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Differential psychopathology and patterns of cerebral glucose utilisation produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET)

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Abstract

Until recently, racemic ketamine (*S*-ketamine/*R*-ketamine=50:50) has been used to study NMDA receptor hypofunction in relation to pathophysiological models of schizophrenia. Ketamine given to normal humans in subanesthetic doses produces a model psychosis including both positive and negative symptoms of schizophrenia. More recently it has been shown that at subanesthetic doses the pure (*S*)- and (*R*)-ketamine enantiomeres interact differently with the NMDA and sigma receptor sites in human brain. It was found that (*S*)-ketamine binds with a 3–4 time higher affinit to the PCP binding site of the NMDA receptor than (*R*)-ketamine, and that at these concentrations (*R*)-ketamine interacts also weakly with the sigma receptor sites, where (*S*)-ketamine binds only negligibly. To further investigate the role of NMDA-receptor mediated neurotransmission in schizophrenic psychosis, the effects of pure (*S*)- and (*R*)-ketamine enantiomeres on brain energy metabolism in normal humans using positron emission tomography and [^{18}F]fluorodeoxyglucos (FDG) are reported here. Psychotomimetic doses of (*S*)-ketamine increased cerebral metabolic rates of glucose (CMRglu) markedly in the frontal cortex including the anterior cingulate, parietal and left sensorimotor cortex, and in the thalamus. The metabolic changes in the frontal and left temporal cortex correlated with ego-disintegration and hallucinatory phenomena. Equimolar doses of (*R*)-ketamine tended to decrease CMRglu across brain regions and significantl suppressed CMRglu in the temporomedial cortex and left insula. (*R*)-ketamine did not produce psychotic symptoms, but a state of relaxation. The (*S*)-ketamine-induced metabolic hyperfrontality appears to parallel similar metabolic finding in acute psychotic schizophrenic patients and encourages further investigations of glutamatergic disturbances in schizophrenia.

Keywords: Model psychosis; Schizophrenia; Glutamate; (*S*)- and (*R*)-ketamine enantiomeres; *N*-Methyl-D-aspartate (NMDA) receptor; Sigma receptor; Cerebral glucose metabolism; Frontal cortex; PET (Positron emission tomography); [^{18}F]Fluorodeoxyglucose (FDG)

1. Introduction

Phencyclidine (PCP) and its congener ketamine are two anesthetics that can uniquely produce a psychosis-like mental state in normal humans, including both positive and negative symptoms of schizophrenia (Luby et al., 1959; Domino et al., 1965). At subanesthetic doses, ketamine primarily blocks the PCP binding site of the *N*-methyl-D-aspartate (NMDA)-sensitive glutamate receptor giving strong support for a glutamate deficienc hypothesis in schizophrenia (Anis et al., 1983). The glutamate hypothesis is further supported by the findin of a decreased glutamate concentration in cerebrospinal flui of schizophrenics (Kim et al., 1980), alterations in cortical and subcortical NMDA receptor densities (Deakin et al., 1989; Kornhuber et al., 1989; Simpson et al., 1992; Ishimaru et al., 1994), and reduced glutamate release in postmortem schizophrenic brain preparations (Sherman et al., 1991). Moreover, pharmacological models of schizophrenia incorporating the thalamic filte theory propose that blockade of

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NMDA receptors located on frontostriatal pathways by ketamine should theoretically lead to an information overload of the frontal cortex and thereby to psychotic symptoms and cognitive fragmentation as seen in ketamine-induced mental states and naturally occurring psychoses (Carlsson and Carlsson, 1990; Vollenweider, 1992). This hypothesis is supported by our previous FDG-PET finding demonstrating that administration of racemic ketamine in normal volunteers leads to a marked metabolic hyperfrontality which is related to derealisation and depersonalisation phenomena (Vollenweider et al., 1996). This hyperfrontality findin is of particular interest, because recent PET- and SPECT- studies of drug-naive and chronic schizophrenics in acute episodes actually revealed a hyperfrontal metabolic pattern (Volkow et al., 1986; Cleghorn et al., 1989; Ebmeier et al., 1993; Parellada et al., 1994). Most intriguingly, hyperfrontal acutely ill schizophrenics appear to have more positive than negative symptoms (Cleghorn et al., 1989; Kaplan et al., 1993) suggesting that metabolic hyperfrontality could be an important pathophysiological manifestation of positive symptom formation in acute psychotic episodes.

More recently it has been shown that the relative psychotomimetic potency of subanesthetic doses of the pure (*S*)- and (*R*)-ketamine enantiomeres parallels their relative affinit at the NMDA receptor complex (Øye et al., 1992; Mathisen et al., 1995), and their relative potency to block NMDA-mediated neurotransmission in animal studies (Zeilhofer et al., 1992). In particular, it was found that (*S*)-ketamine binds with a 4 to 5 times higher affinit to the PCP binding site of the NMDA receptor complex in human brain than (*R*)-ketamine. In addition, it was found that at these concentrations (*R*)-ketamine has also a weak affinit for the sigma receptor sites, where (*S*)-ketamine binds only negligibly (Øye et al., 1991). Thus by using the pure (*S*)-ketamine enantiomere instead of racemic ketamine, it should be possible to separate out the putative sigma effects of (*R*)-ketamine on mental state and cerebral glucose metabolism. This is of particular importance, because the sigma receptor system has been suggested to be an alternative candidate in the pathophysiology of schizophrenia, since certain benzomorphanes are thought to produce their dissociative effects through sigma receptor interaction (Debonnel, 1993).

In the present FDG/PET study we have reevaluated the role of NMDA receptor blockade in the generation of metabolic hyperfrontality and its relation to acute psychotic symptoms by investigating the effects of the pure (*S*)- and (*R*)-ketamine enantiomeres on CMRglu in healthy volunteers using FDG-PET. We have hypothesized that (*S*)-ketamine in equipotent psychotomimetic doses to racemic ketamine should lead to a similar metabolic hyperfrontality associated with derealisation and depersonalisation phenomena as previously reported for racemic ketamine (Vollenweider et al., 1996), while (*R*)-ketamine in equimolar doses to (*S*)-ketamine might only slightly increase CMRglu or lead to different effects.

2. Materials and method

The study was approved by the Ethics Committee of the Psychiatric University Hospital Zürich. The subjects were examined at the Research Department of the Psychiatric University Hospital Zürich (PUK), the MRI Center of the University Hospital of Zürich, and the PET Department of the Paul Scherrer Institute Villigen (PSI).

2.1. Subjects

Ten healthy volunteers (male=6, female=4) with a mean age of 30.4 years (range 24–42) were recruited. All subjects gave informed consent prior to participation. The subjects were screened by psychiatric interview to assure that the subjects had neither personal nor family histories of major psychiatric disorders in first-degre relatives. Subjects with a history of illicit drug abuse were excluded from the study. The ‘openness’ and ‘neuroticism’ scales of the Freiburg Personality Inventory (FPI) (Fahrenberg et al., 1984) were also used as an exclusion criteria (Table 1). Subjects were healthy according to physical examination, electrocardiogram, blood, and urine analysis. All subjects had a normal MRI.

2.2. Experimental design

A within-subject, placebo controlled, counterbalanced design was used. The subjects were tested in two phases: a preliminary drug exposure phase (I) at the PUK was followed by a PET phase at the PSI (II). The subjects were free to withdraw from the study at any time. In phase (II), subjects were blind to the drug conditions and received counterbalanced at monthly intervals three PET scans: a baseline (placebo), an (*S*)- and an (*R*)-ketamine PET scan.

