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The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia

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ABSTRACT

Background: Declarative memory disturbances, known to substantially contribute to cognitive impairment in schizophrenia, have previously been attributed to prefrontal as well as hippocampal dysfunction.
Aims: To characterize the role of prefrontal and mesolimbic/hippocampal dysfunction during memory encoding in schizophrenia.
Method: Neuronal activation in schizophrenia patients and controls was assessed using functional magnetic resonance imaging (fMRI) during encoding of words in a deep (semantic judgement) and shallow (case judgment) task. A free recall (no delay) and a recognition task (24 h delay) were performed.
Results: Free recall, but not recognition performance was reduced in patients. Reduced performance was correlated with positive symptoms which in turn were related to increased left hippocampal activity during successful encoding. Furthermore, schizophrenia patients displayed a hippocampal hyperactivity during deep encoding irrespective of encoding success along with a reduced anterior cingulate cortex (ACC) and dorsomedial prefrontal cortex (DMPFC) activity in successful encoding but an intact left inferior frontal cortex (LIFC) activity.
Conclusions: This study provides the first evidence directly linking positive symptoms and memory deficits to dysfunctional hippocampal hyperactivity. It thereby underscores the pivotal pathophysiological role of a hyperdopaminergic mesolimbic state in schizophrenia.

1. Introduction

Since the original description of schizophrenia by Bleuler (1911) the psychopathological concept of this disease has been developed substantially. Most notably, cognitive deficits such as attention deficits and memory impairment have been recognized as core features that persist and importantly contribute to disease-related disability. Declarative memory impairment is one of the most disabling cognitive deficits in schizophrenia (Heckers et al., 1998).

Schizophrenia patients exhibit functional and structural abnormalities in brain structures that subserve declarative memory, most notably the prefrontal cortex and the hippocampus (Bogerts et al., 1991). In declarative memory, two experimentally discriminable forms have been described: familiarity-based recognition and recollection of context rich memory (Yonelinas, 1999a, 1998). They are mediated by partly dissociable neural structures, with the hippocampus being particularly critical in recollection, but not familiarity (Yonelinas, 1999a, 1998).

Memory encoding can be investigated using a levels of processing (LOP) encoding paradigm (Craik and Lockhart, 1972). At this, verbal stimuli are encoded incidentally, using either a perceptual task (shallow level, e.g. counting syllables, case judgment) or a more elaborate semantic task (deep level, e.g. pleasantness/animacy rating). Depth of encoding has been shown to correlate with memory performance (Craik and Lockhart, 1972).

Up to now, studies of neuronal activation in schizophrenia-related impairment of declarative memory have yielded heterogeneous results with respect to prefrontal as well as hippocampal hyper- or hypoactivation (Kubicki et al., 2003; Ragland et al., 2004). Recent hypotheses regarding the major role of disturbed dopaminergic mesolimbic function in schizophrenia have postulated that psychotic symptoms arise from a hyperdopaminergic state. It has also been established that memory encoding critically depends on novelty detection which is again mediated by the mesolimbic dopaminergic circuitry.

In this context the present study aims to explore whether hippocampal dysfunction contributes to schizophrenia-related

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encoding deficits and whether this effect is related to psychotic symptoms that reflect hyperdopaminergic mesolimbic activity. Furthermore, it addresses the role of prefrontal cortex dysfunction.

2. Methods

2.1. Subjects

A clinically well characterized group of patients with paranoid-hallucinatory schizophrenia ($n=11$, 4 female, mean age 29 years, medicated with atypical neuroleptic drugs, no benzodiazepines, see also Table 1) (International classification of diseases Release 10 (ICD-10) F20, no neuropsychiatric comorbidities) and healthy volunteers ($n=13$, 6 female, mean age 25 years) participated in the experiment on two consecutive days. All participants had normal or corrected-to-normal vision, were right-handed and native speakers of German. All participants were checked for MRI contraindications and gave written informed consent to participate. The study was approved by the institutional review board of the medical faculty, Otto-von-Guericke University, Magdeburg. Control subjects underwent routine clinical interview for history of neurological and psychiatric illnesses. Subjects with present or past neurological or psychiatric disorders or the use of any drugs were excluded.

Control subjects were matched with the patients in age, education and handedness. Controls and patients did not significantly differ with respect to age, education (years in school) and gender (see Table 1).

Diagnosis of paranoid-hallucinatory schizophrenia was established by psychiatric evaluation. According to the positive and negative syndrome scale (PANSS) (Kay et al., 1987) and the brief psychiatric rating scale (BPRS) (Overall and Gorham, 1962) all patients were mildly to moderately impaired (see Table 1).

2.2. Behavioural tasks

2.2.1. LOP paradigm with free recall

On the first day, participants performed an incidental encoding paradigm with an LOP manipulation, that has previously been applied identically in several studies, and is specifically designed to assess neuronal activation during encoding (Schott et al., 2004, 2006). In order to investigate the correlates of successful memory formation neural responses to novel words in two different study tasks (deep and shallow study of items) were compared as a function of subsequent remembering or forgetting in a free recall task directly after the encoding and in a recognition task 24 h later (Schott et al., 2004).

