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ORIGINAL INVESTIGATION

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Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence

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Abstract *Rationale*: Despite animal studies implicating 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in serotonergic neurotoxicity, there is little direct evidence of changes in neural function in humans who use MDMA as a recreational drug. *Objective*: The present study investigated whether there is a correlation between quantitative EEG variables (spectral power and coherence) and cognitive/mood variables, and level of prior use of MDMA. *Methods*: Twenty-three recreational MDMA users were studied. Resting EEG was recorded with eyes closed, using a 128-electrode geodesic net system, from which spectral power, peak frequency and coherence levels were calculated. Tests of intelligence (NART), immediate and delayed memory, frontal function (card sort task), and mood (BDI and PANAS scales) were also administered. Pearson correlation analyses were used to examine the relationship between these measures and the subject's consumption of MDMA during the previous 12-month period. Partial correlation was used to control for the use of other recreational drugs. *Results*: MDMA use was positively correlated with absolute power in the alpha (8–12 Hz) and beta (12–20 Hz) frequency bands, but not with the delta (1–3 Hz) or theta (4–7 Hz) bands. MDMA use was negatively correlated with EEG coherence, a measure of synchrony between paired cortical locations, in posterior brain sites thought to overly the main visual association pathways of the occipito-parietal region. MDMA use did not correlate significantly with any of the mood/cognitive measures except the card sort task, with which it was weakly negatively correlated. *Conclusions*: Alpha power has been shown to be inversely related to mental function and has been used as an indirect measure of brain activation in both normal and abnormal states. Reduced coherence levels have been associated with dysfunctional connectivity in the brain in disorders such as dementia, white-matter disease and normal aging. Our results may indicate altered brain function correlated with prior MDMA use, and show that electroencephalography may be a cheap and effective tool for examining neurotoxic effects of MDMA and other drugs.

Key words MDMA · Ecstasy · Human · EEG · Power · Coherence

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Introduction

There is considerable concern over the widespread recreational use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), usually as an adjunct to dancing in clubs. According to some estimates around half a million Ecstasy tablets are consumed each weekend in the UK, and grave doubts have been expressed about the safety of the drug. These doubts concern both the well-publicised acute effects of the drug, which include hyperthermia, hyponatraemia and tachycardia and which have occasionally proved fatal (Henry et al. 1992; Kessel 1993; Dafters 1996), and the possibility of neurotoxicity in humans.

Fears about possible neurotoxicity in human recreational users derive from studies showing that in several animal species, MDMA causes degeneration of serotonergic neurons in the brain (Schmidt and Kehne 1990; Ricaurte and McCann 1992; Green and Goodwin 1996). Since disruption of serotonin systems has been implicated in a variety of disorders such as memory loss, depression and psychotic conditions, it is important to establish whether the drug is also neurotoxic in humans at recreational doses, and whether this may produce lasting changes in brain function, cognition and behaviour. However, well-designed prospective

studies using random subject assignment, double-blind procedures and placebo controls are rarely possible, because MDMA is an illicit, schedule A drug. The few published studies of cognitive and mood changes have produced variable results, although there have been several reports of memory impairments (Curran and Travill 1997; Parrott et al. 1998). Impulsivity has been reported to increase (Morgan 1998; Schifano et al. 1998), decrease (McCann et al. 1994), or show no change (McCann et al. 1994) after MDMA use. Physiological evidence for brain serotonergic toxicity following MDMA use is based mainly on indirect measures such as reduced levels of the transmitter or its metabolites in cerebrospinal fluid (McCann et al. 1994), or reduced serotonin production in response to injected precursor, L-tryptophan (Price et al. 1986). Recently, there have been promising developments in the use of brain imaging techniques such as positron-emission tomography (PET) to detect changes in serotonin uptake sites in the brain following drug use (Szabo et al. 1995a,b; McCann et al. 1998), but blood flow changes are indirect measures of neural activity and no direct evidence of altered neuronal function has been presented to date. In addition, because PET and metabolic neuroimaging techniques have a poor temporal resolution, they are unlikely to reveal the fundamental mechanisms of normal and pathological brain function which occur on a millisecond time scale. Electroencephalography (EEG) has the necessary temporal resolution and, with new 128-channel, dense-mapping electrode arrays, has a spatial resolution approaching that of PET. Furthermore, at a fraction of the cost of other imaging techniques such as MEG (magnetoencephalography), PET, or fMRI (functional magnetic resonance), only EEG holds out the hope of routine diagnosis and screening for neurotoxicity in the short term. Quantitative EEG measures, such as spectral power analysis and coherence, are being widely used to identify abnormal brain states which underlie many different pathological states including depression, dementia, and AIDS (Duffy et al. 1995; Cook and Leuchter 1995; Newton et al. 1997). We show here that such measures may also prove useful in the identification and characterisation of drug-induced brain changes.