In a pilot study we found that the relative potency of (*S*)- and racemic ketamine to induce comparable psychotic symptoms in normal volunteers is about 1:0.6 (mg/kg). The dose for (*S*)-ketamine selected amounted 60% of the racemic dose used in our previous study and was high enough to assure psychotic reactions including illusions, hallucinations, and ego-disintegration (Vollenweider et al., 1996). The dose of (*R*)-ketamine was equimolar to (*S*)-ketamine. Because of the large distribution volume of (*S*)/(*R*)-ketamine in the body, each subject received i.v. during 5 min a standard dose of 15 mg (*S*)- or (*R*)-ketamine in 20 ml saline solution for induction of psycho-(patho)logical reactions. This initial ‘induction’ phase was followed by a 5 min lasting ‘equilibration’ phase with no further ketamine supply. Then, (*S*)- or (*R*)-ketamine saline solution was continuously infused i.v. at a subanesthetic

Table 1
Demographic features and global psychopathological scores under *S*- and *R*-ketamine

Baseline condition					*S*-Ketamine		*R*-Ketamine	
Volunteer no.	Sex	Age	FPI openness	FPI neuroticism	APZ global	EPI global	APZ global	EPI global
1	F	30	8	6	25	10	10	0
2	M	40	3	6	47	25	16	1
3	M	30	8	3	27	25	9	1
4	M	42	11	6	37	39	11	1
5	F	26	8	1	46	24	15	1
6	M	24	11	2	27	17	10	0
7	F	25	3	2	38	27	8	0
8	M	34	11	2	33	10	15	1
9	M	24	10	6	47	21	29	3
10	F	28	6	1	55	48	33	5
Mean		30.4	7.9	3.5	37.0	24.6	15.6	1.3
S.D.		6.4	3.1	2.2	12.6	11.8	8.6	1.6

The FPI (Freiburg personality inventory) scores for openness (O) and neuroticism (N) for 10 volunteers receiving (*S*)- and (*R*)-ketamine.
Means and S.D. of normative data of healthy controls, sex- and age-matched, are for openness 6.79±2.79 for males and 6.05±2.87 for females, and for neuroticism 5.52±3.52 for males and 6.73±3.65 for females. The APZ (altered state of consciousness) and EPI (ego-pathology inventory) global scores refer to the phase during PET investigation.

dose (0.014–0.02 mg/kg/min) using an infusion pump to maintain the initially induced psycho(patho)logical symptoms over a period of 53 min.

2.3. Substances

(*S*)- and (*R*)-ketamine enantiomeres were prepared by E. Ratti-Moberg, Department of Pharmacology, University of Oslo, Norway, and dissolved in 0.9% sterile NaCl, the concentrations used were 1 mg/ml for each (*S*)- and (*R*)-ketamine.

2.4. Psychometric scales

All subjects were examined by an experienced psychiatrist to assess scores in baseline (placebo) and drug conditions using the 'Ego Pathology Inventory' (EPI) (Scharfetter, 1990a) and the inventory of the 'Association for Methodology and Documentation in Psychiatry' (AMDP) (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie AMDP, 1981). From the AMDP inventory two total scores for 'manic-depression' and 'schizophrenia' (syndrome scores) and 12 subscale scores for 'apathy', 'hallucinatory-disintegration', 'thought disorder', 'mania', 'depression' etc. can be derived. The 'Ego Pathology Inventory' (EPI) reliably measures ego pathology and related behavior (Scharfetter, 1981; Weber and Scharfetter, 1984; Scharfetter, 1990b). The EPI yields a global score (EPglo) and 5 subscale scores measuring 'ego identity' impairment, 'ego demarcation', 'ego consistency', 'ego activity', and 'ego vitality'. The ego identity subscale includes changes or loss of one's own identity in respect to 'gestalt', physiognomy, gender, and biography. Ego demarcation refers to one's uncertainty or lack in differentiating between ego and non-ego spheres concerning the thought process, affective state and body experience. The ego consistency subscale comprises the dissolution, splitting and destruction in experiencing a coherent self, body, thought process, chain of feelings and a structured external world. Ego activity refers to the defici in one's own ability or power for self-determined acting, thinking, feeling and perceiving. The ego vitality subscale includes the experience or fear of one's own death, of the fading away of liveliness, of ruin of mankind or of the universe.

The EWL (Eigenschaftswörterliste) mood rating scale (Janke and Debus, 1978) and the 'Altered States of Consciousness Questionnaire' (APZ) (Dittrich, 1985, Dittrich, 1994) were applied as a self-assessment inventory to evaluate drug effects as changes from the pre-drug condition. The EWL mood rating scale measures various types of mood states and related behavior: 'efficiency' 'deactivation', 'extroversion', 'introversion', 'well being', 'irritability', and 'anxiety'. The APZ-questionnaire yields a global score (APZglo) and three subscale scores measuring shifts in mood and changes in the experience of the self/ego and of the environment in altered states of consciousness (ASC). The firs subscale OSE ('oceanic boundlessness') measures derealisation and depersonalisation phenomena associated with a positive basic mood ranging from heightened feelings to sublime happiness. The second subscale AIA ('dread of ego-dissolution') measures ego-disintegration, loss of autonomy and self-control variously associated with arousal, anxiety, and paranoid feelings of being endangered. The third subscale OSE ('visionary restructuralization') refers to auditory and visual illusions, (pseudo)-hallucinations, synaesthetic phenomena, as well as to changes in the meaning of various percepts (Dittrich, 1994). The APZ dimensions OSE, AIA and VUS have shown to be independent of etiology, e.g.

the inducing factor(s) of ASC (Dittrich et al., 1981, Dittrich et al., 1985).

2.5. Phase I: Preliminary drug exposure

In order to reduce risks and anxiety, and in order that subjects could get trained to lie still for about 50 min under the influenc of psychotomimetic dose of (*S*)-ketamine, subjects received a preliminary drug exposure in a recreational environment at the PUK. Upon arriving at the PUK Research Department, subjects completed the EWL mood rating scale. In the subsequent drug session, subjects were examined by an experienced psychiatrist before and at regular intervals after substance administration using the Ego Pathology (EPI) and the AMDP inventory. The APZ and the EWL were also completed at the end of the session.

2.6. Phase II: PET studies

Each subject underwent at monthly intervals three FDG-PET scans, receiving on each occasion placebo (baseline), (*S*)- or R- ketamine. Upon arriving at the PSI PET Department (1100 h), subjects were examined using the EWL rating scale. Following this baseline measure, placebo or drug infusion was started according the scheme described above. Subjects had their eyes closed and their ears plugged during PET scanning. Subjects were examined immediately after PET scanning using the AMDP and EPI rating scales. Each subject completed the EWL and APZ questionnaire after the drug effects had completely subsided.

FDG-PET scans were performed in 10 volunteers using a CTI (Siemens 933/04-16) tomograph. The scanner measures seven contiguous planes (width, 8 mm) simultaneously with an in-plane transaxial resolution of 8 mm (full width half-maximum) after image reconstruction. Before tracer administration, a transmission scan was performed using an external germanium 68/gallium 68 ring source with the fiel of view parallel to and from 20 to 76 mm above the orbitomeatal line (OM line) and in a second position displacing the fiel of view 40 mm in the cranial direction. A 'dynamic scan' procedure with a series of consecutive scans with increasing time duration was performed during the firs 48 min after tracer infusion. This scan was followed by one 5-min scan in the second position, 50 to 106 mm above the OM line ('static scan'). At each scan, seven planes were recorded simultaneously but, because of two planes overlapping after axial displacement, the total number of recorded planes was twelve. FDG was infused slowly through an arm vein over 3 minutes using an infusion pump simultaneously with the beginning of the dynamic scan. The mean administered FDG dose was 177.6 MBq (min=107.3, max=244.2). Twenty-three arterial blood samples were collected from an indwelling radial artery catheter (Teflon 0.8 mm) for determination of blood plasma radioactivity, glucose concentration, and drug levels. A urethane foam head-holder was made for each subject to fi the subject's head parallel to the OM line, and to allow repeated PET experiments in virtually the same head position.

Using planes from the last time point of the dynamic measurement, 43–48 min, and from the static measurement performed between 48 and 53 min after injection, a contiguous set of 12 planes was formed representing uptake in a volume with an axial fiel of view of 112 mm long. The autoradiographic method described by Rhodes et al. (1983) was used to form parametric images of rCMRglu for each of the planes independently on a pixel-by-pixel basis.

The images were transformed into the standard stereotaxic space described by Talairach and Tournoux (1988) using a combination of linear and non-linear transformations after automatic localization of the AC-PC line. Feature localization is determined by intercomparison of the image volume with a set of standard templates (Friston et al., 1989, Friston et al., 1991).

