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ORIGINAL PAPER

Effects of ketamine-induced psychopathological symptoms on continuous overt rhyme fluency

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Abstract The *N*-methyl-D-aspartate receptor (NMDAR) has been implicated in the pathophysiology of schizophrenia. Administered to healthy individuals, a subanesthetic dose of the noncompetitive NMDAR antagonist ketamine reproduces several psychopathological symptoms commonly observed in patients with schizophrenia. In a counterbalanced, *placebo*-controlled, double-blind, within-participants study, fifteen healthy subjects were administered a continuous subanesthetic *S*-ketamine infusion while cortical activation was measured using functional magnetic resonance imaging. While being scanned, subjects performed an overt word generation task. Ketamine-induced psychopathological symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). Ketamine administration elicited effects on psychopathology, including difficulties in abstract thinking, lack of spontaneity and flow of conversation as well as formal thought disorder. On a behavioral level, verbal fluency performance was unaffected. The PANSS score for formal thought disorder positively correlated with activation measures encompassing the left superior temporal gyrus, the right middle and inferior frontal gyrus and the precuneus. Difficulty in abstract thinking was correlated with pronounced activations in prefrontal as well as in anterior cingulate regions, whereas hyperactivations in the left superior temporal gyrus were found in association with a lack of spontaneity and flow of conversation. In the absence of behavioral impairments during verbal fluency, NMDAR blocking evoked psychopathological symptoms and cortical activations in regions previously reported in schizophrenia patients. The results provide further support for the hypothesis of an NMDAR dysfunction in the pathophysiology of schizophrenia.

Keywords *N*-methyl-D-aspartate receptor · Ketamine · fMRI · Speech production · Schizophrenia · Glutamate

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Introduction

The *N*-methyl-D-aspartate receptor (NMDAR) has been implicated in the pathophysiology of schizophrenia [62]. In healthy individuals, a subanesthetic dose of the noncompetitive NMDAR antagonist ketamine produces several psychopathological symptoms, including formal thought disorder and disorganized symptoms usually observed in patients with schizophrenia (for review see: [38]). Evidence for an NMDAR involvement in the disorder is primarily based on past studies investigating the effects of phencyclidine (PCP) [46]. Administered to healthy individuals, PCP leads to various psychopathological symptoms such as paranoid ideations, hallucinations, and formal thought disorder similar to those observed in patients with schizophrenia [20, 30, 45, 59]. Based on these

observations, the NMDAR blockade was used as an experimental model in human research studies attempting to characterize the contributions of NMDAR dysfunction to human cognition and behavior [38]. Because of the strong toxicity of PCP [57], the dissociative anesthetic ketamine is more widely used in humans. In animal studies, however, the PCP as well as the MK801 (dizocilpine) model of glutamatergic dysfunction is frequently applied, mimicking positive as well as negative symptoms [6, 22, 53]. These animal studies strongly support the use of NMDAR antagonists to model cognitive dysfunctions and psychopathological symptoms of schizophrenia [53].

Ketamine is clinically available as a racemic mixture of two enantiomers. The (*S*)-isomer has 2–4 times greater affinity and selectivity for the NMDAR along with a greater clinical potency than the (*R*)-isomer [39, 58]. Further, *S*-ketamine as opposed to *R*-ketamine was shown to induce metabolic hyperfrontality similar to metabolic findings in acute psychotic schizophrenic patients [69].

Ketamine-induced psychopathological phenomena particularly comprise positive and negative thought disorder [3–5, 27, 41, 47]. Accordingly, recent ketamine studies reported symptoms of disorganization [4, 12, 39, 41, 54, 67, 68] resulting in difficulties "to put thoughts in words" [46]. In general, verbal productivity was found to be significantly decreased due to ketamine administration [4], as measured with the Scale for the Assessment of Thought, Language and Communication (TLC) [7]. Apart from a reduction in the fluency of speech, deficits in abstract thinking were reported in previous ketamine studies [39, 70]. Krystal et al. [39] reported a ketamine-induced deficit in abstract thinking evaluated by means of a proverb interpretation task. Subjects' proverb interpretations revealed significant ketamine effects on two different aspects, concreteness as well as bizarreness. In a similar manner, patients with schizophrenia are found to have difficulties interpreting the figurative meaning of proverbs and metaphors [35].

In the past years, a number of functional magnetic resonance imaging (fMRI) studies have measured the effects of ketamine on cerebral activation using different cognitive tasks [1, 2, 15, 21, 23, 27, 29, 55]. Fu et al. [23] applied an overt lexical verbal fluency task while the blood oxygenation level dependent (BOLD) contrast was measured with fMRI. On the neural level, an interaction of task demand with ketamine was observed in the anterior cingulate cortex (ACC) as well as in frontal and striatal regions [23]. So far, no study has directly targeted the interaction of ketamine-induced psychopathological phenomena related to both speech production and neural activation (Table 1).