The fMRI experiment (= LOP-encoding with free recall task) consisted of three runs lasting 20 min, respectively. Each run comprised three sessions with a deep study task (pleasantness judgment: indication of a pleasant or unpleasant word) and three sessions with a shallow study task (phonemic syllable counting: indication of a word consisting of exactly two syllables), presented in an alternating manner. Subjects responded via button press using their right and left index fingers. Response hands were counterbalanced across participants. Each session consisted of the presentation of a central fixation cross for 250 ms, a word for 1500 ms, and a further fixation cross for 1000 ms. Twenty words were presented during each session. Those were followed by a distractor task consisting of four moderately difficult arithmetic operations in order to prevent internal rehearsal of studied words. Specifically, subjects indicated via button press whether the presented result of two- to three-digit additions was correct or not. After the distractor task, subjects were prompted to freely recall all studied words they could remember and respond overtly. The duration of the free recall phase was 90 s. Overt responses were recorded using a microphone at the bottom of the head coil and scored off-line.

For both tasks (LOP-encoding with free recall and recognition task) 540 words were selected randomly from a pool of 600 substantives, adjectives and verbs (neutral meaning, frequency of occurrence = 46) (Baayen et al., 1993).

2.2.2. Recognition task

The recognition experiment was conducted 24 h after the LOP-encoding with free recall task. It consisted of 540 words including 360 of the LOP-encoding task (180 deeply and 180 shallowly encoded words that previously had to be recalled in the fMRI experiment) and 180 new words and was conducted outside the scanner. The task was divided into 9 sessions of 60 words each and a short break of 60 s after each session. Words were presented in a randomized way beginning with a central fixation cross for 1000 ms, a word for 4000 ms and a further fixation cross for 1000 ms. The participants had to decide via button press using either their right index finger if the present word was old/known or their right middle finger if it was new (or vice versa). Again, response fingers were counterbalanced across participants.

Behavioural data (including the number of correct/incorrect answers and reaction times) of the free recall and the recognition paradigms were analysed using the SPSS statistical software package. We included only subjects with a performance above chance level as indicated by the discriminability index (d')>0.5 (Swets, 1964; Green, 1966). Within-group effects and between-group differences (patients vs. healthy participants) were tested using the non-parametric Wilcoxon test.

2.3. fMRI image acquisition and analysis

FMRI data were acquired during tacit encoding of words as described above. The experiment was conducted in a GE 1.5 T Signa MRI system (General Electric Medical Systems) using a standard quadrature head coil. Echo-planar images (EPIs) were acquired at a TR of 2.0 s and a TE of 35 ms. Images consisted of 23 interleaved axial slices parallel to the AC–PC plane (matrix 64×64; field of view 22 cm; slice thickness 5 mm; 1 mm gap; 544 volumes per session). SPM2 (Wellcome Dept. of Imaging Neuroscience, Institute of Neurology, London, UK) was used for pre-processing and data analysis. EPIs were corrected for acquisition delay, realigned, normalized to the MNI stereotactic reference frame (Montreal Neurological Institute; voxel size: 3×3×3 mm), smoothed (Gaussian kernel, 8 mm), and high-pass-filtered (128 s). Statistical analysis was carried out using a two-stage mixed effects model. In the first stage, neural activity was modelled by a δ function at stimulus onset for each individual subject. The ensuing blood-oxygen-level-dependent (BOLD) response was modelled by convolving these δ functions with a canonical hemodynamic response function (hrf). The resulting time courses were down-sampled for each scan to form covariates in a General Linear Model (GLM). The covariates of the GLM for individual subjects' contrasts were the conditions of interest, one covariate time-locked to each speech event (overt response in free recall), six for the rigid-body movement parameters derived from realignment, a 20 s epoch for the distractor task, and a constant

Table 1
Demographic and clinical characteristics of the subjects.

	Control subjects		Schizophrenic subjects	
	Mean	S.D.	Mean	S.D.
Age	25.00	4.67	29.00	10.98
Education	12.80	0.43	10.82	1.78
Verbal IQ	111.38*	6.86	100.64*	8.78
PANSS	–	–	79.91	23.58
BPRS	–	–	33.09	14.27
Chlorpromazine equivalent of daily neuroleptic dose [mg/d]		–	449.78	232.33
Number of hospitalizations			4.45	4.25
Age of onset	–	–	22.91	7.46
Male	–	–	21.43	4.79
Female	–	–	25.50	11.21

* One-way ANOVA: $F(1,22)=11.903$; $P=0.002$.

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representing the mean over scans. In order to specifically investigate mechanisms related to level of processing and successful encoding as assessed in the free recall task, respectively, difference and thus no baseline contrasts (t statistics for deep vs. shallow processing and remembered vs. forgotten, respectively) were used for all second level comparisons. To assess overall effects of LOP and subsequent memory performance, contrast images [LOP contrast: (deep hits + deep misses) vs. (shallow hits + shallow misses); subsequent memory contrast: (deep hits + shallow hits) vs. (deep misses + shallow misses)] were entered into one-sample t-tests.

