Psychopharmacology (2008) 200:573–583
DOI 10.1007/s00213-008-1237-1

ORIGINAL INVESTIGATION

Pharmacological modulation of the neural basis underlying inhibition of return (IOR) in the human 5-HT_{2A} agonist and NMDA antagonist model of psychosis

Jörg Daumann · Karsten Heekeren · Anna Neukirch · Christiane M. Thiel · Walter Möller-Hartmann · Euphrosyne Gouzoulis-Mayfrank

Received: 5 February 2008 / Accepted: 11 June 2008 / Published online: 24 July 2008

Abstract
Rationale Attentional deficits are common symptoms in schizophrenia. Recent evidence suggests that schizophrenic patients show abnormalities in spatial orienting of attention, particularly a deficit of inhibition of return (IOR). IOR is mostly thought to reflect an automatic, inhibitory mechanism protecting the organism from redirecting attention to previously scanned, insignificant locations. Pharmacologic challenges with hallucinogens have been used as models for psychosis.
Objectives The aim of this study was to investigate the neural correlates underlying orienting of attention in the human *N*-methyl-D-aspartic acid antagonist and 5-HT_{2A} agonist models of psychosis.
Materials and methods Fourteen healthy volunteers participated in a randomized, double-blind, cross-over event-related functional magnetic resonance imaging (fMRI) study with dimethyltryptamine (DMT) and *S*-ketamine. We administered a covert orienting of attention task with nonpredictive peripheral cues, and we scanned the subjects on two separate days at least 14 days apart with a placebo and a verum condition on each day.
Results DMT, but not *S*-ketamine, slowed down reaction times significantly. IOR was blunted after DMT, but not after *S*-ketamine. Relative to placebo, *S*-ketamine increased activation in the IOR condition in the right superior frontal gyrus, left superior temporal gyrus, and right midfrontal frontal gyrus.
Conclusions The discrepancy between the behavioral and functional imaging outcome indicates that pharmacological fMRI might be a sensitive tool to detect drug-modulated blood oxygenation level-dependent signal changes in the absence of behavioral abnormalities. Our findings might help to further clarify the contradictory findings of IOR in schizophrenic patients and might, thus, shed more light on possible differential pathomechanisms of schizophrenic symptoms.

Keywords Ketamine · Dimethyltryptamine · Experimental psychosis · Orienting of attention · Inhibition of return · Pharmacological fMRI

J. Daumann (✉) · K. Heekeren · A. Neukirch · E. Gouzoulis-Mayfrank
Department of Psychiatry and Psychotherapy,
University of Cologne,
Kerpener Strasse 62,
50924 Cologne, Germany
e-mail: joerg.daumann@uk-koeln.de

C. M. Thiel
Institute of Medicine, Jülich Research Centre,
Jülich, Germany

W. Möller-Hartmann
Department of Radiology, University of Cologne,
Cologne, Germany

Introduction

Attentional deficits are common symptoms in schizophrenia and important predictors of the long-term clinical and sociorehabilitative outcome of patients (Addington and Addington 1998). Besides deficits of sustained and selective attention, some recent studies suggest that schizophrenic patients show abnormalities of spatial orienting of attention, particularly a deficit of inhibition of return (IOR) (Huey and Wexler 1994; Carter et al. 1994; Sapir et al. 2001; Larrison-Faucher et al. 2002; Gouzoulis-Mayfrank et al. 2004, 2006a, 2007).

The phenomenon of IOR can be demonstrated in covert orienting of attention tasks (COVATs) that use nonpredictive, exogenous, i.e., peripheral cues, which attract attention automatically (e.g., luminance changes). Exogenous cues facilitate the processing of validly cued targets at cue–target intervals (stimulus onset asynchrony [SOA]) of 100–300 ms, which is due to a reflexive shift of attention toward the source of stimulation. At SOAs greater than 300 ms, the pattern reverses and valid cues result in longer reaction times (RTs) to the subsequent target. This latter phenomenon is commonly referred to as IOR (Posner and Cohen 1984). Although the mechanism of IOR is not entirely understood, it is hypothesized that it mediates visual search: after attention has been withdrawn from a cued location, it is inhibited from returning there. Hence, the organism is protected from being distracted by redundant stimuli from previously scanned, insignificant locations (Rafal et al. 1989; Klein 2000).

IOR has been closely linked to both attentional processing and oculomotor programming. Evidence from both animal and human lesion studies suggests that the superior colliculus (SC) is crucial for the generation of IOR (Klein 2000; Sapir et al. 1999; Fecteau et al. 2004). In addition, recent functional neuroimaging studies demonstrate an involvement of frontal premotor (oculomotor) and parietal areas, the cerebellum, the temporoparietal junction, and the ventrolateral nucleus of the thalamus in IOR (Rosen et al. 1999; Lepsien and Pollmann 2002; Mayer et al. 2004a, b). Besides these brain regions, Müller and Kleinschmidt (2007) were able to demonstrate an involvement of the visual cortex in IOR by applying an innovative paradigm in an attempt to avoid confounds from sensory cue–target interaction. Interestingly, across several visual areas assessed, the authors showed that, in short SOA, target stimuli yielded a stronger transient blood oxygenation level-dependent (BOLD) signal increase at the cued location, whereas, in long SOA, targets at the uncued location generated the larger signal (Müller and Kleinschmidt 2007).

