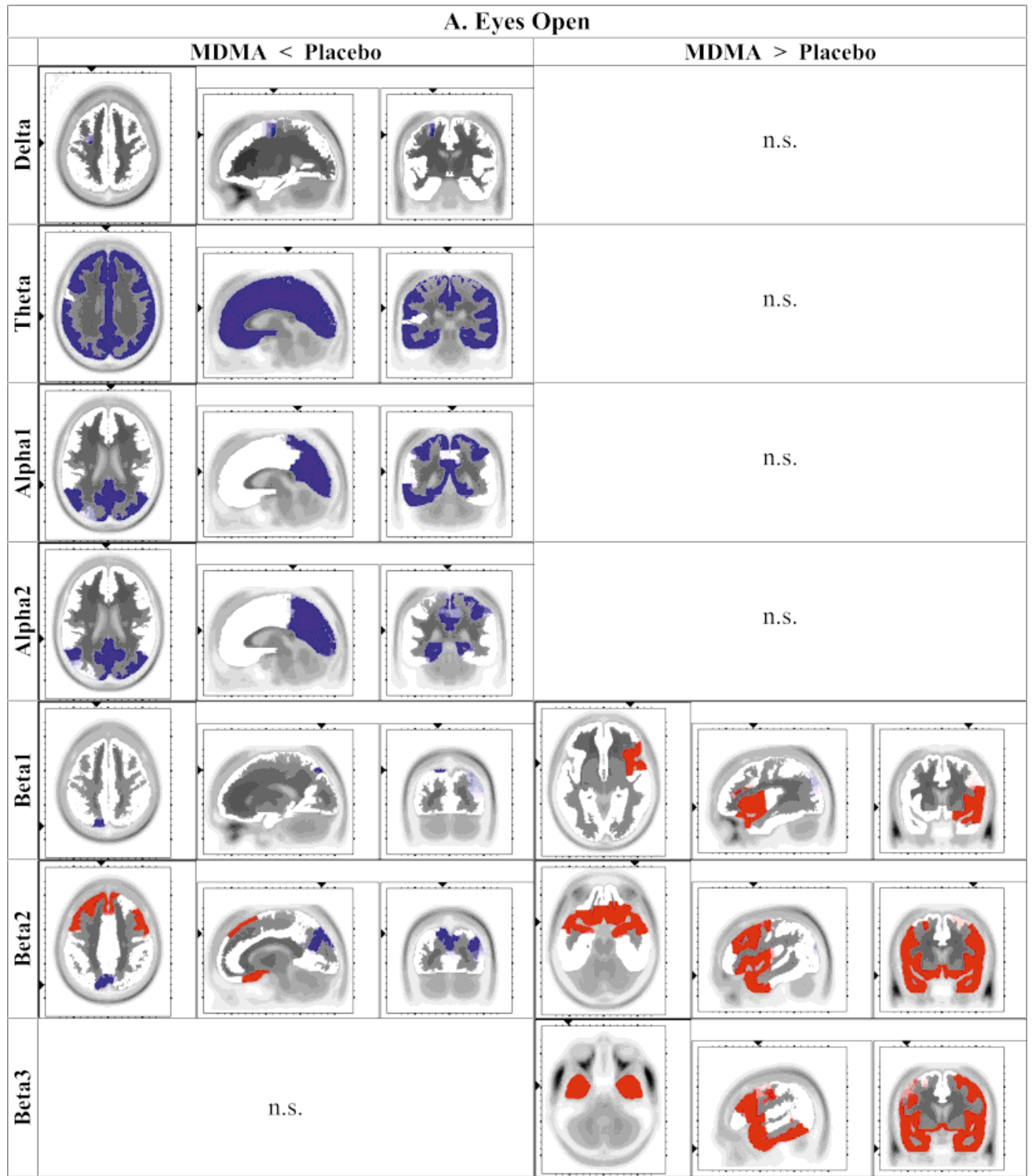


Figure 2.
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