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Enantio-selective cognitive and brain activation effects of N-ethyl-3,4-methylenedioxyamphetamine in humans

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Abstract

In a randomised double-blind trial the subjective, neuropsychological and brain activation effects of the two enantiomers of the MDMA (ecstasy-) like drug N-ethyl-3,4-methylenedioxyamphetamine (MDE) were studied in fiv normal subjects using functional magnetic resonance imaging (fMRI). (S)-MDE produced elevated mood, impairments in conceptually driven cognition and marked right frontal activation. In contrast, (R)-MDE produced increased depression, enhanced visual feature processing, and activation of visual cortical and left frontal areas. Plasma concentrations were higher for the (R)-enantiomer. The so-called entactogenic effects of MDE are likely to be caused by the (S)-enantiomer, whereas (R)-MDE appears to be responsible for neurotoxic effects.

Keywords: (S)-MDE; (R-)MDE; Functional imaging; Neuropsychology; Neurotoxicity; MDMA

With the advent of cognitive neuroscience and functional brain imaging, the subjective as well as objective brain activation effects of psychotropic agents can be studied in unprecedented detail in human subjects.

Substituted amphetamine derivatives, such as N-methyl-3,4-methylenedioxyamphetamine (MDMA, ecstasy) widely used as a recreational drug and N-ethyl-3,4-methylenedioxyamphetamine (MDE, eve) induce subjective effects that are described by users as different from classic hallucinogens such as lysergic acid diethylamide (LSD) and stimulants such as amphetamine (Nichols, 1986). These effects consist of changes in affect, perception, and cognitive style described as 'oceanic boundlessness' and peaceful experiences of emotional closeness, and were confirme in controlled double-blind experiments with normal subjects (Gouzoulis-Mayfrank et al., 1999a,b). Pharmacologically, these agents affect the serotonergic (5-HT) as well as catecholaminergic system, releasing 5-HT as well as dopamine from presynaptic terminals (Johnson et al., 1986; Hegadoren et al., 1995).

There is now an increasing body of evidence that the repetitive use of MDMA causes a series of psychopathological and neuropsychological deficit in abstinent users, such as depression (Curran and Travill, 1997) and impairments in higher executive processing (Morgan, 1999; Parrot, 2000; Gouzoulis-Mayfrank et al., 2000; Wareing et al., 2000). These deficit are generally believed to be the result of serotonergic neurotoxicity (Sprague et al., 1998) concluded from animal and human studies (Parrot et al., 1998; McCann et al. 1998, 2000; Ricaurte et al., 2000).

While MDMA and MDE share a similar acute psychoactive profile MDE is known to be less neurotoxic than MDMA (Ricaurte et al., 1987). MDE exists in two enantiomers because of an asymmetric C-atom in C9-position. Behavioural studies in mice have shown enan-

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tiomer-specif c effects, suggesting stereo-specif c drug–receptor interactions. In particular, the hallucinogenic effects of MDE have been completely attributed to the (R)-enantiomer, whereas the (S)-enantiomer has been related to amphetamine-like effects (Nichols, 1994). Given the practical importance of the use of ecstasy in society, the limited knowledge of its mechanisms of action, and the complete absence of data on enantiomer-specif c effects in humans, we used functional magnetic resonance (fMRI) during a language and a perceptual task, in addition to neuropsychological tests and subjective rating scales, to study the differential effects of the (R)-MDE and (S)-MDE in a double-blind randomised study.

While the mood-elevating effects of (S)-MDE may be caused by dopaminergic projections to the frontal cortex, high densities of 5-HT uptake sites in subcortical regions (Scheffel et al., 1998) and in primary visual cortex (Morrison and Hof, 1992; Nauta and Feirtag, 1990) provide a possible mechanism of the visual hallucinogenic effects of the (R)-MDE. Accordingly, we reasoned that the subjective effects of both enantiomers should be dissociable on a subjective, neuropsychological, and brain imaging level. Therefore, we have chosen experimental paradigms tapping into the respective processes of low level vision and high level cognitive functioning. Outside the MR scanner, standard neuropsychological paradigms were used (visual pop-out search, Wisconsin Card Sorting Test, semantic priming paradigm) whereas for use within the MR scanner, a semantic and a perceptual paradigm were adapted according to our previous experiences (Spitzer et al., 1996).

To assess early and supposedly automatic visual processes as functions of occipital visual cortical areas, a visual popout search task was used. For the assessment of controlled conceptual thought processes, supposedly subserved by frontal brain areas, the Wisconsin Card Sorting Test (WCST) was administered. In order to assess the effects of the two MDE enantiomers on semantic processing independently of the task used in the MR-scanner, reaction times for associated, indirectly associated and non-associated words were recorded in a semantic priming task. In order to investigate perceptual effects, supposedly related to hallucinogenic activity, as well as substance related actions on higher cognition, a colour and a semantic discrimination task were used during data acquisition in the MR-scanner (Fig. 2a). Subjective and behavioural effects of the drugs were studied using self-rating scales before and after drug intake.

