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The P3 in 'ecstasy' polydrug users during response inhibition and execution

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Abstract

Substance abuse and associated externalizing disorders are characterized by behavioural disinhibition and low impulse control, with reduced neural inhibition postulated to be the common underlying brain mechanism. The P3 component of event-related potentials (ERPs) is a widely used neurophysiological measure thought to reflect inhibitory brain processes, but as yet has not been assessed in ecstasy users. We recorded ERPs evoked by a Continuous Performance Test (CPT) in 16 current ecstasy polydrug users and 17 controls. The CPT included conditions where a prepared motor response had to be executed (Go) or inhibited (NoGo). Both controls and ecstasy users showed normal, robust patterns of P3 anteriorization and delay in the NoGo compared to the Go condition. Ecstasy users had lower P3 amplitudes at midline electrodes and a less anterior location of NoGo P3 peaks. These effects became weaker after statistically controlling for age, educational level and lifetime cannabis use. While lower P3 amplitudes are consistent with higher levels of neural disinhibition in ecstasy polydrug users, the normal switch pattern between response execution and inhibition, and the less anterior location of the NoGo P3, do not indicate disturbed inhibitory brain mechanisms.

Keywords

ecstasy, MDMA, ERP, P3, response inhibition, drug abuse

Introduction

'Ecstasy' is the name of a widespread recreational drug whose main psychoactive constituent is the serotonergic agonist 3,4-methylenedioxymethamphetamine (MDMA). Over the course of the last decade, the possibility of persistent neurotoxicity and concomitant cognitive dysfunction in chronic ecstasy users has become the focus of intense epidemiological, neuropsychological, neuroendocrine and neuroimaging research. Only little attention, however, has been paid to electrophysiological measures. Dafters *et al.* (1999) examined the resting electroencephalogram (EEG) of 23 ecstasy users and found positive correlations of alpha and beta wave activity with drug exposure, but not with depression, memory and intelligence scores. Gamma *et al.* (2000) compared the EEG of ecstasy polydrug users and control subjects using scalp-based and source localization methods. A global elevation of fast beta power and a localized right temporal-occipital increase in fast alpha activity were found in ecstasy users. Gijsman *et al.* (2002) recorded resting EEG before and after a d-fenfluramine challenge in heavy and moderate ecstasy users and controls, and found stronger d-fenfluramine-induced reductions in frontal-central alpha activity in heavy users compared to moderate and non-users. Two studies investigated the intensity dependence of the auditory evoked N1/P2 dipole source amplitude (Tuchtenhagen *et al.*, 2000; Croft *et al.*, 2001). Both reported increased slopes of the amplitude/intensity gradient in ecstasy users, indicative of central serotonergic dysfunction.

An important component of the event-related potential (ERP) widely studied in other substance abusers, the P3, has been neglected so far in ecstasy research. The P3 amplitude has overarching significance in psychophysiological research on substance use, particularly alcoholism. Many studies showed reductions in the P3 response in children at risk for alcoholism (Begleiter *et al.*, 1984; Polich *et al.*, 1994; Hill *et al.*, 1999). Therefore, diminished P3 was initially assumed to be a marker for alcoholism risk. More recent studies, however, have increasingly pointed to a broader role of the P3 amplitude as a marker for behavioral and possibly neural disinhibition, which are seen as predisposing to externalizing and impulsive behaviours, including drug abuse (Begleiter and Porjesz 1999; Iacono *et al.*, 1999, 2002; for a review see Gamma

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and Liechti, 2002). Parrott (2000) applied this view to ecstasy use, speculating that a lack of neural inhibition may be the common substrate underlying various abnormalities in ecstasy users, in particular impulsivity and reduced response inhibition leading to faster responses and/or greater error rates (Parrott 2000).

The goal of the present study was to examine response inhibition and its underlying neuroelectric substrate in regular ecstasy users by studying the P3 in a Go/NoGo paradigm. We employed a cued version of the Continuous Performance Test (CPT A-X) that includes conditions in which a prepared motor response must be inhibited ('NoGo' condition) or executed ('Go' condition). Previous research has shown that both these conditions elicit a P3 (Simson *et al.*, 1977; Fallgatter *et al.*, 1997; Strik *et al.*, 1998). A very robust effect is that the NoGo P3 is located anterior to the Go P3, peaks about 30 ms later (Roberts *et al.*, 1994; Fallgatter *et al.*, 1997) and yields frontal source localizations in the anterior cingulate (Strik *et al.*, 1998; Fallgatter *et al.*, 2002). Therefore, scalp anteriorization, frontal brain sources and delay of the P3 are associated with normal response inhibition. The matched probabilities of Go and NoGo trials in this CPT version further ensure that inhibitory control is measured without confounds due to increased novelty or rareness.