After spatial standardization, a standardized set of regions of interest (ROls) (5.6 to 10.4 mm) using the Talairach coordinate system were placed exactly as previously reported symmetrically in cortical and subcortical regions in both hemispheres (Vollenweider et al., 1996). The coordinates according to Talairach of the following ROIs were determined and drawn in a number of adjacent planes (n=number of adjacent planes): frontomedial (n=8) and frontolateral cortex (n=8); insula (n=1); anterior (n=1) and posterior (n=1) cingulate; parietal cortex (n=2); somatosensory cortex (n=1); motor cortex (n=1); temporal lateral (n=4) and temporal medial cortex (n=2); temporal pole (n=1); occipital medial cortex including occipital medial anterior and posterior (n=2); occipital lateral cortex (n=2); caudate nucleus (n=3); putamen (n=2); thalamus (n=3); cerebellum (n=3); and white matter (n=2). For each plane one total image ROI was determined.

Due to the variable number of planes, the total inter-individual number of ROIs varied from 88 to 94 for both brain hemispheres, but the intraindividual number of ROls in the left and right hemispheres was always equal in a series of PET scans. The ROls were determined either on the last frame of the dynamic sequence (45 min after tracer injection) or in the static image obtained in the second head position. For each time frame, the ROI value was determined, decay corrected, and expressed in Bq/ml. In addition to the individual ROI values, ROIs in adjacent planes were pooled. Furthermore, all ROIs define in the frontal, temporal, and occipital cortex were pooled to a frontal, temporal, and occipital average.

Regional glucose utilization was expressed as glucose metabolic rate in μmol per 100 g per min. Relative glucose metabolic rate (ratio of absolute glucose metabolic rate to whole brain mean glucose metabolic rate) were determined

to control for intra- and interindividual global variations in metabolism. Whole brain mean glucose metabolic rate was calculated as the mean of three total image ROIs which cut through the basal ganglia. To compare the present data with our previous results (Vollenweider et al., 1996) and with data from schizophrenic patients, metabolic ratios such as the frontal to occipital ratio were calculated by dividing glucose metabolic rate in frontal cortex by glucose metabolic rate of the occipital cortex in the same hemisphere as described for schizophrenic patients by Buchsbaum et al. (1990). Changes of absolute or relative metabolism, and changes of metabolic ratios from a baseline to a ketamine scan were assessed as per cent difference from baseline.

2.7. Plasma ketamine assay

Plasma ketamine levels were measured using a gas chromatography-mass spectrometry method with a sensitivity of 10 ng/ml for ketamine (Feng et al., 1995). During PET scanning the volunteer's plasma was collected using the cannula in the radial artery after 0, 10, 30, 48 and 54 min. All plasma samples were stored at −20°C until analysis.

2.8. Statistical analysis

All analyses were performed by computer using SAS and STATISTICA/w™, version 5.0 (StatSoft™, 1995). In this study, each subject served as his or her own control to minimize the effect of interindividual variation in metabolic rates and psychopathology scores. To examine the a priori hypothesis that (*S*)-ketamine subjects would show increases in CMRglu in the frontal cortex the Wilcoxon matched pairs test was used. The same statistical approach was used to explore the significanc of changes within other brain regions and in psychopathology scores from placebo to ketamine conditions. The Spearman correlation coefficien was used to evaluate correlations between changes in metabolic rates or ratios and psychopathology scores and to retest our previous findin of significan correlations between metabolic hyperfrontality and ego-disorders (Vollenweider et al., 1995, Vollenweider et al., 1996). Since no correction for the number of comparisons were made, the results should be regarded as exploratory rather than confirmatory

3. Results

3.1. Plasma ketamine levels

The plasma levels of the (*S*)- and (*R*)-ketamine ranged from 269 to 523 ng/ml (mean 379±71 ng/ml) and from 280 to 508 ng/ml (mean 389±74 ng/ml) between subjects. Plasma levels between individuals remained within the same range of magnitude during ketamine infusion. The mean time that elapsed from the start of the (*S*)-ketamine infusion to the appearance of psychotic symptoms was about 5 min at a mean plasma ketamine level of 539 ng/ml.

3.2. Psychopathology

3.2.1. (S)-Ketamine

Continuously supplied subanesthetic doses of (*S*)-ketamine produced acute psychotic reactions including depersonalisation and derealisation phenomena, visual disturbances, thought disorders, and apathy as measured by the APZ, AMDP and EPI rating scales (Fig. 1). Visual disturbances ranged from pseudohallucinations to elementary and complex hallucinations. Auditory distortions were rather illusions (hyperacusis) than true hallucinations. Subjects reported that background noise was unusually loud and sometimes influence their content of thought and inner experience. During (*S*)-ketamine-induced psychosis, directed attention and thinking became difficult and most of the subjects lost their interest in the experimental situation, showed flattene affects, and became progressively emotionally withdrawn. The results of the mood rating scale (EWL) showed increased scores for 'deactivation' ($P<0.01$), introversion' ($P<0.05$), negative and dysphoric feelings ('emotional irritability') ($P<0.05$), and anxiety ($P<0.01$) (Fig. 2). All of the subjects reported distortion of the body-image, loosening of ego-boundaries, and alterations of the sense of time and space variously associated with emotional changes ranging from heightened feelings to euphoria (30%), indifference (30%) or heightened anxiety (40%).

3.2.2. (R)-Ketamine

Equimolar doses of (*R*)-ketamine did not produce any psychotic symptoms in the same subjects under investigation. Most of the subjects experienced, however, a state of relaxation during (*R*)-ketamine infusion, which is indicated by the small but not significan increase of the APZ score for OSE (oceanic boundlessness; $P<0.06$) and the EWL scores for 'well-being' ($P<0.09$), as well as by the slight decrease of the EWL scores for 'emotional irritation' ($P<0.08$).

3.3. Absolute and relative cerebral metabolic rates of glucose

(*S*)-ketamine treatment increased cerebral metabolic rates of glucose (CMRglu: (mol/100 mg/min) in most of the brain regions examined. This metabolic stimulation was, however, not uniform across brain regions. Cortical brain regions were about 2–3 times more stimulated than subcortical regions, while within the cortical regions, frontal regions were about twice as stimulated as posterior regions (Fig. 3 and Fig. 4). As seen in Fig. 4, metabolic