1. Methods

1.1. Subjects

The study was carried out in accordance with the Declaration of Helsinki. We obtained permission from the Local Internal Review Board (Landesärztekammer, Baden-Württemberg) as well as the German Drug Agency to investigate f ve healthy young male physicians with no history of drug abuse and psychiatric or neurologic disorders. All subjects were right-handed according to the Oldf eld (Oldf eld, 1971) handedness quotients (range between: +95 and +100). None had any sign of colour blindness or visual f eld defects. All subjects gave written informed consent prior to the study.

1.2. Study design

A f xed dose of 70 mg MDE hydrochloride (59 mg base) of either enantiomer was given to each subject in a randomised double-blind design. On the days before each test session subjects were well trained on parallel versions of the neuropsychological tasks and familiarised with the instructions of both the tasks and the psychopathometric scales. On test day baseline measures were taken before drug application at 09:00 a.m. fMRI measurements took place about 90 min thereafter. Immediately after scanning the neuropsychological tests as well as the psychometric scales were administered in a randomised order across subjects and test days. Blood samples were collected from a cannulated forearm vein immediately before drug intake and 10 min, 20 min, 30 min, 60 min, 90 min, 2 h, 4 h, 6 h, 10 h, 12 h, 14 h, 24 h, 30 h, and 34 h thereafter. Plasma concentrations were measured using a new established enantioselective HPLC method with f uorimetrical detection. Pharmacokinetic data were calculated according to the standard noncompartmental model with the TopFit 2.1 program (Heinzel et al., 1993). After a washout phase of at least 2 weeks the same procedure was replicated for the other enantiomer.

1.3. Experimental behavioural procedures

To measure *visual pop-out search* (Treisman and Sato, 1990; Derrington, 1996) an oblique white bar was embedded within a display of vertical white bars of the same height and width. The number of distractors were 4, 8, 12, 16, resulting in four different set sizes. There were 12 trials with and 12 without a feature target for each set size, giving a total of 96 trials in randomised order. Subjects responded with their right index f nger when a target was present. Pre- and post-drug reaction time analyses revealed non-signif cant parallel slopes of mean reaction time over increasing set sizes. Therefore, to enhance statistical power individual mean reaction times for target search were calculated for each set size under the two drug conditions. After pooling both pre-sessions data analysis was conducted by means of a one-factor MANOVA with repeated measures (pre, post-(S)-MDE, post-(R)-MDE). For post-hoc analyses Newman–

Keuls tests were used to correct for multiple comparisons (nominal p level, $p<0.05$).

A computerised version of the *Wisconsin Card Sorting Test* was used very parallel to the test modus proposed by Nelson (Nelson, 1976). This modif cation eliminates all ambiguous cards, reducing the number of trials (48-card pack). Alternations of the sorting rule after six correctly sorted single trials are presented by the PC. Owing to this modif cation the number of sorting errors is rather small in young healthy controls. Reaction times after each rule alternation were used to calculate switching costs for rule alternations. The median of the last three correctly sorted trials before a change of the sorting criterion was calculated. These values were subtracted from the reaction time of the f rst correctly sorted card after rule change. After pooling the data from both premeasures, drug effect analyses were computed by means of a one-factor MANOVA for repeated measures with three levels (pre, post-(S), post-(R)). For post-hoc analyses the Newman–Keuls test was used to correct for multiple comparisons (nominal p level, $p<0.05$).

The *priming tasks* (Spitzer et al., 1993) consisted of four conditions: directly associated, indirectly associated, non-associated words and pseudo-words. Subjects had to decide whether or not a word following a prime word was a correct word of the German language (lexical decision). Reactions were done by button press. Reaction times were measured by a PC. There were 18 trials for each of the non-pseudo word conditions and 54 trials embedding pseudo-words. The prime was always a correct German word and was presented for a duration of 200 ms. Immediately afterwards the target word appeared centred on the PC monitor. The time frame for a response was limited to 1500 ms. The intertrial interval was 100 ms. There were two identical parallel forms with different stimuli. Trials for each of the four conditions were randomly mixed to avoid repetition effects on reaction times. Median reaction times were calculated for each condition per subject and drug enantiomer. To reduce the number of factors, differences in reaction times between pre- and post-drug measurements were calculated for the non-pseudo-word conditions. Owing to the small sample sizes, the Wilcoxon test for paired samples was conducted to test for signif cance of the difference times between the (S)- and (R)-enantiomers.

1.4. Psychopathometric rating scales

Four self-rating psychopathometric scales were used. The Depression Scale (DS) (von Zerssen, 1976a) consists of 16 items regarding depressive symptoms and dysphoria. There are two parallel forms allowing repeated tests to measure symptom change. The Actual Subjective Mental State Scale (BfS) (von Zerssen, 1976b) has two parallel forms which makes it suitable for repeated measurements. A set of 28 pairs of contradictory adjectives allows the subject to describe the actual subjective mental state ranging from mania to depression. The list of Somatic Complaints (BL) (von Zerssen, 1976c) has two parallel forms, each consisting of 24 items. Finally, the subjects f lled out a questionnaire concerning Altered States of Consciousness (OAV, a revised version of the ASCs; Dittrich, 1998) at the end of the test days. Subjects had to range their experiences after drug application retrospectively on a visual analogue scale from zero to ten. The construct of ‘oceanic boundlessness’ (OSE) was measured by items such as ‘I felt myself to be in a wonderful world’ and ‘All things seemed to come together in one total whole’. Owing to the small number of subjects statistical comparisons between the difference scores for the (R)- and (S)-enantiomer were computed by means of Wilcoxon tests for paired samples.

