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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: $F(1,22)=11.903$; $P=0.002$.