Interrelated neuropsychological and anatomical evidence of hippocampal pathology in the at-risk mental state

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Background. Verbal learning and memory deficits are frequent among patients with schizophrenia and correlate with reduced magnetic resonance imaging (MRI) volumes of the hippocampus in these patients. A crucial question is the extent to which interrelated structural-functional deficits of the hippocampus reflect a vulnerability to schizophrenia, as opposed to the disorder *per se*.

Method. We combined brain structural measures and the Rey Auditory Verbal Learning Test (RAVLT) to assess hippocampal structure and function in 36 never-medicated individuals suspected to be in early (EPS) or late prodromal states (LPS) of schizophrenia relative to 30 healthy controls.

Results. Group comparisons revealed bilaterally reduced MRI hippocampal volumes in both EPS and LPS subjects. In LPS subjects but not in EPS subjects, these reductions were correlated with poorer performance in RAVLT delayed recall.

Conclusions. Our findings suggest progressive and interrelated structural-functional pathology of the hippocampus, as prodromal symptoms and behaviours accumulate, and the level of risk for psychosis increases. Given the inverse correlation of learning and memory deficits with social and vocational functioning in established schizophrenia, our findings substantiate the rationale for developing preventive treatment strategies that maintain cognitive capacities in the at-risk mental state.

Introduction

Recent meta-analyses of magnetic resonance imaging (MRI) studies of the medial temporal lobe (MTL) in patients with first-episode psychosis (Steen *et al.* 2006; Vita *et al.* 2006; Vita & de Peri, 2007) and non-psychotic first-degree relatives of schizophrenia patients (Boos *et al.* 2007) document significant decreases in hippocampal volume. The MTL is critical for declarative episodic memory (Scoville & Milner, 1957; Squire *et al.* 2004), and in schizophrenia patients, lower scores on neuropsychological measures of declarative episodic memory correlate with reduced MRI volumes of the hippocampus (Kuroki *et al.* 2006;

Nestor *et al.* 2007). While Kraepelin (1919) and Bleuler (1911) considered memory functions to be relatively preserved in schizophrenia, current concepts of the disorder classify deficient declarative episodic memory among the core symptoms of the clinical phenotype (Aleman *et al.* 1999; Boyer *et al.* 2007) and emphasize its validity as outcome predictor (Green, 1996; Niendam *et al.* 2006). Observations that declarative episodic memory is impaired in schizophrenia patients in a manner similar to patients with surgical MTL lesions, have even led to proposals of a schizophrenic amnesia (McKenna *et al.* 1990). Evidence from functional MRI studies converges on abnormal associative encoding of arbitrary information in the hippocampus as a potential underlying pathomechanism (Achim & Lepage, 2005; Achim *et al.* 2007).

While interrelated structural-functional abnormalities of the hippocampus have been identified in

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schizophrenia, the timing of their emergence and the extent to which they are related to vulnerability to the disorder as opposed to psychotic illness itself is unclear. The prevailing research paradigms to identify vulnerability to schizophrenia are the genetic and the clinical at-risk strategy, with the latter targeting at the identification of prodromal symptoms and behaviours (Cannon, 2005). Operationally, the prodrome or at-risk mental state (ARMS) is defined by duration of time, starting with the onset of decline in the baseline level of functioning and ending with the transition to first-episode psychosis (Yung & McGorry, 1996). The average duration of the ARMS is about 3 years across studies (McGlashan, 1996). Accumulating evidence from cross-sectional and longitudinal MRI studies indicates that the ARMS is associated with smaller hippocampal volumes (Pantelis *et al*. 2003; Borgwardt *et al*. 2007) as well as emerging learning and memory deficits, particularly in the verbal modality (Brewer *et al*. 2005; Keefe *et al*. 2006; Lencz *et al*. 2006; Eastvold *et al*. 2007).

As the ARMS can be conceptualized as a continuum of progressive accrual of morbidity, that culminates in first-episode psychosis (Keshavan *et al*. 2005), hippocampal volume reduction should be paralleled by a progressive worsening of verbal learning and memory, as prodromal symptoms and behaviours accumulate, and the level of risk increases. To test this hypothesis within a cross-sectional study design, we used structural MRI and the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941; German adaptation by Helmstaedter *et al*. 2001) to investigate 36 never-medicated individuals suspected to be in early (EPS) or late prodromal states (LPS) relative to 30 healthy controls.

Method

Subjects

The present work was conducted as part of the early detection and intervention programme of the German Research Network on Schizophrenia (GRNS; Hafner *et al*. 2004). Subjects with symptoms suggestive of either EPS or LPS were recruited as previously described (Hafner *et al*. 2004). In brief, subjects with suggestive complaints were screened by general practitioners, counselling services or secondary health-care providers using the 17-item Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos) checklist, which was created for this purpose (Hafner *et al*. 2004). Subjects scoring ⩾6 points were referred to the early recognition and intervention centres established at the Departments of Psychiatry, at the Universities of Bonn and Cologne, for detailed assessment with the 110-item ERIraos symptom list (Hafner *et al*. 2004), which includes items derived from the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Gross & Huber, 1985) and from the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Hafner *et al*. 1992). EPS diagnostic criteria were based either on the presence of basic symptoms with a positive predictive value of >0.7 and a specificity of >0.85 for the transition to first-episode psychosis (Klosterkotter *et al*. 2001) and/or a reduction of the Global Assessment of Functioning (GAF) in conjunction with the presence of a first-degree relative with a psychotic disorder or a history of obstetric complications. While other studies also label individuals to be clinically at ultra-high-risk if they have a genetic risk plus functional decline (McGorry *et al*. 2002), the additional use of basic symptoms allows prediction of transition to first-episode psychosis already in an earlier prodromal state (Hafner *et al*. 2004). In contrast, subjects experiencing attenuated positive symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) were considered to be in the LPS, which is consistent with conventional ultra-high-risk criteria used in clinical studies (McGorry *et al*. 2002). A detailed synopsis of inclusion and exclusion criteria is presented in Table 1.