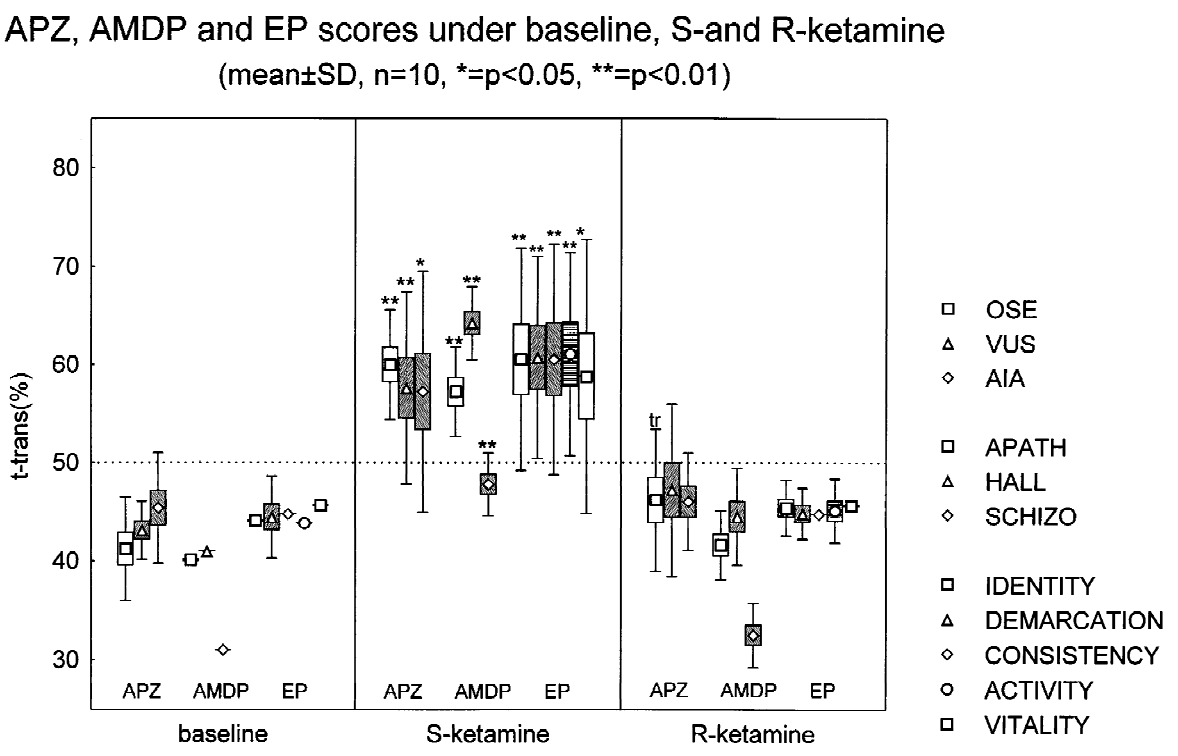

Fig. 1. Mean scores of selected APZ, AMDP and EPI subscales under baseline, (*S*)- and (*R*)-ketamine conditions during PET scanning (mean±S.D.). While (*S*)-ketamine administration resulted in a psychosis-like syndrome, equimolar doses of (*R*)-ketamine produced a state of relaxation as indicated by the slight, but only marginal increase of the APZ subscale score for OSE (oceanic boundlessness) (tr: $P=0.06$). Boxes indicate mean±S.E., significan changes are indicated by Wilcoxon's, $*P<0.05$, $**P<0.01$).

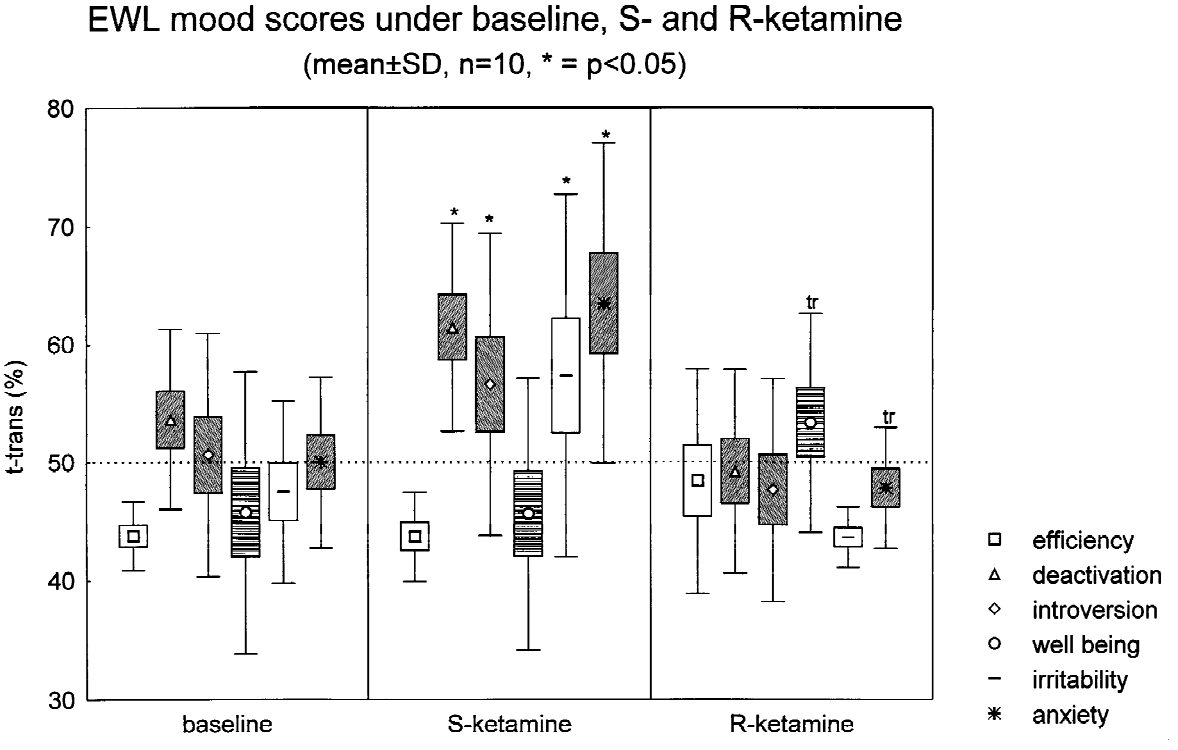

Fig. 2. Mean *t*-transformed scores of the EWL mood rating scale under baseline (placebo), (*S*)- and (*R*)-ketamine conditions during PET scanning (mean±S.D.). While (*S*)-ketamine significantl increased scores for 'emotional irritability' and 'anxiety', equimolar doses of (*R*)-ketamine tended to increase scores for 'well being' ($P<0.09$) and to decrease scores for 'emotional irritability' ($P<0.08$). Boxes indicate mean±S.E., significan changes are indicated by Wilcoxon's, $*P<0.05$, $**P<0.01$).