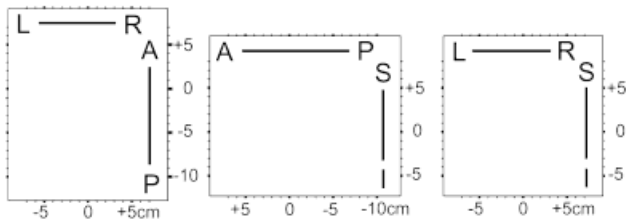
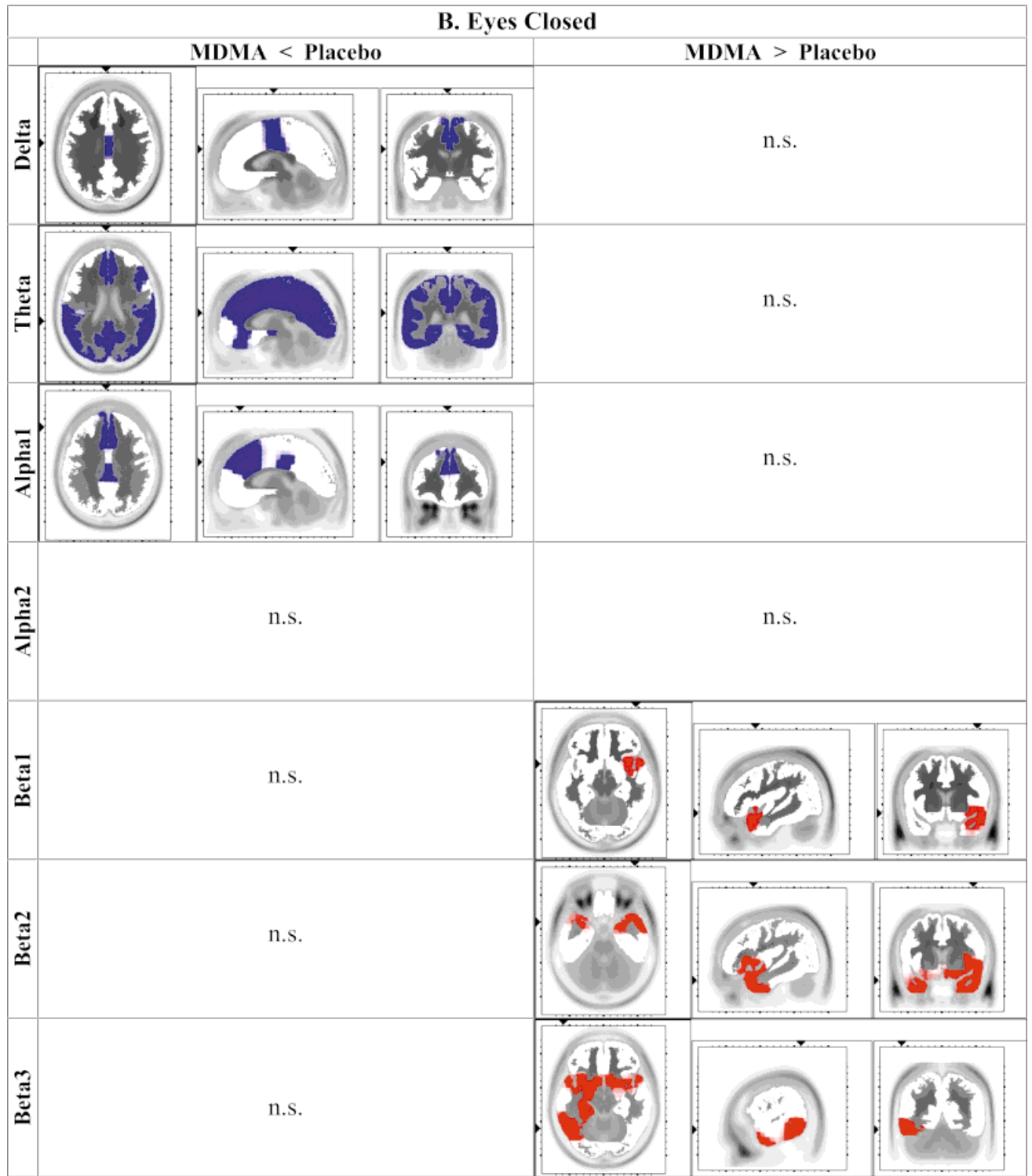