Clinical work indicates that the NoGo anteriorization is reduced in patients with chronic schizophrenia (Fallgatter and Muller 2001) and with obsessive-compulsive disorder (Herrmann *et al.*, 2003), and that the NoGo P3 is attenuated in children with Attention Deficit Hyperactivity Disorder (ADHD) (Brandeis *et al.*, 2002), particularly in those with comorbid conduct disorder (Banaschewski *et al.*, 2004). In addition, more anterior Go P3 locations in healthy subjects correlate with higher impulsivity, and more anterior NoGo P3 locations with a polymorphism leading to lower serotonin transporter (SERT) expression (Fallgatter *et al.*, 1999; Fallgatter and Herrmann 2001). These P3 changes are often not paralleled by performance changes, which emphasizes the increased sensitivity of functional brain mapping. Since higher levels of impulsivity (Morgan 1998; Parrott *et al.*, 2000; Tuchtenhagen *et al.*, 2000; Daumann *et al.*, 2001; Morgan *et al.*, 2002; Butler and Montgomery, 2004) and lower levels of SERT (Semple *et al.*, 1999; Reneman *et al.*, 2001; Buchert *et al.*, 2003; Thomasius *et al.*, 2003) have been found in ecstasy users, one might expect a more anterior location of either the Go- or the NoGo-related P3 or both in the current sample of ecstasy users. Given the ubiquity of reduced P3 amplitudes in drug users, we also hypothesized lower P3 amplitudes in ecstasy polydrug users than in controls. On the behavioural level, a more impulsive response style with reduced response inhibition was expected to manifest as increased reaction times and/or error rates in the CPT.

To the extent that P3 measures of response control indeed reflect neural inhibition, which seems plausible (Halgren *et al.*, 1986; Woodward *et al.*, 1991; Rockstroh *et al.*,1992; Roberts *et al.*, 1994) but difficult to test, our data will be relevant to Parrott's hypothesis of neural disinhibition in ecstasy users. In any event, however, our results will directly speak to the issue of possible abnormalities in behavioral inhibition or response control and its underlying brain electric implementation, whatever the exact involvement of neural inhibition.

Material and methods

Subjects

Current ecstasy users were recruited at local rave parties and among university students through postings and word of mouth. To be considered for the study, applicants had to have taken at least 40 tablets of ecstasy. Exclusion criteria as assessed by medical examination and a semi-structured psychiatric interview were: current DSM axis I diagnosis, current or past professional treatment for a psychiatric disorder, current or past major medical problems, abnormal medical status, electrocardiogram (ECG) or blood chemistry, current or past alcohol abuse or dependence. Control subjects were recruited among university students. The same exclusion criteria applied, with the additional requirement of no past or current use of ecstasy. Seventeen control and 16 ecstasy subjects were thus selected for the study. Compared to ecstasy users, controls were slightly older and more highly educated, and had a less extensive use of illicit drugs other than ecstasy. Subject information and drug use are shown in Table 1. All subjects gave written informed consent. The study was approved by the local Ethics Committee.

Experimental protocol

All subjects agreed to abstain from psychoactive drugs, except nicotine and alcohol, for at least one week before testing. No confirmatory urine screening was conducted. ERPs and spontaneous EEG were recorded while subjects were lying in a Positron Emission Tomography (PET) scanner in a dimly lit room. The EEG and PET findings are reported elsewhere (Gamma *et al.*, 2000; Gamma *et al.*, 2001). ERPs were evoked by a cued Continuous Performance Test (CPT A-X) displayed on a computer screen mounted above the scanner bed at a viewing distance of approximately 50 cm. The CPT was performed twice, with ERPs being recorded each time. Experiments were carried out in accordance with the ethical standards laid down in the Declaration of Helsinki.