Particularly, both oculomotor abnormalities and frontal cortex dysfunction belong to the most robust findings of biological schizophrenia research (Holzman 1985; Sereno and Holzman 1995; Arolt et al. 1998; Weinberger et al. 1986, 2001). More recently, abnormalities of thalamic and cerebellar function and abnormalities in the functional circuits of different areas such as the prefrontal and temporolimbic cortex, the thalamus, the basal ganglia, and the cerebellum have also been suggested as indicative of the schizophrenic disorder (Meyer-Lindenberg et al. 2001; Schlosser et al. 2003; Ragland et al. 2004; Hulshoff et al. 2004).

In spite of the partial overlap of the neural circuits involved in IOR and schizophrenia, to our knowledge, no published neuroimaging findings of IOR in patients with schizophrenia are currently available. However, as mentioned above, some behavioral studies reported blunted or delayed IOR (Huey and Wexler 1994; Carter et al. 1994; Sapir et al. 2001; Larrison-Faucher et al. 2002; Gouzoulis-Mayfrank et al. 2004, 2006a, 2007), but other studies reported a normal amount of IOR (Carter et al. 1992; Maruff et al. 1998; Fuentes and Santiago 1999; Fuentes et al. 1999), and one study reported blunted IOR only in patients with the paranoid, but not with the undifferentiated, type of schizophrenia (Carter et al. 1994). These inconsistencies may relate on both task- and subject-related methodological issues. For example, early studies did not always differentiate between tasks with exogenous and endogenous cues. A typical endogenous cue may be an arrow located centrally and pointing to one peripheral box where the target is going to appear with high probability (predictive cue). Endogenous cues depend on conscious, directed mechanisms of shifting attention toward the source of stimulation and IOR does not come up in tasks with such cues. Furthermore, some early studies used mixed paradigms with exogenous, but predictive cues (e.g., 80% probability that the target will appear at the same location as the foregoing cue), thus precluding interpretation of their findings in respect to the underlying attentional mechanisms (Posner et al. 1988; Strauss et al. 1991, 1992; Gold et al. 1992; Liotti et al. 1993; Oie et al. 1998). Additional differences in the tasks used across the different studies are also likely to account for some inconsistencies (e.g., single cue vs. cue-back paradigms, see Fuentes and Santiago 1999; Fuentes et al. 1999). Finally, subject-related issues such as the biological heterogeneity of the schizophrenic disorder, different medications and aspects of the age of onset, and long-term course of the disorder may also account for some discrepancies across the literature.

In respect to these latter subject-related methodological issues, human experimental studies with hallucinogenic drugs are considered to be a valuable, complementary research strategy to studies with patients. Hallucinogenic drug states resemble clinical manifestations of schizophrenia, and therefore, pharmacological challenges with hallucinogens have often been used as models for psychosis (Snyder 1988; Gouzoulis-Mayfrank et al. 1998, 1999; D'Souza et al. 1999; Carpenter 1999). Intraindividual comparisons of the off- and on-drug state help to minimize the variability of data and offer a unique opportunity to study fundamental neurobiological mechanisms of psychoses. Interestingly, the two major classes of hallucinogens (phencyclidine [PCP]-type: glutamate *N*-methyl-D-aspartic acid (NMDA) receptor antagonists and LSD-type: serotonin 5-HT_{2A} receptor agonists or partial agonists) have partially different psychotropic profiles, and therefore, they may model different aspects or types of schizophrenia. The NMDA antagonist state (PCP, ketamine) is thought to be an appropriate model for undifferentiated or disorganized

psychoses with both positive and negative symptoms, while the 5-HT_{2A} agonist state (LSD, dimethyltryptamine [DMT], psilocybin) may be an appropriate model for the paranoid subtype of schizophrenia (Javitt and Zukin 1991; Krystal et al. 1994; Abi-Saab et al. 1998; Gouzoulis-Mayfrank et al. 2005).

Most recently, in a study using the human 5-HT_{2A} agonist and NMDA antagonist model of psychosis, we found blunted IOR after both DMT and *S*-ketamine (Gouzoulis-Mayfrank et al. 2006b). This abnormality was more pronounced in the serotonin (DMT) model. The aim of the present experiment was to study the neural basis underlying the pharmacological modulation of IOR by the two major classes of hallucinogens. Both drugs can be given intravenously and have similar pharmacokinetics with rapid onset at the beginning and rapid fading of action at the end of the infusion. Hence, it is possible to study the effects of the two drugs in a randomized, double-blind, cross-over design. Given the partial overlap of the multifaceted neural circuits involved in IOR and schizophrenia, this approach allows us to further specify the IOR-associated cortical alterations in experimental hallucinogen psychoses and in naturally occurring schizophrenia disorders. Furthermore, we aimed at further clarifying the inconsistent findings of IOR in schizophrenia by making use of a human experimental study design with two different classes of drugs modeling different aspects of schizophrenic symptoms. Based on our previous findings, we expected blunted IOR after both DMT and *S*-ketamine, yet differences in terms of IOR-accompanied cortical alterations due to differential pharmacodynamic profiles of both drugs. To our knowledge, this is the first study on the pharmacological modulation of the neural circuits involved in IOR.