Figure 2. (cont'd)
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Alpha1 activity included the parietal and occipital cortex and was maximal in the posterior cingulate. The Alpha2 band showed a right-centered decrease in the parietal cortex, and in the temporo-occipital cortex extending into the hippocampal formation, with a maximal decrease in the posterior cingulate. Beta1 frequency activity was increased in the right orbitofrontal and anterior temporal cortex, but decreased in the left precuneus (parietal cortex). Beta2 increase was bilateral and more widespread, comprising the anterior temporal and posterior orbitofrontal cortex and extending into the insula and posterior frontal lobe. Beta2 activity also showed a decrease in the parietal cortex. The Beta3 band showed a bilateral increase in the anterior temporal, orbitofrontal, prefrontal and fusiform cortex with maximal activity in the temporal gyrus.

Eyes closed

In general, changes seen under the eyes-closed condition (Table I and Fig. 2B) were similar to those under the eyes-open condition. Delta band activity was decreased bilaterally in the cingulate and precentral gyrus. Theta showed a widespread bilateral decrease centered at the posterior cingulate and including the entire cingulate gyrus, the parietal cortex, the posterior temporal lobe and in addition, on the right side, the occipital, fusiform and hippocampal cortices. There was a maximal decrease in Alpha1 activity in the frontal cortex with additional decreases in the

Figure 2.

Low resolution electromagnetic tomography (LORETA) functional images of the differences between regional brain electric activity after MDMA and after placebo during (A) open eyes (12 subjects) and (B) closed eyes (14 subjects) in the seven EEG frequency bands 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). For each frequency band, three orthogonal slices through the location of maximal increase or decrease, respectively, are displayed. Decreased activity after MDMA compared to placebo is labeled blue, increased activity red. Images are color-coded non-parametric statistical maps corrected for multiple testing, registered to the stereotaxic Talairach space and overlaid on a structural MRI scan. Color coded are the cortical voxels at corrected $P < 0.1$ (see Table I). The Talairach coordinates of minimal or maximal t -values are indicated by black triangles on the coordinate axes. Calibration (left lower corner in A) in cm of the Talairach atlas. Talairach x axis: L, left; R, right. Talairach y axis: P, posterior; A, anterior. Talairach z axis: I, inferior; S, superior. Note that in general, after MDMA there was predominant decrease in Delta, Theta, Alpha1 and Alpha2 frequency bands, and a predominant increase in the three Beta frequency bands.

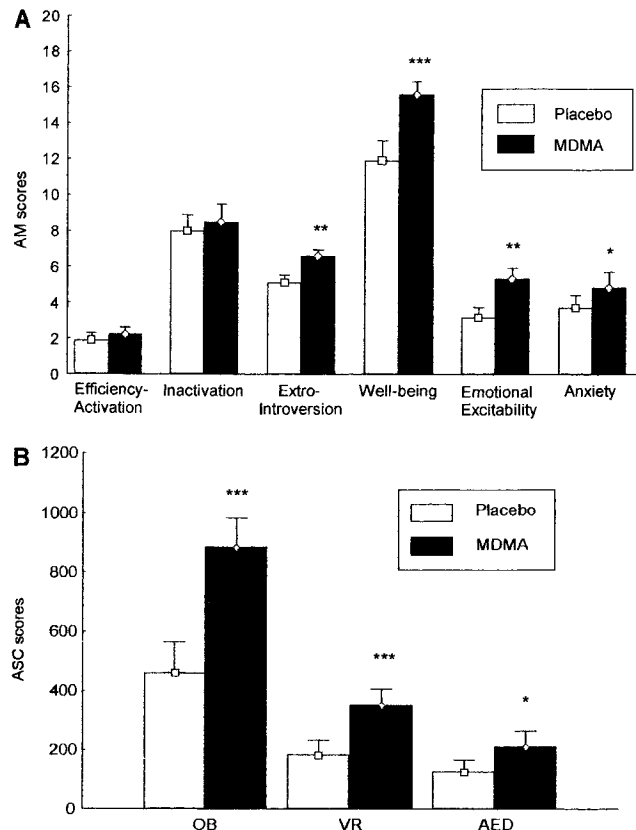


Figure 3.