Continuous performance test

The stimulus set consisted of the 11 capital letters A, B, C, D, E, F, G, H, J, L, X, which appeared in a seemingly random sequence on the screen. These letters were presented between two vertical bars of 10 mm length that were permanently visible in order to facilitate central fixation. The stimulus duration and interstimulus interval were 150 and 1500 ms, respectively. The task was to press a mouse button with the right index finger every time the target sequence A–X appeared. The letter A therefore served as a cue inducing the preparation of a motor response. If followed by the target letter X, this response had to be executed ('Go' condition), if followed by another letter, the response had to be inhibited ('NoGo' condition). The total stimulus set comprised 400 letters: 80 cues A, 40 times followed by the target letter X (Go condition) and 40 times followed by another letter except A or X (NoGo condition). Two hundred letters were meaningless distractors, the remaining 40 letters were X without a preceding A. The 11 min

Table 1 General subject information and drug use

	Ecstasy polydrug users	Controls	*P*
No. of females/males	8/8	7/10	0.7
Age	22.6 (19–27)	26.0 (22–30)	0.001
Education level[a]	2.6 (1–4)	3.8 (3–4)	0.001
Lifetime drug use			
Ecstasy (no. of tablets)	270.2 (43–1500)	0	–
Cannabis (no. of 'joints')	332.1 (0–1000)	84.9 (0–500)	0.02
Amphetamine [mg]	309.4 (0–3000)	0	–
Cocaine [mg]	614.7 (0–2250)	160.9 (0–2500)	0.07
LSD (no. of 'occasions')	5.4 (0–20)	0.1 (0–1)	0.01
'Mushrooms' (no. of occasions)	3.1 (0–20)	0.8 (0–8)	0.1

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

test was run twice, which resulted in 80 NoGo and 80 Go trials over 22 min. The data of the two CPT sessions was averaged for subsequent analysis. A short training session preceded the experimental task. All subjects were instructed to favour accuracy over speed, since fast motor responses could interfere with the ERP signal.

ERP recording and processing

ERPs were recorded from 31 channels using a Nihon-Kohden Neurofile system with 1–50 Hz bandbass filtering and a sampling rate of 256 Hz. The electrodes were applied in an extended 10/20 array including FP1/2, FPZ, F3/4, F7/8, FZ, FT9/10, FC5/6, TP9/10, C3/4, CZ, CP5/6, P3/4, PZ, PO9/10, O1/2, OZ. F3 and F4 served as common recording reference. An additional electrode was placed below the left eye to register eye movements.

The continuous EEG was digitally low-pass filtered at 30 Hz (−24 dB/octave), after interpolating bad channels (less than 0.5%) from their nearest neighbours and transformed to the average reference. A topographic blink correction retaining frontal EEG activity (Berg and Scherg, 1994), and technical zero baselines (rather than pre-stimulus baselines) were used to avoid topographic distortion. Segments containing amplitudes exceeding 80 micV were then rejected. The artifact free event-related 2s epochs (−0.125 to 1.875s) were averaged separately for the Go and the NoGo conditions. For users, these averages contained a mean of 73.6 Go trials (range 44–80) and 72.9 NoGo-trials (range 43–80). For controls, 73.3 (range 40–80) Go trials and 72.8 (range 40–80) NoGo trials were averaged. Global Field Power (GFP) was computed to measure map strength (Lehmann and Skrandies, 1980). The few trials with performance errors (on average, 0.6 out of 400 in controls, 1.3 out of 400 in users) were not excluded to allow comparisons with the PET results.

ERP responses to the letter following the cue letter A were used for analysis. The size of the P3 response was computed as the mean amplitude between 250 and 450 ms after stimulus onset. In order to obtain a measure of P3 latency, individual P3 amplitude peaks were identified by computer algorithm as the maximal positive deflection of the GFP curve between 250 and 450 ms post-stimulus. For topographic analysis, the centroids of the Go and the NoGo P3 positivity were computed (Fallgatter *et al.*, 1997; van Leeuwen *et al.*, 1998).