In addition to a voxel-based analysis we used spherical regions of interest (ROI) analysis for temporal structures (hippocampus, and superior temporal gyrus) and for prefrontal regions (left inferior prefrontal cortex, LIFC; dorsomedial prefrontal cortex, DMPFC; and anterior cingulated cortex, ACC) of both hemispheres. The centers of the spherical ROIs were placed in the SPM-identified maxima for each relevant contrast within both groups. Given the considerable size differences of the brain structures of interest, the radius of the spherical ROIs was set to 15 mm for the frontal regions (LIFC; dorso lateral prefrontal cortex, DLPFC; DMPFC), 7 mm for the hippocampus, and 10 mm for the superior temporal gyrus. The significance level for the overall group analyses was set to 0.05 (uncorrected), with an extent threshold of 5 adjacent voxels.

In order to display the time course of the hrf BOLD signal time courses of the hippocampus (spherical ROI 7 mm) were produced by averaging the time course of each subject across multiple voxels during deep encoding.

2.4. Psychopathological assessment

Patients were also tested for disease severity at the time of participation using the PANSS (subscales: positive symptomatic, negative symptomatic and general psychopathology) and the BPRS.

2.4.1. Psychopathology, memory impairments and hippocampal activity

A correlation analysis was conducted in order to test for a relation of actual psychotic symptoms with behavioural and neuronal measures of memory impairment. Two-tailed spearman rho correlation coefficients were calculated in the patients between schizophrenia symptoms (PANSS: subscales positive and negative symptomatic) and memory performance as well as neuronal activation (fMRI BOLD signal) in the hippocampus during encoding. Again, the significance level was set to 0.05.

3. Results

3.1. Behavioural results

3.1.1. Free recall task

Overall, schizophrenia patients freely recalled significantly less of the studied words than controls (16% vs. 32%, $F(1,22) = 32.34$; $P<0.001$). Both groups remembered a larger proportion of deeply encoded words as compared to shallowly encoded words (LOP effect in controls: $\text{mean}_{\text{deep}} = 68.77$ words (38%) $\text{mean}_{\text{shallow}} = 46.38$ words (26%); $F(1,12) = 82.86$; $P<0.001$; schizophrenia subjects: $\text{mean}_{\text{deep}} = 32.91$ words (18%); $\text{mean}_{\text{shallow}} = 23.45$ words (13%) $F(1,10) = 12.59$; $P = 0.005$). Schizophrenia patients benefitted less from deep in comparison to shallow encoding than controls (Group × LOP, $F(1,22) = 13.67$; $P = 0.001$) (see Fig. 1).

3.1.2. Delayed recognition task

In the delayed recognition task (24 h after the encoding and free recall task) the number of correctly recognized words (collapsed over deep and shallow words) did not differ between the patients (mean = 128.69 words; 72%) and controls (mean = 142.91 words, 79%) ($F(1,17) = 2.66$; $P = 0.121$) for those subjects with a performance above chance level (as indicated by $d' > 0.5$). Accordingly, 11 controls and 9 patients were included in this subanalysis. Controls again showed a robust LOP effect ($\text{mean}_{\text{deep}} = 153.18$ words (86%) $\text{mean}_{\text{shallow}} = 132.63$ words (73%); $F(1,10) = 20.13$; $P = 0.001$), while for the patients this effect could only be seen as a statistical trend ($\text{mean}_{\text{deep}} = 133.88$ words (75%); $\text{mean}_{\text{shallow}} = 123.50$ words (69%); $F(1,8) = 4.79$; $P = 0.053$) (see Fig. 2).

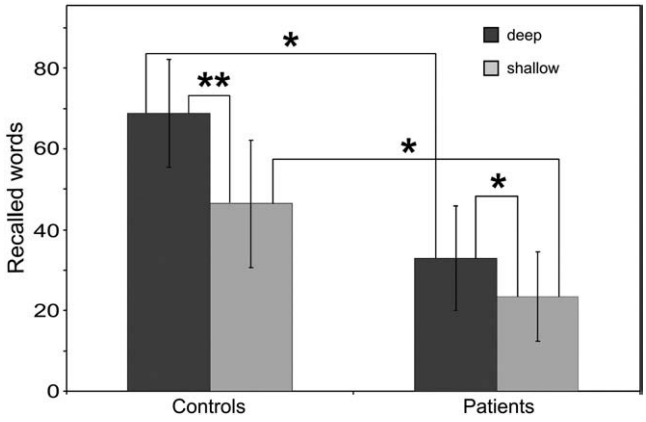

Fig. 1. Mean number of freely recalled words for control and schizophrenia subjects. * *General linear model repeated measure*: $P<0.01$; **$P<0.001$; $\alpha = 0.05$.

3.2. Imaging data

3.2.1. Controls: LIFC activation during deep encoding

During memory encoding in control subjects, deep as compared to shallow processing (contrast: deep vs. shallow, collapsed over hits and misses) was associated with an increase of cerebral blood flow in the LIFC and DMPFC (voxel-wise t statistics; $P<0.001$, respectively).