Spectral analysis uses a fast Fourier transform to calculate the power or amplitude of the EEG signal in different frequency bands, typically, delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–20 Hz). Absolute power levels of each band and relative values (the percentage of total power in a given band) are typically presented and have shown changes in normal aging, in dementia and in depression. Topographical characteristics, such as left-frontal alpha power versus right-frontal alpha power, may also have diagnostic value, for example in depression (Davidson et al. 1985; Henriques and Davidson 1990). EEG coherence is defined as the cross-power spectrum per frequency of two electrode positions recorded simultaneously at different sites on the scalp. It is a measure of the synchronisation of activity of the two locations in terms of both phase and amplitude of the signal, and can provide information about the coupling of two locations. Thus, two electrodes which have the same average spectral profile over a given period may have coherence values ranging from 0 to 1 depending on whether or not their frequency values were synchronised over the relevant period. Coherence is widely interpreted as an indication of the functional interaction or connectivity of the two sites and has proved useful in detecting brain pathology in a variety of conditions where neuronal dysfunction is implicated. For example, neurological changes resulting from vascular or degenerative changes in the elderly are associated with reduced coherence (O'Connor et al. 1979; Leuchter et al. 1987). Thus, it may be predicted that drug-induced neurotoxicity will also result in reduced coherence. We report here evidence for changes in both spectral EEG power and EEG coherence in long-term MDMA users.

Materials and methods

Subjects and drug histories

Subjects were university students or their friends (mean age = 24 years, range 18–42), recruited via a "snowball" effect (Callow 1996) in which initial volunteers were asked to recruit additional volunteers from among their friends. Subjects were asked to participate in an experiment on the physiological and cognitive effects of recreational drug use. The subjects were recruited by one experimenter (C.B.) who took drug use histories which were not revealed to the other experimenters so that testing could be carried out "blind". Drug histories were obtained using a structured instrument which listed questions about a variety of different drugs. Subjects estimated their prior use of the drugs in the previous week, month, year and lifetime. Subjects were screened in this way for use of MDMA, alcohol, tobacco, amphetamines, temazepam, cocaine, heroin, LSD, magic mushrooms, diazepam, ketamine, nitrites and solvents. Subjects with a history of neurological disorder, head injury, or diseases previously linked to EEG abnormalities such as cardiovascular disease or diabetes were eliminated, as were those on prescribed medication, and those reporting MDMA or other drug use (except alcohol or tobacco) within 7 days of the test session. The subjects completed a consent form, were coded to maintain anonymity, and were then given an appointment for the EEG and other tests. The procedures used were in accordance with the ethical guidelines of the British Psychological Society and with the Helsinki Declaration of 1975 and were approved by the local ethics board.

Experimental procedure

On arriving at the Brain Electrophysiology Laboratory, subjects completed a consent form and were fitted with a 128-electrode geodesic sensor net for EEG analysis (Netstation v1. 4; Electrical Geodesics Incorporated, Eugene, Oregon, USA). This multi-channel EEG acquisition system has been described in the literature and simulation studies have emphasised its advantages for topographical studies of the EEG over the traditional ten-twenty electrode system (Tucker 1993; Srinivasan et al. 1998). Six 60-s epochs of resting, eyes-closed EEG were recorded with the subject seated in

a small, sound-attenuated room with 20-s re-arousal periods between epochs. The sensor net was then removed and the subject was taken immediately to an adjacent room where the cognitive tests and mood tests were given. The experimental session lasted approximately 1 h and subjects were then debriefed, paid for their participation, and released from the experiment.