Statistical analysis

Unpaired t-tests and chi-square tests were used to compare demographic and drug use data. A one-way repeated measures MANOVA was used to assess main and interaction effects of group and task condition on P3 amplitudes. In order to control experimental type I error rate, we restricted further analysis to planned univariate comparisons of (1) the midline electrodes Fz-Cz-Pz, where the P3 in both Go and NoGo conditions has previously been found to be maximal, and of (2) the four quadrants of the scalp potential field, for each of which the averaged P3 amplitude was computed. The anterior left quadrant comprised electrodes Fp1, F3, F7, FC5 and FT9, and the anterior right quadrant the corresponding electrodes on the right side. The posterior left quadrant included electrodes P3, O1, T5, CP5, TP9, PO9, and the posterior right quadrant the corresponding right-sided electrodes. Separate univariate ANOVAs were conducted for P3 latencies and centroid locations. To control for the potential confounding effects of age, educational level and lifetime cannabis use (which all significantly differed between the two groups), all analyses of variance were repeated using these variables as covariates. CPT performance was compared across groups using unpaired t-tests. Pearson correlations between ERP characteristics or CPT performance and self-reported cumulative lifetime use of ecstasy and cannabis, which is a major confounder in ecstasy studies, were computed. All analyses were done in STATISTICA 6.0 (StatSoft, Inc. (2004), www.statsoft.com).

Results

P3 amplitude and centroids: Go vs. NoGo condition

There was a highly significant main effect of condition. Planned contrasts showed more positive NoGo than Go amplitudes at Fz

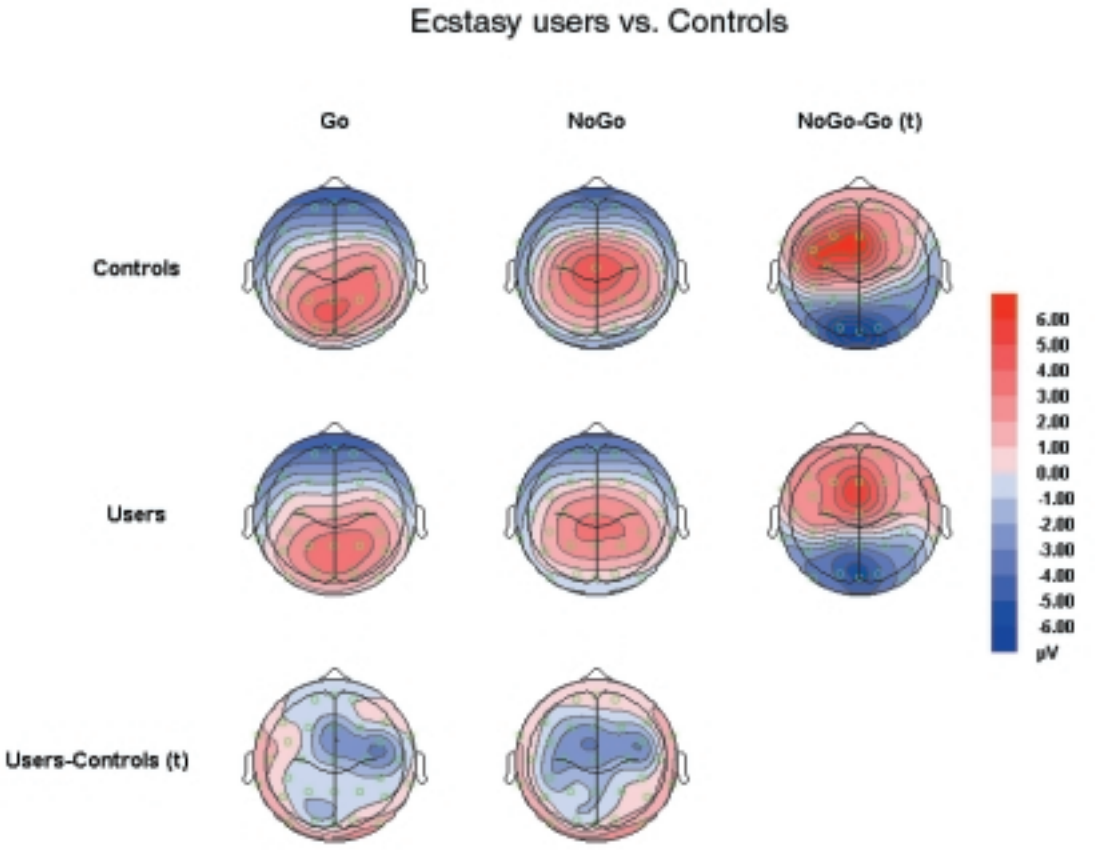

Figure 1 Topographic maps of mean P3 amplitude in ecstasy polydrug users and controls during response execution ('Go') and inhibition ('NoGo'). Difference maps (right-most column and bottom row) show values of the t-statistic ($p < 0.05$ for $t > 2.13$). Open green circles indicate electrode positions. Note the similar anteriorization of the P3 peak during response inhibition in both groups

