



Hippocampal volume reduction and autobiographical memory deficits in chronic schizophrenia

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ABSTRACT

Although autobiographical memory (AM) deficits and hippocampal changes are frequently found in schizophrenia, their actual association remained yet to be established. AM performance and hippocampal volume were examined in 33 older, chronic schizophrenic patients and 21 healthy volunteers matched for age, gender and education. Psychopathological symptoms and additional neuropsychological parameters were assessed by using appropriate rating scales; magnetic resonance imaging (MRI) 3-T data were analyzed via an automated region-of-interest procedure. When compared with the control subjects, patients showed significantly decreased left anterior and posterior hippocampal volumes. Episodic but not semantic AM performance was significantly lower in the patients than in the healthy controls. Both episodic and semantic AM deficits were significantly correlated with volume of the left hippocampus in the patient group. In contrast, deficits in verbal memory, working memory and remote semantic memory observed in the patients did not relate to hippocampal volume. Our findings indicate that AM deficits in chronic schizophrenia are associated with hippocampal volume reductions and underline the importance of this pathology in schizophrenia.

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1. Introduction

Although memory deficits are generally considered to be a core feature of schizophrenia (Reichenberg and Harvey, 2007), autobiographical memory (AM) was scarcely investigated and primarily younger patients with schizophrenia were examined (Feinstein et al., 1998; Elvevag et al., 2003; Riutort et al., 2003; Danion et al., 2005; Wood et al., 2006). AM includes both personal episodic and semantic memories; while the former refers to events (e.g. “my first day at school”), the latter comprises personal facts (e.g. “where I went to school”). The ability to recall autobiographical memories is considered to be crucial for the continuity of the self and the development of personal identity, a process which may be disturbed in patients with schizophrenia due to the onset of the disease in early adulthood (Conway and Pleydell-Pearce, 2000; Wilson and Ross, 2003; Cuervo-Lombard et al., 2007; Berna et al., 2011). Corresponding to previous results we demonstrated in a preliminary study with a sample of middle-aged patients that schizophrenia is associated with deficits of both personal episodic and semantic

memory (Seidl et al., 2009). However, little is known about the cerebral correlates of AM deficits in schizophrenia.

The neuroanatomy of remote episodic and semantic memory is discussed by two theoretical approaches: The standard model of consolidation and the multiple trace theory (Squire and Alvarez, 1995; Nadel and Moscovitch, 1997; Frankland and Bontempi, 2005; Moscovitch et al., 2006). The former posits that the hippocampal formation plays a time-limited role for all forms of declarative memory and as time passes after learning, memories stored in neocortical sites gradually become independent of the medial temporal lobe (MTL). In contrast, the multiple trace theory assumes that vivid autobiographical memories require the hippocampal system no matter how old they are. Semantic memories, however, benefit from hippocampal contribution for some time before they can be retrieved independently of this structure. The majority of studies on this question did not find a remoteness effect as proposed by the standard model, therefore supporting the multiple trace theory (Conway et al., 1999; Maguire et al., 2001; Ryan et al., 2001; Gilboa et al., 2004; Piolino et al., 2004; Viard et al., 2007). In accordance with these reports, evidence from patients with MTL lesions shows spared personal semantic memory but impaired personal episodic memory without a temporal gradient (Viskontas et al., 2000; Steinvorh et al., 2005; Noulhiane et al., 2008).

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Brain morphological changes have been frequently reported in patients with schizophrenia: Based on 37 studies, which utilized voxel-based morphometric analysis of data, Fornito and colleagues reported gray matter reduction in a network of frontal, temporal, thalamic and striatal regions (2009). Moreover, changes in brain structure were identified at different stages of the disorder. Individuals at high risk of developing schizophrenia showed frontotemporal structural abnormalities, with more extensive changes in first-episode and chronic schizophrenia (Chan et al., 2011). Comparing gray matter volume between first-episode and chronic patients the authors of another meta-analysis found progression of cortical changes while temporolimbic pathology seemed to be rather stable (Ellison-Wright et al., 2008). More specifically, hippocampal volume reductions in patients with schizophrenia were reported in an earlier meta-analytic study (Nelson et al., 1998). These results underline the importance of this region in schizophrenia and are consistent with declarative memory deficits frequently observed in this patient group. However, although chronic patients were examined in a wide range of studies, older patients with a duration of illness of more than 20 years were only investigated in a few studies, which consistently found significantly smaller hippocampal volumes in patients versus controls (Sachdev et al., 2000; Weiss et al., 2005; Prestia et al., 2011).

Given the acknowledged role of the hippocampus in episodic memory (Scoville and Milner, 1957; Milner et al., 1998; Eichenbaum et al., 2007) and structural alterations of this region in schizophrenic patients (Nelson et al., 1998; Wright et al., 2000; Honea et al., 2005) we decided to investigate AM deficits with respect to hippocampal volume reductions in chronic schizophrenia. Performance in other neuropsychological parameters was considered for comparison. We hypothesized that (i) hippocampal volume reductions are also found in older patients with chronic schizophrenia when compared to controls carefully matched for age, gender and education; and (ii) that patients with chronic schizophrenia show AM deficits, which are associated with hippocampal volume reductions.

