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Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA

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Abstract

Serotonin (5-HT) release is the primary pharmacological mechanism of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') action in the primate brain. Dopamine release and direct stimulation of dopamine D2 and serotonin 5-HT_{2A} receptors also contributes to the overall action of MDMA. The role of 5-HT_{1A} receptors in the human psychopharmacology of MDMA, however, has not yet been elucidated. In order to reveal the consequences of manipulation at the 5-HT_{1A} receptor system on cognitive and subjective effects of MDMA, a receptor blocking study using the mixed beta-adrenoreceptor blocker/5-HT_{1A} antagonist pindolol was performed. Using a double-blind, placebo-controlled within-subject design, 15 healthy male subjects were examined under placebo (PL), 20 mg pindolol (PIN), MDMA (1.6 mg/kg b.wt.), MDMA following pre-treatment with pindolol (PIN-MDMA). Tasks from the Cambridge Neuropsychological Test Automated Battery were used for the assessment of cognitive performance. Psychometric questionnaires were applied to measure effects of treatment on core dimensions of Altered States of Consciousness, mood and state anxiety. Compared with PL, MDMA significantly impaired sustained attention and visual-spatial memory, but did not affect executive functions. Pre-treatment with PIN did not significantly alter MDMA-induced impairment of cognitive performance and only exerted a minor modulating effect on two psychometric scales affected by MDMA treatment ('positive derealization' and 'dreaminess'). Our findings suggest that MDMA differentially affects higher cognitive functions, but does not support the hypothesis from animal studies, that some of the MDMA effects are causally mediated through action at the 5-HT_{1A} receptor system.

Key words

3,4-methylenedioxymethamphetamine; 5-HT_{1A}; cognition; ecstasy; human study; MDMA; pindolol

Introduction

The neurochemical mechanisms of action of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') are well studied *in vitro* and in experimental animals (for comprehensive reviews, see Baumann, *et al.*, 2007; Colado, *et al.*, 2004; Green, *et al.*, 1996, 2003; Morton, 2005).

MDMA causes an increase of extracellular levels of brain serotonin (5-HT) (Nichols, *et al.*, 1982) and – to a lesser extent – of dopamine (DA) (Kankaanpää, *et al.*, 1998; Koch and Galloway, 1997; Yamamoto and Spanos, 1988) and norepinephrine (NE) (Fitzgerald and Reid, 1990) by promoting non-exocytotic release of these neurotransmitters from storage vesicles (Rothman and Baumann, 2002). The increase of extracellular 5-HT, DA and NE levels in the brain can be seen as the 'primary neurochemical effects' of MDMA (Muller, *et al.*, 2007). Because the increase of extracellular 5-HT concentration as well as the subjective and cardiovascular effects of MDMA can be blocked by pretreatment with Selective Serotonin Reuptake Inhibitors (Liechti, *et al.*, 2000a; Liechti, *et al.*, 2001), it is generally believed that this elevation of 5-HT involves serotonin-transporter (SERT)-mediated release (Gudelsky and Nash, 1996; Hekmatpanah and Peroutka, 1990; Rudnick and Wall, 1992), although inhibition of 5-HT reuptake is considered to be a contributory factor (Iravani, *et al.*, 2000). Furthermore, MDMA reversibly inhibits the enzyme complex monoaminooxidase A (MAO A) and hence,

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slows down the metabolic degradation of 5-HT. Moreover, MDMA also inhibits tryptophan hydroxylase and decelerates the formation of 5-HT in serotonergic nerve cells (Schmidt and Taylor, 1987). Moreover, animal studies indicate a role for 5-HT$_{2A}$ receptors in the profile of action of MDMA (Nash, *et al*., 1988; Schmidt, *et al*., 1990). Moreover, our finding that some of the effects of MDMA (e.g. perceptual changes and emotional excitation) are blocked by pre-treatment with ketanserin (Liechti, *et al*., 2000b) suggests some involvement of 5-HT$_2$ receptors. The role of the 5-HT$_{1A}$ receptor subsystem in the pharmacodynamic mechanism of action of MDMA and congeners, however, is far less understood.

In vitro single-unit recording studies have demonstrated that MDMA dose-dependently increases extracellular 5-HT concentrations in the region of somatodendritic 5-HT$_{1A}$ autoreceptors leading to an inhibition of firing of 5-HT neurons in the dorsal raphe nucleus (DRN) (Sprouse, *et al*., 1989). In rats, early evidence suggested an inhibitory effect of 5-HT$_{1A}$ receptor antagonist pre-treatment with pindolol on MDMA-induced hyperlocomotion (Callaway, *et al*., 1992). Moreover in rats, the inhibitory effect of MDMA on 5-HT neuron firing can be reversed by the selective 5-HT$_{1A}$ receptor antagonist WAY 100635 (Gartside, *et al*., 1997). Pre-treatment of rats with WAY 100635 also prevents some – but not all – MDMA-induced behavioural effects, such as increased social interaction (Morley, *et al*., 2005). This finding indicates that the prosocial effects of MDMA may involve 5-HT$_{1A}$ receptors. Thompson, *et al*. (2007) bring forward the argument that oxytocin release – stimulated by MDMA through activation of postsynaptic 5-HT$_{1A}$ receptors in the hypothalamus – may play a key role in the prosocial effects of MDMA. Finally, Millan and Colpaert (1991) found that the 5-HT$_{1A}$ receptor antagonists BMY 7378 and NAN-190 both dose-dependently abolished spontaneous tail-flicks in rats selectively evoked by pre-treatment with MDMA. As *in vivo* receptor-binding experiments also revealed a moderate affinity of MDMA itself to 5-HT$_{1A}$ receptors ($K_i \sim 23\ \mu M$), it is conceivable that MDMA also directly stimulates the 5-HT$_{1A}$ receptor subtype leading to a modulation of serotonergic neurotransmission. Primary aim of this study was to better characterize the acute effects of MDMA on cognition, core dimensions of Altered States of Consciousness, mood and state anxiety. Moreover, we wanted to specifically assess the contribution of the 5-HT$_{1A}$ receptor system in the complex pharmacological mode of action of MDMA in the healthy human brain. We, therefore, investigated the effects of antecedent blockade of 5-HT$_{1A}$ receptors with the mixed ß-adrenergic/5-HT$_{1A}$ receptor antagonist pindolol on MDMA-induced acute alterations in perception, mood and cognition. Based on the aforementioned investigations *in vitro* and in experimental animals, we hypothesized that pre-treatment with pindolol might lead to an attenuation/modulation of MDMA-induced effects also in human subjects, especially in affective and cognitive domains with an important involvement of 5-HT$_{1A}$ receptors, such as mood, state anxiety and working memory.