In the contrast between subsequently remembered and forgotten words (contrast: hits vs. misses, collapsed over deep and shallow), healthy controls showed a stronger activation in the left hippocampus (ROI-analysis 7 mm sphere; $P = 0.02$) during the encoding of later remembered words. Previously deeply encoded and later remembered words (contrast: deeply encoded words only — hits vs. misses) were associated with activation of the left ACC (ROI-analysis, 10 mm sphere; $P = 0.008$), and LIFC (ROI-analysis, 15 mm sphere; $P = 0.011$) (see Table 2 and Fig. 3).

3.2.2. Schizophrenia patients: preserved LIFC activity

Similar to healthy controls, schizophrenia patients showed increased activation of the LIFC (ROI-analysis 15 mm sphere;

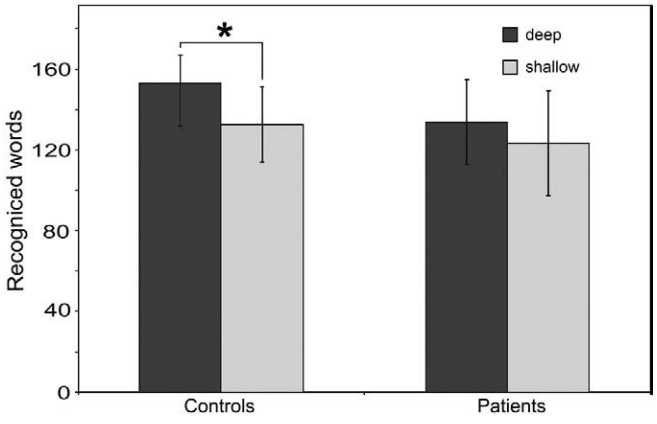

Fig. 2. Mean number of recognized words for control and schizophrenia subjects. * *General linear model repeated measure*: $P<0.01$; **$P<0.001$; $\alpha = 0.05$.

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Table 2
Volume and region of interest (ROI) analysis within control group: local maxima of blood-oxygen-level-dependent fMRI signal change in healthy comparison subjects; extent threshold: $k=5$ voxel; threshold: 0.01; $P_{uncorrected}<0.05$.

	Talairach coordinates			
Volume analysis: Contrast and anatomical region	*x*	*y*	*z*	*t*-value
Deep vs. shallow				
Left inferior prefrontal cortex	−43	14	−1	7.62
Left dorsomedial prefrontal cortex	−6	54	40	9.53
Hits vs. misses				
Right dorsomedial prefrontal cortex	5	40	43	4.69
Left anterior cingulate cortex	−9	34	−5	7.75
Shallow only; hits vs. misses				
Left anterior cingulate cortex	−6	38	0	6.27
Right anterior cingulate cortex	5	35	3	5.15
Hits only; deep vs. shallow				
Left inferior prefrontal cortex	−49	20	−4	7.48
Left dorsomedial prefrontal cortex	−3	53	37	7.01
Left inferior temporal gyrus	−43	−15	−23	4.80
Left superior temporal gyrus	−31	17	−20	5.69
Misses only; deep vs. shallow				
Left medial temporal gyrus	−62	−52	25	6.07
Left inferior prefrontal cortex	−46	14	0	5.73
	−38	28	−13	5.73
Left dorsomedial prefrontal cortex	−6	54	37	4.80
ROI-analysis: Contrast and anatomical region				
Hits vs. misses				
Left hippocampus	−24	−3	−17	4.80
Deep only; hits vs. misses				
Left anterior cingulated cortex	−3	39	16	3.22
Left inferior prefrontal cortex	−9	34	−5	4.92

$P=0.028$), left DLPFC (ROI-analysis, 15 mm sphere; $P=0.045$) and left DMPFC (ROI-analysis, 15 mm sphere; $P=0.007$) during deep encoding (contrast: deep vs. shallow, collapsed over hits and misses). Compared to the encoding of words that were later forgotten (see Table 3), the neural activation of left superior temporal gyrus (ROI-analysis, 10 mm sphere; $P=0.047$) was more pronounced during the encoding of later remembered words (contrast: hits vs. misses) (see Table 3, Fig. 4).

3.2.3. Group comparison: hypoactivity in ACC and DMPFC, but unspecific left hippocampal hyperactivity in schizophrenia

In a subsequent volume analysis between groups, healthy controls had in comparison to patients a significantly higher activation in the left ACC and the right DMPFC (volume analysis; $P=0.025$, respectively) for the contrast hits vs. misses. A ROI-analysis between groups showed a stronger activation of the left hippocampus (ROI-analysis 7 mm sphere; $P=0.031$) in the patient group during deep encoding which did not differ between words that were later remembered and those that were later not remembered (contrast: deep vs. shallow, collapsed over hits and misses) (see Table 4 and Fig. 5). Hippocampal hyperactivity is also shown in Fig. 6 which displays the hrf time courses of schizophrenia patients and healthy controls during deep encoding (stimulus onset = 0 s).