and Cz in both groups, and less positive positive NoGo amplitudes at Pz, the latter being significant only in users. Averaged amplitudes in all four quadrants of the scalp potential field also differed significantly between conditions: in both groups, amplitudes became more positive in the anterior, and less positive in the posterior half-field during response inhibition in the NoGo condition. As expected, the P3 positivity in the NoGo condition in controls was anteriorized relative to the Go condition. This effect was present in the group mean data and in 15 out of 17 control subjects individually. The maximal amplitude was at Pz for the Go, and at Cz for the NoGo condition. The same NoGo-related changes were found in ecstasy polydrug users. An anterior shift of the P3 scalp maximum was present in the group mean data and in 12 out of 16 users. The centroid analysis indicated a NoGo anteriorization in every single subject and in the group data. Including age, educational level and cannabis use as covariates did not change the results, which are shown in Fig. 1 (first and second row) and Table 2.

P3 amplitude and centroids: controls vs. ecstasy polydrug users

The main effect of group for P3 amplitude was not significant. Planned comparisons showed, however, significantly less P3 positivity at Fz in ecstasy polydrug users in the Go condition. In the NoGo condition, ecstasy polydrug users showed significantly less P3 positivity at Fz and Cz. The results for Fz just missed statistical significance ($p = 0.08$) when controlling for age, education and cannabis use. Quadrant analysis revealed only one significant difference: ecstasy polydrug users showed more NoGo P3 positivity in the posterior-right quadrant of the scalp potential field (comprising electrodes P4, O2, T6, CP6, TP10, PO10). This result became non-significant when controlling for confounders. The centroid analysis showed significant main effects of group and condition. NoGo centroids were significantly less anterior in ecstasy users than in controls. This result became non-significant ($p = 0.07$) when controlling for confounders. We also computed 'NoGo anteriorization' as the difference between the anterior–posterior locations of the P3 centroids in the Go vs. NoGo

Table 2 P3 characteristics in ecstasy polydrug users

	Means (SD)				Statistics			
	Go		NoGo					
	Ecstasy users (E)	Controls (C)	Ecstasy users (E)	Controls (C)				
P3 amplitude					*MANOVA effects*			
					Group	Condition		Interaction
					R(7,25) = 1.9	R(7,25) = 17.0**		R(7,25) = 1.2
					P*lanned contrasts*			
					Go	NoGo	E	C
Fz	−1.06 (0.79)	−0.34 (0.86)	0.55 (1.26)	1.48 (1.26)	E < C*[b]	E < C*	Go < NoGo***	Go<NoGo***
Cz	1.70 (1.02)	2.39 (1.54)	3.02 (1.37)	4.77 (2.61)	–	E < C*	Go < NoGo***	Go < NoGo***
Pz	3.83 (1.23)	4.09 (1.74)	2.71 (1.26)	3.31 (1.88)	–	–	Go > NoGo**	–
Anterior left	−1.99 (0.70)	−2.06 (0.86)	−1.22 (0.95)	−1.11 (0.86)	–	–	Go < NoGo***	Go < NoGo**
Anterior right	−1.71 (0.86)	−1.53 (1.23)	−1.10 (0.72)	–1.09 (1.06)	–	–	Go < NoGo**	Go < NoGo*
Posterior left	1.42 (0.83)	1.21 (0.69)	0.53 (0.74)	0.33 (0.54)	–	–	Go > NoGo**	Go > NoGo***
Posterior right	1.42 (0.70)	1.16 (0.80)	0.73 (0.86)	0.16 (0.63)	–	E > C*[b]	Go > NoGo***	Go > NoGo***
P3 latency					ANOVA effects			
					Group	Condition		Interaction
					F(1,31) = 0.39	F(1,31) = 12.01**		F(1,31) = 0.55
					Planned contrasts			
					Go	NoGo	E	C
	323.24 (43.58)	335.02 (35.74)	353.76 (33.42)	354.78 (30.67)	–	–	Go < NoGo*	Go < NoGo*
P3 centroids (coordinates)					MANOVA effects			
					Group	Condition		Interaction
					F(2,30) = 3.34*	F(2,30) = 59.68***		F(2,30) = 0.44
					Planned contrasts			
					Go	NoGo	E	C
X (left–right)[a]	6.06 (0.42)	6.31 (0.75)	5.96 (0.95)	6.00 (0.50)	–	–	–	–
Y (anterior–posterior)[a]	7.89 (0.52)	7.59 (0.27) –	6.97 (0.52)	6.58 (0.50)		E more posterior than C*[b]	Go more posterior than NoGo***	Go more posterior than NoGo***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