2. Methods

2.1. Subjects

Thirty-three patients with DSM-IV schizophrenia ($n=24$) or schizoaffective disorder ($n=9$) were recruited among the inpatients treated at the section of Geriatric Psychiatry at the University of Heidelberg and the residential care St. Thomas e.V., Heidelberg. Psychopathology was assessed by means of the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984b), the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1984a), the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962) and the Apathy Evaluation Scale (AES, Marin et al., 1991), respectively. Negative symptoms were predominating in our sample. The majority of patients (75.75%) were chronically hospitalized. The patients received an antipsychotic medication with a mean dose of 674.28 (S.D.=554.30) mg chlorpromazine (CPZ) equivalents (Woods, 2003). Atypical antipsychotic monotherapy was administered to 18 patients, while 10 patients received a combination of atypical and typical antipsychotics. Two patients were treated with typical antipsychotics only and three patients were not receiving any antipsychotic medication at the time of examination. Antidepressants and benzodiazepines were prescribed as an additional medication in 15 patients and 3 patients, respectively. Patients were excluded from the study if they had (1) a lifetime history of neurological disorder, head injury or substance dependency, (2) a current axis I mood or anxiety disorder, mental retardation and/or a concurrent axis II disorder, or (3) were not fluent in German.

Twenty-one healthy comparison participants were recruited through newspaper advertisement. Healthy subjects had no history of axis I and/or axis II disorders, neurological or medical illness, head injury or substance abuse and were not first-degree relatives of patients diagnosed with schizophrenic spectrum disorders. All subjects were right-handed (Oldfield, 1971). The study was approved by the local ethics committee. After full explanation of the study procedure written informed consent was obtained from all subjects. The groups

Table 1

Demographic and clinical characteristics of patients and healthy controls.

	Patients $n=33$ Mean (S.D.)	Controls $n=21$ Mean (S.D.)	t d.f.=52	P
Age, years	52.03 (8.76)	53.67 (8.0)	-0.69	0.49
Education, years	12.62 (2.81)	13.90 (2.12)	-1.79	0.08
Sex, % male	69.7	57.1		$n. sig.^a$
Duration of illness, years	29.55 (11.05)			
Psychopathology				
BPRS	37.06 (10.07)			
SAPS	16.76 (16.18)			
SANS	32.03 (21.46)			
AES	25.48 (11.10)			

BPRS= Brief Psychiatric Rating Scale; SAPS= Scale for the Assessment of Positive Symptoms; SANS= Scale for the Assessment of Negative Symptoms; AES= Apathy Evaluation Scale.

^a χ^2 -test.

were closely matched with respect to age, gender and level of school education (Table 1).

2.2. Autobiographical memory assessment

AM was tested with a semi-structured autobiographical interview adapted from Kopelman, Wilson and Baddeley (AMI; Kopelman et al., 1990); German version: Erweitertes Autobiographisches Gedächtnisinventar (E-AGI) (Fast et al., 2007). The E-AGI interview addresses five lifetime periods, to obtain patterns of AM throughout the lifespan: preschool (up to 6 years of age), primary school (from 6 to 11 years of age), secondary school (from 11 years of age to school graduation), early adulthood (from graduation to 35 years of age) and recent 5 years. From each lifetime period the participants were asked for one autobiographical event, which was scored concerning detail, maximal 11 points were given. The scores were distributed as follows: one point for remembering a mental image associated with the event (1), if the participant could remember his age at the time of the event (1), season (1) and place where the event happened (1), environmental details (1), its time of day (1) and duration (1), the climate or temperature at that day (1), which other people were involved (1), preceding events or consequences (1), own or others thoughts/emotions/reactions (1). Subjects were not requested to tell specific events from their past, instead they were free to report whatever they want and were free to take their time to remember the details. To control for delusional memories, we consulted staff members and reviewed the patients' case notes and psychiatric reports, when it was not clear whether a memory was intrusive. Besides these autobiographical events the subjects should indicate five autobiographical facts from each period, e.g. names of friends or addresses of their past (max. 5 points). To ensure an adequate consolidation of the memory contents, we restricted our analyses to memories from the first four lifetime periods. For our analyses we used the total score of the remembered details of each event (max. 44 points) and the total score of personal facts (max. 20 points). A previous study of our group revealed a sufficient internal reliability (Cronbach's α) of the scales. The inter-rater reliability ranged from 0.954–0.979 (Ahlsdorf, 2009).

The AM task was part of a comprehensive neuropsychological test battery, which also addressed verbal memory, short-term and working memory as well as remote semantic memory. To assess verbal memory we conducted the subtests logical memory I and II from the Wechsler Memory Scale-Revised (WMS-R, Härting et al., 2000). Digit span forward and backward from the WMS-R were used to measure short-term memory and working memory, respectively. Remote semantic memory was assessed by testing recognition of famous people using the Bielefelder Famous Faces Test (BFFT, Jänicke, 2001). This test includes grayscale portrait photographs of famous individuals from different decades (10 photographs per decade, max. 7 decades) and corresponding verbal cues. For every item subjects could achieve 0–3 points (max. 30 points for every decade). We calculated mean scores dividing the sum score of all decades through the number of items, as the number of presented decades varies with age. A group of 17 control subjects also completed the BFFT.

2.3. MRI data acquisition

The magnetic resonance imaging (MRI) scans were obtained at the German Cancer Research Center with a 3.0 Tesla scanner (SIEMENS MAGNETOM TrioTim syngo MR B15) using a high-resolution T1-weighted magnetization prepared rapid gradient echo sequence (MP-RAGE, 160 sagittal slices, voxel size=1.0×1.0×1.0 mm³, image matrix=256×256, flip angle 9°, TR=2300 ms, TE=2.98 ms, TI=900 ms).

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