3.3. Psychopathology, memory performance and neuronal hippocampal activity

In schizophrenia patients, the severity of prevalent positive symptoms was negatively correlated with the number of freely recalled words ($r=-0.627$; $\alpha=0.05$; 2-tailed). Additionally, more pronounced positive symptoms were associated with a stronger BOLD response in the left hippocampus during successful semantic encoding in the patients ($r=0.626$; $\alpha=0.05$; 2-tailed). No correlation was found between negative symptoms and memory performance or BOLD responses.

4. Discussion

In the present study we observed a remarkable relation of memory impairment, neuronal activity, and psychopathology in schizophrenia patients. Memory impairments in the patients came along with a peculiar hippocampal activation pattern: left hippocampal activity was unspecifically increased during deep encoding. Furthermore, memory impairment was related to more pronounced positive symptoms which in turn were associated with stronger left hippocampal activation in the more infrequently occurring events of successful semantic encoding.

Overall, the patients displayed an impaired performance and a reduced LOP effect in the free recall task, which were accompanied by relatively unaltered neuronal LIFC activations, but decreased ACC and DMPFC activity during encoding.

4.1. Differential impairment of recall and recognition

We observed a dissociation of free recall and recognition memory impairment in schizophrenia patients. Behavioral data of both tasks indicate that declarative memory deficits in schizophrenia patients mainly affect recall, while recognition remains relatively intact. In the framework of the dual-process model of declarative memory this deficit pattern could be accounted for by a relatively selective impairment of recollection, but relative sparing of familiarity-based memory retrieval (Yonelinas, 1999a,b). It has previously been shown that patients with a frontal lobe damage have difficulties in the active recollection of memory traces but not in familiarity-based recognition (Yonelinas, 1999a,b). Cytoarchitectonic abnormalities and fronto-temporal volume reductions are a well-replicated finding in schizophrenia patients (Bogerts et al., 1991). Given that storage and recall of declarative memory rely critically on the interaction of frontal and limbic brain regions (Düzel et al., 2001) structural alterations in these regions in schizophrenia might lead to memory deficits that share features with those observed after frontal lobe damage. Nevertheless, previous findings as well as our study cannot clearly elucidate whether the memory deficit is attributable to disturbed encoding or retrieval processes.

Alternatively, the selective recall deficit in the patients might be related to disturbed hippocampal integrity. Investigations in patients with selective hippocampal damage and fMRI studies in healthy humans suggest that the hippocampus might be particularly critical for recollection-based memory processes, such as recall, but not familiarity-based recognition (Düzel et al., 2001). Both, schizophrenia patients and controls generally benefited from deep encoding in the free recall task even though this LOP effect was less pronounced in the patient group. This reduction of both overall memory performance and LOP effect in the patients might be related to separable pathomechanisms. While the overall recall deficit, evident in the deep and shallow condition, might be best explained by structural hippocampal deficits in schizophrenia, the reduced LOP effect might be related to impaired interaction between frontal and limbic components of the declarative memory networks.

In contrast to the impaired free recall in the patients, the number of recognized words did not differ between both groups, indicating an intact recognition performance in the patients. Thus, our data show that recollection and familiarity are differentially affected in schizophrenia. The assumption of two separate and hence independently vulnerable processes underlying recognition and recollection is in line with multiple previous findings in healthy controls (Yonelinas, 1999a,b). In contrast to our data, other studies described an intact LOP effect for schizophrenia subjects in recognition tasks which tested item recognition directly after encoding (Heckers et al., 1998; Ragland et al., 2003). Our data show this effect only in a statistical trend and it may thus be detectable when examining larger samples.

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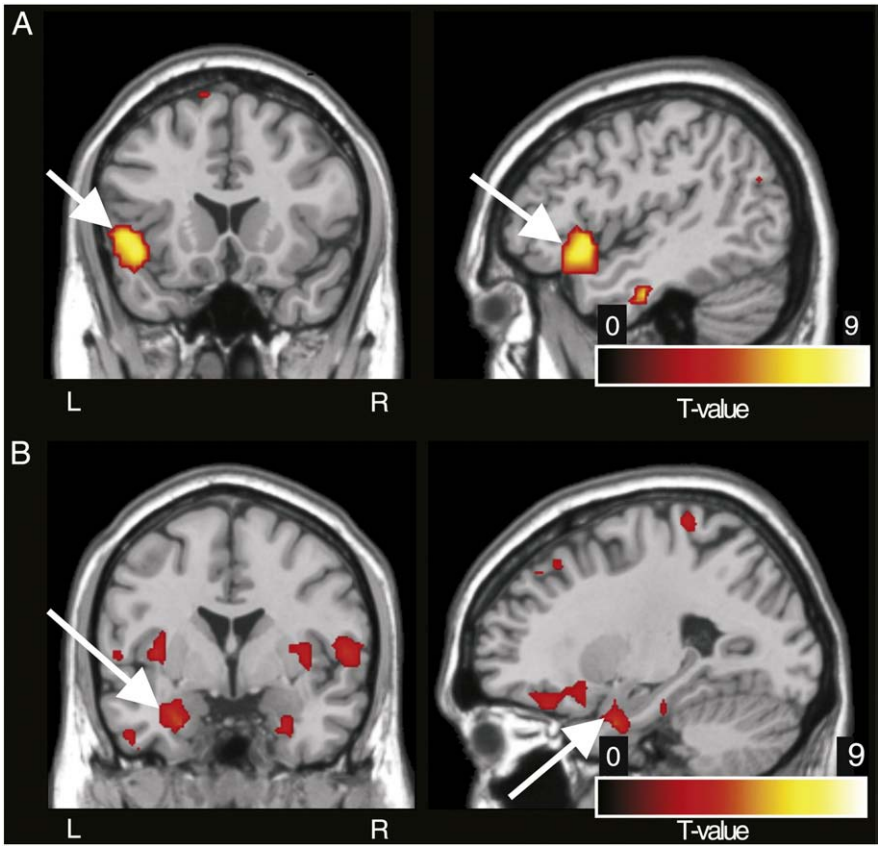