MDMA-induced alterations of subjective experience during EEG measurements. **A:** MDMA-induced affective and emotional changes as measured by the Adjective Mood Profile Questionnaire (AM). **B:** MDMA-induced changes in dimensions of the Altered States of Consciousness Questionnaire (ASC). OB, 'Oceanic Boundlessness'; VR, 'Visionary Restructuralization'; AED, 'Anxious Ego Dissolution'. See text for further explanation. * $P < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

entire cingulate cortex. Beta1 activity was increased in the right anterior temporal and posterior orbitofrontal cortex. Bilateral Beta2 increase was found in the anterior temporal and posterior orbitofrontal cortex, extending on the right side into the insular cortex. Beta3 activity showed a bilateral increase in the anterior superior temporal gyrus, a left sided increase in the inferior temporal and parahippocampal gyrus, and a right sided increase in the subcallosal gyrus.

Psychological measures

MDMA significantly elevated the AM scores (main effect treatment $F = 57.6$, $df = 1,15$, $P < 0.001$). Tukey's post hoc tests (Fig. 3A) showed significant increases for well-being ($P < 0.001$), extroversion ($P = 0.001$), emotional excitability ($P < 0.001$) and anxiety ($P =$

0.037). The subscale scores heightened mood ($P < 0.001$) and self-confidence ($P < 0.001$) of the well-being scale were also significantly increased.

Elevated extroversion scores reflected an increased openness for social communication such as being more 'sociable,' 'outgoing,' 'friendly,' and 'talkative.' Although AM anxiety scores were increased under MDMA, subjects did not explicitly report feelings of anxiety. Analysis of the anxiety subscales revealed that the overall increase in anxiety was mainly due to an increase in thoughtfulness-contemplativeness scores ($P < 0.002$), whereas the apprehension-anxiety and dejection scores were not significantly changed.

MDMA also produced significantly increased ASC scores (main effect of treatment $F = 31.7$, $df = 1,15$, $P < 0.001$). Post hoc comparisons (Fig. 3B) revealed significant increases for OB ('Oceanic Boundlessness'; $P < 0.001$), VR ('Visionary Restructuralization'; $P < 0.001$) and AED ('Anxious Ego Dissolution'; $P = 0.015$). The increase in OB scores was due to a prominent increase in items for positive basic mood and moderate increases in items for derealization and depersonalization. Although VR scores were elevated, none of the subjects reported hallucinations, whereas visual illusions and an intensification of tactile awareness were experienced frequently. Increased AED scores were due to thought disorder and first signs of loss of body control associated with slight anxiety. Contrary to anecdotal report of MDMA-induced psychomotor stimulation [Solowij et al., 1992], most subjects did not report an increased psychomotor drive and even felt calmer or more relaxed in our experimental setting.

DISCUSSION

Comparing the scalp power maps for MDMA and placebo via the non-parametric cluster statistics, significant differences in the spatial distribution of brain electric activity were found in all seven frequency bands, both during eyes open and closed. The application of LORETA functional tomographic imaging for 3D localization of intracranial electrical activity determined distinct frequency- and region-specific changes in line with reports of clinical and research applications of LORETA [Anderer et al., 2000; Gamma et al., 2000; Pascual-Marqui et al., 1999; Pizzagalli et al., 2001; Worrell et al., 2000]. Changes in brain activity occurred in frontal areas (Delta), frontal and posterior areas (Alpha), frontotemporal areas (Beta) and over the whole brain (Theta). In general, the activity in the slow and medium EEG frequency bands was decreased, in the fast bands increased after MDMA. Concomitant with these electrophysiological changes,

MDMA produced a state of enhanced mood and increased extroversion. Moreover, it is noteworthy that MDMA increased the overall AM anxiety score, but this increase was mainly due to an increase in the thoughtfulness-contemplativeness subscale score but not due to an increase in the apprehension-anxiety and dejection subscale scores. Indeed, most subjects did not report feelings of anxiety. Nevertheless, some anxiety was related to concerns of loss of body control as measured by the AED rating scale.