Materials and methods

Participants

Fourteen healthy, right-handed volunteers (eight men; mean age 32.1 years, range 26–42 years) with no current physical and no current or previous history of neurological or psychiatric disorder (axis I according to the DSM-IV criteria; APA 1994) were included in the study. There was no overlap between the current sample and the sample involved in our recently published study (Gouzoulis-Mayfrank et al. 2006b). Subjects with a positive family history of psychotic or major affective psychiatric disorder in first-degree relatives, a personal history of current or previous neurological or psychiatric disorder (axis I according to the DSM-IV criteria), or under regular medication were excluded. All subjects were screened with a medical history, a standardized psychiatric interview (SCID), a physical examination, ECG, and a routine laboratory testing. No subject had been under medication or subject to excessive caffeine intake and/or stressful life events in the 4 weeks prior to the study. The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee at the Medical Faculty of the University of Cologne, Germany and the Federal Health Administration (Bundesinstitut für Arzneimittel und Medizinprodukte, Bundesopiumstelle Berlin, Germany). Written informed consent was obtained from all subjects following detailed description of the experimental procedures and assurance that they could withdraw from the study at any time without having to explain the reasons.

Drugs

Dimethyltryptamine fumarate (DMT) was synthesized in the Pharmaceutical Institute, University of Tübingen (Germany) and prepared as solution for intravenous use by Wülfing Pharma (Gronau, Germany). The *S*-ketamine solution (Ketanest® S, Parke-Davis, Karlsruhe, Germany) was purchased from the hospital pharmacy. The S-isomer of ketamine has two to four times greater affinity for the NMDA receptor and stronger hallucinogenic potency than the R-isomer (Øye et al. 1991, 1992; Vollenweider et al. 1997). The appropriate dosages for both DMT and *S*-ketamine were determined in a previous study so as to evoke psychosis-like symptoms, such as hallucinations and transient delusional misinterpretations of the experimental situation (Gouzoulis-Mayfrank et al. 2005). The individual dosages were titrated during every experiment within the defined ranges so as to obtain relatively uniform psychopathological profiles across subjects. The two dose regimens were: (1) DMT: bolus injection of 0.15 mg/kg over 5 min followed by a break of 1 min, followed by continuous infusion with 0.01 up to 0.01875 mg/kg min over 20 min, (2) *S*-ketamine: bolus injection of 0.1 mg/kg over 5 min, followed by a break of 1 min, followed by continuous infusion with 0.0066 up to 0.015625 mg/kg min over 20 min. With these doses, the psychological effects of both drugs developed fully within about 10 min from the start of the injection and were then kept relatively constant over the functional magnetic resonance imaging (fMRI) scanning session.

Study design

Subjects were scanned on two separate days at least 14 days apart with a placebo and a verum condition on each day (double-blind, randomized order between and within sessions) with a 2-h break between both conditions to

avoid potential residual drug effects. The subjects were instructed to take a light breakfast in the morning. As soon as they arrived, an intravenous catheter was placed in a forearm vein. Subjects were at all times in the company of an experienced psychiatrist who was blind to the substance used (placebo, DMT, or *S*-ketamine). The drugs were administered by a second physician who was a member of the research team and was not blind as to the substance. He had no other role in these experiments and did not communicate with the subjects and the other members of the research team. Drugs were administered intravenously by an automatic infusion pump (Perfusor®, B. Braun, Melsungen, Germany). Systolic and diastolic blood pressure was measured before and after fMRI scanning. Within a few minutes of stopping the drug infusion, the psychological effects vanished. During the break between the verum and the placebo session, subjects were served a light standardized meal. Subjects remained in the research center under medical supervision during this break between and for at least 2 h after termination of the second dose. During that time, we completed interviews on the drug effects and both subject and researcher completed the psychometric ratings relating to the period during which significant effects from the drugs were experienced. At discharge, subjects were instructed to contact the researcher whenever problems possibly related to participation in the study should occur during the following days. On the day after the experiment, all subjects were interviewed on possible delayed effects.

Psychopathological evaluation and clinician ratings

Psychological effects were assessed using two self-rating scales. The Hallucinogenic Rating Scale (HRS; Strassman et al. 1994) comprises six subscales: somaesthesia, affect, perception, cognition, volition, and intensity. The Abnormer Psychischer Zustand (or altered state of consciousness [APZ-OAV]; Dittrich et al. 1985) covers common experiences of hallucinogenic drug-induced and other similar altered states of consciousness. The items form three subscales: Ozeanische Selbstentgrenzung (or oceanic boundlessness [OSE]) measures pleasant ecstatic experiences; Angst vor Ich-Auflösung (or dread of ego-dissolution [AIA]) describes a disintegrative, anxious state; Visionäre Umstrukturierung (or visionary restructuralization [VUS]) includes visual phenomena and experiences of altered meaning.

Furthermore, we used four psychiatric scales for the assessment of schizophrenia-like symptoms by clinicians. The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) comprises fives subscales: activity, anxiety/depression, anergy, hostility, and thought disorder. The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984) includes one global score and five subscales: hallucinations, delusions, bizarre behavior, positive formal thought disorders, and inappropriate affect. The Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983) consists of one global score and five subscales: affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. Finally, we used the Schizophrenia Proneness Instrument—Adult Version (SPIA; Schultze-Lutter et al. 2007), which describes subtle, subclinical subjective symptoms, complaints, and perceptional alterations occurring in prodromal stages of psychosis.