Subjects, materials and methods

Subjects

Fifteen male volunteers (24.3 ± 4.5 years, range 20–36 years) were recruited from University Hospital staff or were students at the Medical School of the University of Zurich. All subjects provided written consent after being thoroughly informed about aims and design of the study, effects and possible adverse effects of MDMA and pindolol. In particular, our volunteers were informed about the results of previous pharmacological studies addressing the assumed neurotoxic potential of MDMA, and case studies reporting occasional psychiatric sequelae following MDMA use [ethical aspects of administration of MDMA to healthy subjects are discussed in Vollenweider, *et al*. (1999a) and Lieberman and Aghajanian (1999)]. All study participants were healthy according to medical history, physical examination, electrocardiogram and blood analysis, and were screened by a structured psychiatric interview based on the DIA-X computerized diagnostic expert system (Wittchen and Pfister, 1997). Exclusion criteria were personal or family histories of psychiatric disorders. The screening procedure was supplemented by standard psychometric instruments [Freiburg Personality Inventory (FPI) (Fahrenberg, *et al*., 1984), State-Trait Anxiety Inventory (STAI) – Trait form STAI-X2 (Spielberger, *et al*., 1970) and Hopkins Symptom Checklist SCL-90 (Derogatis, *et al*., 1976)].

Because the personality trait factors 'rigidity' and 'emotional ability' were identified to be predictors of negative experiences during altered states of consciousness (Dittrich, 1994), scores exceeding two SD from the mean value of normative data in the respective subscales of the FPI (i.e. 'openness' and 'neuroticism') were used as exclusion criteria. Apart from sporadic use of cannabis, one subject reported a single previous experience with MDMA, five others had a single experience with hallucinogenic drugs (LSD or psilocybin), two subjects had previously used both MDMA and a hallucinogen, and seven subjects were drug-naive.

MDMA and pindolol capsules

Pharmaceutically pure racemic MDMA HCl [(±) 3,4-methylenedioxymethamphetamine hydrochloride)] was obtained from the Swiss Federal Office of Public Health, Bern, and prepared as gelatin capsules (10 and 50 mg) at the Pharmacy of the Hospital of Canton Lucerne, Switzerland. MDMA was administered in a dosage of 1.6 mg/kg b.wt. (absolute doses 122 ± 14 mg). This regimen, representing a typical recreational dose of ecstasy (Greer and Tolbert, 1986; Schuster and Wittchen, 1996), was found to robustly induce distinct subjective effects in earlier studies (Vollenweider, *et al*., 1998a, 1999b).

When administered to human subjects in doses of 20 mg, the mixed 5-HT$_{1A}$ receptor antagonist/beta-adrenoreceptor blocker pindolol exhibits no *in vivo* selectivity for the DRN 5-HT$_{1A}$ autoreceptors over postsynaptic 5-HT$_{1A}$ binding sites.

(Rabiner, *et al*., 2000). Due to its beta-receptor blocking properties, pindolol is clinically used as an antihypertensive drug in doses of 10–45 mg (Sanghavi, *et al*., 1995). To ensure an adequate occupation of cerebral 5-HT$_{1A}$ receptors, a fixed dose of 20 mg pindolol (for blinding purposes prepared as gelatine capsules from Visken® 5 mg tablets) was administered in the blocking experiments.

Study design

The study protocol was approved by the Ethics Committee of the University Hospital of Zürich. Administration of MDMA to healthy subjects was authorized by the Swiss Federal Office of Public Health, Bern, Switzerland. In order to investigate the role of 5-HT$_{1A}$ receptors in the pharmacodynamic mode of action of MDMA, we have chosen a repeated-measures within subject design with a counter-balanced succession of experimental conditions to avoid time order effects. With a temporal spacing of at least 2 weeks, every subject underwent each of the following four treatment conditions: placebo-placebo (PLA), pindolol-placebo (PIN), placebo-MDMA (MDMA) and pindolol-MDMA (PIN-MDMA). Capsules containing either placebo or 20 mg pindolol (medication 1) were administered to the subjects at the beginning of each study day (usually at 9 a.m.). One hour later, MDMA capsules (1.6 mg/kg body weight) or placebo were given (medication 2). Both volunteers and investigators were blind with respect to the experimental condition. As shown in Figure 1, psychometric ratings [Adjective Mood Rating Scale (AMRS) and STAI] were assessed 5, 135 and 170 min as well as 24 h after the first medication. Neuropsychological testing was accomplished 180 min after administration of the pre-treatment medication, and the '5D-ASC questionnaire' (5 Dimensions of Altered States of Consciousness) was filled in by the subjects 210 min after the first medication. As a safety measure, blood pressure, heart rate and body temperature were measured every 30 min throughout the study day. Our subjects have not been discharged from the experiments before all psychotropic effects have completely subsided, and all cardiovascular parameters were back to predose levels.

Psychometric scales

Assessment of altered states of consciousness The '5D-ASC questionnaire' (Dittrich, 1998; Dittrich, *et al*., 1985) is a visual-analogue scale consisting of 94 items, suited to depict the core dimensions of altered states of consciousness, independent of their aetiology. This psychometric instrument is constructed of five subscales comprising several item clusters: The 5D-ASC dimension, 'Oceanic Boundlessness' (OB, 27 items) measures derealization and depersonalization phenomena associated with positive emotional states ranging from heightened mood to euphoric exaltation. The corresponding item clusters are 'positive derealization', 'positive depersonalization', 'changed percept of time', 'positive basic mood' and 'mania-like experience'. The 5D-ASC dimension 'Anxious Ego Dissolution' (AED, 21 items)