In patients with schizophrenia, the degree of formal thought disorder was found to correlate with a widespread neural network [8, 32, 33, 36, 43]. Enhanced BOLD responses were predominantly found in fronto-temporal brain regions. A recent fMRI study investigated the neural correlates of formal thought disorder using a discourse processing paradigm [61]. Relative to controls, clinical high-risk participants for developing psychosis showed increased neural activity in a network of language-associated brain regions such as the left inferior frontal and middle temporal gyrus, among others. Interestingly, increased activity in the superior temporal gyrus, caudate and left inferior frontal gyrus was found to predict those subjects who subsequently developed psychosis [61].

Similarly, the neural correlates of abstract linguistic processing were investigated in a number of fMRI studies. Especially the frontal cortex was associated with abstract reasoning, such as rule generation [10] and the monitoring and integration of subgoals during a verbal working memory task [11]. In patients with schizophrenia, the lack of abstract reasoning as during proverb interpretation or metaphor processing is clinically referred to as "concretism" and associated with the left inferior frontal gyrus [35].

Animal models of schizophrenia revealed ketamine-induced psychopathological effects due to the NMDAR hypofunction (for review see [53]). For chronic ketamine administration, significant effects were reported for the immobility dimension in mice. In contrast, the acute NMDAR blockade resulted in hyperlocomotory responses in the absence of any negative symptoms [13]. On the cognitive level, chronic ketamine exposure was found to impair working memory in mice, which leads to the assumption of a ketamine-induced disruption of neurotransmission in the prefrontal cortex [44, 49, 66]. A current pharmaco-imaging study in rats revealed a significant increase in BOLD signals in prefrontal as well as in cingulate regions during the ketamine condition as opposed to saline administration [14]. For patients with schizophrenia, an elevation of blood flow in frontal brain regions was previously reported [25].

So far, no pharmaco-imaging study has investigated the neural correlates of ketamine-induced psychopathological phenomena during an online speech production task. The cognitive demands of the underlying continuous overt rhyme generation on pronounceable pseudoword stimuli encompass linguistic processes (word selection and generation) as well as extralinguistic processes (verbal working memory, selective as well as sustained attention) [34]. Therefore, the phonological verbal fluency task (rhyming) can be regarded as a highly sensitive tool to access ketamine-induced psychopathological phenomena, such as the lack of abstract thinking as well as dysfluent speech production pattern along with symptoms of formal thought disorder, henceforth being referred to as conceptual disorganization (CD).

In analogy to the symptomatology of patients with schizophrenia, we hypothesized ketamine-induced enhanced BOLD responses in the temporal cortex for the lack of

Table 1 Previous pharmacoimaging study results

Authors	Task	Behavioral results	Imaging result (Ket > Pla)
Abel et al. [1]	Face discrimination	No effect on task performance	No significant activations
Abel et al. [2]	Face discrimination	No effect on task performance	Left superior occipital gyrus for fearful faces
Corlett et al. [15]	Causal associative learning task	Ketamine perturbs error-dependent learning activity in the right frontal cortex	Subjects showing the highest degree of frontal activation with placebo show the greatest occurrence of drug-induced perceptual aberrations and ideas or delusions of reference
Daumann et al. [18]	Orienting of attention task with nonpredictive peripheral cues	Inhibition of no return was not significantly blunted after *S*-ketamine	*S*-ketamine increased activation in the right superior frontal gyrus, left superior temporal gyrus, and right mid-frontal frontal gyrus
Daumann et al. [19]	Target detection task	Ketamine slowed down reaction times significantly	Increased cortical activation in the left insula and precentral gyrus in the auditory modality
Deakin et al. [21]	–	–	Ketamine induced a decrease in ventromedial frontal cortex, orbitofrontal cortex, and subgenual cingulate, which strongly predicted dissociative effects and increased activity in mid-posterior cingulate, thalamus, and temporal cortical regions
Fu et al. [23]	Lexical verbal fluency	No significant impairment	Interaction of task demand with ketamine was observed in the anterior cingulate, prefrontal, and striatal regions
Honey et al. [29]	Verbal working memory task	No significant main effect of drug	Task-specific effect of ketamine on working memory in the frontal cortex, parietal cortex, and putamen
Honey et al. [28]	Memory encoding and retrieval task	Overt behavior is unimpaired	Left frontal activation is augmented by ketamine when elaborative semantic processing is required at encoding
Honey et al. [27]	Verbal working memory task, sustained attention, semantic generation, verbal self-monitoring	RTs were significantly slower	Different activations in the neural network demonstrate precise and predictive brain markers for individual profiles of vulnerability to drug-induced psychosis
Musso et al. [51]	Visual oddball task	On the behavioral level, reaction hit and false alarm rate perfectly separated the two drug conditions	BOLD responses were diminished in the ketamine condition in cortical regions being involved in sensory processing/selective attention
Northoff et al. [55]	Episodic memory retrieval task	No significant differences in the RTs	Significantly smaller BOLD signal changes in the posterior cingulate, precuneus, and anterior cingulate in the ketamine group during the retrieval of episodic memory

Ket ketamine, *Pla* placebo

spontaneity and flow of conversation. For the lack of abstract thinking, we proposed a similar pattern of frontal lobe involvement for the ketamine group, as previously found for patients with schizophrenia [35]. Since the NMDAR blockade primarily induces symptoms of CD, we expected a global hyperactivation in the fronto-temporal language network countervailing ketamine-induced cognitive dysfunctions.