Cognitive mood tests

Subjects completed the National Adult Reading Test (NART) component of the Wechsler Adult Intelligence Scale (WAIS), which involves reading 50 words of decreasing frequency in the English language; the Rivermead Behavioural Memory Test (Wilson et al. 1985), of which version A of item 6 A (story-immediate) and 6B (story-delayed) were given, in which subjects were required to recall a prose passage immediately and following a task-filled interval; the Behavioural Assessment of the Dysexecutive Syndrome (BADS)–rule shift cards test (Nelson 1976), a derivative of the Wisconsin Card Sorting Task involving a sudden change to a new sorting rule and which is designed to examine frontal executive function; an in-house version of the Memory Span task (Turner and Engle 1989), a working memory span task requiring recall of words following distraction with mathematical problem in which subjects were presented with a series of cards which contained either a word or a mathematical problem to solve. Recall of the words was tested at appropriate points throughout the task. Two mood state questionnaires were administered: the BDI (Beck's Depression Inventory), and the PANAS (Positive and Negative Affect Scale) The latter consists of a list of ten negative and ten positive word items on which subjects rate their general mood on a 4-point scale. The scale has been validated and shown to be highly internally consistent and stable over a prolonged time period, and highly correlated with other mood state questionnaires (Watson et al. 1988).

EEG measures

Spectral 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 movement minimised by means of a chin rest. EEG was collected from 128 channels at 125 samples/s using an averaged reference and with a lowpass filter of 40 Hz. For each subject, one relatively artefact-free 60-s period was visually selected for spectral analysis using a fast Fourier transform. The analysis was carried out on 1-s epochs, which were additionally software-filtered to eliminate those where amplitude fluctuations exceeded 100 μV, and with fewer than 110 good channels, then averaged to obtain a frequency spectrum for that individual. Spectral power for the four brain quadrants was taken as the mean power in each frequency band for an appropriate triplet of electrodes which most closely approximated standard ten-twenty positions in the 128-channel array, that is, left frontal (electrodes Fp1, F3 and F7), right frontal (electrodes Fp2, F4 and F8), left posterior (electrodes O1, P3 and T5), and right posterior (electrodes O2, P4 and T6). A grand mean of all 12 positions was also taken for each frequency band. Relative power values were calculated as the ratio of mean power in a particular band to that in the entire spectrum.

Coherence

To avoid the "combinatorial explosion" problem and type 1 statistical error inherent in qEEG studies where many electrodes and many variables may lead to "significant" values arising by chance (Duffy et al. 1994), coherence measures were based on the method