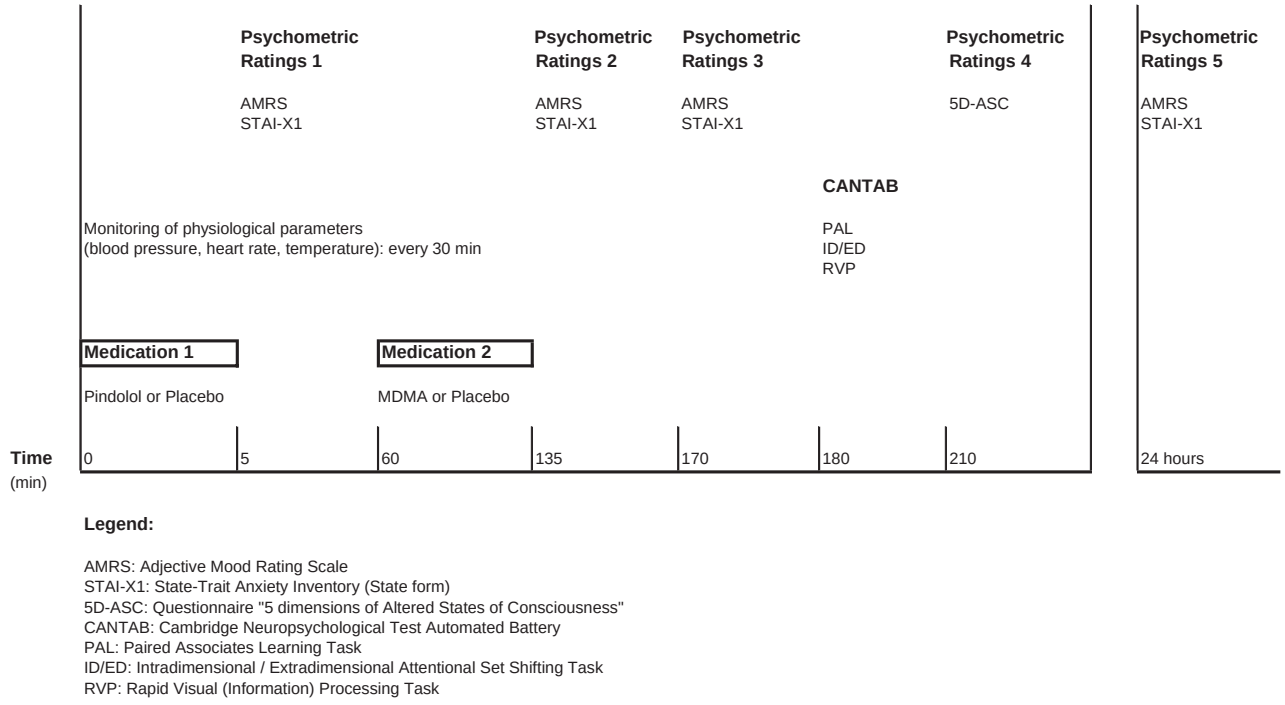

Figure 1 Study design and experimental procedure.

summarizes ego-disintegration and loss of self-control phenomena associated with anxiety. The corresponding item clusters are 'thought disorders', 'loss of thought control', 'loss of body control', 'negative derealization' and 'delusions'. The 5D-ASC dimension 'Visionary Restructuralization' (VR, 18 items) consists of the item clusters 'visual (pseudo)-hallucinations or visions', 'synesthesia', 'changed meaning of percepts', 'facilitated recollection' and 'facilitated imagination'. Finally, the subscale 'Auditory Alterations' (AA, 16 items) subsumes auditory (pseudo-)hallucinations empirically found during ASCs, and the subscale 'Reduction of Vigilance' (RV, 12 items) describes states of drowsiness and impairment of alertness and cognitive performance. The scale 'global ASC score' (G-ASC) is constructed by addition of the scores from the OB, AED and VR scales. Our subjects were asked to complete 5D-ASC rating scales 210 min after administration of the first medication (t_0) and instructed to retrospectively rate their experience. To facilitate comparison of scales among each other, 5D-ASC data are presented as percentage values indicating percentage of maximum absolute scores.

Assessment of mood states The AMRS (Janke and Debus, 1978) consisting of 60 adjectives depicting mood states (e.g. 'serene', 'absent-minded', 'carefree') represents a multidimensional psychometric test developed for repeated measurement of mood states. In our study, the AMRS list was presented to the subjects 5, 135, 170 min as well as 24 h after administration of the first medication. The subjects were instructed to choose from four possible answers ('not at all', 'somewhat', 'quite' or 'strongly' appropriate) to gradually rate to what extent each adjective characterizes their actual mood state. The AMRS consists of 15 subscales that can be subsumed interpretatively to seven domains of affective states: performance-related activity, general inactivation, extroversion-introversion, general well-being, emotional excitability, anxiety-depressiveness and dreaminess.

The STAI (Spielberger, *et al*., 1970) is a psychometric instrument consisting of two independent scales. The state anxiety scale (STAI X1) is designed for the measurement of acute, situational and transient anxious mood states characterized by stress, solicitude, nervousness, tension and fear of future events. In contrast, the trait anxiety scale (STAI X2) assesses a relatively stable individual 'proneness' to anxiety in terms of a characteristic trait. The items of the STAI X2 scale are, therefore, phrased in a general way, not referring to the current mood state. Both anxiety scales consist of 20 items and each item is rated on four possible levels ('not at all', 'somewhat', 'quite' or 'strongly appropriate'). The STAI X2 scale was used in the screening procedure to estimate trait anxiety, whereas the STAI X1 scale was repeatedly used to assess state anxiety during the experiments (ratings at 5, 135 and 170 min, and 24 h after administration of the first medication).

Neuropsychological testing

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computer-based test system for the assessment of cognitive functions and provides tasks measuring attention, vigilance, associative learning, (visual) working memory and planning. It has been shown that the CANTAB battery is well suited to study alterations of cognitive functions as a consequence of pharmacological intervention (Mehta, *et al*., 2001; Robbins, *et al*., 1997). Normative CANTAB data are given in Robbins, *et al*. (1998). In order to become familiar with the CANTAB tasks, all subjects underwent a training phase during the initial screening procedure (using tests with subsets of stimuli different from those presented later during the experiments). To minimize the effect of learning, different sets of stimuli – if available – were used for each experiment. Three CANTAB tasks were chosen for the assessment of acute effects of pharmacological manipulation on cognitive functions: Rapid Visual (Information) Processing task (RVP), Paired Associates Learning task (PAL) and Intradimensional/Extradimensional Attentional Set Shifting Task (ID/ED). The CANTAB tests used in this study will only be briefly described here. For detailed description of this neuropsychological test battery, we refer to Robbins, *et al*. (1994). The RVP measures sustained visual attention and vigilance, and also involves components of working memory for its successful execution. Predominantly fronto-parietal networks seem to underlie RVP (Coull, *et al*., 1996). In the test phase, fast alternating monadic digits are presented in a pseudorandom order and subjects are instructed to detect pre-defined sequences of digits over a period of four min. The RVP task provides three relevant parameters: the number of correct responses to target stimuli (RVP total hits; RVP-TH [n]), the sensitivity for errors, expressing the subjects ability to detect target sequences (RVP-A' [range 0.00 (poor detection) to 1.00 (excellent detection)]), and the mean latency between presentation of target sequence and response (RVP mean latency; RVP-ML [ms]). The PAL measures recognition of visual patterns under activation of visual-spatial memory functions. Conditioned learning is also involved in the PAL test. The PAL test is described in more details by Park and Holzman (1993). A successful performance in the PAL test requires both the elaboration of 'frontal strategies' and the 'mnemonic processes' of the medial temporal lobe (Jakala, *et al*., 1999). PAL provides the following two relevant test scores: the total amount of errors (PAL total error score; PAL-TE [n]), and the total number of trials needed to reach test criterion (PAL total trials to criterion; PAL-TT [n]). Based on the Wisconsin Card Sorting Test, the CANTAB ID/ED assesses the cognitive capacity to selectively focus attention and the ability to flexibly shift attention to a previously irrelevant stimulus dimension. The ID/ED task is considered to primarily assess aspects of executive functions, such as anticipation, planning and general problem solving. The following ID/ED test scores are generated: number of errors committed after switching of the relevant stimulus dimension (ID/ED extradimensional shift errors, EDS-E [n]), number of errors committed before switching of the relevant stimulus dimension (ID/ED pre-extradimensional shift errors, Pre-EDS-E [n]) and number of successfully completed stages (ID/ED stages completed; ID/ED-SC [n]).