MDMA decreased the Delta activity in the frontal cortex including the anterior cingulate. Delta activity in awake adults is associated with functional inhibition and is seen in pathological conditions [Fisher-Williams, 1993; Sharbrough, 1993], but also in normal sleep. Thus, the observed Delta decrease suggests that MDMA might involve functional disinhibition of frontocortical areas and possibly arousal. This is supported by our findings that after MDMA, subjects had higher scores for emotional excitability, and that a Delta decrease was found also with the stimulant *d*-amphetamine [Fink et al., 1971; Saletu et al., 1993] and with the NA uptake inhibitors tandamine and clovoxamine [Saletu, 1982].

A global decrease in the Theta band activity centered around the cingulate cortex was seen after MDMA. Decreased Theta activity has been found after the psychostimulant *d*-amphetamine [Saletu et al., 1993] and the NA agonists tandamine [Saletu, 1982] and clovoxamine [Saletu, 1982] in humans. Further, increased Theta activity in adults was linked to decreased vigilance or anxiety [Kirov et al., 1996; Mizuki et al., 1992]. Theta decrease in our results may therefore relate to MDMA-induced arousal or to slight anxiety, which was found in association with concerns of loss of body control (AED) under MDMA. On the other hand, frontal midline Theta reportedly is generated during focused attention, and is mainly related to bilateral medial prefrontal cortices, including the anterior cingulate [Ishii et al., 1999]. The global decrease during eyes open and the decrease during eyes closed in the anterior cingulate in our study might also indicate a decrease of focused attention during MDMA.

In the eyes-open condition, MDMA reduced Alpha activity in posterior regions of the parietal, cingulate, occipital and temporal cortex, whereas in the eyes-closed condition, Alpha decrease was seen in frontal regions and in the entire cingulate cortex. The functional significance of the Alpha frequency is not completely clarified, all the more because the absence of Alpha in a minority of healthy people is not associated with relevant functional deviations. Alpha activity is normally prominent during states of relaxed wakeful-

ness [Niedermeyer, 1997]. Others found increased left frontal Alpha activity and increased parietal Alpha activity while subjects listened to narratives eliciting anxious arousal [Heller et al., 1997]. Furthermore, Alpha activation has been reported as being typical for the arousing action of psychostimulants such as *d*-amphetamine [Saletu et al., 1993] and methamphetamine [Saletu et al., 1980], and has been associated to stimulant-induced feelings of euphoria [Lukas et al., 1995]. Thus, the functional significance of the observed Alpha band decreases after MDMA is unclear, although these decreases indicate that MDMA can be differentiated from psychostimulants with regard to its effects on Alpha band frequencies.

All Beta frequencies that are generally associated with excitatory processes during focused attention [Lopes da Silva et al., 1970; Murthy and Fetz, 1992], arousal [Sheer, 1984] and vigilance [Bouyer et al., 1987; Rougeul-Buser et al., 1983] showed a marked increase after MDMA ingestion. Beta increase was present in both the eyes-closed and eyes-open condition, and was most pronounced in the anterior temporal lobe and orbitofrontal cortex. These regions are closely interconnected parts of the limbic system that plays an important role in the regulation of mood and emotion [Le Doux, 1991]. Increased activity of these limbic areas is likely to reflect the observed mood enhancement and emotional arousal after MDMA. Furthermore, the anterior temporal lobe and orbitofrontal cortex have been linked to social expression and perception [Brothers, 1996; Deakin, 1996], and their increased activity may be related to the MDMA-induced increase in extraversion that was reflected by items describing openness for social interaction such as being "friendly," "sociable," "outgoing," "talkative," etc. Further studies on correlations between social behavior and cerebral activity in these areas are needed to substantiate this hypothesis.