[a]x-coordinate is defined in units of left-right electrode position, ranging from 1 (leftmost) to 11 (rightmost); y-coordinate is defined in an analogous manner, ranging from 1 (most anterior) to 11 (most posterior).

[b]No longer significant when controlling for age, educational level and cumulative lifetime cannabis use.

condition. ANOVA with and without covariates showed no difference in NoGo anteriorization between users and controls. The lack of both a significant group × condition interaction and of a significant group difference in NoGo anteriorization confirmed that ecstasy users did not differ electrophysiologically from controls with regard to how their brains switched between executive and inhibitory response control. Results are shown in Fig. 1 (first and second column) and Table 2.

Latencies

There was no group difference or interaction for P3 latency. In both groups, the P3 peak was delayed by 20–30 ms when the response had to be inhibited as opposed to executed (Table 2).

CPT performance

Performance did not differ between the groups. The percentage of total errors (missed targets and false alarms) was 0.34% (SD 0.40%) in ecstasy users and 0.15% (SD 0.25%) in controls ($p = 0.12$). Reaction time for targets was 689 ms (SD 153.1 ms) for ecstasy users and 631 ms (SD 141.7 ms) for controls ($p = 0.28$). Ecstasy users achieved 97.2% (SD 3.8%) correct responses to targets as compared to 99.0% (SD 2.3%) in controls ($p = 0.11$). Ecstasy users incorrectly responded to non-targets as follows: 0.03% (SD 0.09%) to non-A/X followed by non-A/X, 0.16% (SD 0.43%) to A followed by non-A/X, 0.08% (SD 0.21%) to A alone (before the next letter appeared), and 0.8% (SD 0.31%) to non-A followed by X. The corresponding percentages for controls were: 0.06% (SD 0.19%), 0.08% (SD 0.31%), 0.0% (SD 0.0%) and 0.08% (SD 0.31%). Group comparison for these errors were non-significant (all $p > 0.15$).

Correlations with drug use

Self-reported cumulative lifetime use of MDMA or cannabis did not significantly correlate with any of the ERP characteristics or any CPT performance measure.

Discussion

This study compared ecstasy polydrug users with non-drug using controls and found (1) similar neuroelectric mechanisms (e.g., P3 delay and anteriorization) of response inhibition compared to response execution in the two groups, (2) in ecstasy polydrug users, lower P3 amplitudes at central midline electrodes regardless of task, higher NoGo amplitudes over right posterior cortex, and less anterior NoGo centroids. These results became weaker when statistically controlling for age, level of education and lifetime cumulative cannabis use. No significant differences in P3 latency and CPT performance, and no significant correlations of ERP and CPT variables with lifetime ecstasy and cannabis use emerged.

The previously observed robust anteriorization and delay of the P3 during response inhibition in healthy subjects was replicated in this study. There was an anterior shift of the P3 peak in the NoGo condition in control subjects, which was observed both in the group mean and individual data using both amplitude and centroid analyses. The latency of the NoGo peak was increased by 20 ms in controls. The same pattern of NoGo-related changes was observed in ecstasy polydrug users: anteriorization and delay of the inhibitory P3 response. The lack of a significant interaction between group and task condition further supports the idea that the same brain electric substrate underlies the switching between inhibitory and executive response mechanisms in both groups.