Statistics

Statistical calculations were performed by use of the STATISTICA® for windows computer software version 6.0 (StatSoft, 1995). For each test scale (dimension), univariate repeated measures analysis of variance (ANOVA) with pre-treatment (PLA vs. PIN) and treatment (PLA vs. MDMA) as within-subject factors were used to analyse the 5D-ASC, AMRS and CANTAB data. Scores from the state anxiety profile (STAI X1) were analysed by use of two-way repeated measures ANOVA with the factors 'treatment' and 'rating time'. When significant main effects or interactions were apparent after ANOVA procedure, *post hoc* pairwise comparisons were performed by use of Tukey HSD tests. The criterion for significance was set at $p < 0.05$.

Results

Dimensions of altered states of consciousness

Figure 2 shows the effect of pre-treatment (PLA vs. PIN) and treatment (PLA vs. MDMA) on core-dimensions of Altered States of Consciousness according to Dittrich (1998) and Dittrich, *et al*. (1985), as assessed with the 5D-ASC questionnnaire. ANOVA revealed a significant main effect of treatment for all five dimensions of the 5D-ASC rating scale, as well as for the composed 5D-ASC global scale [G-ASC; $F(1,14) = 45.34$; $p < 0.001$]. MDMA treatment caused the most pronounced increase of scores in the scales 'OB' [$F(1,14) = 48.79$; $p < 0.001$], followed by the scales 'VR' [$F(1,14) = 24.70$; $p < 0.001$], 'AED' [$F(1,14) = 12.91$; $p < 0.01$], 'AA' [$F(1,14) = 10.56$; $p < 0.01$] and 'RV' [$F(1,14) = 9.87$; $p < 0.01$]. The increase of scores in the 5D-ASC scale OB is primarily based on enhanced scores in the OB-item-cluster 'Positive Basic Mood' [$F(1,14) = 73.21$; $p < 0.001$]. The item-clusters 'Positive Derealization' [$F(1,14) = 39.63$; $p < 0.001$], 'Altered Perception of Space and Time' [$F(1,14) = 39.27$; $p < 0.001$] and 'Positive Depersonalization' [$F(1,14) = 35.47$; $p < 0.001$] also contributed to the increase of total OB scores under the acute influence of MDMA. The MDMA-induced increase of scores in the 5D-ASC scale VR could be attributed mainly to the item-clusters 'Facilitated Imagination' [$F(1,14) = 28.82$; $p < 0.001$] and 'Changed Meaning of Percepts' [$F(1,14) = 26.14$; $p < 0.001$]. In the anxiety-depicting 5D-ASC domain AED, most pronounced increases were found in the item groups 'Thought Disorder' [$F(1,14) = 20.64$; $p < 0.001$] and 'Fear of Loss of Body Control' [$F(1,14) = 13.54$; $p < 0.01$].

Significant main effects of pre-treatment were found for the 5D-ASC dimensions 'OB' [$F(1,14) = 7.26$; $p < 0.05$] and 'RV' [$F(1,14) = 6.06$; $p < 0.05$], but not for other 5D-ASC dimensions. Attenuation of OB-scores as a consequence of pre-treatment with PIN was primarily based on score reductions in the OB item-clusters 'Positive Derealization' [$F(1,14) = 12.40$;

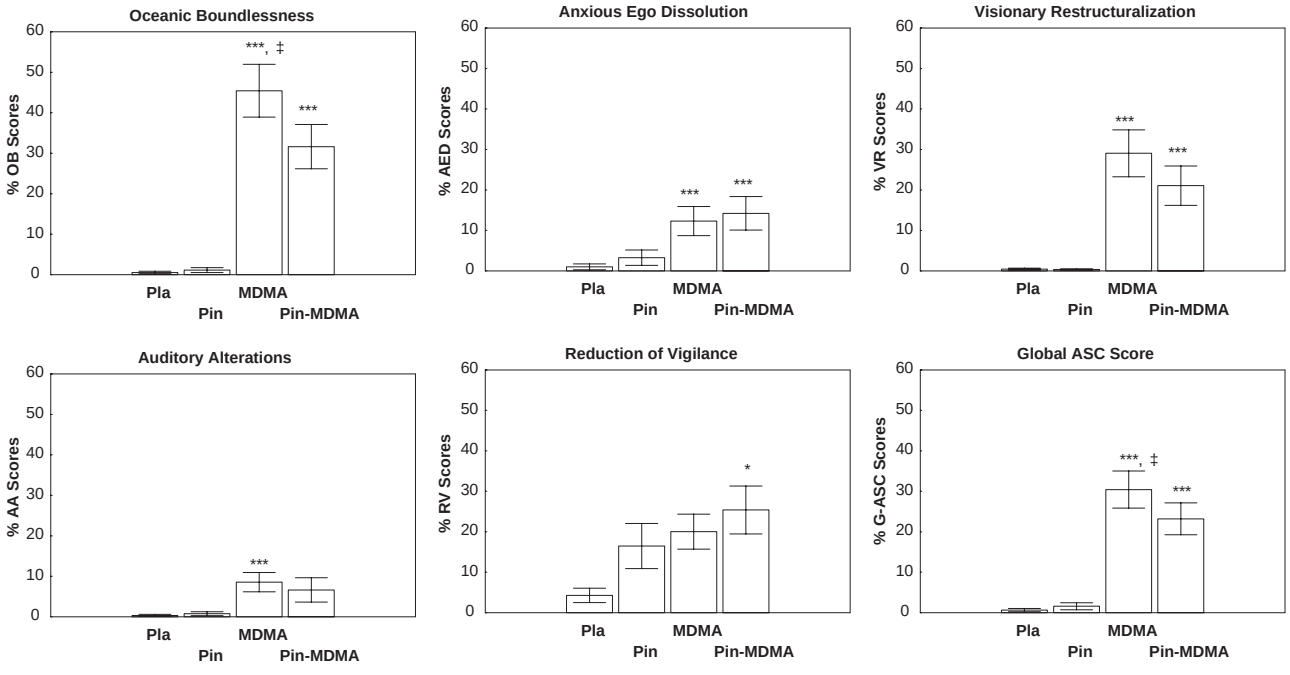

Figure 2 Effect of pre-treatment (placebo vs. pindolol) and treatment (placebo vs. MDMA) on core-dimensions of Altered States of Consciousness, as assessed with the 5D-ASC questionnaire (mean ± SEM, $n = 15$). Scores indicate percentage of theoretical scale maxima.

$p < 0.01$], followed by 'Positive Basic Mood' [$F(1,14) = 6.40$; $p < 0.05$] and 'Mania-like Experience' [$F(1,14) = 6.22$; $p < 0.05$]. Comparing MDMA and PIN-MDMA conditions, *post hoc* tests revealed significant differences only for the scales OB ($p < 0.01$) and G-ASC ($p < 0.01$). Treatment-dependent *F*-and *p*-values for all 5D-ASC scales and its constituent item-clusters, as well as statistical indices for pre-treatment ×treatment interactions are shown in Table 1.