Stimuli and fMRI paradigm

We administered a covert orienting of attention task (COVAT) with nonpredictive peripheral cues and two stimulus onset asynchronies (SOA=100 and 800 ms). In this task, three identical boxes were presented on the screen throughout the experiment: one box in the center of the screen with the fixation point in it and two peripheral boxes (schematic illustration in Fig. 1). The experiment consisted of 200 trials, each presented randomly every 2,000 ms. Out of these trials, 40 were baseline trials (null events) with no cue or target occurring. These trials serve two different purposes: they effectively lead to variable SOAs and, in addition, avoid accumulation of BOLD signal by returning the hemodynamic response function (HRF) to baseline during the experimental session. In the remaining 160 trials, either the right or the left box was brightened with equal probability (cue) and the target followed either 100 or 800 ms after cue onset either in the brightened box or opposite to the brightened box (valid or invalid trial, respectively) with equal probability. Stimuli were projected onto a screen in front of the participant in the MRI scanner. Viewing distance was approximately 29 cm. During performance of the task, subjects were instructed to maintain fixation on the centrally presented cross. The task was to respond as rapidly as possible to the target by pressing a single key. The target was a star, which appeared on each trial within one of the two peripheral square boxes at about 5° right or left from the central fixation cross, and

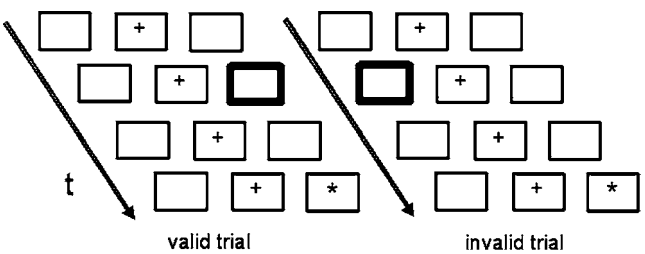

Fig. 1 Schematic illustration of the COVAT with nonpredictive peripheral cues

remained present for 200 ms. Eye position was monitored during scanning using an MR-compatible infrared eye tracker (ASL Model 540, Applied Science, Bedford, MA, USA). Before entering the scanner, a practice experiment consisting of 40 trials was performed with no RTs recorded. In an additional run, we administered a centrally cued target detection task, which will be reported separately.

Data acquisition

A Sonata MRI system (Siemens, Erlangen, Germany) operating at 1.5 T was used to obtain T_2*-weighted echoplanar (EPI) images with BOLD contrast (matrix size=64×64, pixel size=3.12×3.12 mm^2). The 172 volumes of 24 4-mm-thick axial slices were acquired sequentially with a 0.8-mm gap (repetition time=2.5 s, echo time=66 ms). For anatomic reference, we additionally obtained a T_1-weighted 3-D inversion recovery sequence (imaging parameters: TR=2,200 ms, TE=4 ms, TI=400 ms, flip angle=15°). Head movements were minimized in all subjects using foam pads and Velcro straps. Images were acquired using a standard head coil. The first five volumes were discarded to allow for T_1 equilibration effects. Images were spatially realigned to the first volume to correct for head movements, interpolated in time (temporal realignment to the middle slice), and normalized to a standard EPI template volume (resampled to 2×2×2 mm^3 voxels). The data were then smoothed with a Gaussian kernel of 8 mm full-width half-maximum to accommodate intersubject anatomical variability. Raw time series were detrended by the application of a high-pass filter (cut-off period=128 s).

Data analyses

Behavioral data were analyzed by means of repeated-measures analysis of variance (ANOVA) and paired *t* tests implemented in the SPSS 15.0 software (SPSS, Chicago, IL, USA). For cognitive performance, trials with RTs less than 100 ms or exceeding 1,000 ms were excluded because they were considered either anticipatory or most likely to be due to brief periods of general inattention to the task. Trials with eye movements registered in the EOG were also excluded. Median RT values of the remaining trials were calculated for each subject, drug condition, and type of trial. p values ≤ 0.05 were considered significant.

Functional imaging data were analyzed with the Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6 (Mathworks, Sherborn, MA, USA) employing a random effects model. At the first level, all four sessions (twice placebo, *S*-ketamine, DMT) were incorporated into one design matrix. For each session, eight event types were defined: short SOA+right cue+valid target, long SOA+right cue+valid target, short SOA+left cue+valid target, long SOA+left cue+valid target, short SOA+right cue+invalid target, long SOA+right cue+invalid target, short SOA+left cue+invalid target, and long SOA+left cue+invalid target. This design matrix was specified applying the HRF with dispersion and time derivatives to every event type. In order to identify the cortical basis underlying IOR, we analyzed the main effect of SOA (Lepsien and Pollmann 2002). The underlying rationale was that IOR-related activity should accumulate over time and that this process is independent from the validity of cues. Thus, events with long SOA were directly compared to conditions with short SOA. In order to explore the differences between different drug conditions, the computed contrasts of each subject were entered into two separate within-subjects second-level analyses (paired *t* tests for placebo and verum condition). All random effects analyses contrasts were computed with the commonly used height threshold of $p<0.05$ corrected for multiple comparisons). Minimum cluster size was set to 20 voxels. Because the MNI coordinates do not accurately match the brain of Talairach and Tournaoux (1988), we used the Matlab function *mni2tal* by M. Brett for the nonlinear transformation of MNI to Talairach coordinates.