In general, LORETA activity changes under MDMA were more pronounced under the eyes-open condition. The decreases in Delta, Theta and Alpha1 and the increases in Beta1, 2 and 3 were common to both recording conditions. For the Alpha2, Beta1 and Beta2 bands, however, LORETA decreases were found only with eyes open. In the Alpha1 band, there was a shift of MDMA-induced changes to frontal areas in the eyes-closed as compared to the eyes-open condition. Apparently, the MDMA effect in the EEG is manifested in different regions and is amplified when subjects open their eyes, which probably leads to a general increase in brain activity and in complexity of processing. A similar effect has been clinically observed under hallucinogenic drugs where psycho-

tropic effects were more distinct during the eyes-open condition [Leuner, 1981]. This should be further clarified by studying drug-induced subjective and cognitive effects separately with closed eyes and open eyes.

To clarify the relative contributions of different transmitter systems to the electrophysiological and psychological effects of MDMA, we compared MDMA effects with effects of various agonists of the 5-HT, DA and NA systems that have been implicated in the action of MDMA.

d-Fenfluramine is a structurally related serotonergic agonist [Saletu et al., 1993] which, like MDMA, produces a strong release and uptake inhibition of 5-HT in animals. *d*-Fenfluramine also has similar, although weaker, effects on mood in humans such as increased contentment, dreaminess, and calmness [Bond et al., 1995]. The MDMA-evoked pattern of region- and frequency-specific changes closely parallels that found in a study using a single dose of 30 mg *d*-fenfluramine in healthy subjects under resting condition with eyes closed [Saletu et al., 1993]. In that study, *d*-fenfluramine produced a decrease of slow waves (Delta, Theta) over frontal, central and posterior regions, and increased fast Beta activity over frontal and temporal regions, changes that are nearly identical to those seen after MDMA. Alpha band changes induced by MDMA and *d*-fenfluramine were less similar: whereas *d*-fenfluramine had no overall effect on Alpha power under the eyes-closed condition, MDMA selectively affected the Alpha1 frequency band, while having no effect on Alpha2. This apparent discrepancy may be due to differences in neuroreceptor or release profiles of the two drugs, which may be related to differences in psychological effects. Also, methodological differences between the studies may account for the lack of *d*-fenfluramine effects on Alpha activity. Alpha1 and 2 were not analyzed separately, but merged into one single frequency band in the *d*-fenfluramine study, so that a possible differential effect on Alpha1 and Alpha2 may have been averaged out.

Surprisingly, acute administration of the selective 5-HT uptake inhibitors (SSRIs) fluvoxamine and fluoxetine in healthy subjects was reported to produce EEG profiles that were entirely different from that seen under MDMA in this study. Fluvoxamine produced opposite frequency changes with an increase of the Delta, Theta and Alpha band and a decrease in the Beta band [Saletu, 1982]. After Fluoxetine, Alpha activity was increased and Beta activity was decreased, and no changes were seen in slow wave activity [Saletu, 1982]. The differences between these EEG profiles and that under MDMA might partly be explained by the fact that MDMA is thought to act primarily as a

potent 5-HT releaser, whereas fluvoxamine and fluoxetine are 5-HT uptake inhibitors producing a much weaker enhancement of 5-HT neurotransmission. Furthermore, contrary to MDMA, these two SSRIs have no or only negligible acute effects on mood [Cook et al., 1994; Saletu et al., 1996]. Finally, differences in methodology may contribute to the observed EEG differences.

Animal studies show that, besides the 5-HT system, other neurotransmitter systems are involved in the effects of MDMA. It has been demonstrated particularly that MDMA produces a dose dependent increase in DA levels in the striatum and nucleus accumbens [Yamamoto and Spanos, 1988]. Moreover the high affinity of MDMA for Alpha-2 receptors in rats [Battaglia et al., 1988] suggests that NA may also play a role in the mediation of MDMA effects in humans.