Profiles of affective states

Scores of the AMRS were analysed by two-factorial ANOVA with pre-treatment and treatment as within-subject factors. Regarding the rating times 5 min and 24 h after commencement of the experiments, neither significant main effects of treatment (PLA vs. MDMA) nor significant main effects of pre-treatment (PLA vs. PIN) were apparent. AMRS scores assessed during peak effects of the second medication (t_0 + 135 min) revealed that administration of MDMA alone (treatment) led – compared with placebo condition – to a significant increase of score-sums of the scales 'excitability' [$F(1,14) = 41.09$; $p < 0.001$], 'heightened mood' [$F(1,14) = 18.64$; $p < 0.001$], 'sensitivity' [$F(1,14) = 11.89$; $p < 0.01$] and 'dreaminess' [$F(1,14) = 13.52$; $p < 0.01$]. Moreover, a significant decrease of 'tiredness' was seen under the acute influence of MDMA [$F(1,14) = 5.12$; $p < 0.05$]. Pindolol alone (pre-treatment) solely led to a significant increase of scores in the scale 'drowsiness' [$F(1,14) = 9.1$; $p < 0.01$], when compared with placebo. Pre-treatment with pindolol produced a statistically significant attenuation of MDMA-induced 'dreaminess' [$F(1,14) = 6.10$; $p < 0.05$]. Similar to rating 2, ANOVA of AMRS scores from rating 3 (t_0 + 170 min) revealed significant main effects of treatment (MDMA vs. PLA) for the subscales 'heightened mood' [$F(1,14) = 11.17$; $p < 0.01$], 'excitability' [$F(1,14) = 51.18$; $p < 0.001$], 'sensitivity' [$F(1,14) = 11.11$; $p < 0.01$] and 'dreaminess' [$F(1,14) = 11.25$; $p < 0.01$]. 'Introversion' scores significantly decreased due to MDMA treatment at t_0 + 170 min [$F(1,14) = 7.99$; $p < 0.05$], but not at t_0 + 135 min. For AMRS rating 3, 'pre-treatment' (PIN alone) solely led to a significant decrease of scores in the subscale 'introversion' [$F(1,14) = 6.91$; $p < 0.05$]. For the same rating time, a significant treatment × pre-treatment interaction was found only for the AMRS scale 'dreaminess' [$F(1,14) = 8.44$; $p < 0.05$]. AMRS data as well as relevant statistical indices are presented in Table 2.

State anxiety

Two-way ANOVAs with the factors 'medication' (PLA, PIN, MDMA, PIN-MDMA) and 'rating time' (5, 135 and 170 min, and 24 h after the administration of the pre-treatment medication) revealed a significant main effect of medication for our psychometric data depicting state anxiety (STAI X1) [$F(3,42) = 5.16$; $p < 0.01$]. However, Tukey HSD *post hoc* tests revealed no significantly state anxiety for any given rating time.

Table 1 Statistical indices for effects of treatment and pre-treatment on 5D-ASC scales and its constituent item-clusters

5D-ASC dimensions and item-clusters	Treatment (MDMA) $F(1,14)$	Pre-treatment (Pindolol) $F(1,14)$	Treatment × pre-treatment $F(1,14)$
Oceanic boundlessness (OB)	**48.79*****	**7.26***	**10.36****
Positive derealization	**39.63*****	**12.40****	**13.84****
Positive depersonalization	**35.47*****	0.02 (n.s.)	0.52 (n.s.)
Altered perception of space and time	**39.27*****	1.29 (n.s.)	3.73 (n.s.)
Positive basic mood	**73.21*****	**6.40***	**6.81***
Mania-like experience	**18.60*****	**6.22***	**5.91***
Anxious ego-dissolution	**12.91****	1.50 (n.s.)	0.02 (n.s.)
Anxious derealization	**5.77***	3.29 (n.s.)	0.29 (n.s.)
Thought disorder	**20.64*****	0.00 (n.s.)	0.72 (n.s.)
Delusion	3.53 (n.s.)	1.07 (n.s.)	0.75 (n.s.)
Fear of loss of body control	**13.54****	1.17 (n.s.)	0.12 (n.s.)
Fear of loss of thought control	**7.24***	0.47 (n.s.)	1.26 (n.s.)
Visionary restructuralization	**24.70*****	4.40 (n.s.)	4.49 (n.s.)
Elementary visual hallucinations	**10.87****	0.35 (n.s.)	0.51 (n.s.)
Complex visual hallucinations	3.26 (n.s.)	0.16 (n.s.)	0.21 (n.s.)
Changed meaning of percepts	**26.14*****	3.60 (n.s.)	3.35 (n.s.)
Facilitated recollection	**14.19****	2.44 (n.s.)	2.17 (n.s.)
Facilitated imagination	**28.82*****	4.07 (n.s.)	3.72 (n.s.)
Auditory alterations (AA)	**10.56****	0.42 (n.s.)	1.42 (n.s.)
Reduction of vigilance (RV)	**9.87****	**6.06***	0.57 (n.s.)
Global ASC Scale (G-ASC)	**45.34*****	3.98 (n.s.)	**10.00****

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

Table 2 Effect of pre-treatment and treatment on domains of mood states from the Adjective Mood Rating Scale (AMRS)

	Rating 2 (t_0 + 135 min)			Rating 3 (t_0 + 170 min)		
Domains of mood states from the AMRS	Treatment (MDMA) $F(1,14)$	Pre-treatment (Pindolol) $F(1,14)$	Treatment × pre-treatment $F(1,14)$	Treatment (MDMA) $F(1,14)$	Pre-treatment (Pindolol) $F(1,14)$	Treatment × pre-treatment $F(1,14)$
Performance-related activity						
Efficiency-activation	1.29 (n.s.)	0.91 (n.s.)	0.64 (n.s.)	1.11 (n.s.)	0.87 (n.s.)	0.14 (n.s.)
Concentration	0.29 (n.s.)	2.98 (n.s.)	1.26 (n.s.)	0.06 (n.s.)	0.08 (n.s.)	0.15 (n.s.)
General inactivation						
Inactivation	0.01 (n.s.)	2.98 (n.s.)	0.74 (n.s.)	0.05 (n.s.)	5.13 (n.s.)	0.25 (n.s.)
Tiredness	**5.12***↓	0.71 (n.s.)	0.82 (n.s.)	2.80 (n.s.)	2.38 (n.s.)	0.59 (n.s.)
Drowsiness	3.48 (n.s.)	**9.14****↑	0.28 (n.s.)	0.68 (n.s.)	4.44 (n.s.)	1.90 (n.s.)
Extroversion/introversion						
Introversion	4.04 (n.s.)	1.92 (n.s.)	0.07 (n.s.)	**7.99***↓	**6.91***↑	2.42 (n.s.)
Extroversion	1.59 (n.s.)	1.67 (n.s.)	0.00 (n.s.)	1.54 (n.s.)	0.55 (n.s.)	0.07 (n.s.)
General well being						
Self-confidence	4.30 (n.s.)	0.05 (n.s.)	0.09 (n.s.)	3.07 (n.s.)	0.27 (n.s.)	0.17 (n.s.)
Heightened mood	**18.64*****↑	0.14 (n.s.)	1.07 (n.s.)	**11.17****↑	0.14 (n.s.)	1.68 (n.s.)
Emotional excitability						
Excitability	**41.09*****↑	0.22 (n.s.)	0.02 (n.s.)	**51.18*****↑	0.11 (n.s.)	0.21 (n.s.)
Sensitivity	**11.89****↑	0.03 (n.s.)	0.83 (n.s.)	**11.11****↑	0.32 (n.s.)	0.75 (n.s.)
Angriness	1.89 (n.s.)	1.67 (n.s.)	0.00 (n.s.)	4.24 (n.s.)	0.12 (n.s.)	1.03 (n.s.)
Anxiety/depressiveness						
Anxiety	1.38 (n.s.)	0.26 (n.s.)	1.46 (n.s.)	4.02 (n.s.)	0.26 (n.s.)	0.00 (n.s.)
Depressed mood	0.38 (n.s.)	0.01 (n.s.)	0.07 (n.s.)	0.83 (n.s.)	1.90 (n.s.)	0.39 (n.s.)
Dreaminess	**13.52****↑	0.62 (n.s.)	**6.1***	**11.25****↑	0.27 (n.s.)	**8.44***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; ↑, increase of scale scores; ↓, decrease of scale scores.