Fig. 3. Healthy controls: A. Enhanced neural activity of left (*L*) inferior prefrontal cortex (*white* arrow) during semantic encoding. B. Increased left (*L*) hippocampal blood flow (*white* arrow) during successful encoding.

4.2. Normal LIFC activity, but unspecifically increased hippocampal activity and DMPFC hypoactivity

Interestingly, during semantic encoding schizophrenia subjects showed a neural activation of LIFC comparable to healthy controls (see Figs. 3 and 4). Hippocampus and LIFC represent a semantic network. Whereas the hippocampus plays a crucial role in general successful encoding, independently of encoding depth (Schacter et al., 1996), the LIFC shows neural activation during semantic encoding (Kapur et al., 1994). An activation increase in the LIFC appears to be associated with a successful semantic encoding (Ragland et al., 2001). The apparently normal activation of LIFC in the patients suggests that patients are successfully engaged in deep vs. shallow processing in our study, which is reflected by the presence of a behavioural LOP effect.

Notably, hippocampal activation in schizophrenia patients was not specific to successful encoding, but occurred as an overall effect of LOP, irrespective of encoding success. This result is in line with a previously observed increased mediotemporal fMRI activation in schizophrenia subjects that was not related to task performance (Kubicki et al., 2003; Ragland et al., 2006). An important function of the hippocampus increasingly gaining attention is to detect novelty by comparing incoming with stored information. This novelty detection again triggers the firing of neurons in the ventral tegmental areal (VTA) which is connected to the hippocampus by dopaminergic projections. These projections appear to trigger dopamine release in the hippocampus, which in turn is crucial for consolidation processes of long-term memory (Lisman et al., 2008). Accordingly, in schizophrenia patients an increased hippocampal activity might disturb this delicate circuit resulting in insufficient novelty detection and thus a deficient encoding (Bunzeck et al., 2007). In case of such a continuous dopaminergic activity the comparator function of the hippocampus, distinguishing new from stored information, might be impaired. Thus, information could be encoded only randomly and infrequently, leading to the reduced memory performance of schizophrenia subjects in the free recall task.

During semantic encoding, schizophrenia subjects showed an activation of left DMPFC similar to healthy controls in addition to normal neural activity of LIFC. However, this activation of DMPFC was

Table 3
Volume and region of interest (ROI) analysis within patient group: local maxima of blood-oxygen-level-dependent fMRI signal change in schizophrenic subjects; extent threshold: $k = 5$ voxel; threshold: 0.01; $P_{uncorrected} < 0.05$.

	Talairach coordinates			
Volume analysis: Contrast and anatomical region	*x*	*y*	*z*	*t*-value
Misses only; deep vs. shallow				
Left medial temporal gyrus	−63	−45	7	4.38
	−54	−36	1	4.26
ROI-analysis: Contrast and anatomical region				
Deep vs. shallow				
Left inferior prefrontal cortex	−49	19	13	4.54
Left dorso lateral prefrontal cortex	−15	41	51	3.79
Left dorsomedial prefrontal cortex	−6	58	26	4.34
Hits vs. misses				
Left superior temporal gyrus	−46	−3	−4	4.09
Shallow only; hits vs. misses				
Right anterior cingulate cortex	2	28	14	4.77
Hits only; deep vs. shallow				
Left hippocampus	−20	−37	−6	4.50
Misses only; deep vs. shallow				
Left inferior prefrontal cortex	−47	19	−7	6.55

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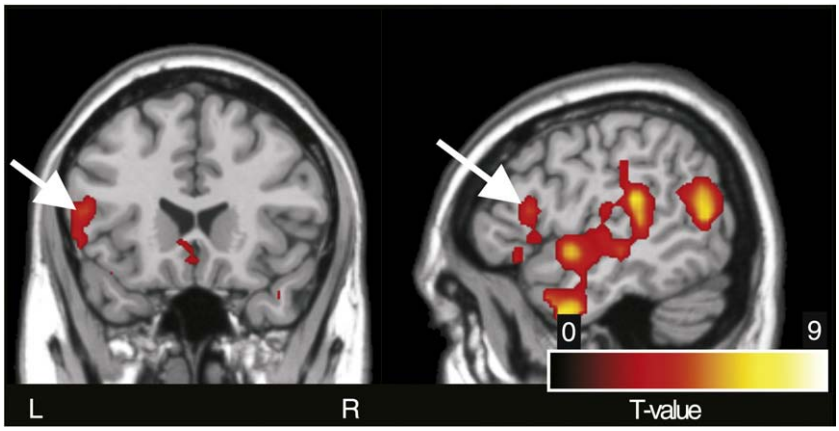