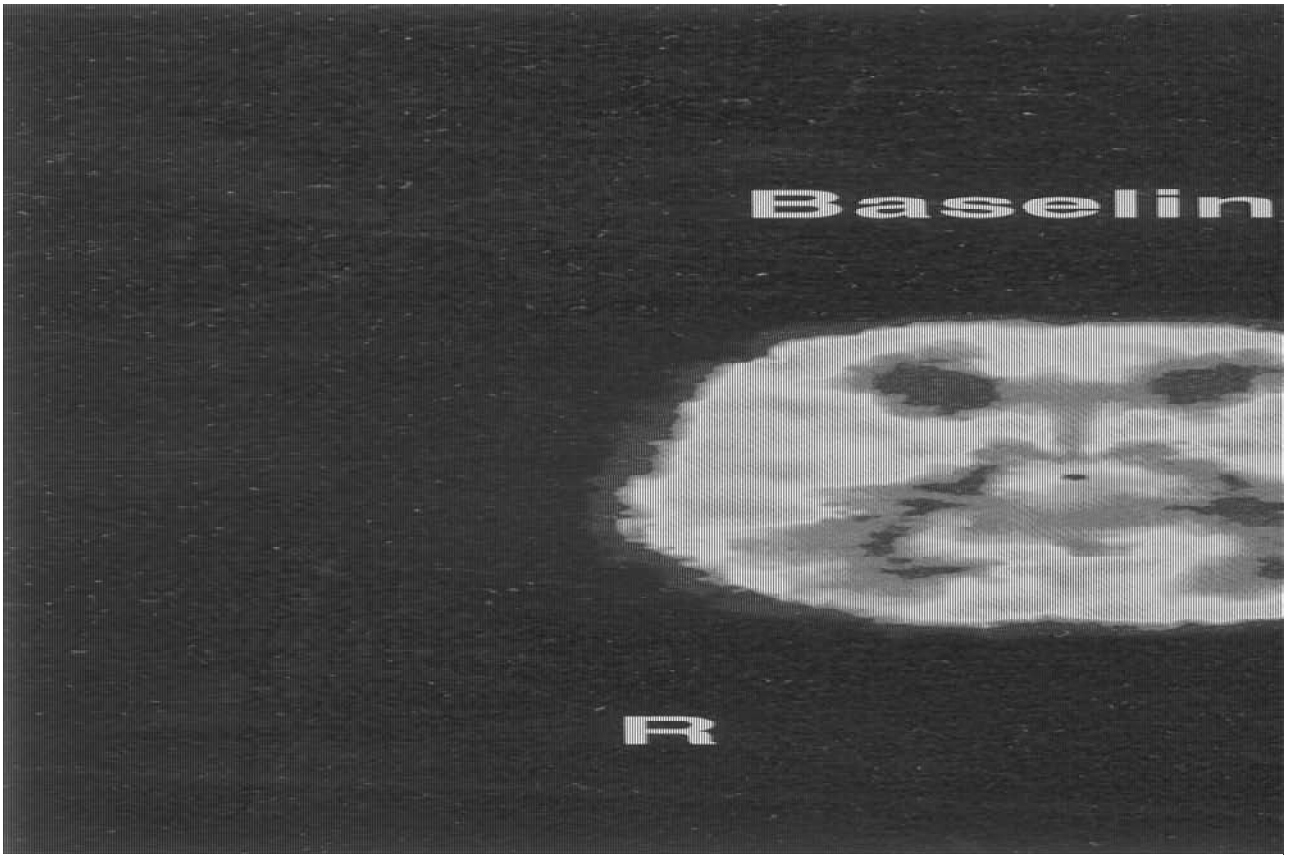

Fig. 3. [^{18}F]FDG-PET images at the level of the basal ganglia from the same subject under baseline, (*S*)- and (*R*)-ketamine conditions. (*S*)-Ketamine and (*R*)-ketamine had opposite effects on absolute CMRglu (CMRglu: μmol/100 mg/min), while (*S*)-ketamine increased global CMRglu, (*R*)-ketamine tended to decrease CMRglu in corresponding brain regions. (*S*)-Ketamine stimulated CMRglu markedly in the frontal and parietal cortex, while the occipital cortex was only moderately affected (hyperfrontality). The thalamus was the only subcortical region that showed a trend level increase in CMRglu. (*R*)-Ketamine decreased CMRglu significantl in the temporomedial cortex and left insula.

rates of glucose were markedly increased in the frontomedial (19.6%), frontolateral (20.1%), cingulate anterior (23.5%), cingulate posterior (24.0%), and parietal (27.35%) cortices in both hemispheres (%=mean change of the left and right hemisphere). The somatosensory (21.1%) and motor (23.0%) cortex were stimulated significantl in the left hemisphere only. Although (*S*)-ketamine also tented to stimulate subcortical structures such as the caudate nucleus or the putamen, the thalamus was the only region that showed bilaterally a trend level increase in CMRglu (17%, $P<0.07$). Whole brain metabolism was not increased significantl by (*S*)-ketamine (12%, $P<0.09$). Relative CMRglu (CMRglu/whole brain) were also increased bilaterally in the frontomedial (7.7%), frontolateral (8.4%), and cingulate posterior (12.5%) cortices, and in the left parietal cortex (18.2%), but decreased in the left temporomedial cortex (4.8%, all $P<0.05$).

Although (*R*)-ketamine tended, in contrast to (*S*)-ketamine, to decrease CMRglu across brain regions, whole brain CMRglu was not reduced significantl (−9.8%, $P<0.07$) (Fig. 3 and Fig. 4). As seen in Fig. 5, significan reductions in absolute CMRglu were found bilaterally in the temporomedial cortex (−13.4%) and left insula (−14%). Relative CMRglu were also decreased signifi cantly in the right temporal cortex (−4.0%, $P<0.05$) and bilaterally in the cerebellum (−5.0%/−4.0%, $P<0.05$).

3.4. Cortico-cortico and cortico-subcortical metabolic ratios

To look for a hyper- or hypofrontal pattern of metabolism, ratios of metabolic rates (‘metabolic gradients’) between brain regions were calculated (Table 2). Mean changes from a baseline to a (*S*)- or (*R*)-ketamine scan were assessed as per cent changes from baseline. Metabolic ratios were investigated to control for interindividual fluctuation and to compare the present data with those obtained in our previous study using racemic ketamine (Vollenweider et al., 1996). As seen in Table 2, (*S*)-ketamine significantl increased the fronto-temporal ratios between 7% and 14% and the fronto-occipital ratios about 10% in both hemispheres, indicating a hyperfrontal pattern. Of the frontocortical-subcortical ratios, the ratio between the left frontolateral cortex and caudate nucleus (16.0%) and the ratios between the right frontomedial/-lateral

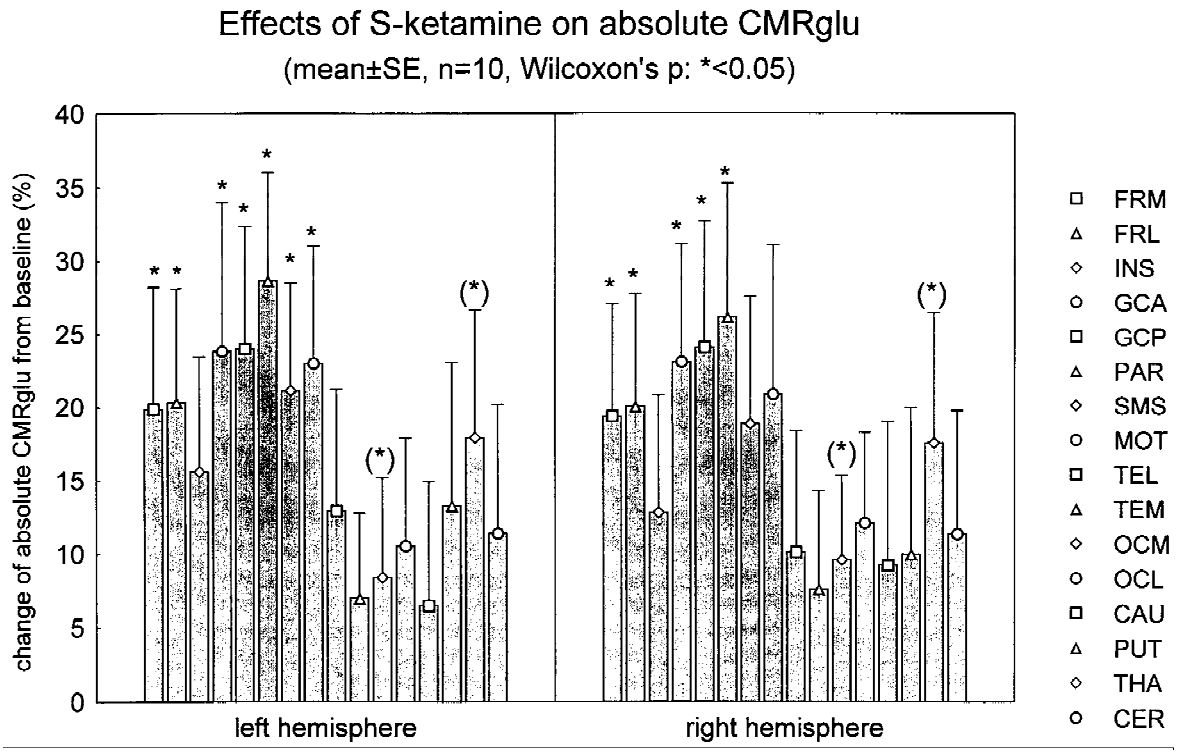

Fig. 4. Mean changes of absolute CMRglu from baseline to (*S*)-ketamine conditions. Metabolic rates of glucose were markedly increased in the frontal cortex including the cingulate anterior and posterior, in the parietal and in the left somatosensory cortex. The thalamus and the occipitomedial cortex were also stimulated, but only with marginal significanc ($P<0.07$). Significan increases are indicated by Wilcoxon's, *$P<0.05$. FRM, frontomedial xortex; FRL, frontolateral cortex; CGA, cingulate anterior; CGP, cingulate posterior; PAR, parietal cortex; SMS, somatosensory cortex; MOT, motor cortex; TEL, temporlateral cortex; TEM, emporomedial cortex; OCM, occipitomedial cortex; OCL, occipitolateral cortex; CAU, caudate nucleus; PUT, putamen; THA, thalamus; CER, cerebellum.

cortex and putamen (12.3 and 13.2%) were significantl increased.

As seen in Table 2, (*R*)-ketamine treatment resulted also in small increases of the fronto-temporal ratios. These increases averaged between 3% and 7% and were signifi cant predominantly in the right hemisphere. The ratios between the frontomedial/-lateral cortex and the putamen were significantl increased in the left hemisphere (6.4% and 6.3%).