Neuropsychological testings

Effects of pre-treatment and treatment on cognitive performance, as assessed with the CANTAB are shown in Table 3 and Figure 3. In the 'Rapid Visual Processing' (RVP) task, statistically significant main effects of treatment (placebo vs. MDMA) were found for the test parameters 'total hits' [RVP-TH; $F(1,14) = 4.75$; $p < 0.05$] and 'error sensitivity' [RVP-A'; $F(1,14) = 4.58$; $p < 0.05$], but not for the test score 'mean latency' (RVP-ML). No significant main effect of pre-treatment (placebo vs. pindolol) and no significant interactions treatment × pre-treatment were found for any RVP parameter.

Table 3 Main effects of pre-treatment (placebo vs. pindolol) and treatment (placebo vs. MDMA) on cognitive performance, as assessed with the CANTAB battery

Cambridge Neuropsychological Test Automated Battery (CANTAB) Tasks	Treatment (MDMA) $F(1,14)$	Pre-treatment (Pindolol) $F(1,14)$	Treatment × pre-treatment $F(1,14)$
Rapid visual processing (RVP)			
RVP-TH [n]	**4.75***	1.44 (n.s.)	1.44 (n.s.)
RVP-A' [n]	**4.58***	1.64 (n.s.)	1.64 (n.s.)
RVP-ML [n]	0.12 (n.s.)	0.05 (n.s.)	0.05 (n.s.)
Paired associates learning (PAL)			
PAL-TE [n]	**23.06*****	0.28 (n.s.)	0.28 (n.s.)
PAL-TT [n]	**21.37*****	0.01 (n.s.)	0.01 (n.s.)
Intradimensional/extradimensional attentional shift (ID/ED)			
EDS-E [n]	1.44 (n.s.)	1.23 (n.s.)	1.23 (n.s.)
Pre-EDS-E [n]	1.79 (n.s.)	0.03 (n.s.)	0.03 (n.s.)
ID/ED-SC [n]	1.62 (n.s.)	1.62 (n.s.)	1.62 (n.s.)

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

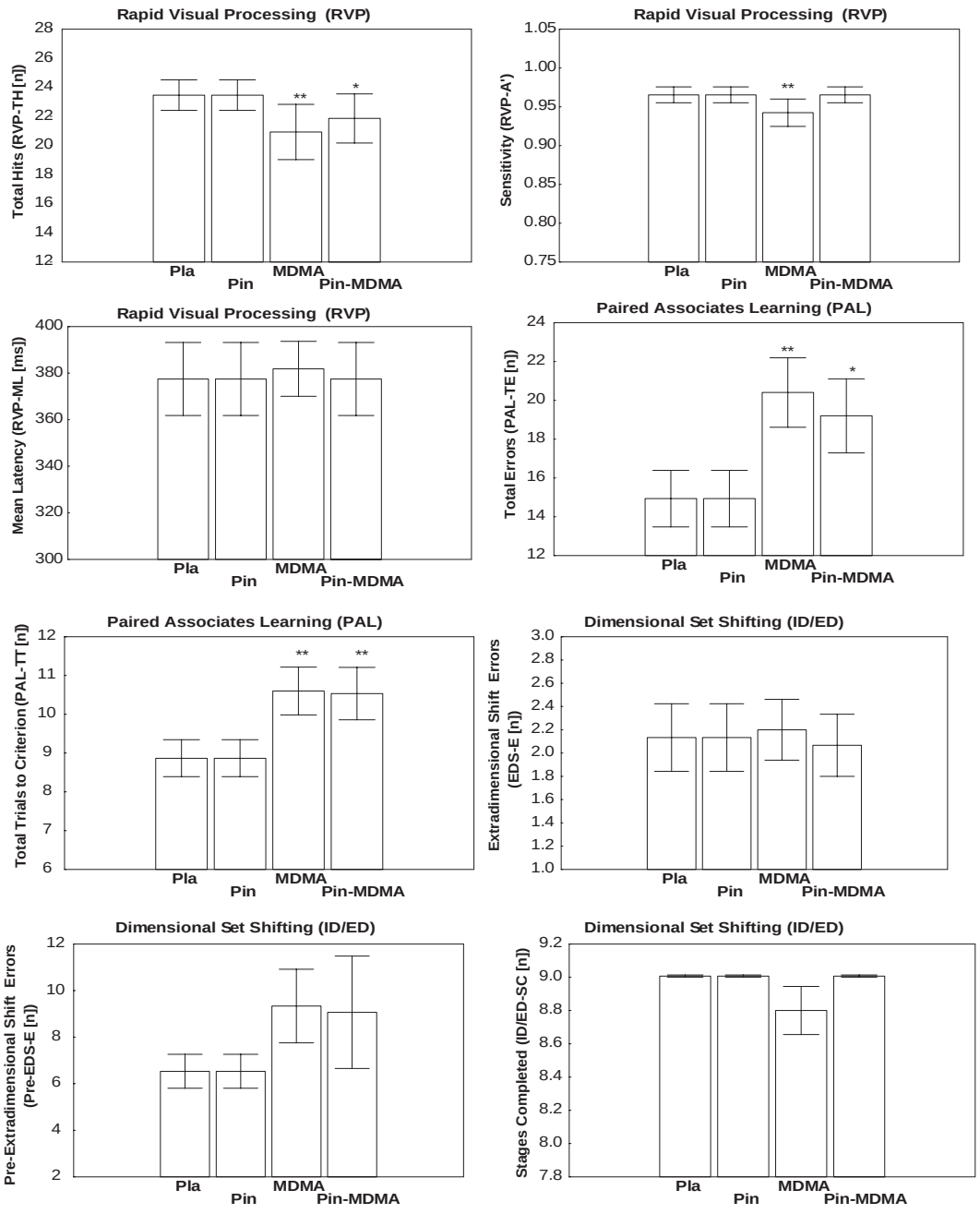

Figure 3 Effect of pre-treatment (placebo vs. pindolol) and treatment (placebo vs. MDMA) on cognitive performance, as assessed with the CANTAB test battery (mean ± SEM, $n = 15$).