Results

Psychological effects

All subjects who entered the study completed both experimental days without any complications. Both drugs induced psychosis-like symptoms. In accordance with our recently published study on the psychological effects of the two drugs (Gouzoulis-Mayfrank et al. 2005), perceptional abnormalities were more pronounced after DMT (HRS perception: $t(14)=2.58$, $p=0.022$; APZ-OAV VUS: $t(14)=2.63$, $p=0.021$), and phenomena resembling negative symptoms of schizophrenia, body perception disturbances, anxiety, and affective blunting were stronger after *S*-ketamine (HRS somaesthesia: $t(14)=-3.05$, $p=0.009$; APZ-OAV AIA: $t(14)=-4.38$, $p<0.001$; BPRS anergy: $t(14)=-3.481$, $p=0.004$; SANS global: $t(14)=-4.36$, $p<0.001$; SANS affective blunting: $t(14)=-4.25$, $p<0.001$). An overview of all psychological effects is given in Table 1.

Cognitive performance

Anticipatory responses (RTs less than 100 ms) and trials with brief periods of general inattention to the task (RTs exceeding 1,000 ms) were observed in 3.2% of trials. On an additional 4.3% of trials, eye movements were registered.

Table 1 Psychometric scores (mean and standard deviation) for DMT and *S*-ketamine administration (n=14)

	DMT (mean±SD)	Ketamine (mean±SD)	t value	p value
Hallucinogenic rating scale				
Somaesthesia	12.60±5.14*	17.33±7.18*	−3.047*	0.009*
Affect	21.23±9.42	18.89±8.14	1.578	0.210
Perception	29.67±10.54*	19.53±9.44*	2.578*	0.022*
Cognition	15.47±5.96	19.80±8.25	−1.810	0.092
Volition	10.60±3.66	12.40±4.61	−1.790	0.095
Intensity	7.87±1.88	7.73±1.98	0.197	0.846
Altered state of consciousness				
Oceanic boundlessness	26.99±19.80	31.12±17.40	−0.718	0.485
Dread of ego-dissolution	8.72±7.68*	20.13±13.18*	−4.377*	0.001*
Visionary restructuralization	35.14±17.85*	18.42±14.26*	2.62*	0.021*
Global	23.30±11.85	24.15±12.20	−0.209	0.838
Brief psychiatric rating scale				
Activity	6.64±3.30	5.71±2.79	0.975	0.347
Anxiety/depression	8.14±2.14	7.86±2.38	0.409	0.689
Anergy	6.79±2.83*	11.14±4.17*	−3.481*	0.004*
Hostility	4.57±2.98	4.29±2.30	0.302	0.767
Thought disorders	12.29±4.98	12.21±4.49	0.033	0.974
Global	38.43±8.21	41.21±10.17	−0.756	0.463
Assessment of positive symptoms				
Hallucinations	8.64±5.54	8.29±5.57	0.161	0.875
Delusions	3.29±5.01	7.64±10.57	−1.376	0.192
Bizarre behavior	0.14±0.36	0.00±0.00	1.472	0.165
Positive formal thought disorders	12.14±8.17	14.36±9.17	−0.535	0.602
Inappropriate affect	0.21±0.55	0.12±0.22	1.526	0.184
Global	25.64±15.99	31.07±24.54	−0.602	0.558
Assessment of negative symptoms				
Affective flattening or blunting	0.85±1.14*	11.00±8.49*	−4.247*	0.001*
Alogia	2.08±2.78*	7.69±5.48*	−4.083*	0.002*
Avolition/apathy	0.83±2.12	1.83±2.58	−1.732	0.111
Anhedonia/asociality	0.33±0.81	0.13±0.45	1.00	0.363
Attention	4.83±4.15	7.50±3.84	−1.943	0.078
Global	9.31±7.76	27.31±16.52	−4.353	0.001
Schizophrenia proneness instrument				
Overstrain	10.73±6.04	13.80±5.54	−1.844	0.086
Emotional deficits	7.27±3.34	7.53±3.56	−0.267	0.793
Cognitive impediments	4.13±4.34*	7.33±4.11*	−2.152*	0.049*
Cognitive disturbances	5.86±4.58	6.71±4.98	−0.432	0.673
Body perception disturbances	8.53±7.46*	13.53±7.66*	−2.230*	0.043*
Estrangement	17.64±7.78	14.64±2.61	1.075	0.302

*p<0.05; significant differences

RT time data from the remaining 92.5% of trials were used in the statistical analyses.

Cognitive performance is presented in Fig. 2. Performance for both placebo conditions did not differ and was, therefore, pooled. An initial 3×2×2 repeated-measures ANOVA of drug (placebo, *S*-ketamine, DMT)×validity (valid, invalid)×SOA (100 and 800 ms) revealed significant main effects for drug [F(2,13)=14.53, p<0.001], validity [F(1,14)=11.68, p=0.004], and SOA [F(1,14)=7.23, p=0.018]. Hence, like in our previous study (Gouzoulis-Mayfrank et al. 2006b), both drugs prolonged RTs, this effect being more pronounced after DMT (p<0.001) than after *S*-ketamine (p=0.107). The significant interaction between validity and SOA [F(1,14)=40.41, p<0.001] reflects the dependence of RT facilitation and inhibition by peripheral cues from the SOA. Interactions of validity and SOA with drug were not significant: drug×validity [F(2,13)=2.70, p=0.105]; drug×SOA [F(2,13)=2.16, p=0.156]. However, the higher order interaction drug×validity×SOA approached significance [F(2,13)=2.79, p=0.098]. Inspection of the descriptive data suggests that this interaction may have been due to a missing validity effect