3.5. Psychopathology and correlations with metabolism

To explore the relationship between (*S*)- and (*R*)-ketamine-induced reactions and metabolic alterations, scores for hallucinatory-disintegration, ego-dissolution, and mood changes of the APZ, AMDP and EPI rating scales were correlated with changes of metabolic ratios ('gradients') or absolute metabolic rates of glucose.

3.5.1. (S)-Ketamine

The APZ score for OSE referring to derealisation and depersonalisation phenomena, showed a positive correlation with the increase of absolute CMRglu bilateral in the frontomedial cortex (left/right: $P<0.05/P<0.07$) and in the right temporomedial cortex ($P<0.05$). Similarly, the ego-pathology score for 'ego-identity' impairment showed a positive correlation with the increase of absolute CMRglu in the frontomedial ($P<0.04/P<0.04$), frontolateral ($P<0.05/P<0.04$), cingulate anterior ($P<0.01/P<0.004$) and cingulate posterior ($P=$ns$/P<0.04$) cortices. With respect to hallucinatory phenomena, scores for VUS and 'hallucinatory-disintegration' showed bilaterally positive correlations with the increase of absolute CMRglu in the occipitomedial (VUS: $P<0.07$/hall: $P<0.06$) and occipitolateral (VUS: $P<0.06$/hall: $P<0.05$) cortices. The 'apathy' score correlated positively with the increase of the absolute CMRglu in the left and right parietal cortices ($P<0.01/P<0.04$) and in the left insula ($P<0.04$).

As seen in Table 2, the (*S*)-ketamine-induced scores for hallucinatory phenomena and ego-dissolution ('hall', 'schizo' and AIA) correlated predominantly with the hyperfrontality findin in the left hemisphere. For example, the AMDP subscale score 'hallucinatory-disintegration' (hall) which refers to hallucinations and ego-dissolution correlated negatively with the left fronto-temporal ratios. Similarly, the APZ scores for AIA comprising items for an anxious ego-dissolution, and the APZ scores for VUS including predominantly items for illusions and hallucinations showed also negative correlations with the increases of the fronto-temporal ratios in the left hemisphere.

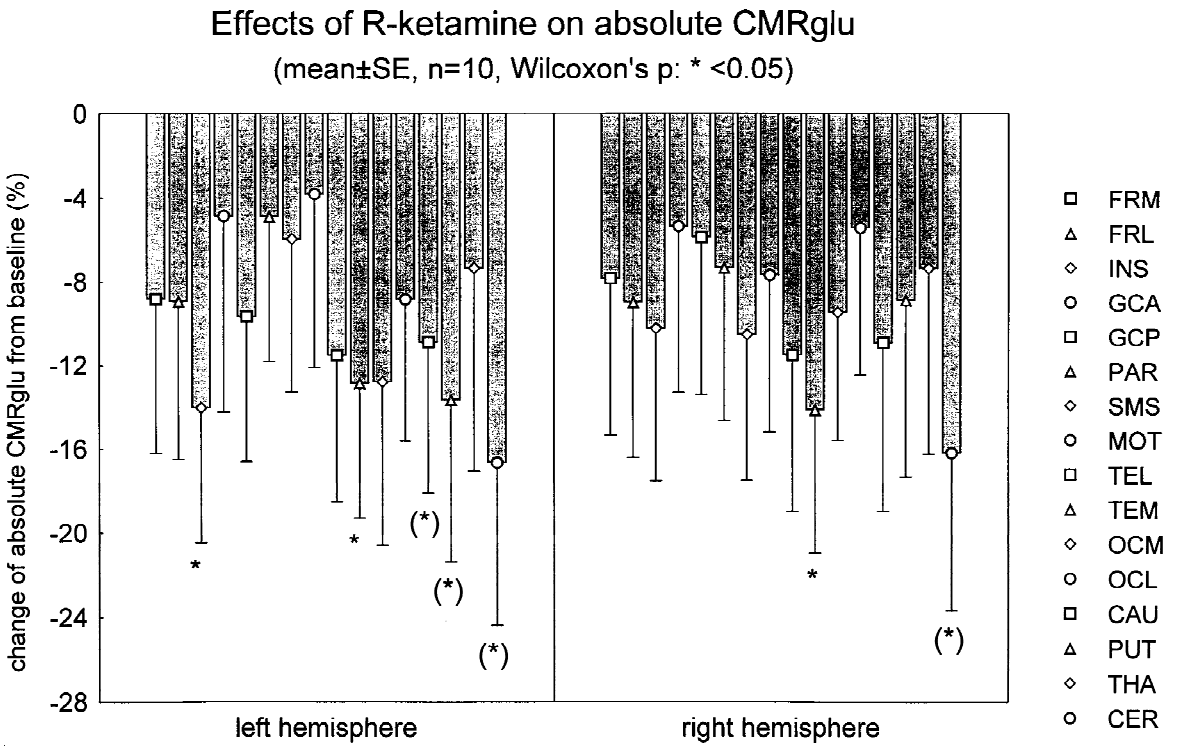

Fig. 5. Mean changes of absolute CMRglu from baseline to (*R*)-ketamine conditions. Significan decreases of CMRglu were found in the temporomedial cortex and in the left insula. Moderate, but not significan decreases were also found in the cerebellum and the left caudate-putamen ($P<0.07$). Significan decreases are indicated by Wilcoxon's, $*P<0.05$. For legend see Fig. 4.

The 'schizophrenic' syndrome of the AMDP rating scale and the AMDP subscale score 'hallucinatory-disintegration', which is included in the item pool of the 'schizophrenic' syndrome, correlated negatively with the increase of the frontomedial-occipitomedial ratio in the left hemisphere. The ratio between the frontolateral cortex and

Table 2
Correlations between changes of metabolic gradients and psychopathology scores under *S*- and *R*-ketamine conditions ($n=10$)

Metabolic gradients (ratios)	*S*-Ketamine								*R*-Ketamine							
	Left hemisphere				Right hemisphere				Left hemisphere				Right hemisphere			
	Change of gradients		Correlations with syndromes		Change of gradients		Correlations with syndromes		Change of gradients		Correlations of syndromes		Change of gradients		Correlations with syndromes	
	%	*P*(w)		*r*(sp)	%	*P*(w)		*r*(sp)	%	*P*(w)		*r*(sp)	%	*P*(w)		*r*(sp)
FM-OM	10.7	tr	Hall	−0.04	9.1	ns	Hall	−0.08	6.00	ns			1.2	ns		
			Schizo	−0.05			Schizo	−0.07								
FL-OL	11.7	a			9.8	ns			5.80	ns			0.1	ns		
FM-TM	12.8	b	Hall	−0.01	14.0	a			4.40	ns			7.4	a		
			VUS	−0.04												
FM-TL	6.8	tr	AIA	−0.03	9.4	b			3.20	A	AIA	−0.08	4.6	a		
FT-TL	7.6	b	Hall	−0.02	10.2	b			2.90	ns			3.2	a		
			VUS	−0.04												
FL-CA	16.0	a	Intro	0.04	14.2	ns			2.20	ns	Intro	0.06	3.3	ns		
			Deac	−0.04			Deac	−0.05			Deac	−0.05			Deac	−0.02
FM-PU	7.4	tr			12.3	a			6.40	b			2.6	ns		
FL-PU	8.2	tr	Hall	−0.02	13.2	a	Hall	−0.001	6.30	a			1.2	ns		

FM, frontomedial cortex; FL, frontolateral cortex; GA, cingulate anterior; CA, caudate nucleus; PU, putamen; TM, temporomedial cortex; TL, temporolateral cortex; OM, occipitomedial cortex; Hall, hallucinatory-desintegration syndrome (AMDP subscale score); Schizo, schizophrenic syndrome (AMDP syndrome score); AIA, dread of ego dissolution (APZ scale); VUS, visionary restructuralisation (APZ scale); Deac, deactivation (EWL scale); Intro, introversion (EWL scale).

Significan changes of metabolic gradients are indicated by $^{a}P<0.05$; $^{b}P<0.01$; trend level (tr), $0.05<P<0.07$; ns, no significanc (Wilcoxon); significan correlations are indicated by Spearmans roh *r*(sp), values are not corrected for multiplicity of tests.

putamen was the only cortical-subcortical ratio that showed a significan negative correlation with the 'hallucinatory-disintegrative' syndrome in the left ($P<0.02$) and right ($P<0.001$) hemisphere.