1.5. Imaging protocols

Data were acquired with a 1.5 Tesla Magnetom VISION (Siemens, Erlangen, Germany) whole-body MRI system equipped with a head volume coil. T2*-weighted functional MR images were obtained using echo-planar imaging in axial orientation (TE=50 ms). Image size was 64 by 64 pixels (3.6 by 3.6 mm pixels). The volume consisted of 38 slices (TR=3.480 ms). Slice thickness was 2 mm, with a gap of 1.2 mm. For anatomical reference T2 weighted Turbo-Spin-Echo-images (256 by 256; 38 slices; voxel-size: 0.9×0.9×3.2 mm) were obtained. In total, 264 volumes were acquired per session. The f rst six volumes of each session were discarded to allow for T1 equilibration effects. Image preprocessing and statistical analysis were carried out with Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK; www.f l.ion.ucl.ac.uk) executed in MATLAB 5.3 (The MathWorks, Natick, MA). All individual functional images of one session were corrected for motion artefacts by realignment to the f rst volume of the session. A sinc interpolation was used to reslice the realigned volumes. A T2-weighted structural MRI was coregistered to the mean image of the realigned volumes. Functional images of each session were spatially normalised to a standard T2-template of 2×2×2 mm voxels. Finally, images were spatially smoothed with an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel. The fMRI protocol was a block design. Each activation epoch lasted 21 s (equivalent to six whole-brain fMRI volume acquisitions). For each session the variance of each and every voxel was estimated according to the general linear model using a box-car model convoluted with the hemodynamic response function as the predictor. Images were globally scaled to 100 and low frequency drifts were removed via a high pass f lter using low-frequency cosine functions with a cut-off of 378 s.

Differences of drug-dependent brain activations for the semantic and colour similarity decisions were computed using linear contrasts. Signif cant voxels were thresholded at a p level of $p<0.001$, uncorrected for multiple comparisons. At the cluster level, signif cance was set to an uncorrected p level of $p<0.05$. Areas were labelled using the nomenclature of Talairach and Tournoux (1988) and Brodmann (1909).

1.6. fMRI task

Word pairs were created belonging to three categories of semantic relations: directly related ('table–chair'), indirectly related ('beer–grape') or not semantically related ('cloud–dog'). For decisions on the similarity of colours an analogous set of pairs of coloured asterisks was created (identical, similar, non-identical). Behavioural results (number of correct responses and reaction time) indicated that the task diff culties of both conditions were comparable, and thus psychometrically equivalent (Spitzer et al., 1996). In total, 120 word pairs and 120 pairs of asterisks were created with 40 trials for each of the three categories. The whole test was split into two half forms of an equal number of conditions, trials and task diff culty. The sequence of semantic and colour similarity decisions was pseudorandomised such that no more than two blocks of the same modality were allowed to follow each other. Blocks of activation consisted of six trials. Directly/identical and indirectly related/similar trials were always combined with non-related/non-identical trials within each block to prevent response repetition effects. Presentation times of stimuli were controlled by the subjects. The maximum presentation time was set to 2850 ms. The intertrial interval was set to 150 ms. The control condition consisted of pairs of identical words. For colour similarity trials, two strings of identically coloured asteriks served as control condition. Block presentation order was at random but constant across subjects and sessions. The sequence of blocks of semantic and colour decisions was different between both parallel versions. Each activation epoch was followed by a controlled rest condition of the same length. Responses were given by button press. The stimulation protocol was realised by means of Experimental Run Time System (ERTS, Jörg Beringer, Frankfurt, Germany) on a standard personal computer. Semantic as well as colour items were presented as coloured bitmaps. Signal transduction to the PC was realised by means of a f ber-optic system and an opto-coupler. Before scanning, subjects were instructed and trained to become familiar with the tasks. In the scanner stimuli were presented by LCD video-goggles (Resonance Technologies, Northridge, CA). Onset of the PC-stimulation epochs was controlled by the fMRI scanner emitting a 50 ms lasting TTL pulse prior to each volume acquisition.

2. Results

Both enantiomers of MDE could be detected in the plasma samples taken, and pharmakokinetic data revealed comparable times of maximum activity and half lives for both. Owing to the signif cantly increased clearance for the (S)-enantiomer, plasma levels of the (R)-enantiomer were signif cantly larger (Table 1).

The (R)- and the (S)-enantiomers of MDE led to markedly different subjective-behavioural, brain imaging, and neuropsychological effects.