Methods and materials

Ethics statement

Informed written consent was obtained from all participants. The study was approved by the local ethics committee at the faculty of medicine, RWTH Aachen University (EK143-06), the federal drug agency (403 1706) as well as by the European Union Drug Regulating Authorities Clinical Trials (EUDRACT: 200 600 469 235).

Participants

Fifteen healthy, right-handed (Edinburgh Inventory of Handedness, [56]), native German-speaking male volunteers participated in the fMRI study. The mean age of the participants was 27.87 (SD = 3.68) years. Subjects with a history of substance abuse or general MRI incompatibility (e.g., metal implants) were excluded. Participants were found to be free of medical diseases, which was confirmed through an in-depth interview, physical examination, ECG,

and blood examination conducted by the principal investigator. The blood sample analysis had to show normal values of liver enzymes and kidney function as well as no signs of current infection. Structured diagnostic interviews (SCID for DSM-IV) were conducted in order to exclude psychiatric disorders of the participants (neither personal nor family histories of psychiatric disorders) by a psychiatrist.

Tasks and stimuli

Subjects were required to overtly articulate as many words as possible beginning with a visually presented pseudoword (e.g., *OITE*) while BOLD-signal changes were measured with fMRI. In constructing the pseudowords for the novel rhyming task, it was ensured that word trunks differed from the usual way of spelling regular German words. All nonsense rhyme trigger words had different endings and could be described as pronounceable nonwords according to the rules of grapheme-to-phoneme conversion in German language (for detailed information see [34, 37, 52]). Variability of the stimuli due to differences in length was controlled by using items of four letters only. Words considered homophonous to German words were excluded from the set (e.g., *HOITE* was not used because of German homophones HEUTE (today) or HÄUTE (skin)) [37]. During the low-level baseline condition, participants had to "rest" whenever the instruction "resting phase" appeared.

Procedure

A block design was used in order to measure differences in BOLD activation between the ketamine and the *placebo* condition. The experimental conditions consisted of seven blocks alternating with "resting" baseline. At the beginning of each block, an instruction slide was displayed via MRI-compatible video goggles (VisuaStim XGA, Resonance Technology, Inc., CA, USA http://www.mrivideo.com/) for 3,000 ms. Then, a fixation cross appeared in the center of the screen for 12,000 ms, indicating the word generation phase. Within this time window, participants were required to generate as many words as possible while verbal responses were audiotaped with a MRI-compatible headset microphone (funcLab, Resonance Technology, Inc., CA, USA). Presentation of stimuli was controlled by a computer using the Presentation 11.0 software package (Neurobehavioral Systems, Albany, CA, USA, http://www.neurobs.com/). In order to ensure optimal visual acuity, participants were offered fMRI-compatible glasses that could be fixed to the video goggles.

Prior to scanning, all subjects performed two test trials, in which all items used for training differed from the experimental stimuli in the fMRI study. This task has been used successfully in a previous study of ours [34].

Speech recordings

Subjects were initially instructed to speak clearly and to respond as fast as possible. The participants' speech production was recorded using the headset microphone of the goggle system. The cable from the microphone as well as the cable from the MR trigger box was plugged into an audio splitter, from which one cable led to the intercom and one to the line-in port of an external sound card attached to a Siemens notebook used for digital recording. All verbal responses were filtered (Adobe Audition 3, Adobe Systems Software Ireland Limited, http://www.adobe.com/) and transcribed. These recordings were used for quantitative analyses of the participants' overt responses in each condition, yielding information about what was said and how many items were generated.

fMRI image acquisition

All scanning was performed on a 3 T scanner (3-T Philips Achieva) using standard gradients and a circular polarized phase array head coil. Participants lay in supine position, while head movement was limited by foam padding within the head coil. For each participant, a series of 210 EPI-scans lasting 7 min was acquired.

Scans covered the whole brain parallel to the AC/PC line with the following parameters: number of slices (NS), 34; slice thickness (ST), 3.5 mm; interslice gap (IG), 1 mm; matrix size (MS), 64 × 64; field of view (FOV), 230 mm; echo time (TE), 29 ms; repetition time (TR), 2.0 s.

fMRI data analysis

Functional scans were analyzed using Statistical Parametric Mapping software (SPM5; http://www.fil.ion.ucl.ac.uk) implemented in MATLAB 7.0 (Mathworks Inc., Sherborn, MA). All images were realigned to the first image to correct for head movement. After realignment, volumes were normalized into standard stereotaxic anatomical MNI-space by using the transformation matrix calculated from the first EPI-scan of each subject and the EPI-template. Afterward, the normalized data with a resliced voxel size of 2 × 2 × 2 mm was smoothed with an 8 mm FWHM isotropic Gaussian kernel.