3.5.2. (S)- and (R)-Ketamine

Under both (*S*)- and (*R*)-ketamine conditions, the EWL score for 'introversion' showed a negative correlation with the increase of the absolute CMRglu in the left caudate nucleus ($P<0.05$), and a positive correlation with the increase of the fronto-caudate ratio in the left hemisphere. While the EWL score for 'deactivation' correlated negatively with the increase of the fronto-caudate ratio in both hemispheres.

4. Discussion

4.1. Psychopathology

(*S*)-Ketamine administration in healthy volunteers produced an acute psychosis-like syndrome including ego-dissolution, illusions and hallucinations, thought disorders, paranoid ideations, and changes of mood and affect. The (*S*)-ketamine-induced hallucinatory-disintegration, loss of self-control over the thought processes and intentionality, perceptual alterations in the sense of time and space, and changes in the meaning of surroundings resembled in many ways acute schizophrenic decompensation (Bowers and Freedman, 1966; Scharfetter, 1987; Gouzoulis et al., 1994). In particular, loosening of ego-boundaries and/or visual hallucinations were associated in some of the subjects (30%) with euphoria and heightened awareness, while other subjects reacted to depersonalisation and derealisation phenomena with a feeling of indifference (30%), anxiety and/or paranoid feelings of being endangered (40%). The difficult in reality appraisal and impairment of ego-functioning was transient and occurred with varying intensity across subjects, possibly because (*S*)-ketamine subjects-unlike schizophrenics-could at least in part recognize derealisation and depersonalisation phenomena as abnormal experiences and attribute them to the drug. Emotional disturbances and disorganization of thought appeared to be secondary to and influence by derealisation and depersonalisation phenomena. At the doses tested, visual disturbances ranged as previously reported for racemic ketamine from illusions to elementary and complex hallucinations (Collier, 1972; Ghoneim et al., 1985; Hansen et al., 1989; Øye et al., 1992; Krystal et al., 1994; Mathisen et al., 1995; Vollenweider et al., 1996). The association between heightened awareness, euphoria and visual hallucinations is in line with the view that the earliest affective changes in schizophrenic patients are often pleasurable (Chapman, 1966; Bowers, 1968; Hermle et al., 1992; Gouzoulis et al., 1994) and that visual hallucinations occur significantl more often in acute than in chronic schizophrenic patients (McCabe et al., 1972; Freedman and Chapman, 1973; Gouzoulis et al., 1994). Also consistent with previous reports suggesting that ketamine and PCP can mimic some negative symptoms of schizophrenia, (*S*)-ketamine produced apathy, emotional withdrawal, and a feeling of indifference (Collier, 1972; Corssen et al., 1968; Krystal et al., 1994). Interindividual differences in these responses might have been due either to variations in dosage or personality trait (Dittrich, 1994).

Comparison of the ego-pathology (EPI) scores (mean values) of the present study with EPI scores obtained in firs episode schizophrenic patients revealed that the ego-pathology scores 'ego-consistency', 'ego-identity' and 'ego-demarcation' of the present study were about 2/3 of the values seen in schizophrenic patients. Scores for the dimension 'ego-activity' (one's self-determined acting, thinking, feeling and perceiving) and scores for 'ego-vitality' were clearly less affected in (*S*)-ketamine subjects than in schizophrenic patients (Scharfetter, 1995). Taken together, the present finding support the view that NMDA receptor antagonists such as ketamine can produce positive and negative symptoms in healthy volunteers that are associated with schizophrenia, but that there are also differences, particular in the quality and quantity of ego-disorders at least at the doses tested.

Equimolar doses of (*R*)-ketamine did-in contrast to (*S*)-ketamine-not produce psychotic symptoms, but a state of relaxation and a feeling of well being. Although (*R*)-ketamine increased the scores of the EWL mood rating scale only a at trend level, a shift towards a positive basic mood was apparent. Subjects could well differentiate their (*R*)-ketamine experience from baseline (placebo) measurements. In addition, some of the subjects described their (*R*)-ketamine experience as a state of heightened awareness and sensitivity that was characterized by facilitated introspection, and a slight change in the sense of time, comparable to a meditative state. These subjective reports are in line with the moderate, but not significan increase of the OSE (oceanic boundlessness) score in fiv of the ten subjects.

Finally, the psychic effects of (*S*)-ketamine occurred at serum concentrations that suggest a primary interaction with the PCP binding site of the NMDA receptor complex (Øye et al., 1991). The fact that at 60% of a racemic dose (*S*)-ketamine produced virtually the same psychotic reactions as racemic ketamine strongly suggests that (*S*)-ketamine is the predominant psychotomimetically active agent in racemic ketamine.

4.2. Metabolism

The present PET data demonstrate that equimolar subanesthetic doses of the pure (*S*)- and (*R*)-ketamine enantiomeres produce opposite effects on CMRglu. While psychotomimetic doses of (*S*)-ketamine increased absolute CMRglu in most of the brain regions investigated, equimo-

lar doses of (*R*)-ketamine tended to decrease CMRglu in corresponding brain regions.

(*S*)-Ketamine produced a hyperfrontal metabolic pattern as indicated by the marked increase of absolute and relative CMRglu in the frontal cortex and by the increased fronto-occipital metabolic ratios. This (*S*)-ketamine-induced hyperfrontality and the overall pattern of metabolic changes seen after (*S*)-ketamine are very similar to those previously reported for racemic ketamine (*S*/*R*=50:50) (Vollenweider et al., 1996). Since at the doses tested, (*S*)-ketamine selectively blocks the NMDA receptor, it is possible to assume that the metabolic finding induced by (*S*)- and racemic ketamine are predominantly due to excessive NMDA receptor blockade. This interpretation is supported by fact that ketamine, PCP and the high affinit NMDA receptor antagonist MK-801 resulted in similar metabolic activations of the frontal cortex, limbic system and subcortical structures in rats (Nelson et al., 1980; Hammer et al., 1982; Tamminga et al., 1987; Piercey and Ray, 1988; Piercey et al., 1988).

A similar stimulation of the frontal cortex, the anterior cingulate, the temporomedial cortex, and the thalamus as seen in the present study, was also found in the psilocybin model of psychosis (Vollenweider et al., 1995), although psilocybin primarily activates 5-HT2 and 5-HT1 serotonin receptors. Thus the common hyperfrontality findin seen in both the ketamine and psilocybin models of psychosis strongly suggests that hyperfrontality reflect a fina metabolic manifestation (pathway) in acute psychosis that might be due to a disruption of a common pathway of sensory and cognitive processing. In this respect, cortico-striato-thalamic feedback loops controlling a thalamic filte function have been proposed to provide an anatomical substrate that gates the information flo via the thalamus to the frontal cortex. Filtering deficit of the thalamus have been linked to schizophrenia (Carlsson and Carlsson, 1990). The thalamic filte theory of schizophrenia suggests that disruption of cortico-striato-thalamic (CST-) feedback loops by ketamine or psilocybin should theoretically lead to an opening of the thalamic filte and a consecutive information overload of the frontal cortex and its limbic relay stations. Since both ketamine and psilocybin have been shown to activate indirectly the dopaminergic system, and since activation of the dopaminergic pathways may lead to a disruption of the information flo in CST-loops, the possibility remains that dopamine may still play a role in the pathogenesis of acute psychotic symptom formation (Meltzer et al., 1978, Meltzer et al., 1981).