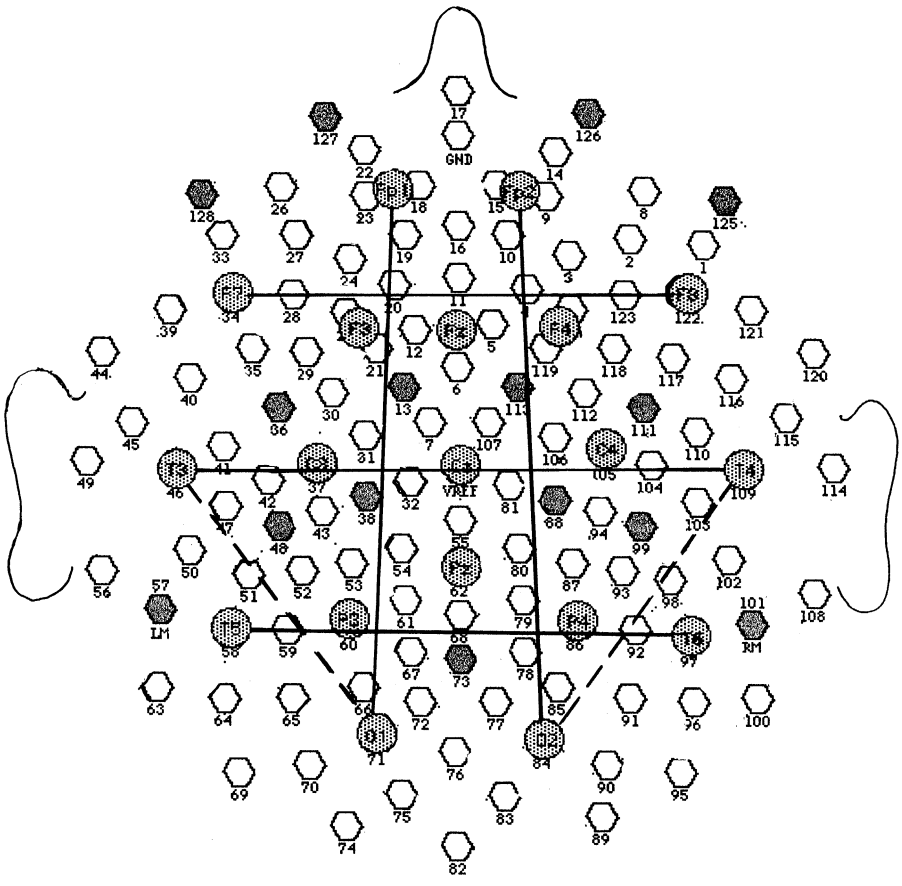

Fig. 1 Two-dimensional head model showing 128-channel electrode locations and standard ten-twenty locations (*large filled circles*). *Continuous lines* join electrode pairs used for Trans-callosal and Fascicle coherence estimates; *dashed lines* join electrode pairs used for Visual coherence estimates

of Leuchter and colleagues (Leuchter et al. 1994; Cook and Leuchter 1995) in which electrode pairs are selected for analysis on the basis of presumed underlying white-matter fibre tracts. Thus, coherence (for frequencies between 2 and 20 Hz) between anterior and posterior sites in each hemisphere which approximate the endpoints of the superior longitudinal fasciculus (the so-called Fascicle coherence measure) was calculated, as was coherence between occipital and temporal sites in each hemisphere thought to overly projections of the visual association pathways (the so-called Visual coherence measure). Interhemispheric (Trans-callosal) coherence was also measured for three corresponding electrode pairs (ten-twenty locations F7–F8; T3–T4; T5–T6). Figure 1 shows a two-dimensional view of the sensor array with superimposed ten-twenty electrode positions. The continuous lines and dotted lines link the electrodes used for the calculation of Trans-callosal/Fascicle and Visual coherence, respectively.

Results

A 60-s, artefact-free period of EEG could not be obtained from one subject, and statistical analysis was therefore performed on the remaining 23 subjects. Since there was great individual variability in consumption of drugs, it was decided to use correlational analysis to study the relationship between MDMA use and EEG and cognitive variables rather than to attempt an arbitrary division into groups based on level of consumption. However, for illustrative purposes only, averaged data from "high" MDMA users (>20 units in lifetime) and "low" MDMA users (<20 units in lifetime) were taken and used to generate Figs 2 and 3. In addition to MDMA, the only drugs consumed by a significant number of subjects (>5) in the previous year were alcohol (unit = 1 drink), tobacco (unit = 1 cigarette), amphetamine (unit = 1 tablet), LSD (1 tablet) and cannabis (unit = 1 joint) see Table 1. Annual consumption (units in previous year) was used as the dependent measure for drug consumption, since subjects expressed higher levels of confidence about the accuracy of these figures than their estimate of lifetime use. The data were analysed using the Statistica CSS software package. Individual Pearson correlation coefficients were calculated comparing all the combinations of annual drug use measures, age and gender. Correlation analysis on the annual consumption of these drugs showed that MDMA use was independent of use of any other drug, and also independent of age and gender ($P > 0.05$ in each case). Table 2 shows the Pearson correlation matrix. For each of the significant correlations, a multiple regression equation was conducted with EEG power as the dependent measure and MDMA and other drug use measures (alcohol, tobacco, amphetamine, LSD and cannabis) as the independent variables. This was repeated for each of the EEG power bands as the dependent variable. This allowed calculation of what are technically semi-partial correlations (i.e. correlations drawn from the multiple regression equation) between the EEG power bands and MDMA with the effects of other drug use measures removed from the MDMA variable. The results of the semi-partial correlations and their significance values are shown in Table 2 in parentheses.