However, NoGo centroids and several local amplitude measures of the P3 response differed between the groups. Both the inhibitory and executive P3 midline responses were reduced in ecstasy polydrug users, while the inhibitory P3 was increased selectively over the right posterior brain. The latter finding is consistent with a selective increase in fast alpha EEG activity in the same location previously reported in this group (Gamma *et al.*, 2000). A reduced size of the inhibitory midline P3 in ecstasy users is consistent with the conception of P3 as a marker for deficient inhibitory brain mechanisms underlying disinhibited pathologies such as antisocial personality, sensation-seeking and drug-taking behaviours (Begleiter and Porjesz, 1999; Iacono *et al.*, 1999). Applying this conception to ecstasy, Parrott (2000) suggested that a lack of cortical inhibition could be the common brain mechanism underlying the pattern of neurocognitive and behavioural disturbances found in ecstasy users. According to Parrott, this pattern is characterized by decreased memory performance, increased impulsivity and impairments in strategic and planning abilities. Taken as a whole, however, our results are ambiguous with regard to the disinhibition hypothesis. While reduced inhibition-related midline P3 responses are consistent with the possibility of reduced cortical inhibition, the fact that the neuroelectric pattern associated with the switch between inhibitory and executive responses in users were normal does not support a lack of cortical inhibition. Moreover, the less anterior NoGo P3 centroids in ecstasy users reflect a pattern found in less, not more, impulsive subjects (Fallgatter and Herrmann, 2001).

Error rates in the CPT were low in both groups, and not significantly different between the groups. Since we instructed subjects to favour accuracy over speed in order to prevent motor artifacts in the ERP signals, the reported reaction times cannot be taken at face value. Even so, it can be expected that more impulsive subjects would still on average respond earlier. However, there was no significant difference in reaction times, and therefore no indication of a more impulsive response style in ecstasy users. It should be noted that we did not independently assess impulsivity using psychometric measures. Impulsivity is a heterogeneous construct, and different, possibly independent, aspects of it can be evaluated (Evenden, 1999). The majority of studies (Morgan 1998; Parrott *et al.*, 2000; Tuchtenhagen *et al.*, 2000; Daumann *et al.*, 2001; Morgan *et al.*, 2002; Butler and Montgomery, 2004) found heightened levels of various forms of psychometric and behavioural impulsivity in ecstasy users. It may be that the present ecstasy polydrug users were more impulsive than non-users in one or more of these aspects, without this showing in the response behaviour in the CPT. If so, then maybe lowered midline P3 amplitudes may underlie this/these aspect(s) of impulsivity, while

the normal anteriorization and latency of the P3 could reflect the lack of behavioral disinhibition/impulsivity in the CPT.

A different possible explanation for diminished P3 responses in ecstasy polydrug users are MDMA-induced neurotoxic alterations in brain serotonergic systems. Animal studies have repeatedly documented a depletion of central serotonin content and loss of presynaptic serotonin transporters following high or repeated doses of MDMA (Ricaurte *et al.*, 2000; Green *et al.*, 2003). Recent human brain imaging studies using radioligands for the SERT have been consistent with animal experiments in showing lower SERT densities in the brains of current ecstasy users (Semple *et al.*, 1999; Reneman *et al.*, 2001; Buchert *et al.*, 2003; Thomasius *et al.*, 2003). Since the methodology used in these studies has been questioned (Kish 2002), the correct interpretation of these findings is not completely clear, but the results are at least consistent with the possibility of MDMA-related neurotoxic changes also in humans.

However, our more posterior NoGo P3 centroids in ecstasy users contrast with findings showing that a genetic polymorphism causing less SERT expression is associated with a more anterior, not posterior, NoGo P3 centroid in the CPT (Fallgatter *et al.*, 1999). It is also worth noting that a causal relationship between these serotonergic abnormalities and physiological, cognitive or mood impairment has not been established (for example, serotonergic abnormalities do not seem to parallel memory deficits (Semple *et al.*, 1999; Reneman *et al.*, 2001; Thomasius *et al.*, 2003)). Likewise in the present study, no correlation of ERP and CPT measures with lifetime ecstasy use emerged, which could point to a causal relationship.

Moreover, the fact that the finding of low P3 amplitude is almost ubiquitous among users of a variety of substances such as alcohol, cocaine, opiates, nicotine, cannabis and amphetamines (see Gamma and Liechti, 2002) suggests that its neural basis is an unspecific mechanism common to various drugs, not particular to MDMA/ecstasy. This would make serotonergic neurotoxicity an unlikley candiate. More promising candidates may be found in common non-toxic effects of these drugs on brain reward systems, or in pre-existing, possibly heritable, neural and personality characteristics predisposing to disinhibited behaviours such as substance use.