As shown in Figure 3, *post hoc* analysis (Tukey HSD) revealed that RVP performance under the acute influence of MDMA alone was significantly reduced for the test scores RVP-TH and RVP-A' ($p < 0.01$). Also following pre-treatment with pindolol, scores of the test parameter RVP-TH were significantly lowered ($p < 0.05$) under the acute influence of MDMA, when compared with placebo condition (but not statistically different from the respective scores under the experimental condition MDMA alone). For both relevant test parameters of the CANTAB PAL task, ANOVA procedures revealed significant main effects of treatment [PAL-TE: $F(1,14) = 23.06$; $p < 0.001$; PAL-TT: $F(1,14) = 21.37$; $p < 0.001$]. Again, neither significant main

effects of pre-treatment nor significant interactions treatment × pre-treatment were found. Compared with placebo condition, our subjects committed significantly more errors under MDMA (PAL-TE score; $p < 0.01$) and under the experimental condition pindolol-MDMA ($p < 0.05$), and needed more trials to reach the test criteria (PAL-TT score; $p < 0.01$ for both MDMA and Pin-MDMA). However, neither PAL-TE nor PAL-TT test scores measured under the treatment conditions MDMA and Pin-MDMA differed in a statistically significant way. For none of the three test scores (EDS-E; Pre-EDS-E; ID/ED-SC) from the ID/ED task neither a main effect of treatment, nor a main effects of pre-treatment, nor a significant interaction pre-treatment × treatment was found.

Discussion

Acute effects of MDMA on subjective experience, mood and state anxiety

In all study subjects, administration of a moderate dose of 1.6 mg MDMA/kg body weight reliably induced a specific and unique set of alterations of conscious experience typical for the class of psychoactive compounds termed 'entactogens' (derived from the Greek, meaning 'touching within'; Nichols, 1986). The subjective effects reported were in good agreement with observations from previous studies (Gouzoulis-Mayfrank, 1999; Hermle, *et al*., 1993; Liechti, *et al*., 2000a, 2001; Peroutka, *et al*., 1988; Vollenweider, *et al*., 1998a). MDMA induced strong affective changes in terms of heightened mood, increased self-awareness and intense feelings of happiness (mania-like experience), a profound state of relaxation and an intensified sense of empathy and closeness to others. This positively experienced derealization is depicted in high rating scores for both the 5D-ASC dimension 'OB' as well as for the AMRS subscales 'heightened mood', 'excitability', 'sensitivity' and 'dreaminess'. Administration of MDMA also significantly increased scores of the 5D-ASC dimension 'VR'. Although more complex (psychedelic) perceptive alterations were absent, perceptive changes in terms of intensified perception of visual, acoustic and tactile stimuli, and an altered perception of space and time were commonly reported. As hallucinatory perceptive alterations induced by 'classic' hallucinogens, such as LSD and psilocybin, are known to be bound to drug interactions with the 5-HT$_{2A}$ receptor system (Nichols, 2004; Roth, *et al*., 1999; Vollenweider, *et al*., 1998b), it is reasonable to assume a role for 5-HT$_{2A}$ receptors also for the pharmacodynamic mode of action of MDMA. This hypothesis is supported not only by animal studies (Nash, *et al*., 1988; Schmidt, *et al*., 1990) but also by an own earlier human study showing that pre-treatment with the 5-HT$_2$ receptor antagonist ketanserin leads to a reduction of MDMA-induced 5D-ASC scale scores (Liechti, *et al*., 2000b). As MDMA itself shows only low affinity to HT$_{2A}$ receptor sites (K_i >10 μM for racemic MDMA, Sadzot, *et al*., 1989), it is likely that the MDMA-induced release of 5-HT from storage vesicles leads to synaptic serotonin concentrations high enough to stimulate the 5-HT$_{2A}$ receptor system.

Case studies of subjects acutely reacting to MDMA with anxiety, panic or paranoid thought content have been published (Whitaker-Azmitia and Aronson, 1989; Williamson, *et al*., 1997). In none of our study subjects such an adverse acute reaction was seen, neither was state anxiety under MDMA – as assessed with the STAI X1 questionnaire – significantly different from placebo levels. A minority of subjects, however, reported temporary tenseness and thought disturbances as well as transient fears of losing control, mostly at the onset of drug effects. These momentary anxiety-related effects are depicted in increased scores of the 5D-ASC dimension 'AED'. The magnitude of MDMA effects on AED-scale scores, however, is only about 1/3 compared with the impact of MDMA on the 5D-ASC dimension OB (~15% and ~45% of theoretical scale maxima, respectively). As expected, both PIN alone and PLA had no to minimal effects on scores of the 5D-ASC scales.

Acute effects of MDMA on cognition

Our investigation clearly demonstrated that under the acute influence of a moderate dose of MDMA, diverse aspects of cognitive function are affected to varying degrees. Compared with placebo, MDMA induced a pronounced impairment of visual-spatial memory. In the CANTAB PAL task, the total number of errors was significantly increased, and under MDMA more trials were used to reach test criteria. MDMA also led to a marked decline of the ability to maintain sustained attention, as expressed in the test scores of the CANTAB RVP task. On the more complex executive functions, however, as examined with the CANTAB ID/ED attentional set shifting task, our treatment with MDMA had no measurable impact. Pre-treatment with pindolol led to no statistically significant alteration (neither deterioration nor improvement) of MDMA-induced impairments in the neurocognitive tasks. The administration of pindolol alone led, as expected, to no altered cognitive performance when compared with placebo condition.

A wealth of investigations suggests that alterations of the serotonergic system cause malfunctions in all aspects of learning involving several types of memory (Jacobs and Azmitia, 1992; Meneses, 1999). The MDMA-induced cognitive deficits in humans shown in our study are in line with the findings of Santucci, *et al*. (1996), who have demonstrated that in rats, 5-HT release rather than depletion leads to memory impairment. In some aspects, however, our results are in contrast to findings from previous studies investigating the cognitive effects of MDMA. Downing (1986) found no effects of MDMA on short-term memory in normal human volunteers. Moreover, Hermle, *et al*. (1993), who have studied the acute cognitive effects of MDEA (3,4-methylenedioxyethylamphetamine, an entactogenic amphetamine with pharmacological properties similar to MDMA), found no acute impairment of memory

performance as operationalized with the Benton task. Their finding could be explained by a lower sensitivity of the Benton test, compared with the CANTAB PAL task. In a study by Tei, *et al.* (1993) investigating memory functions of MS patients with both the Benton and the PAL tasks, only test scores of the PAL, but not the Benton task, were reduced compared with normal controls.