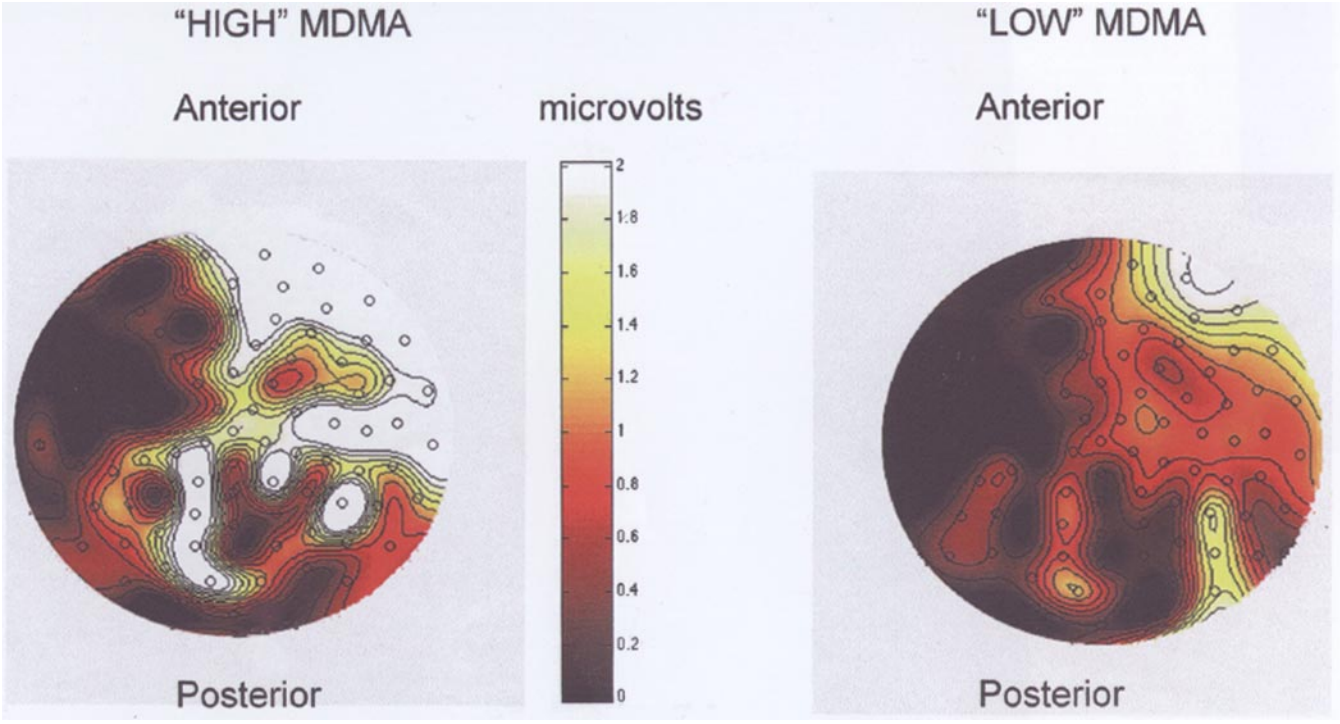

Fig. 2 Topography of mean alpha (9 Hz) power. *Left*, "high" MDMA users; *right*, "low" MDMA users (scale in μV; $n = 11$ and 12, respectively). Front of the head is at the top in each figure

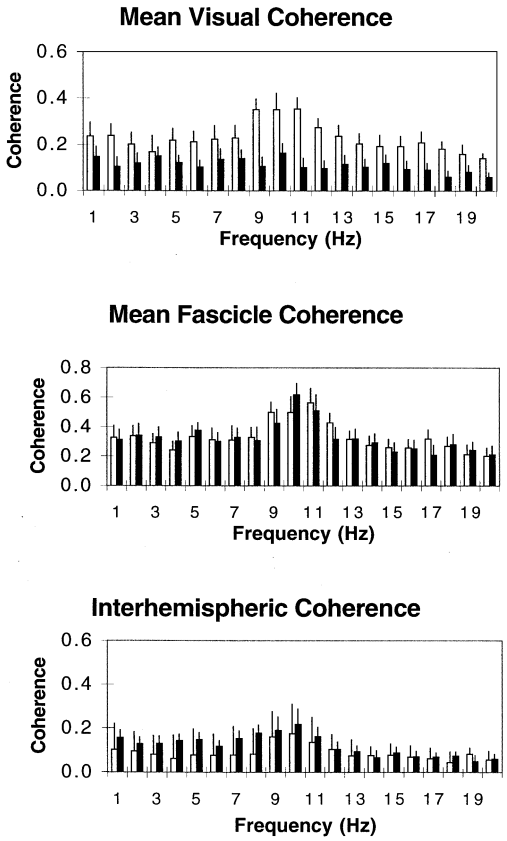

Fig. 3 Mean coherence values for the three different kinds of pairing. *Filled columns*, "high" MDMA users; *unfilled columns*, "low" MDMA users