MDMA shares some of its EEG effects with the DA releaser *d*-amphetamine, notably a deactivation of slow Delta/Theta waves and an augmentation of Beta frequencies [Fink et al., 1971; Saletu et al., 1993]. MDMA, however, can be clearly discriminated from *d*-amphetamine and its congener methamphetamine by its effect on the Alpha band. Whereas MDMA reduced Alpha activity, *d*-amphetamine [Fink et al., 1971; Lukas et al., 1989; Saletu et al., 1993] and methamphetamine [Saletu et al., 1980] have been demonstrated to produce an activation of Alpha frequencies. An increase in Alpha activity has been discussed as typical for psychomotor stimulant drugs [Saletu et al., 1993]. Thus, the present Alpha decrease seen after MDMA may be attributable to the fact that subjects in our study experienced relaxation rather than psychomotor stimulation. This observed relaxation contrasts with anecdotal reports of ecstasy-induced psychomotor activation [Solowij et al., 1992]. Thus, it is possible that higher doses of MDMA may lead to psychomotor activation potentially associated with an increase in DA release and Alpha band activity. On the other hand, as mentioned above, an Alpha increase, rather than decrease, is normally associated with a state of relaxed wakefulness. This apparent discrepancy indicates that Alpha changes may not simply reflect changes on the axis relaxation-stimulation, but that there may be a yet unknown common functional denominator of the Alpha changes observed in these different states. Possibly, the divergent effects of MDMA and *d*-amphetamine on Alpha power are related to differences in mood effects of these drugs. Whereas euphoria and grandiosity are typical for amphetamines, MDMA was characterized by a state of increased emotional and sensory aware-

ness, heightened mood but not euphoria, in our setting.

Interestingly, the two NA uptake inhibitors and antidepressants tandamine and ciclopramine produced a nearly identical EEG frequency band pattern under resting condition as MDMA [Saletu, 1982]. All substances showed a Delta, Theta, and Alpha band decrease and a Beta band increase. This similarity suggests that NA is involved in the mediation of MDMA effects. Nevertheless, despite similar EEG patterns, mood effects of tandamine and MDMA are only partially overlapping. Both show a mood enhancing effect, which, however, is more pronounced after MDMA. Tandamine produced an increase in attention, concentration and psychomotor activity [Saletu, 1982] whereas, under MDMA, attention and concentration were reduced as indicated by the slight increase of errors in a Continuous Performance Test performed immediately before the EEG recordings (data not shown). The similarities in EEG patterns and the concomitant differences in mood between tandamine and MDMA imply that their EEG patterns do indeed reflect effects other than only mood effects.

In conclusion, the MDMA-specific EEG pattern shows strong similarities to that of the 5-HT releaser *d*-fenfluramine and the NA uptake inhibitors tandamine and ciclopramine and weaker similarities with the DA agonists *d*-amphetamine and methamphetamine. This suggests that MDMA effects on the EEG, and possibly also its mood and behavioral effects, are mediated predominantly by the 5-HT and also the NA system and, to a lesser degree, by the DA system. This interpretation is supported by our recent finding that citalopram, a serotonin uptake inhibitor, markedly attenuated the effects of MDMA in humans [Liechti et al., 2000]. It remains unclear why SSRI-specific EEG effects are nearly opposite to those of MDMA.

A general difficulty in comparing the EEG of different drugs is the fact that EEG patterns after drug administration can vary substantially over time. There is no best predetermined time point after administration to compare EEG effects. One possibility is to measure and compare the time course of drug-specific EEG changes. This is not possible for the present study, however, because our measurements were restricted to one point in time.

In conclusion, using 3D brain electromagnetic tomography LORETA that provides information in both the EEG frequency domain and the brain space domain, we found distinct region- and frequency-specific EEG changes in healthy human subjects treated with the mood-enhancing agent MDMA as compared to placebo. Particularly, the observed increase of Beta

band activity in limbic and paralimbic areas may contribute to the marked enhancement in mood observed after MDMA. Comparisons with the serotonergic agonist *d*-fenfluramine, the NA uptake inhibitors tandamine and ciclopramine and the dopaminergic stimulants *d*-amphetamine and methamphetamine indicate that serotonin, noradrenaline and, to a lesser extent, dopamine contribute to the effects of MDMA on the EEG, and possibly also on mood and behavior.

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