Equimolar doses of (*R*)-ketamine generally decreased CMRglu across brain regions. Significan decreases of CMRglu were, however, only found bilaterally in the temporomedial cortex and in the left insula, two brain regions with high NMDA receptor densities. Similar, but not significan decreases of CMRglu were also observed in the cerebellum and caudate nucleus. It has been shown that at the doses tested (*R*)-ketamine does not only interact with the PCP binding site of the NMDA receptor, but also has a weak affinit to the sigma receptor sites. Thus the reduction of CMRglu in response to (*R*)-ketamine might be interpreted to be due to a moderate blockade of NMDA receptor mediated excitatory neurotransmission or to an additional interference with the sigma receptor sites. The involvement of the sigma receptor is supported by the fact that administration of the high affinit sigma receptor ligand d-NANM resulted in a similar reductions of CMRglu in rat brain, and particularly in brain regions with high sigma receptor densities such as the cerebellum (London et al., 1988; Weissman et al., 1988).

4.3. Hyperfrontality and psychopathology

The present findin of an association between metabolic hyperfrontality, derealisation phenomena and impaired ego-functioning in (*S*)-ketamine subjects confirm our previous results seen in the ketamine (racemic mixture) and psilocybin models of psychosis. For example, in the present study we found that the scores for 'oceanic boundlessness' (OSE) referring to depersonalisation and derealisation phenomena correlated positively with the increase of CMRglu in the frontomedial cortex. Moreover, scores for 'ego-identity' impairment showed a positive correlation with the increase of absolute CMRglu that extended from the left frontomedial cortex to right frontolateral cortex including the cingulate anterior cortex. These finding are similar to those reported in our previous ketamine and psilocybin studies where OSE and 'ego-identity' impairment correlated with the increase of CMRglu in the right frontomedial cortex, while the global 'ego-pathology' score correlated with the increased CMRglu in the frontomedial and frontolateral cortex (Vollenweider et al., 1995, Vollenweider et al., 1996). In the ketamine and psilocybin models of psychosis, 'ego-identity' impairment correlated also with the increase of the frontomedial-anterior cingulate ratio in the left and with the frontomedial-temporomedial ratio in the right hemisphere. In the present study, however, these correlations were similar in direction but were not significant perhaps because of the small sample size, differences in drug mechanism, or the variability of psychopathological responses.

The present hyperfrontality findin is of particular interest, because recent SPECT- and PET-finding suggest that metabolic hyperfrontality rather than hypofrontality is associated with positive symptoms, particularly in first episode schizophrenics. For example, a hyperfrontal pattern of CBF (Ebmeier et al., 1993; Parellada et al., 1994) or increased frontal to parietal ratio of CMRglu was found under resting conditions and associated with positive psychotic symptoms in acute unmedicated firs episode schizophrenics (Cleghorn et al., 1989; Kaplan et al., 1993). Similarly, a hyperfrontal metabolic pattern (Ebmeier et al., 1993) and a positive correlation between increased cere-

bral blood flo (CBF) in the right anterior cingulate cortex and a 'disorganization' syndrome was found in medicated and unmedicated chronic schizophrenic patients during acute psychotic episodes (Liddle et al., 1992; Ebmeier et al., 1993). Finally, ketamine administration in haloperidol-stabilized schizophrenics also resulted in a transient increase of CBF in frontomedial cortex including the anterior cingulate, concomitant with an exacerbation of positive psychotic symptoms (Lahti et al., 1995). Thus the (*S*)-ketamine-induced hyperfrontality does not only corroborate similar finding obtained with racemic ketamine and psilocybin, but appears to parallel comparable metabolic changes related to acute psychotic episodes in schizophrenic patients and contrasts with the hypofrontality findin in chronic schizophrenics.

The AMDP subscale 'hallucinatory-disintegration' which concomitantly measures ego-dissolution and hallucinations, showed bilaterally a negative correlation with the increase of the frontomedial-occipitomedial and the fronto-putamen ratios, and with the fronto-temporal ratios in the left hemisphere. A similar pattern of correlations with emphasis in the left hemisphere was also found in the ketamine and psilocybin models of psychosis (Vollenweider et al., 1995, Vollenweider et al., 1996). In the present study, we found, however, that both the AMDP subscale score for hallucinatory-disintegration and the syndrome score for schizophrenia showed-in contrast to our previous finding with racemic ketamine or psilocybin-only a trend level positive correlation with the increase of absolute CMRglu in the left temporal cortex and putamen (data not shown). Differences in the results with (*S*)-ketamine, racemic ketamine and psilocybin might be due to differences in the small sample size, dosage, drug mechanisms, or the variability in psychopathological responses. Nevertheless, the correlations between 'hallucinatory-disintegration' and the fronto-temporal and fronto-putamen ratios suggest that neuronal dysfunctions in remote areas of the frontal cortex such as the temporal lobe and the basal ganglia are critically involved in the pathophysiology of ego-disorders and hallucinations.

The negative correlations between 'hallucinatory-disintegration' and the fronto-occipital ratio seems surprising, but might be due to the fact that illusions and hallucinatory phenomena which are included in this syndrome are more related to metabolic changes in the occipital than in the frontal cortex. This interpretation is supported by both our present and previous findings namely that the APZ subscale VUS, which predominantly refers to illusions and visual hallucinations, tended to show a positive correlation with the increase of CMRglu in the occipital cortex (Vollenweider et al., 1995; Vollenweider et al., 1996).

(*S*)-Ketamine subjects showed a positive correlation between the 'apathy' score and the increases of absolute CMRglu in left insula and in both parietal cortices. Interestingly, a similar correlation was found between Liddle's 'poverty' factor referring to emotional withdrawal, blunted affects and motor retardation and metabolic changes in the left prefrontal and parietal cortex in acute psychotic drug-naive schizophrenic patients (Kaplan et al., 1993). This similarity provides additional support for the suggestion that (*S*)-ketamine administration can mimic negative symptoms seen in schizophrenia.

At the doses tested, (*R*)-ketamine produced a state of relaxation and elation which was correctly identifie as drug effect by all of the subjects, although (*R*)-ketamine changed scores for mood only with marginal significance Likewise, (*R*)-ketamine decreased absolute CMRglu only moderately in most of the cortical and subcortical brain regions. Significan absolute decreases were found in the left insula, and the temporomedial cortex, which has been suggested to play a role in the pathophysiology of schizophrenia. Surprisingly, neither of these decreases correlated significantl with the EWL mood rating scales or any other scales used in the present study. We found however, that the EWL score for 'introversion' tended to correlate with the increase of the left frontolateral-caudate ratio, while the score for 'deactivation' showed a negative correlation with the same ratio in both hemisphere (Table 2). This is an interesting findin because these were the only two correlations that were also found in (*S*)-ketamine subjects. However, the relatively weak effects of (*R*)-ketamine on mood and cerebral metabolism have to be interpreted with caution, since the sample size was small and the alterations in mood were discrete. Nevertheless, the present finding are in line with similar overall decreases in cerebral glucose metabolism associated with a state of relaxation seen after ethanol and diazepam (de Wit et al., 1990, de Wit et al., 1991). Whether the present correlations reflec neuronal activity specificall related to ketamine's mood-altering effects has to be tested in future PET studies.

In conclusion, the present data suggest that the (*S*)-ketamine-induced metabolic hyperfrontality as well as the metabolic changes in the left temporomedial and lateral cortex, basal ganglia, and occipital cortex are associated with derealisation phenomena, ego-disintegration, and hallucinations. Equimolar doses of (*R*)-ketamine produced opposite effects on CMRglu and a state of relaxation. The possibility that the sigma receptor is also involved in the (*R*)-ketamine-mediated metabolic effects is an interesting issue that remains to be investigated in further PET studies using more specifi sigma receptor ligands. Comparison of the metabolic effects of (*S*)- and racemic ketamine revealed that the pure (*S*)-ketamine enantiomere affected CMRglu more circumscribed than equipotential psychotomimetic doses of racemic ketamine, in particular that the number of areas with significan metabolic changes is more limited and restricted to brain regions with high NMDA receptor densities. Thus the present data strongly suggest that the pure (*S*)-ketamine enantiomere provides a more appropriate tool to study the relationship of NMDA receptor hypofunction and psychotic symptom formation. And finally the similarity between the (*S*)-ketamine-in-

duced metabolic hyperfrontality and the recent hyperfrontality findin in acute psychotic schizophrenic patients supports a number of growing evidence considering a glutamatergic dysbalance at the NMDA receptor complex in the pathophysiology of schizophrenia.

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