Subjective behavioural effects as indicated by self-rating scales are summarised in Fig. 1. When comparing drug induced alternations from baseline of both enantiomers against each other, the (R)-MDE led to numerically increased scores on a depression scale (DS) whereas the (S)-enantiomer decreased depressiveness and dysphoria (P=0.22; Wilcoxon test). With respect to subjective mental states (BfS) the difference between (R)-MDE causing depressive, and (S)-MDE causing manic mood was signif cant ($P<0.05$; Wilcoxon test). In the BL scale there was a trend towards more somatic symptoms of dysphoria under (R)-MDE while the (S)-enantiomer led to decreases in somatic complaints ($P<0.07$; Wilcoxon test). The OAV questionnaire revealed signif cant differences for the scale of 'oceanic boundlessness' ((S)-MDE: 86.1; (R)-MDE: 3.9, $P<0.05$, Wilcoxon test for paired samples). Taken together, the (S)-enantiomer produced the entactogenic subjective effects of increased talkativeness, openness, and elevated mood whereas the (R)-enantiomer mainly caused dysphoria and somatic complaints.

Functional MRI data were assessed by comparing the effects of the two enantiomers directly against each other (Fig. 2b and Table 2). During the semantic judgement task, (R)-MDE caused signif cant activation of right visual and left frontal areas. In contrast, the (S)-enantiomer caused right frontal and bilateral temporoparietal activation. In the colour discrimination task, no increased activation was seen under (S)-MDE, whereas under (R)-MDE the same occipital visual areas as during the semantic task became more active (data not shown).

Neuropsychological data on low-level visual processes and on switching costs in the WCST are summarised in Fig. 3. A MANOVA for repeated measures on reaction times for pop-out search revealed a signif cant main effect of the factor drug ($F(2,38)=9.16$; $P<0.001$). Newman–Keuls post-hoc analyses demonstrated that the decrease of visual search time under (R)-MDE was signif cant when compared with pre-drug (P=0.001) as well as the (S)-enantiomer (P=0.001). The slight increase in scanning times after application of the (S)-enantiomer compared with pre-drug was not signif cant ($P>0.10$) (Fig. 3a). For switching costs in the WCST a MANOVA for repeated measures showed a signif cant main effect of drug ($F(2,42)=5.45$, $P<0.01$). Post-hoc analyses

Table 1
Results[a] of plasma samples (mean±SD)

	(S)-MDE	(R)-MDE	*p*
C_{max} (ng/ml)	80.0±29.49	127.80±34.16	<0.05
T_{max} (h)	2.61±0.58	2.76±0.94	0.67
$T_{1/2}$ (h)	4.18±1.44	7.45±2.38	0.08
AUC (ng/h/ml)	535.41±262.51	1706.81±896.88	<0.04
Total Cl (ml/min)	2258.0±1032.21	718.20±340.16	<0.04

[a] C_{max}, maximum concentration; T_{max}, corresponding time to maximum plasma concentration; $T_{1/2}$, elimination half life; AUC, area under the curve; Total Cl, total clearance; *P*, level of signif cance (non-parametric Wilcoxon tests for paired samples).

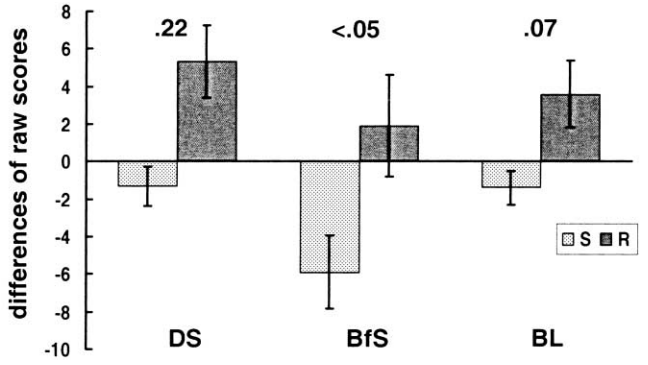

Fig. 1. Results of psychopathometric rating scales. Self rating scales were administered before and after drug application. Scores are scaled to baseline (pre-drug) such that bars below the *x*-axis ref ect a decrease and bars above the *x*-axis ref ect an increase (DS: Depression Scale; BfS: actual subjective mental state scale; BL: list of somatic complaints).

revealed that switching costs were signif cantly increased by the (S)-enantiomer when compared with baseline ($P<0.05$) and with the (R)-enantiomer ($P<0.01$). The decrease of mean switching costs under application of the (R)-enantiomer was not signif cant when compared with baseline ($P>0.05$) (Fig. 3b). To assess the effects of the two MDE enantiomers on semantic processing, reaction times for the three conditions (associated, indirectly associated and non-associated) obtained in the pre-drug session were compared with the corresponding reaction times under (R)- and (S)-MDE. Only in the indirectly related condition was a trend for differential effects found ($P=0.067$) in that there was a 38% decrease in reaction time under the (S)-enantiomer, and a 5% increase under (R)-MDE, indicative of a tendency towards a larger degree of activation of remote associations under the inf uence of (S)-MDE.

3. Discussion

The present study demonstrated differential effects on various measures assessing alterations of psychopathology, neuropsychological performance and brain activation patterns after ingestion of (R)- and (S)-MDE.