Fig. 4. Schizophrenia patients: Increased neural activity during semantic encoding in left (*L*) inferior prefrontal cortex (*white* arrow).

not specific to successful encoding, as we could show in the control group. The DMPFC is sensitive to emotional stimuli and seems to be involved in higher-order emotional processing (Davidson, 1995). The use of a pleasantness judgment during the semantic encoding task might explain the activation of neural networks implicated in emotion processing, such as the DMPFC. Thus, besides a partly impaired semantic encoding, schizophrenia patients could not benefit from the emotional decision making of a presented stimulus for a later exact remembrance.

Finally, compared to healthy controls, schizophrenia patients showed decreased activation of ACC during successful encoding. As the ACC is crucial for focussing the attention on task-related processes (Crottaz-Herbette and Menon, 2006) such a deficitary ACC activity could result in an insufficient top-down attentional modulation to task-irrelevant processes, and thereby impairing encoding performance.

4.3. Positive symptoms are associated with impaired recall performance and abnormal hippocampal activity

Schizophrenia patients scoring higher in the positive symptom scale of the PANSS had a reduced memory performance during free recall but also showed, beyond that, a stronger BOLD response in the left hippocampus when items were successfully encoded. Taken together, these results indicate that positive symptoms are associated with impaired recollective performance in conjunction with an increased hippocampal neuronal activation, necessary to successfully encode semantic information. This finding supports the hypothesis that in the presence of positive symptoms additional neuronal activity may be needed in order to compensate for dysfunctional medio-temporal processes of memory encoding. Our finding of an unspecifically increased hippocampal activity during semantic encoding thus either may reflect the pathophysiological underpinning of defective medio temporal processes itself or also may reflect a compensatory response to dysfunctional mechanisms. Such a dysfunction may possibly be related to a previously hypothesized disorganized mesolimbic circuit involving a hyperdopaminergic state in schizophrenia that interferes with the encoding of memory information (Lisman and Grace, 2005; Lisman et al., 2008). Thus, the extraordinarily strong neuronal activation which is necessary to exceed the increased threshold for successful encoding, and which is reflected by increased neuronal activation in the patients to successful deep encoding, may explain the considerably decreased encoding success in patients with pronounced positive symptoms.

On the contrary, in the present study negative symptoms were not associated with behavioural or functional impairments in the patients. Even though there have been reports of detrimental effects of negative symptoms that mainly involved affective symptoms such as blunted affect and anhedonia on memory, the results are inconsistent. Some studies that found detrimental effects on memory have addressed emotional memory (Sachs et al., 2004) while others did not find such memory effects for neutral stimuli (Mathews and Barch, 2004) suggesting that possibly the affective component of these tasks may play a role.

Table 4
Volume and region of interest (ROI) analysis between groups: local maxima of blood-oxygen-level-dependent fMRI signal change; extent threshold: $k = 5$ voxel; threshold: 0.01; $P_{uncorrected} < 0.05$.

	Talairach coordinates			
Volume analysis: Contrast and anatomical region	*x*	*y*	*z*	*t*-value
Controls>schizophrenic patients				
Hits vs. misses				
Right dorsomedial prefrontal cortex	2	45	40	4.14
Left anterior cingulate cortex	−3	40	24	3.32
ROI-analysis: Contrast and anatomical region				
Schizophrenic patients>controls				
Deep vs. shallow				
Left hippocampus	−23	−11	−19	3.55
Controls>schizophrenic patients				
Deep only; hits vs. misses				
Right dorsomedial prefrontal cortex	2	54	40	3.68
Left anterior cingulate cortex	−6	40	24	4.01
Shallow only; hits vs. misses				
Right dorsomedial prefrontal cortex	5	46	43	3.45

5. Conclusion

The present study supports the notion that schizophrenia-related deficits of declarative memory encoding are a consequence of a hyperdopaminergic mesolimbic state that in turn is responsible for the occurrence of positive psychotic symptoms in schizophrenia.

Future studies should address whether the temporolimbic hyperactivity is detectable in more acutely ill patients too, and whether it varies as a function of disease activity and may possibly be useful as a biological marker of disease activity.