Spectral analysis

Table 2 shows the correlation matrix between annual MDMA use and power in each EEG frequency band. Separate correlations have been calculated for absolute and relative values. For each of the significant correlations, a partial correlation was also conducted to control for possible interactive effects of the other drugs consumed (alcohol, tobacco, amphetamine, LSD and cannabis). The results of the partial correlations and their significance values are shown in Table 2 in parentheses. In addition, a separate analysis was conducted using the log 10 transformed absolute and relative power values, since it has been argued that this transformation reduces the skew/kurtosis of power data (Leuchter et al. 1993). These data are not shown, since they did not alter the distribution of significant correlations. Clearly, level of MDMA use is positively correlated with a global increase in alpha rhythm power across the brain, although the correlation just fails to reach significance for the right-frontal quadrant. MDMA use also correlated positively with beta rhythm power in the left posterior quadrant, and negatively with relative delta power averaged over the whole scalp.

The contrast in alpha power between relatively "high" MDMA users (doses >= 20, lifetime use) and relatively "low" MDMA users (doses < 20, lifetime use) is clearly seen in Fig. 2, which shows a brainmap plot of the mean power at 9 Hz for each group.

Coherence

Table 2 shows that there were weak but significant negative correlations between MDMA use (in previous 12 months) and EEG coherence between sites located along the Visual tracts (O1–T3,O2–T4). MDMA use did not correlate with coherence in the longitudinal Fascicle tracts or Trans-callosal pairings. Once again, the semi-partial correlation values and significance level controlling for other drug consumption are shown in parentheses. The contrast between Visual and Fascicle pathways is highlighted in Fig. 3, which compares coherence values in "high" and "low" MDMA-use subjects. Note that the decreased Visual coherence in the high-use subjects occurs across the entire frequency band.

Behavioural measures

As Table 2 shows, the only cognitive measure which was significantly correlated with MDMA use was the rule shift cards test for frontal executive dysfunction. Sorting accuracy following a rule change was weakly negatively correlated with MDMA use in the initial correlation analysis, and in the partial correlation analysis where other drug consumption was controlled for ($P < 0.05$, one-tailed, in each case).

Discussion

The principal electrophysiological findings of the study are clear cut. MDMA use in the previous 12-month

Table 1 Table of drug consumption in previous year showing mean units consumed (range in parenthesis)

Drug	Unit	No. of subjects using	Units (previous year)
MDMA	1 tablet	23	14.04 (1–60)
Cannabis	1 joint	21	154 (1–365)
Alcohol	1 drink	23	148.6 (3–250)
Tobacco	1 cigarette	16	3173.9 (1825–9125)
LSD	1 tablet	9	2.82 (1–24)
Amphetamine	1 tablet	20	10.91 (1–48)

Table 2 Pearson correlations of MDMA use with electrophysiological and cognitive/mood variables. Results of semi-partial correlations controlling for the use of other drugs are shown in parenthesis. *$P < 0.05$; **$P < 0.01$. All significance tests are two-tailed except for the coherence measures and the rule-shift-card-sort task where the direction of change was predicted a priori