Within this framework of our experimental neuropsychological data, combined with the subjective-behavioural observations, the differential effects of (R)- and (S)-MDE on brain activation in fMRI are interpreted as follows. The (R)-enantiomer of MDE activates visual areas, thereby facilitating bottom-up driven information processing, as indicated by facilitating parallel visual search. The activation of left frontal areas was paralleled by numerically decreased switching costs and lower priming effects. From the experimental psychology of affective states it is known that bad mood is associated with 'tightening' and focusing of thought processes whereas good mood is concomitant with 'loosening' of thought processes and increased associations (Fiedler, 1991). During cognitive tasks, people in bad mood prefer systematic strategies and show improvement in tasks requiring assiduity and discipline whereas people in good mood prefer heuristic problem-solving strategies and are better at creative tasks. Depression and anxiety, i.e. the main subjective components of (R)-MDE driven experiential changes, promote bottom-up information processing and thereby facilitate automatic feature detection and, in general, scrutiny to environmental signals under the inf uence of possible incipient danger to the organism. Moreover, under the (R)-enantiomer subjects are more depressed and better at performing the WCST.

Although the above mentioned animal data suggest that the hallucinogenic activity of MDE is caused by its (R)-enantiomer, our subjects did not report prominent positive visual non-object bound phenomena such as hallucinations or severe illusory experiences. As both the semantic and the colour task caused increased activation of visual occipital areas under the (R)-enantiomer, we may tentatively conclude that our data do not rule out, but are compatible with, the view that higher doses of (R)-MDE may cause hallucinatory effects in humans by the activation of visual areas. This argument of dose-dependency still holds even with respect to previous studies that applicated hallucinogens in suff ciently high doses. Most of these studies that failed to observe sensory phenomena were so-called resting studies that did not use sensory stimulation that might have been necessary to induce the expected sensory alternations or hallucinations (ffytche et al., 1998).