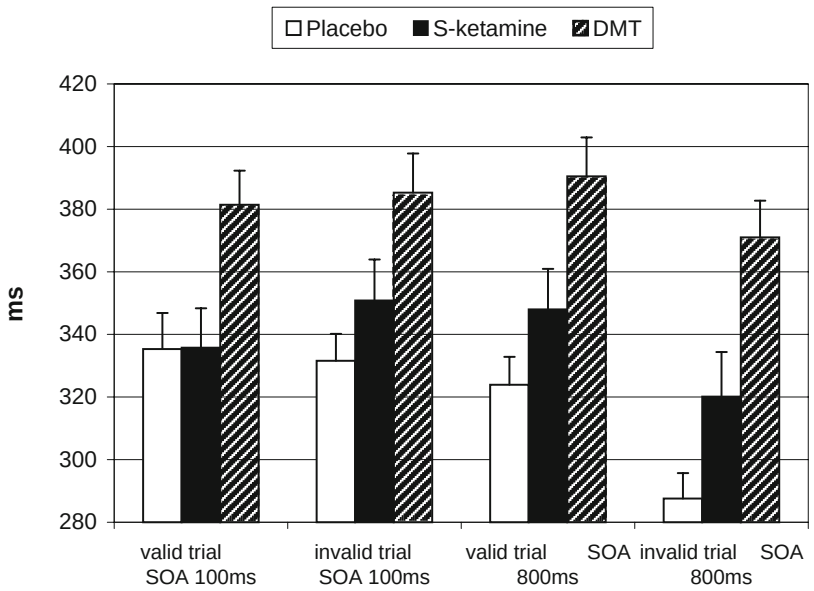

Fig. 2 RTs in ms in the COVAT with exogenous, non-predictive cues (n=14, group means). *SOA* stimulus onset asynchrony is the time from onset of cue to onset of target. *p<0.05, paired t tests with Bonferroni correction (three tests) for trials with valid vs. invalid cues at SOA=800 ms. Significant differences indicate IOR effects for the placebo and the *S*-ketamine conditions. Insignificant difference in the DMT condition indicates blunted IOR

in the placebo condition or due to blunted IOR in the DMT condition. Therefore, we, additionally, performed a 2×2 repeated-measures ANOVA of validity×SOA for the placebo condition. This analysis revealed a highly significant main effect for validity [F(1,14)=24.71, p<0.001] ruling out the possibility of a missing validity effect in the placebo condition. Finally, we tested the RTs in valid vs. invalid trials at the long SOA of 800 ms for each drug condition by means of paired t tests with Bonferroni correction (three tests). The RT difference between valid and invalid trials was significant for the placebo [t(13)=6.54, p<0.001] and the *S*-ketamine condition (t(13)=5.39, p<0.001), but not for the DMT condition [t(13)=2.04, p=0.180]. This finding confirms the blunting of IOR with DMT.

fMRI results

All subjects had a normal structural MRI scan without focal brain lesions or anatomical abnormalities. For both placebo conditions, fMRI for the IOR condition led to significant and localized hemodynamic bilateral changes in frontal premotor (oculomotor) and parietal areas as well as in the temporoparietal junction (Fig. 3), which were already linked to IOR in previous studies (Rosen et al. 1999; Lepsien and Pollmann 2002; Mayer et al. 2004a, b). The contrast between placebo and *S*-ketamine revealed increased activation with *S*-ketamine administration in the right superior frontal gyrus (Z=4.18), the left superior temporal gyrus (Z=3.76) and the right midfrontal gyrus (Z=3.59) (Fig. 3). The contrast between placebo and DMT failed to show any significant IOR-associated activation differences at the chosen threshold.

Discussion

The aim of the present investigation was to study the pharmacological modulation of IOR in two different pharmacological models of psychosis in humans. We administered psychotomimetic doses of the serotonergic hallucinogen DMT and the antiglutamatergic hallucinogen *S*-ketamine to healthy volunteers in a randomized, double-blind, cross-over experimental design. Overall, all subjects tolerated the procedures and we observed no serious immediate or delayed adverse effects after the experiments.

The administration of both hallucinogens was followed by alterations of perception, affect, and cognition, which were similar to many symptoms of patients with schizophrenia. The overall intensity of the hallucinogenic effects of both drugs was similar; however, phenomena that resemble positive symptoms of schizophrenia were more pronounced after DMT and phenomena that resemble negative symptoms of schizophrenia were clearly more pronounced after *S*-ketamine. In general, only DMT, but not *S*-ketamine, slowed down reaction times significantly. Furthermore, IOR was significantly blunted after DMT, but not after *S*-ketamine. Thus, with the present data, we confirm our own recent findings of blunted IOR after exogenous cueing and a long cue–target interval of 800 ms after two different doses of DMT (Gouzoulis-Mayfrank et al. 2006b). However, in the present study, we failed to demonstrate reduced IOR with *S*-ketamine administration. One significant difference between the present and our former study was the duration of drug administration. Hence, it may be speculated that, in an early stage of ketamine administration, subjects are still able to maintain constant cognitive performance resulting in reasonable intact IOR. However, further research is needed to shed