Brain region	Delta (1–4 Hz)	Theta (4–8 Hz)	Alpha (8–12 Hz)	Beta (12–20 Hz)
Spectral power				
Left anterior (Abs)	0.194	0.162	0.483* (0.375*)	0.250
Left anterior (Rel)	0.027	−0.093	0.460* (0.474*)	0.074
Left posterior (Abs)	−0.020	0.332	0.616** (0.750**)	0.530* (0.681**)
Left posterior (Rel)	−0.188	0.056	0.629** (0.810**)	0.446* (0.631**)
Right anterior (Abs)	−0.103	0.011	0.385	0.153
Right anterior (Rel)	−0.333	−0.357	0.220	−0.139
Right posterior (Abs)	−0.041	0.193	0.491* (0.618**)	0.332
Right posterior (Rel)	−0.153	0.067	0.483* (0.598**)	0.255
Whole brain (Abs)	0.016	0.210	0.549* (0.698**)	0.370
Whole brain (Rel)	−0.455*	−0.089	0.599** (0.731**)	0.261
Coherence				
Visual	−0.353* (−0.447*)			
Fascicle	−0.203			
Trans-callosal	−0.158			
Peak frequency				
Left anterior	0.138			
Left posterior	0.024			
Right anterior	0.210			
Right posterior	−0.016			
Cognitive mood measures				
BDI	0.239			
PA	−0.087			
NA	−0.325			
RM	0.004			
RMD	0.068			
WM	0.340			
WAIS (NART)	0.004			
CARD_SORT	−0.396* (−0.413*)			

period correlates with resting brain function as measured with quantitative EEG methods. Specifically, there was a positive correlation between MDMA use and EEG power in the alpha frequency band (8–12 Hz) which was significant in all except the right-anterior quadrant of the brain. There was also a significant positive correlation between MDMA use and power in the beta frequency band (12–20 Hz) in the left-posterior quadrant only, and a significant negative correlation between MDMA use and relative low frequency (1–4 Hz delta band) power across the brain. EEG coherence, a measure of the synchronisation of firing between two locations in the cortex was also negatively correlated with MDMA use, but in a more restricted fashion. The decreased coherence with drug use was found only in sites thought to overly the fibres of the main visual tracts following an occipital-parietal-temporal route. The Visual coherence was reduced across the whole range of the examined frequency spectrum (1–20 Hz). Perhaps surprisingly, these drug/EEG correlations were not accompanied by similar correlations between drug level and measures of mood (BDI, NA, or PA) or cognitive measures. Only performance on the rule-shift-card-test test of frontal executive function was negatively correlated with MDMA use. This fact, taken together with the finding that the general measures of intelligence (WAIS-NART) and memory function (WM, RMI, RMD) were not correlated with MDMA use, suggests that MDMA use may be producing a mild but fairly specific frontal dysfunction related to changes in impulsivity and/or executive function. This would certainly be in accord with previous reports of changes in impulsivity scores and deficits on the Wisconsin Card Sort Task (McCann and Ricaurte 1991; Morgan 1998), and could be attributed to the high density of serotonin terminals in the frontal lobes (Frederick et al. 1995; Frederick and Paule 1997) which may make them particularly sensitive to MDMA's neurotoxic effects. Recent animal experimentation involving in vitro measurement of brain transmitters and their metabolites has also confirmed that changes of activity in both serotonergic and dopaminergic systems in the frontal cortex underlie deficits in attentional and response "switching" tasks (al-Ruwaitea et al. 1997; Puumala and Sivio 1998). It is important to note that our findings do not prove that MDMA use has no effect on mood or memory/cognition. Our study only looked at drug users with different histories of past use. Since we did not examine performance in non-users, it is possible that deficits may have existed in all of our subjects on some of these tasks, but were insufficiently dose-dependent to show up in our correlational

analyses. Indeed, there is published evidence of selective memory impairment in both light and heavy MDMA users (Parrott et al. 1998), and of psychiatric impairment in heavy users (Schifano et al. 1998). Further study is required in this area using control groups of non-MDMA polydrug users.

These results suggest that quantitative EEG is a potentially powerful tool for detecting neurological sequelae of drug abuse. Alpha power has been shown to be inversely related to mental activity and has been used as an indirect measure of brain activation in both normal and abnormal functional states (Lutzenberger 1997; Larson et al. 1998). With regard to normal populations, it is interesting that the pattern of MDMA-related increased desynchronisation of the EEG (increased high frequency activity (alpha and beta) and decreased low frequency (delta)) activity we find here mimics the effects of aging in normal populations. Most recent studies of aging have reported decreased slow wave activity (delta and theta) and increased fast activity (alpha and beta) (Giaquinto and Nolfe 1986; Pollock et al. 1990; Duffy et al. 1993), although some earlier studies reported increased synchronisation (EEG slowing) with age (Roubicek 1977; Otomo and Tsubaki 1996).This discrepancy may have been the result of the earlier studies having incorporated subjects with age-related disease (early dementias, for example) which were responsible for the slowing (Niedermeyer et al. 1982). With regard to clinical populations, it has recently been shown that increased alpha rhythm may be used as an early clinical marker of HIV brain pathology (Baldeweg and Gruzelier 1997). Thus, it is possible that the positive correlation between alpha power and previous MDMA use indicates reduced cortical activity caused by the neurotoxic effects of the drug.