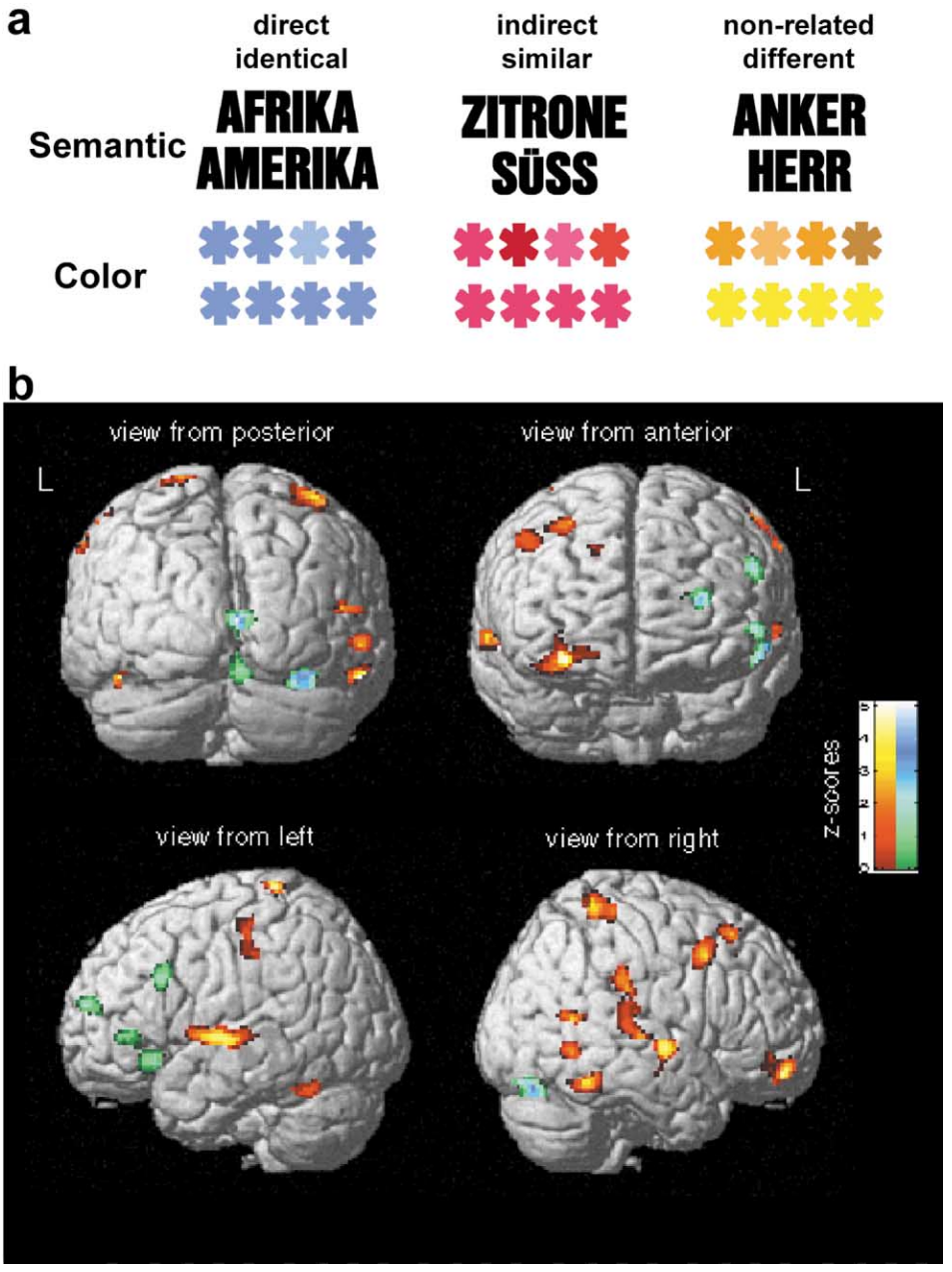

Fig. 2. Stimulus examples of the fMRI task and 3D-rendered fMRI results. (a) Examples of stimuli used within the fMRI experiment. Subjects had to decide whether the words or colours were directly associated/identical (Africa, America), indirectly associated/similar (lemon, sweet) or non-related/different (anchor, gentleman). (b) Three-dimensional rendered standardised brains ref ecting the areas of activity when comparing brain activation during the semantic similarity judgement task. Red-yellow spots demonstrate activity comparing the (S)-enantiomer minus the (R)-enantiomer. Green-blue spots show activity comparing the (R)-enantiomer minus the (S)-enantiomer.

The effects of the (S)-enantiomer are in contrast to the effects of (R)-MDE, producing subjective experiences of elevated mood, a decrease in concept-driven thought processes (as indicated by increased set shifting costs) and some evidence for increased availability of remote associations. This is in line with the activation of right frontal areas that have been found to harbour remote associations in a number of experimental behavioural and neuropsychological studies (Weisbrod et al., 1998). The f nding of a decrease of WCST performance under (S)-enantiomer and an increase of performance under the (R)-enantiomer is consistent with the view of a dynamic balance between two synergistic decision making systems in the frontal lobes: context-dependent in the left hemisphere and context-invariant in the right (Podell et al., 1995). Thus, the increase in right dorsolateral prefrontal functioning under application of the (S)-enantiomer results in a decreased ability to consider contextual cues and to switch between conceptual affordances. (S)-MDE does not cause activation in the visual system in

Table 2
Signif cantly activated brain regions during semantic judgements when comparing both enantiomers against each other

Anatomical region	BA[a]	Talairach-coordinates			z-value
(S)-MDE minus (R)-MDE					
Left		*x*	*y*	*z*	
Superior temporal gyrus	21/22	−56	−14	2	4.81
Superior parietal lobule	7	−20	−40	76	4.50
Cerebellum		−44	−58	−22	4.36
Postcentral gyrus	1/2	−52	−24	56	4.03
Transverse temporal gyrus	41	−28	−32	14	3.63
Right					
Fusiform gyrus	36	58	−50	−20	5.19
Superior parietal lobule	5/7	38	−46	68	5.13
Superior temporal gyrus	21	64	−8	0	4.57
Superior frontal gyrus	11	36	54	−16	4.28
Inferior parietal lobule	40	54	−30	32	4.09
Inferior temporal gyrus	37	60	−58	−4	4.06
Middle frontal gyrus	9	42	10	40	3.96
Superior frontal gyrus	8	32	26	52	3.89
Middle temporal gyrus	39	50	−60	14	3.70
Middle frontal gyrus	8	16	30	40	3.63
(R)-MDE minus (S)-MDE					
Left					
Inferior frontal gyrus	47	−54	26	−10	4.44
Middle frontal gyrus	9	−50	18	32	4.22
Superior frontal gyrus	10	−28	58	18	3.97
Right					
Cuneus	17	8	−84	8	4.94
Fusiform gyrus	36	36	76	−20	4.75

[a] Brodmann's areas.