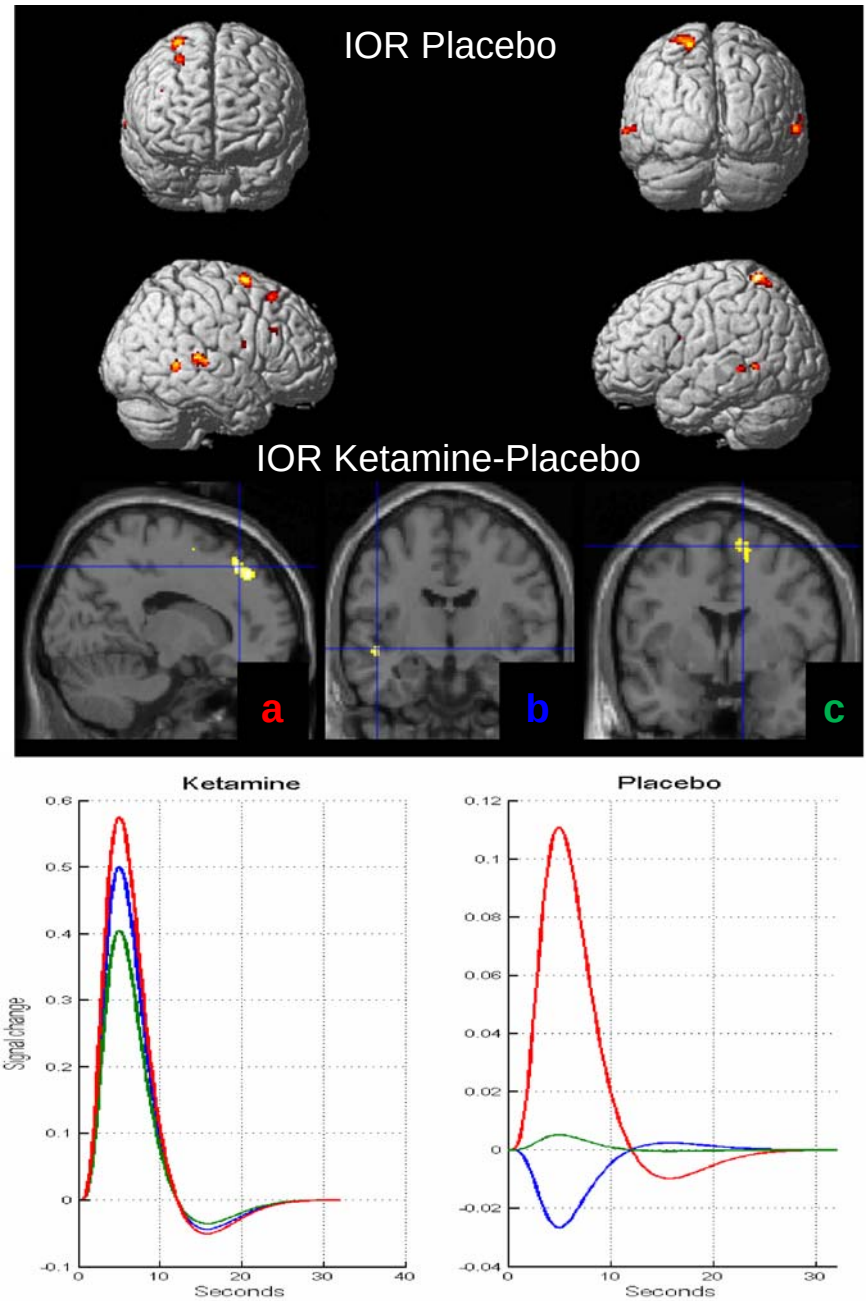

Fig. 3 Summary of the fMRI results for the IOR condition (events with long SOA–events with short SOA): activation patterns in the placebo conditions (*top*), and increased activation with *S*-ketamine administration in relation to the placebo condition and the accompanying time courses in the right superior frontal gyrus (*A*; maximum located at Talairach coordinates 8, 37, 47; Brodmann area 8), the left superior temporal gyrus (*B*; maximum located at Talairach coordinates −55, −17, 2; Brodmann area 22), and the right midfrontal gyrus (*C*; maximum located at Talairach coordinates 8, 5, 60; Brodmann area 6), $p<0.05$ (corrected for multiple comparisons), minimum cluster size=20 voxels

more light on this issue. Interestingly, we found elevated IOR-related cortical activation with the antiglutamatergic hallucinogen *S*-ketamine, yet not with the serotonergic hallucinogen DMT. The DMT-related changes were found in the superior and midfrontal as well as in the superior temporal areas, which are part of the network of areas associated with covert orienting of attention (Rosen et al. 1999; Lepsien and Pollmann 2002; Mayer et al. 2004a, b).

Most recently, a number of studies investigated the effects of acute ketamine administration on brain response in different cognitive tasks (Honey et al. 2004, 2005; Northoff et al. 2005; Fu et al. 2005). In line with our findings, these studies unanimously showed increased ketamine-induced activation in frontal areas involved in episodic memory (Honey et al. 2005; Northoff et al. 2005), working memory (Honey et al. 2004), and verbal fluency (Fu et al. 2005). Interestingly, in theses studies, ketamine administration did not significantly impair task performance relative to placebo. Similarly, we found a task-specific effect of *S*-ketamine on brain activation while overt performance was unimpaired. This finding may facilitate the attribution of the fMRI alterations to an effect of the drug. Otherwise, in pharmacological imaging studies, groups frequently differ in both task performance and drug

condition. Therefore, imaging findings cannot unambiguously be associated with one of these factors, since neural activity may reflect differences in task performance rather than a drug effect. In the present study, however, matched performance across drug conditions allows the interpretation that alterations in BOLD response are likely to reflect a drug effect. This is particularly interesting, since pharmacological fMRI studies may serve as a sensitive tool for detecting subtle cognitive changes that may not be seen behaviorally. Hence, it may be speculated that the task-related hyperactivity during *S*-ketamine administration indicates compensatory mechanisms in order to maintain constant cognitive performance.