The evidence linking reduced coherence with dysfunctional connectivity in the brain is strong, deriving from studies on dementia (Leuchter et al. 1987; Cook and Leuchter 1995), white matter disease in aging (Leuchter et al. 1994a), depression (Leuchter et al. 1994b), and cognitive impairment in HIV (Fletcher et al. 1997). However, there is an important methodological issue in neurophysiology concerning the appropriate reference to use in EEG recordings, and this is particularly relevant where coherences between electrodes are being measured. The problem is that with typical common reference recordings the moment-to-moment activity at the reference electrode (vertex, ear or nose etc.) can influence the measured coherence level (Fein et al. 1988). This arises because, if two recording channels share a common reference, then voltage variance at that reference site will appear as voltage covariance (coherence) between the recording channels. For this reason, where sparse electrode arrays are used (32 channels or less), it has been common practice to measure coherence between close bipolar pairings of electrodes – the bipolar montage. However, simulations have shown that the effect of the reference on coherence is only a factor when its activity level is high, and that mapping of coherence is most reliable when reference electrodes are used (Rappelsberger 1989). With dense-electrode arrays (such as the 128-channel system used here), the problem can also be minimised by using the averaged activity of the whole array as the reference which cancels out local fluctuations. For this reason, we used an averaged reference in both the power and coherence analyses.

The reason for the specificity of the drug effect for fibres of the posterior Visual tract is currently unknown, but similar dissociations between Fascicle and Visual and between intra- and inter-hemispheric coherence values are reported in other studies relating coherence levels to brain pathology in AIDS (Newton et al. 1997), and dementia (O'Connor et al. 1979; Leuchter et al. 1987; Locatelli et al. 1998). In the case of dementia, it has been argued that in Alzheimer's disease, where changes in the long cortico-cortical fibres of the Fascicle tract predominate, cortical fibre damage is mainly responsible, while in vascular dementias, where changes in the Visual tracts predominate, subcortical and subcortical-cortical fibres are mainly affected (Cook and Leuchter 1995). Thus, the loss of Visual coherence reported here may indicate subcortical involvement, and there is evidence from recent PET imaging studies using radioligands selective for serotonin transporters that serotonin transporters are concentrated in subcortical structures such as the midbrain, putamen, caudate nucleus, thalamus and hypothalamus (Szabo et al. 1995a,b). It is assumed that the coherence dissociations reflect regional differences in the underlying modulatory influences of serotonergic neurons thought to be damaged by MDMA use, but more work needs to be done to elucidate the mechanisms, using both animal invasive techniques and human brain imaging studies.

One weakness which applies to all retrospective studies of human MDMA use, including the present one, is that there is no control over the precise dosage and purity of the drug consumed. Thus, the effects described here and elsewhere can only be attributed to the subjects' estimates of the number of tablets consumed which were presumed to contain MDMA. As discussed elsewhere (Curran 1998; Parrot et al. 1998), this weakness is unavoidable when studying category A drugs for which the licensing of placebo-controlled, double-blind studies is problematic, although approval was recently given for a low-dose MDMA-administration study in the UK (Henry et al. 1998). However, in the present study we have avoided the major methodological flaw of most previous investigations of comparing MDMA users with drug-naive subjects. Since most MDMA users are polydrug users, this fails to control for the use of other drugs. Our strategy was to recruit polydrug users, who take MDMA and specifically control for the use of other drugs by means of partial correlation analyses.

Our findings are the first to link quantitative EEG measures with previous consumption of MDMA in human recreational users, and while they must be regarded as preliminary in terms of direct clinical application, we believe they are important in highlighting a potentially powerful and economically viable diagnostic tool which could be used in large-scale screening for drug-induced neurotoxicity.

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