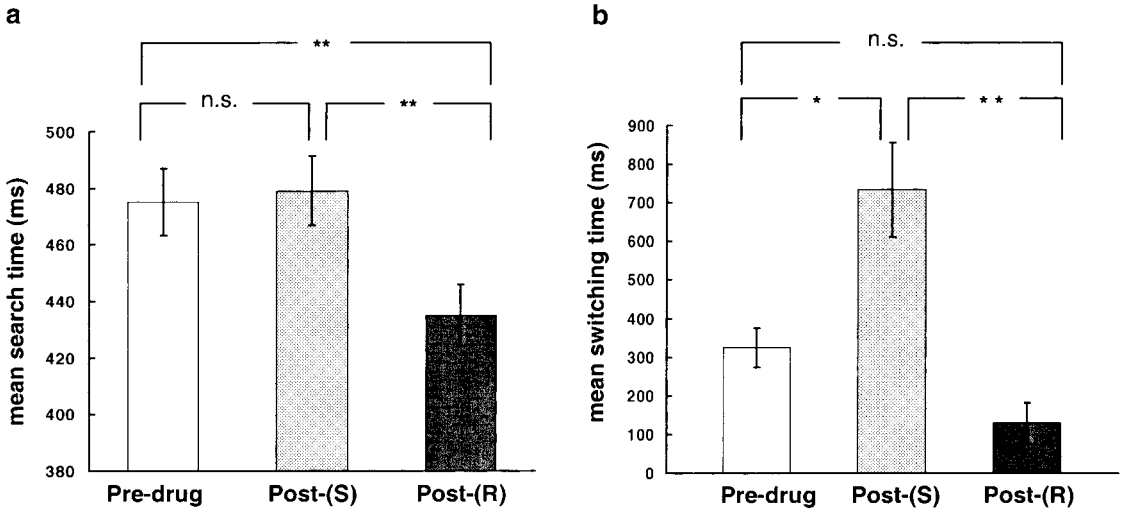

Fig. 3. Results of neuropsychological tasks. (a) Results of the visual pop-out search. Bar graphs represent the pooled reaction times for pop-out search within four different set sizes ranging from four to 16 distracters. Post-(S) and Post-(R) denote the time points of measurement about 90 min after drug application. (b) Results of the Wisconsin Card Sorting Test. Mean switching times performed before drug intake (pre-drug) and under the inf uence of the two MDE enantiomers (S) and (R). (*$P<0.05$, **$P<0.01$).

either (semantic and colour) task, and has no effect upon parallel visual search. Given its positive emotional effect and its influences on cognition, this agent may be responsible for the entactogenic component of the effect of the racemic mixture that is illegally used.

An alternative interpretation of our data, i.e. (R)-MDE has fewer psychotropic effects than the (S)-MDE and, additionally, that enhancements in neuropsychological performance under the (R)-enantiomer are possibly due to repetition effects, is unlikely for the following reasons. The increase of depressiveness after ingestion of (R)-MDE was approximately as pronounced as the decrease in depressive mood after (S)-MDE. Secondly, contrasts of neural activity of both enantiomers against each other's data could distinctly demonstrate that there exist objective patterns of different brain activations after ingestion of (S)- and (R)-MDE. Finally, repetition effects can be ruled out because the sequence of drug application was balanced over sessions. On the first study day, the (R)-MDE was applicated in three subjects ((S)-MDE: two subjects), and consequently in two subjects on the second study day ((S)-MDE: three subjects).

With respect to the neurotoxic effects of substituted amphetamines, our data favour the (R)-enantiomer as a possible candidate for the following reasons. This enantiomer acts upon visual cortical areas into which the 5-HT system preferentially projects. This is in line with a previous single-photon emission computed tomography study demonstrating 5-HT related effects to be prominent in the visual cortex of abstinent MDMA users (Chang et al., 2000). In addition, the (R)-enantiomer affects cortical areas relevant for carrying out those cognitive functions that have been found to be impaired after excessive abuse of MDMA, possibly by causing 5-HT depletion after increased activity of these regions. Finally, the approximately three-fold plasma concentrations of (R)-MDE alone would render this enantiomer as the likely candidate for any neurotoxic effects. Together with the differential psychological effects of the agent, this suggests that any future medical applications of MDE within the framework of psychotherapeutic interventions should make use of the (S)-enantiomer only.

In conclusion, our results link the pharmacological study of psychoactive agents and neuromodulatory systems with the neuropsychology of specific cognitive functions, and with brain activation by cognitively defined paradigms. They fit within the general framework provided by a large number of animal and human data from these fields. Given the wide use of illegal drugs and their potential for biological approaches to the understanding of psychological and psychopathological phenomena, this approach of stereo-specific drug challenge in human subjects, in conjunction with experiential, behavioural, neuropsychological and functional imaging methods, should be further carried on to study the unique features of the human mind.

References

Brodmann, K., 1909. Vergleichende Lokalisationslehre der Großhirnrinde. Barth, Leipzig.

Chang, L., Grob, C.S., Ernst, T., Itti, L., Mishkin, F.S., Jose-Melchor, R., Poland, R.E., 2000. Effect of ecstasy (3,4-methylenedioxymethamphetamine (MDMA)) on cerebral blood flow: a co-registered SPECT and MRI study. Psychiatry Research 98, 15–28.

Curran, H.V., Travill, R.A., 1997. Mood and cognitive effects of ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. Addiction 92, 821–831.

Derrington, A., 1996. Vision: filling in and pop out. Current Biology 6, 141–143.

Dittrich, A., 1998. The standardised psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry 31 (Suppl.), 80–84.

Ffytche, D.H., Howard, R.J., Brammer, J., David, A., Woodruff, P., Williams, S., 1998. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nature Neuroscience 1, 738–742.

Fiedler, K., 1991. In: Forga, J.P. (Ed.), Emotion and Social Judgement, Chapter 5. Pergamon, Oxford.

Gouzoulis-Mayfrank, E., Schreckenberger, M., Sabri, O., Arning, C., Thelen, B., Spitzer, M., Kovar, K.A., Hermle, L., Bull, U., Sass, H., 1999a. Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. Neuropsychopharmacology 20, 565–581.

Gouzoulis-Mayfrank, E., Thelen, B., Habermeyer, E., Kunert, H.J., Kovar, K.A., Lindenblatt, H., Hermle, L., Spitzer, M., Sass, H., 1999b. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental, double-blind placebo-controlled study. Psychopharmacology 142, 41–50.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H.J., Fimm, B., Sass, H., 2000. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). Journal of Neurology, Neurosurgery and Psychiatry 68, 719–725.