At the subject level, BOLD responses for phonological verbal fluency and "resting" baseline were modeled by a boxcar function convolved with the canonical hemodynamic response function employed in SPM5. In addition, the amount of correct words generated during each rhyming block was entered as an additional regressor in the design matrix in order to account for behavioral fluctuations within one participant. The same methodological approach was applied in previous studies of ours [34, 52]. Parameter

estimates (β) and t statistic images were calculated for each subject. At the group level, the individual weighted β-images relating to differences between PVF activation and "resting" baseline were entered into one-sample t tests for both conditions separately, *placebo* as well as ketamine infusion. Psychopathological phenomena (CD, difficulty in abstract thinking, lack of spontaneity and flow of conversation) as scored with the PANSS [31] were entered as covariates in the second-level design matrices of both conditions. Task-related activations under both conditions are reported on whole-brain level of analyses. Correlations of individual differences in PANSS scores and task-related activation during ketamine administration were examined applying a cluster extend threshold of $N = 43$ voxels at $P = .001$ in order to correct for multiple comparisons (see Monte Carlo simulations [63]). In each resulting cluster, β-parameter estimates were extracted at the coordinate of the maximum correlation as an average within a sphere of 3 mm radius. For the *placebo* condition, parameters were extracted using the same coordinates and extraction procedure. The correlations of task activation and PANSS scores were plotted to examine effects of outliers. Afterward, partial correlations between task-related activation and PANSS scores were calculated controlling for the activation during the *placebo* condition. The reported coordinates of strongest correlations were transformed from MNI space to Talairach & Tournoux atlas space [64] by nonlinear transformations (http://www.mrc-cbu.cam.ac.uk).

S-ketamine and placebo infusions

A within-subject, *placebo*-controlled, counterbalanced design was administered. Each subject, for 5 min, received an intravenously (i.v.) administered bolus of 8 mg *S*-ketamine from a 0.5 mg/ml solution of *S*-ketamine in 0.9% NaCl and a pure saline infusion for the *placebo* condition respectively for the induction of psychopathological symptoms. The initial "induction" phase was followed by an "equilibration" phase with no further *S*-ketamine/*placebo* supply lasting for 5 min. Then, the continuous subanesthetic i.v. infusion of 0.01 mg/kg/min *S*-ketamine (using a 0.25 mg/ml solution of *S*-ketamine in 0.9% NaCl) or pure 0.9% NaCl for the *placebo* condition was administered using an infusion pump to maintain the initially induced psychopathological symptoms. The duration of the infusion was approximately 1 h. All participants remained in the research center under medical supervision for at least 2 h after the termination of the *S*-ketamine infusion.

Psychopathological data

Before and immediately after the scan, psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) [31] by a trained psychiatrist (AK-V). For the subsequent fMRI analysis, we focused on the three task-related psychopathological PANSS items CD, difficulty in abstract thinking and lack of spontaneity and flow of conversation.

According to Kay et al. [31], CD is characterized by disruption of goal-directed sequencing, for example, circumstantiality, tangentiality, loose associations, non-sequiturs, gross illogicality, or thought blocking. The lack of spontaneity and flow of conversation is specified by a decrease in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive impairment. These symptoms are manifested by diminished fluidity and productivity of the verbal-interaction process. The evaluation of difficulty in abstract thinking consists of a range of questions on concept formulation (e.g., How are a train and bus alike?) and proverb interpretation, which were varied in content since PANSS was used for repeated assessment (*placebo* and ketamine).

Results

Psychopathology

Ketamine application elicited significant psychopathological effects as assessed by the PANSS. Participants experienced perceptual abnormalities and dissociative states with a range of psychotic symptoms, including difficulties in thinking as well as reality appraisal. Paired-samples t tests revealed a significant increase in positive symptoms (mean = 5.47, SD = 2.42; $t = 8.763$, $P < .01$), negative symptoms (mean = 10.93, SD = 5.73; $t = 7.396$, $P < .01$), general symptoms (mean = 6.53, SD = 2.67; $t = 9.480$, $P < .01$), and total symptomatology (mean = 22.93, SD = 7.21; $t = 12.326$, $P < .01$) for the ketamine in comparison with the *placebo* condition.

Ketamine psychopathological effects for the items of interest were as follows: CD (mean = 3.73, SD = 1.22); difficulty in abstract thinking (AT) (mean = 3.66, SD = 1.50); lack of spontaneity and flow of conversation (SP) (mean = 2.60, SD = 1.68).

Behavioral data

The number of generated rhyming words was slightly reduced under ketamine (mean = 17.6, SD = 8.24) as compared to *placebo* (mean = 19.6, SD = 8.10) administration. However, this difference in performance between the conditions was not statistically significant (paired-samples t test: $t = -0.85$, $P = .41$).