5.1. Limitations

As 'schizophrenia' comprises a spectrum of psychiatric conditions, symptoms as well as neuroanatomical abnormalities differ considerably between individuals. This heterogeneity is very likely reflected in

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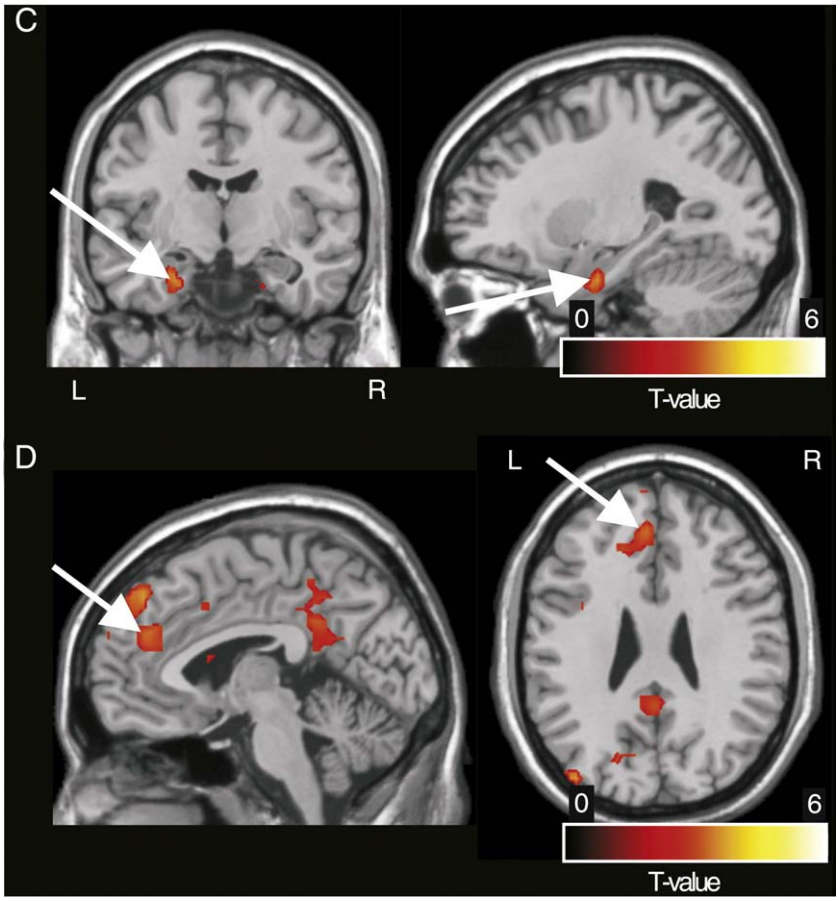

Fig. 5. Group analysis: C. Schizophrenia patients show compared to healthy controls increased neural activity of left (*L*) hippocampus (*white* arrow) during semantic encoding. D. Enhanced cerebral blood flow in the left (*L*) anterior cingulate (ACC) (*white* arrow) during successful encoding in healthy controls in comparison to schizophrenia patients.

different patterns of neural activity. Thus we focussed on a highly homogeneous patient group of mildly symptomatic patients what led to the moderate sample size.

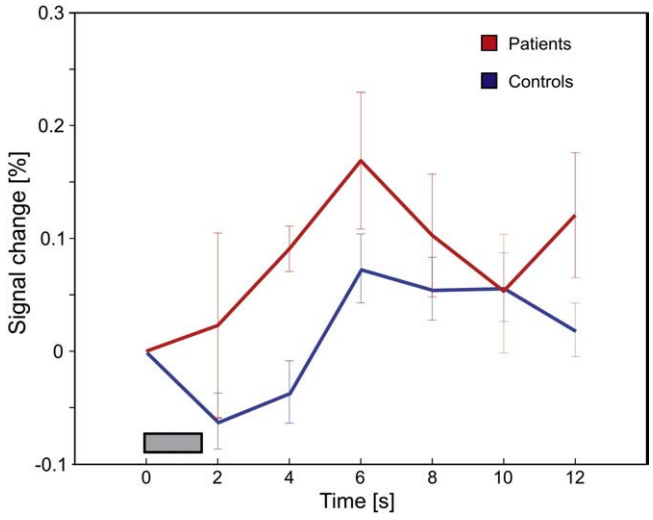

Fig. 6. Mean BOLD activation within the hippocampus across time during deep encoding. Healthy controls are shown in blue, schizophrenia patients in red. Error bars represent standard error of the mean. The gray box above the *x*-axis displays the stimulus length. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Another problem, well known in patient studies, is neuroleptic medication that is known to reduce positive symptoms but has not consistently been associated with memory improvement in schizophrenia (Goldberg et al., 2007). Thus it remains to be explored in future studies whether the improvement of positive symptoms under neuroleptic medication is also associated with normalized hippocampus function and possibly memory improvement in the longer term or whether positive symptom and memory improvement dissociate, hence contradicting a common pathophysiology.

In the light of a recently published paper by Kriegeskorte et al. (2009) our results clearly have to be considered in a differentiated way. At this, the authors demonstrated impressively that problems of circularity arise in neuroimaging analyses when group comparisons are calculated at locations identified in a data driven manner. In the present study, firstly, group comparisons were calculated in strictly a priori defined anatomical regions on the one hand, but, on the other hand, within these regions SPM derived local maxima were used. Thus, these data rather replicate previous findings and should be considered as supportive evidence. Secondly, we conducted correlation analyses at the identified locations that do not underlie this reservation due to circular analysis problems and thus have to be considered as conclusive findings.

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