In the DMT condition, attentional capacity was generally reduced and IOR was blunted, indicating a pronounced disruption of orienting of attention. However, this cognitive impairment was not accompanied by significant alterations in neural activity. This, at first glance, seems surprising. However, it has been shown that subcortical areas and, particularly, the SC are crucial for the generation of IOR (Klein 2000; Sapir et al. 1999; Fecteau et al. 2004). It is possible that DMT caused alterations in the activity of these subcortical areas, which were below the threshold for detection by the administered fMRI procedures.

Both NMDA receptor antagonists and 5-HT_{2A} receptor agonists model naturally occurring schizophrenic symptoms (Abi-Saab et al. 1998), although the NMDA antagonist model of psychosis is more generally accepted than the serotonergic model (Tsai and Coyle 2002). Numerous studies suggest that NMDA receptor hypofunction in frontal cortices and, in general, NMDA receptor-mediated neurotransmission may play a crucial role in the pathophysiology of schizophrenia. Initial evidence for the glutamate theory of schizophrenia derived from early studies in the late 1970s and early 1980s which measured cerebral spinal fluid (CSF) levels of glutamate and postmortem glutamate receptor binding in schizophrenic patients (e.g., Kim et al. 1980). These early results were reappraised when postmortem brain analyses became more differentiated (review in Konradi and Heckers 2003). Furthermore, it became evident that the psychotomimetic drug PCP is an antagonist at glutamate NMDA receptors (Javitt and Zukin 1991). Finally, recent genetic studies have reanimated the idea of NMDA receptor dysfunction in schizophrenia. Several genes associated with an increased risk for psychosis have the property to influence the function of NMDA receptors (Harrison and Weinberger 2005). Although these specific linkages were not fully replicated, influencing the excitatory neurotransmission may be an important conjunction among plausible susceptibility genes for schizophrenia. And, in fact, a disruption in NMDA receptor function might serve as a sophisticated model for the complex behavioral disturbances observed in psychotic patients, since the glutamatergic system is involved in numerous cognitive and other psychological functions.

In addition, a large body of evidence supports a role of the serotonergic system in schizophrenia. Support for serotonin's actions derives from drug mechanisms, post-mortem, and genetic studies. The strongest evidence of serotonin's role in schizophrenia, by far, is the mechanism of atypical antipsychotic drugs like clozapine, which are antagonists at the 5-HT_{2A} receptor and have relatively weak antidopaminergic properties (Horacek et al. 2006). More precisely, it has been suggested that the 5-HT_{2A} receptor is not central to the pathological processes that induce psychoses but may be involved in processes generating some of the symptoms observed in schizophrenic patients (Dean 2003).

There are some limitations in interpreting our data, which are outlined below. First, we cannot fully exclude the possibility that our imaging findings were associated with an unspecific effect of *S*-ketamine on cerebral blood flow. However, recent studies suggest that ketamine administration rather results in an altered BOLD response specific to the cognitive task (Northoff et al. 2005) or the emotional stimuli (Abel et al. 2003) presented than in a nonspecific global effect on cerebral blood flow per se. Further support for this argument comes from animal studies, which also suggest that ketamine has no effects on vascular mechanisms beyond its specific effects on neural activation (Burdett et al. 1995). Secondly, both human and animal studies suggest that ketamine does not affect the glutamatergic system only. In humans, for example, it increases dopamine levels in the striatum (Vollenweider et al. 2000), reduces acetylcholine release (Grunwald et al. 1999), and also binds to 5-HT_2 receptors (Kapur and Seeman 2002). Furthermore, in rodents, acute administration of ketamine increased the release of dopamine in the prefrontal cortex (Moghaddam et al. 1997).

In conclusion, IOR was significantly blunted after DMT, but not *S*-ketamine. This behavioral outcome of our study is in line with studies on deficient IOR in patients with schizophrenia and, specifically, with a report of blunted IOR in paranoid, but not in undifferentiated, patients (Carter et al. 1994). In contrast, administration of *S*-ketamine, yet not DMT, yielded a stronger signal increase in cortical regions involved in the modulation of IOR. The discrepancy between the behavioral and functional imaging outcome of our study is particularly interesting, since it indicates that pharmacological fMRI might be a sensitive tool to detect drug-modulated BOLD signal changes in the absence of behavioral abnormalities. Our findings might help to further clarify the contradictory findings of IOR in schizophrenic patients and might, thus, shed more light on possible differential pathomechanisms of schizophrenic symptoms. Needless to say, the association of our imaging

findings to schizophrenia warrants further analysis of the same fMRI study applied to patients.

Acknowledgements This work was supported by a grant to E. Gouzoulis-Mayfrank from the German Research Foundation (Deutsche Forschungsgemeinschaft DFG, Project No. 6 of a DFG clinical researcher group KFO 112/1/-1, Go 717/5-1).

Financial disclosures All authors certify that there is no actual or potential financial interest in relation to the subject matter or materials discussed in this manuscript.

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