Imaging data

Task and condition specific effects

During *placebo* administration, the PVF task (as compared to "resting" baseline) elicited a neural activation pattern that encompassed the left inferior frontal gyrus, the left middle and superior temporal gyrus, the left occipital lobe as well as the bilateral motor cortex and the cerebellum (whole-brain analysis, FDR-corrected, $P < .05$, extent threshold $k = 40$) (Fig. 1, left).

During ketamine administration, a similar though enhanced pattern of activation was found in the fronto-temporal language network encompassing the left superior temporal as well as the inferior parietal lobe (whole-brain analysis, FDR-corrected, $P < .05$ extent threshold $k = 40$) (Fig. 1, right).

Conceptual disorganization

Under ketamine (KET) administration, CD scores were correlated with activation measures in the temporo-parietal region in the left hemisphere (BA 22), the right middle and inferior frontal region (p. opercularis) (BA 8), and the precuneus (BA 7) (see Table 2; Fig. 2). Importantly, the correlations were still significantly correlated with task-related activation, after controlling for the activation, which was present during the *placebo* condition, where subjects showed no signs of CD.

Difficulty in abstract thinking

Difficulty in abstract thinking scores under ketamine infusion correlated with activation in the right anterior cingulate gyrus (BA 32) as well as the left superior frontal gyrus (SFG) (BA 10) (Fig. 3). Again, after controlling for activation during the *placebo* condition, the partial correlations of AT scores and task-related activation during the ketamine condition remained statistically significant below the threshold level.

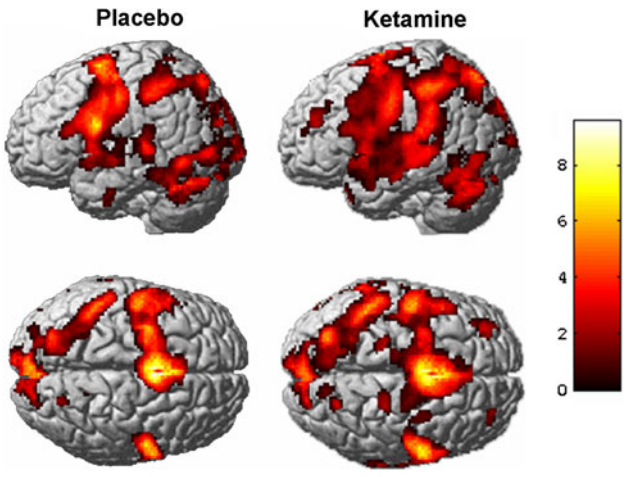

Fig. 1 Cortical activations for PVF (contrasted with "resting" baseline) during *placebo* (*left* graphics) and ketamine administration (*right* graphics) (FDR-corrected, $P < .05$, extent threshold $k = 40$ voxels)

Lack of spontaneity and flow of conversation (SP)

Lack of spontaneity and flow of conversation was correlated with task-related activity in the left superior temporal gyrus (BA 22) (Fig. 4) and remained significant at below threshold level after controlling for activation during the nonketamine condition.

Discussion

The NMDAR blockade was found to evoke clinical symptoms—among others—of CD, an impairment of abstract thinking as well as a reduction in the spontaneity and flow of conversation as assessed with the PANSS. On the level of task performance, the glutamate antagonism revealed a subtle effect on the total quantitative verbal output. However, this difference was not significant.

Ketamine-induced impairments in speech production were found in previous studies [5]. Here, NMDAR blocking led to loss of goal, perseveration, or blocking phenomena being characteristic for schizophrenic speech [48]. Moreover, a discourse analysis of linguistic output from healthy subjects receiving ketamine revealed a decrease in "verb density" resulting in the tendency to speak in noun phrases rather than complete sentences [17]. In addition, Covington and colleagues found a more repetitious speech pattern in association with ketamine administration indicating an impairment of both lexical access and discourse organization. In general, a ketamine-induced influence on verbal productivity was previously reported by Adler et al. [4]. However, some studies also reported nonsignificant effects of NMDAR blockade on executive verbal fluency performance [23, 60], which might be explained by ketamine-induced alterations in perception (see [40]). It can be hypothesized that the preserved performance in verbal fluency performance may rely on the additional recruitment of neural resources counteracting cognitive impairment due to the NMDAR hypofunction.

In the current pharmaco-imaging study, the NMDAR blockade predominantly resulted in a fronto-temporal pattern of BOLD enhancements. Fu et al. [23, 24] reported greater activations in particular in the anterior cingulate as well as in the middle frontal region in patients with acute psychosis as compared to patients in remission during a verbal fluency task and during increased task demands [24]. The authors conclude that schizophrenia is associated

Table 2 Correlations of PANSS items for conceptual disorganization (CD), difficulty in abstract thinking and lack of spontaneity and flow of conversation (SP) with hemodynamic responses during ketamine administration