Hegadoren, K.M., Martin-Iverson, M.T., Baker, G.B., 1995. Comparative behavioural and neurochemical studies with a psychomotor stimulant, an hallucinogen and 3,4-methylenedioxy analogues of amphetamine. Psychopharmacology 118, 295–304.

Heinzel, G., Woloszczak, R., Thomann, P., 1993. TopFit version 2.0: pharmacokinetic and pharmacodynamic data analysis system for the PC. Gustav Fischer, New York.

Johnson, M.P., Hoffman, A., Nichols, D.E., 1986. Effects of the enantiomers of MDA, MDMA and related analogues on [3H]serotonin and [3H]dopamine release from superfused rat brain slices. European Journal of Pharmacology 132, 269–276.

McCann, U.D., Mertl, M., Eligulashvili, V., Ricaurte, G.A., 1998. Positron emission tomographic evidence of toxic effect of MDMA ('Ecstasy') on brain serotonin neurons in human beings. Lancet 352, 1433–1437.

McCann, U.D., Eligulashvili, V., Ricaurte, G.A., 2000. (±) 3,4-methylenedioxymethamphetamine ('ecstasy')-induced serotonin neurotoxicity: clinical studies. Neuropsychobiology 42, 11–16.

Morgan, M.J., 1999. Memory deficits associated with recreational use of 'ecstasy' (MDMA). Psychopharmacology 141, 30–36.

Morrison, J., Hof, P., 1992. The organisation of the cerebral cortex. Discussions in Neuroscience 11, 1–80.

Nauta, W., Feirtag, M., 1990. Neuroanatomie. Spektrum-Verlag, Heidelberg.

Nelson, H.E., 1976. A modif ed card sorting test sensitive to frontal lobe defects. Cortex 12, 313–324.

Nichols, D.E., 1986. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identif cation of a new therapeutic class: entactogens. Journal of Psychoactive Drugs 18, 305–313.

Nichols, D.E., 1994. In: Cho, A.K., Segal, D.S. (Eds.), Amphetamine and Its Analogs, Chapter 1. Academic Press, San Diego, CA.

Oldf eld, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Parrot, A.C., Lees, A., Garnham, N.J., Jones, M., Wesnes, K., 1998. Cognitive performance in recreational users of MDMA of 'ecstasy': evidence for memory def cits. Journal of Psychopharmacology 12, 79–83.

Parrot, A.C., 2000. Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioral indices of change. Neuropsychobiology 42, 17–24.

Podell, K., Lovell, M., Zimmerman, M., Goldberg, E., 1995. The cognitive bias task and lateralized frontal lobe functions in males. Journal of Neuropsychiatry and Clinical Neuroscience 7, 491–501.

Ricaurte, G.A., Finnegan, K.F., Nichols, D.E., DeLanney, L.E., Irwin, I., Langston, J.W., 1987. 3,4-Methylenedioxyethylamphetamine (MDE), a novel analogue of MDMA, produces long-lasting depletion of serotonin in the rat brain. European Journal of Pharmacology 137, 265–268.

Ricaurte, G.A., Yuan, J., McCann, D.U., 2000. (±) 3,4-methylenedioxymethamphetamine ('ecstasy')-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology 42, 5–10.

Scheffel, U., Szabo, Z., Mathews, W.B., Finley, P.A., Dannals, R.F., Ravert, H.T., Szabo, K., Yuan, J., Ricaurte, G., 1998. In vivo detection of short- and long term MDMA neurotoxicity — a positron emission tomography study in the living baboon brain. Synapse 29, 183–192.

Spitzer, M., Braun, U., Hermle, L., Maier, S., 1993. Associative semantic network dysfunction in thought-disordered schizophrenic patients: direct evidence from indirect semantic priming. Biological Psychiatry 34, 864–877.

Spitzer, M., Bellemann, M.E., Kammer, T., Guckel, F., Kischka, U., Maier, S., Schwartz, A., Brix, G., 1996. Functional MR imaging of semantic information processing and learning related effects using psychometrically controlled stimulation paradigms. Cognitive Brain Research 4, 149–161.

Sprague, J.E., Evermann, S.L., Nichols, D.E., 1998. An integrated hypothesis for the serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine. Neurotoxicology 19, 427–441.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Georg Thieme-Verlag, Stuttgart.

Treisman, A., Sato, S., 1990. Conjunction search revisited. Journal of Experimental Psychology, Human Perception Performance 16, 459–478.

von Zerssen, D., 1976a. Depressivitaets-Skala. Beltz, Weinheim.

von Zerssen, D., 1976b. Bef ndlichkeitsskala. Beltz, Weinheim.

von Zerssen, D., 1976c. Beschwerden-Liste. Beltz, Weinheim.

Wareing, M., Fisk, J.E., Murphy, P.N., 2000. Working memory def cits in current and previous users of MDMA. British Journal of Psychology 91, 181–188.

Weisbrod, M., Maier, S., Harig, S., Himmelsbach, U., Spitzer, M., 1998. Lateralized semantic and indirect semantic priming effects in people with schizophrenia. British Journal of Psychiatry 172, 142–146.