Furthermore, we have to consider important limitations of our study which allow further alternative explanations.

First, the two groups were not well matched on a number of variables (age, education, cannabis use), so that we cannot rule these out as possible causes of the group differences. Indeed, when controlling for these variables, the group differences became weaker and in most cases were pushed into statistical non-significance, indicating a confounding effect. While the small differences in age and education may play a certain role, an increasing number of recent studies have pinpointed cannabis as a major confounder in studies of ecstasy use. Concomitant cannabis use may be partly or fully responsible for findings of cognitive impairment in ecstasy users (Croft *et al.*, 2001; Daumann *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2002; Simon and Mattick 2002; Dafters *et al.*, 2003; Daumann *et al.*, 2004). The ecstasy polydrug users in our study had a considerably higher lifetime use of cannabis than the control subjects, and regular cannabis smoking has been linked to reduced P3 responses (Solowij *et al.*, 1991, 1995). Thus, concomitant cannabis use may have contributed to lower P3 amplitudes in ecstasy polydrug users. This conclusion is also supported by an additional analysis including only cannabis as a covariate and showing the same confounding effect as when including all covariates (data not shown). It should be noted, however, that cannabis was not a significant covariate and that there was no correlation of ERP measures with lifetime cannabis use.

Our groups were also not matched for lifestyle. The typical pattern of ecstasy use, involving prolonged phyiscal exercise in crowded and audiovisually over-stimulated environments, lack of sleep and appetite over several days, can lead to sub-acute stress-induced impairments of mood and vigilance, to which ERP recordings are sensitive. One ecstasy study so far has controlled for lifestyle, but found no effect on memory performance and hormone levels (Verkes *et al.*, 2001). However, it is not clear whether this finding extends to electrophysiological measures. Moreover, given that we required subjects to abstain from illicit drugs for at least one week before the experiments, sub-acute effects of ecstasy appear less likely. However, we did not verify abstention time using urine testing. A further and related limitation is that we did not document time since last use of ecstasy, and are thus unable to relate abstention time to ERP and CPT measures and to address the question of reversibility of ERP differences.

Second, there are limitations which are basically unavoidable for research in this field. Our study is retrospective, comparing groups of different subjects at a given point in time. Such designs can in principle not rule out the possibility of pre-existing group differences. In the context of ecstasy research, this possibilty has often taken the form of the suggestion that ecstasy users may be predisposed to use MDMA to self-medicate a premorbid condition. Such a condition may be related to disinhibition, as discussed above, or may be of a different nature. It should also be noted that such a condition could remain subclinical and would therefore not be removed by excluding subjects with psychiatric disorders on the diagnostic level. In support of the general idea of pre-existing group differences, the first prospective community survey addressing ecstasy-related issues recently concluded that 'onset of mental disorder is more likely to precede rather than to follow use of ecstasy and related substances' (Lieb *et al.*, 2002). Therefore, even though the present study does not uniformly support the idea of neurofunctional disinhibition in ecstasy users, the general possibility of pre-existing abnormalites remains valid. Finally, further factors that constrain inferences to the possible role of MDMA are the impurity of ecstasy tablets and the unreliability of retrospective self-reports.

In conclusion, this study examined the inhibitory and executive P3 in a naturalistic sample of ecstasy polydrug users. A lower midline P3 amplitude was found in ecstasy polydrug users during response inhibition and execution, which may be explained by (1) a non-specific effect common to a variety of drugs, (2) concomitant polydrug, particularly cannabis use; this possibility could be a variant of possibility (1), (3) pre-existing neural, personality or psychopathological differences, possibly in the form of reduced

neural inhibition leading to low impulse control and disinhibited behaviours, (4) MDMA-induced neurotoxic impairment of brain serotonergic function and (5) differences in age, education or lifestyle. These explanations are not mutually exclusive. Whatever the correct explanation, the present group difference had limited consequences insofar as both the temporal and spatial neuroelectric pattern of the switch from response execution to inhibition in ecstasy polydrug users was normal, as was task performance in the Go/NoGo paradigm.

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