		MNI-coordinates					t	r^{+}	Partial $r^{\#}$	P
		BA	x	y	z	No. voxels				
CD										
L	Superior temporal gyrus	22	−52	−40	16	134	6.14	0.850	0.822	<.0003
R	Middle frontal gyrus	8	38	16	48	67	5.68	0.828	0.836	<.0002
	Inferior frontal gyrus (p. opercularis)		38	12	40		4.97			
L	Precuneus	7	−10	−80	38	66	4.66	0.750	0.740	<.0025
AT										
R	Anterior cingulate gyrus	32	18	40	−4	47	6.27	0.820	0.751	<.0019
L	Superior frontal gyrus	10	−22	42	26	105	4.84	0.804	0.781	<.0010
SP										
L	Superior temporal gyrus	22	−56	−60	14	48	4.80	0.793	0.789	<.0008

$^{+}$ Pearson correlations of PANSS items with activations in the depicted regions during ketamine administration

First Eigenvariate betas extracted in a sphere of 3 mm; $^{\#}$ Partial correlations after controlling for activation during the placebo condition in the same Area of interest. P values referring to partial correlations

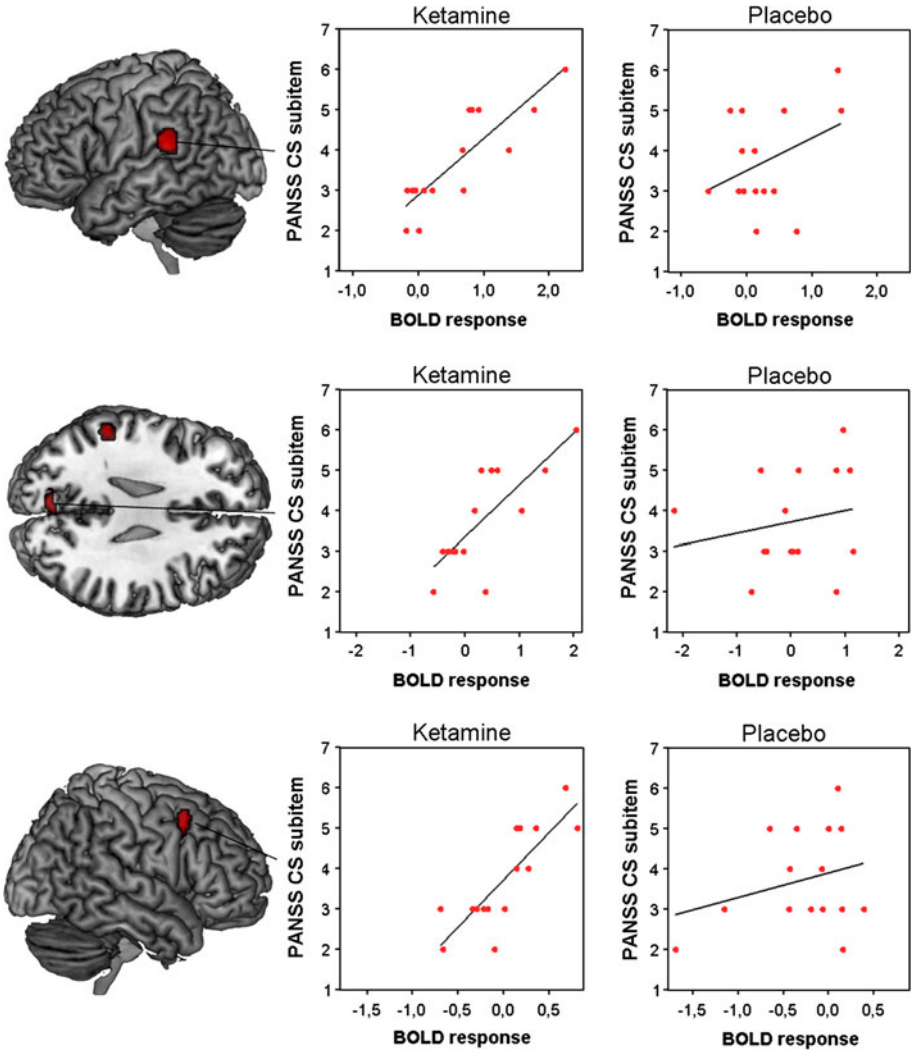

Fig. 2 Conceptual disorganization (whole-brain analysis, MC-corrected, $P < .001$)