Selective serotonin reuptake inhibitors have repeatedly been shown to impair vigilance performance in sustained attention tasks (Riedel, *et al.*, 2005; Schmitt, *et al.*, 2002). For the first time, to our knowledge, the acute effect of MDMA-induced elevated serotonergic neurotransmission on sustained attention has been investigated in this study. As vigilance performance is often reported as being impaired during the acute effects of MDMA and congeners (Peroutka, *et al.*, 1988; Vollenweider, *et al.*, 1998a), the finding of an MDMA-induced deficit in sustained attention, as assessed with the CANTAB RVP task, is not surprising. MDMA seems to hamper attention capacity only when attention is supposed to be kept over an extended period of time. In an earlier study with MDMA-naïve subjects, we could show that 'short-term' selective attention capacity remains unaffected under the acute influence of MDMA (Vollenweider, *et al.*, 1998a). One may speculate that the increased distractability in the RVP task can be attributed to the MDMA-induced facilitation of memory recollection, and that the resulting influx of memory content on the level of conscious processing impairs the ability to deliberately uphold a cognitive focus over a longer period of time. In accordance with this hypothesis, Spearman-correlation analysis of our psychometric and neuropsychological data revealed that increased scores in the 5D-ASC subscales 'facilitated imagination' and 'facilitated recollection', respectively, were negatively correlated with performance in the RVP task ($r = -0.54$, $p < 0.05$ and $r = -0.57$, $p < 0.05$, respectively). Moreover, we also found a significant negative correlation between the parameter values in the AMRS subscale 'dreaminess' and RVP performance ($r = -0.57$, $p < 0.05$). Our finding that pre-treatment with PIN does not significantly attenuate MDMA-induced impairment of sustained attention is in line with results from a recent mechanistic human study investigating the effect of manipulation at the 5-HT$_{1A}$ and 5-HT$_{2A}$ system on vigilance performance (Wingen, *et al.*, 2007). When pre-treatment with 10 mg pindolol failed to alter escitalopram-induced impairment of sustained attention, the authors conclude that the 5-HT$_{1A}$ receptor does not have an additional effect next to a possible effect of additionally increased serotonin levels. With respect to 5-HT$_{1A}$ receptors, however, antagonist studies in animals suggest that this receptor subtype may not be a prerequisite for spatial learning. In rats, for example, no subcutaneous dose of the 5-HT$_{1A}$ receptor antagonist WAY 100135 modified acquisition of spatial learning (Carli, *et al.*, 1995). This view is corroborated by our finding that in humans pre-treatment with PIN does not significantly improve MDMA-induced deterioration in the PAL task performance.

Contribution of 5-HT$_{1A}$ receptors to the human psychopharmacology of MDMA

In contrast to our working hypothesis, pre-treatment with PIN only had a minor modulating effect on psychometric scales affected by MDMA treatment. A significant difference of rating scores assessed under the acute action of MDMA and PIN/MDMA, respectively, was found for two scales only. Pre-treatment with PIN led to a decrease of MDMA-induced positive derealization as assessed with the 5D-ASC scale OB. A detailed analysis of the OB subscales revealed that this reduction was primarily due to a decrease of 'positive basic mood' and 'mania-like experience'. Moreover, administration of PIN prior to MDMA led to a score reduction in the AMRS scale 'dreaminess'. All other psychometric subscales depicting MDMA-evoked changes were not significantly affected by pre-treatment with PIN. Apparently, in our study the antecedent blockade of 5-HT$_{1A}$ receptors with pindolol only marginally altered the subjective experience to MDMA. A similar picture was seen with respect to cognitive performance (Figure 3 and Table 3). Antecedent 5-HT$_{1A}$ receptor blockade with PIN caused no statistically significant change in test performance in any of the cognitive tasks, compared with MDMA alone.

As the 5-HT$_{1A}$ receptor system is known to play an important role in cognitive processing, modulation of mood, and motor behaviour (Barnes and Sharp, 1999) – processes that are all markedly affected by MDMA – it was obvious to investigate the contribution of the 5-HT$_{1A}$ receptor system in the mediation of MDMA effects on subjective experience and cognition. However, our findings are not supporting the hypothesis derived from animal and *in vitro* studies that (direct or indirect) stimulation of this serotonin receptor subtype importantly contribute to the pharmacodynamic mode of action of MDMA. In the experiments of Millan and Colpaert (1991), the influence of the selective 5-HT$_{1A}$ receptor antagonists BMY 7378 and NAN-190 upon MDMA-induced spontaneous tail-flicks in the rat was strictly dose-dependent. One obvious reason for the conflicting results from their investigations and our human study might be that the 20 mg pindolol dose we administered was not high enough to sufficiently occupy the targeted receptor sites. According to a PET study by Rabiner, *et al.* (2000), a single oral dose of 20 mg pindolol leads to an approximately 40% occupation of both pre- and postsynaptic 5-HT$_{1A}$ receptors. Although a higher level of receptor occupancy would have been preferable, we abstained from using more than 20 mg pindolol due to the increased likelihood of occurrence of ß-adrenergic side effects. An additional reason for not administering more than 20 mg pindolol prior to MDMA was the possible risk of inducing paroxysmal elevation of blood pressure due to unopposed alpha-receptor stimulation in the peripheral vasculature. We derived this possible side effect from a case of paroxysmal hypertension after treatment of cocaine intoxication with propranolol (Ramoska and Sacchetti, 1985). Moreover, our MDMA dose of 1.6 mg/kg b.wt. might have been too high compared with the relatively

low dose of pindolol. The excessively high extracellular 5-HT concentration resulting from MDMA administration is likely to have induced a negative feedback on 5-HT synthesis and release through activation of solely partially pindolol-antagonized 5-HT$_{1A}$ autoreceptors. More subtle modulating effects of pindolol, especially on postsynaptic 5-HT$_{1A}$ receptors may, therefore, have been masked. Moreover, we cannot rule out that certain test results (e.g. anxiety scores) have been influenced by the beta-adrenoreceptor blocking properties of pindolol.

However, also animal data on the role of 5-HT$_{1A}$ receptors in the profile of action of MDMA is inconclusive. When the effect of the selective 5-HT$_{1A}$ receptor antagonist WAY 100635 on MDMA-induced hyperlocomotion was studied in rats, no effect was found by McCreary, *et al.* (1999). Accordingly, the conclusion was drawn that the 5-HT$_{1A}$ receptor system is not involved in the mediation of MDMA-induced locomotor activation (Bankson and Cunningham, 2001). Further mechanistic receptor blocking studies using multiple and higher doses of pindolol and other 5-HT$_{1A}$-agonists and -antagonists should be carried out to better understand this issue.

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