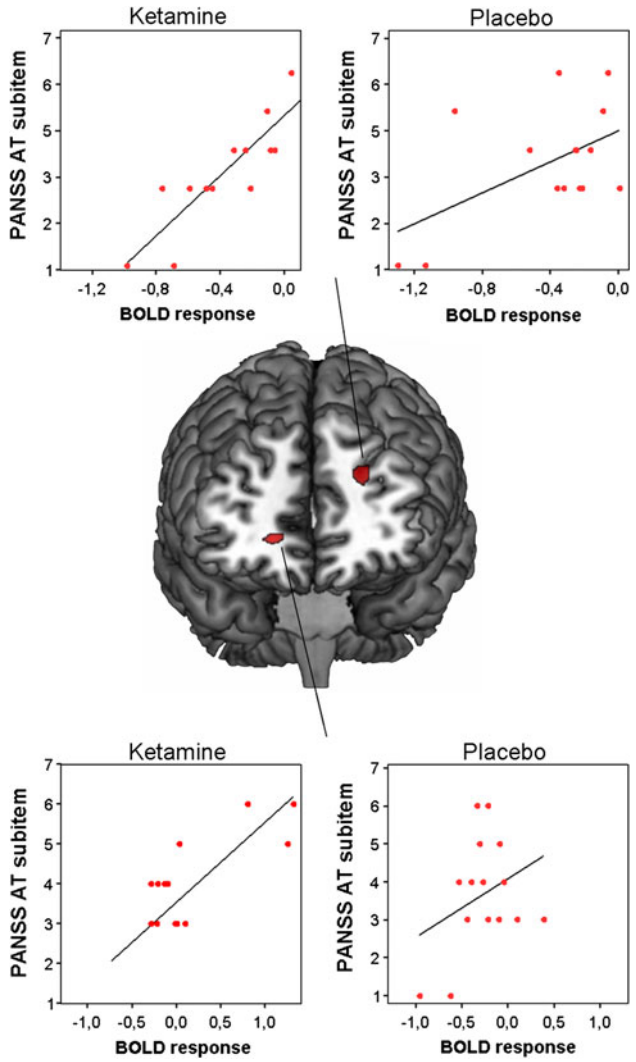

Fig. 3 Difficulty in abstract thinking (whole-brain analysis, MC-corrected, $P < .001$)

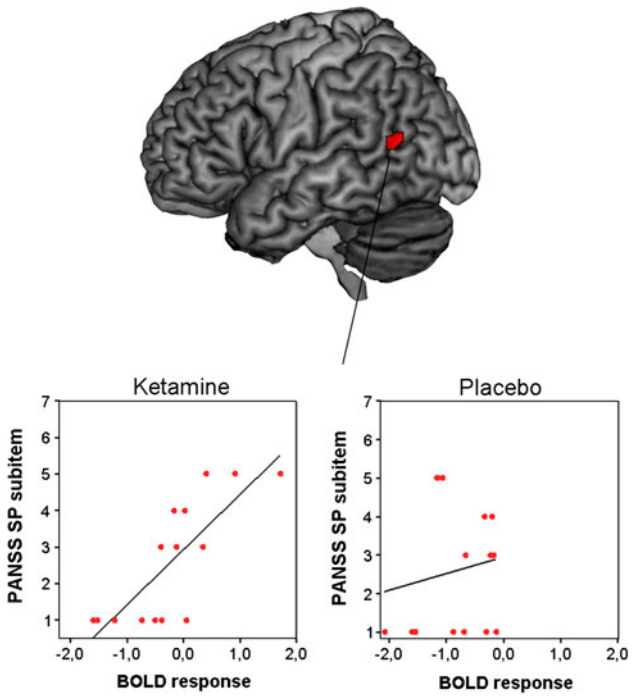

Fig. 4 Lack of spontaneity and flow of conversation (whole-brain analysis, MC-corrected, $P < .001$)

with impaired prefrontal function, but the manifestation depends on both the severity of psychotic symptoms and the level of task difficulty. A recent fMRI study investigating the neural correlates of phonological verbal fluency also found a pattern of altered frontal activation, particularly in the anterior cingulate and the left dorsolateral prefrontal cortex in patients with schizophrenia as compared to healthy controls [16]. The individual associations of psychopathological symptoms with BOLD signal changes are discussed in the following paragraphs.

Association of psychopathological items with hemodynamic responses

Conceptual disorganization

In the past years, a number of ketamine functional imaging studies were conducted [1, 2, 18, 19, 24, 28, 29, 55], implementing different cognitive tasks at different ketamine dosages. In line with previous study results [3, 4, 27, 47], ketamine induced a state of CD in our study. Here, formal thought disorder particularly comprised looseness of thought, but also blocking phenomena as well as *nonsequiturs* resulting in difficulties "to put thoughts into words" [46].

On the neural level, individual differences in expressing these symptoms under ketamine administration were associated with enhanced hemodynamic responses in fronto-temporal language areas. Accordingly, increased BOLD responses encompassed areas of the left superior temporal gyrus as well as the right middle and inferior frontal gyrus including the pars opercularis. Another cluster that was highly associated with the expression of CD was found in the precuneus. According to the hypothesis of neural inefficiency [9, 61], subjects tend to recruit additional brain regions, such as the middle and inferior frontal gyrus as well as the precuneus, in order to compensate cognitive dysfunctions or hyperactivate regions being primarily involved in task performance, respectively. In the context of NMDAR hypofunction, ketamine administration impacts on the supplemental recruitment of key regions being involved in task performance, for example, during encoding and retrieval of episodic memory [28, 55].

Abstract thinking

The AT domain in particular, with regard to proverb interpretation and concept formulation, was found to be

strongly affected by the NMDAR blockade. On the neural basis, AT values revealed enhanced cortical responses encompassing the right ACC as well as the left SFG. Partial correlation results were found to be the highest for the SFG followed by the ACC, which leads to the assumption that both regions are particularly involved in ketamine-induced AT symptom formation.

A recent fMRI study [23] investigated the neural correlates of letter fluency during continuous ketamine infusion. Although the purpose of this paced overt verbal fluency study was primarily based on differences in BOLD response with respect to increasing task demand during ketamine or *placebo*, respectively [23], similar brain regions were reported to be more activated in the ketamine condition. Thus, an interaction of task demand was observed in the ACC as well as in the prefrontal cortical region in the context of ketamine administration [23]. The authors conclude that these results were comparable to verbal fluency findings evident in patients with schizophrenia.

Moreover, enhanced neural responses in prefrontal as well as in anterior cingulate regions were previously found in association with subanesthetic ketamine administration [39, 70]. Furthermore, Honey et al. [28] found a significant effect of ketamine on left frontal neural response. The authors report that left frontal activation was augmented by ketamine when elaborative semantic processing was required at encoding. Likewise, the region of the ACC was associated with the NMDAR blockade, enhanced [26, 69, 70] on the one hand, or deactivated [55] on the other hand. Similarly, ketamine increased regional blood flow in the ACC in patients with schizophrenia as measured with positron emission tomography (PET) [25, 42, 65]. Holcomb et al. [25] concluded that the ketamine-induced reduction in inhibition leads to a marked increase in glutamate release and hypermetabolism in frontal and cingulate cortical regions.

With regard to the neural correlates of verbal fluency in patients with schizophrenia, the ACC was shown to be associated with increased verbal fluency task demand [24]. The authors found an association between impaired prefrontal cortical function depending first on the severity of psychotic symptoms and second on the level of task difficulty. Thus, increasing task demand led to enhanced neural responses in the anterior ACC and middle frontal region in patients with active psychosis in comparison with those in remission [24].

In our study, the degree of AT dysfunction correlated with enhanced hemodynamic responses in two distinct brain regions, which were previously found in healthy subjects receiving ketamine as well as in patients with schizophrenia. Interestingly, these results are based on fundamentally different imaging techniques measuring differences in hemodynamic responses (fMRI) or differences in receptor binding potentials (PET), different cohorts (healthy subjects undergoing neurochemical NMDAR blockade vs. patients with schizophrenia), and different cognitive tasks. In the context of overt rhyme generation the AT dysfunction may have highlighted the above-mentioned regions, first for reason of highly abstract cognitive demands during the continuous rhyme generation on pseudoword stimuli, second for reasons of general augmentation of BOLD responses in the ACC and SFG due to glutamate antagonism.

Lack of spontaneity and flow of conversation (SP)

The ketamine-induced SP symptom expression predominantly occurs in the sense of a reduced verbal productivity [4]. This lack is primarily manifested by diminished fluency and productivity of the verbal-interaction process [31]. On the neural level, again, enhanced cortical responses became evident in the left STG, corresponding to Wernicke's area. As previously argued for the CD activations, a neural inefficiency mechanism may underlie the increased activations in the superior temporal region. Following this hypothesis, subjects with a higher degree of SP impairment necessitate comparatively more resources in order to access or recall appropriate entries from the mental lexicon. In this respect, additional effort is needed to compensate for SP impairment during continuous rhyme generation, which in turn results in pronounced activations in the area of the mental lexicon.

In general, there are remarkable methodological differences between previous pharmaco-imaging studies with ketamine limiting the generalizability of the reported results. First, a distinction between both enantiomers (*R*-) and (*S*-) ketamine has to be made, since the latter was found to bind with a 3–4 time higher affinity to the PCP binding site of the NMDA receptor than (*R*)-ketamine. This in turn results in differential psychopathological symptom formations. Moreover, the individual subanesthetic dosage was found to play an important role inducing cognitive impairment as well as psychopathological symptoms [50].

Limitations

The reported imaging results for the ketamine-induced psychotic states rest upon correlations between psychopathological symptom measures (PANSS) on the one hand, and hemodynamic responses on the other hand. Although we controlled for activations in the same area for *placebo*, the number of participants is still limited such that a second-order error cannot be ruled out. A further limitation of the study consists in the nonblinded evaluation of psychopathological symptoms.

Conclusions

To our knowledge, no functional imaging study has investigated the associations between neural correlates and single ketamine-induced psychopathological syndromes, so far. In our study, focal differences in activation patterns were strongly related to the individual symptom formation. Hyperactivations due to the NMDAR dysfunction can be explained in terms of compensational mechanisms countervailing ketamine-induced psychopathological phenomena. Moreover, similarities to patients with schizophrenia were found supporting the hypothesis of a glutamatergic dysfunction in the pathophysiology of schizophrenia. Therefore, the neurochemical blocking of the glutamatergic NMDAR receptor represents a valid method to mimic specific aspects of symptom formation. Finally, our findings might help to further clarify the pathophysiological mechanisms being involved in psychopathological symptom formation.

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Conflict of interest None.

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