Based on these criteria, we recruited 36 never-medicated ultra-high-risk subjects, of whom 20 (56%) (8 female, 12 male; mean age 27.3±5.1 years; age range 21–45 years) were assigned to the EPS group and 16 (44%) (8 female, 8 male; mean age 26.8±6.2 years; age range 19–41 years) to the LPS group. The mean longitudinal follow-up examination time was 18±3 months. During this period, three EPS subjects (15%) and five LPS subjects (31%) converted to schizophrenia according to DSM-IV diagnostic criteria. This preliminary conversion rate is in agreement with the predictive validity of EPS and LPS diagnostic criteria reported in prospective studies. According to these studies, EPS criteria predict psychosis onset within 12 months in 19% of cases and within 64 months in 70% of cases (Klosterkotter *et al*. 2001), whereas LPS criteria predict psychosis onset within 12 months in 30–54% of cases (Yung *et al*. 2003). The healthy control (CTL) group comprised 30 subjects (7 female, 23 male; mean age 28.2±6.4 years; age range 18–40 years) carefully matched for age, education, and sociodemographic area. They were free of personal as well as first- and second-degree family history of DSM-IV Axis I and II disorders as assessed by experienced clinicians (P.F. and S.R.). Subjects were recruited through local advertisement and excluded from participation if they had previous exposure to psychoactive medication, current substance or alcohol

Table 1. *Synopsis of (A) inclusion criteria and (B) exclusion criteria (Hafner et al. 2004)*

(A) Inclusion criteria
(*a*) Early prodromal state (EPS)
One or more of the following basic symptoms appeared in the last 3 months, several times a week:

- Thought interference or thought perseveration or thought pressure or thought blockage
- Disturbances of receptive language, either heard or read
- Decreased ability to discriminate between ideas and perception, fantasy and true memories
- Unstable ideas of reference (subject-centrism)
- Derealization
- Visual or acoustic perception disturbances

and/or
Reduction in the Global Assessment of Function score (DSM-IV) of at least 30 points (within the past year) *and* at least
  one of the following risk factors:

- First-degree relative with lifetime schizophrenia or schizophrenia-spectrum disorder
- Pre- or perinatal complications

(*b*) Late prodromal state (LPS)
Presence of at least one of the following attenuated positive symptoms (APS) within the last 3 months, appearing several
  times per week for a period of at least one week:

- Ideas of reference
- Odd beliefs or magical thinking
- Unusual perceptual experience
- Odd thinking or speech
- Suspiciousness or paranoid ideation

and/or
Brief limited intermitted psychotic symptoms (BLIPS), defined as appearance of one of the following symptoms for <1 week
  (interval between episodes at least 1 week), resolving spontaneously:

- Hallucinations
- Delusions
- Formal thought disorder
- Gross disorganized or catatonic behavior

(B) Exclusion criteria
APS or BLIPS (early prodromal state)
Present or past diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional or bipolar disorder according to DSM-IV
Present or past diagnosis of brief psychotic disorder according to DSM-IV with a duration ⩾1 week or within the last 4 weeks
  regardless of its duration
Diagnosis of delirium, dementia, amnestic or other cognitive disorder, mental retardation, psychiatric disorders due to somatic
  factors or related to psychotropic substances according to DSM-IV
Alcohol or drug abuse within the last 3 months prior to inclusion according to DSM-IV
Diseases of the central nervous system (inflammatory, traumatic, epileptic, etc.)
Aged <18 yr and >36 yr

abuse or a history of neurological disorder or severe somatic condition. Written informed consent was obtained from all participants prior to the study, and study protocols were approved by the ethics committees of the Medical Faculties of the Universities of Bonn and Cologne.

Psychopathological and neuropsychological instruments

Psychopathological assessment before MRI scanning included the Positive and Negative Syndrome Scale (PANSS), a 30-item rating instrument evaluating the presence/absence and severity of positive, negative, and general psychopathology of schizophrenia (Kay *et al.* 1987); the Montgomery–Åsberg Depression Rating Scale (MADRS), a 10-item semi-structured interview assessing the affective, cognitive, and neurovegetative dimensions of depressive symptomatology (Montgomery & Åsberg, 1979); and the GAF, a 100-point numeric scale implemented in DSM-IV Axis V assessment, that provides an index of overall psychological, social, and occupational functioning (Table 2).

Table 2. *Synopsis of (*a*) demographics and clinical characteristics and (*b*) neuropsychological and brain structural measures*

	CTL		EPS		LPS	
(*a*) Demographics and clinical characteristics						
N	30		20		16	
Female sex	7		8		8	
Age (yr)	28.2	(6.4)	27.3	(5.1)	26.8	(6.2)
IQ (verbal)	108	(12)	107	(15)	106	(11)
PANSS positive	–		8.9	(2.1)	12.8	(4.0)
PANSS negative	–		10.7	(2.9)	15.3	(2.9)
PANSS total	–		28.6	(7.3)	32.6	(5.4)
MADRS	–		18.5	(6.9)	20.2	(6.9)
GAF	–		54.6	(3.4)	52.1	(4.4)
(*b*) Neuropsychological and brain structural measures						
RAVLT						
Trial 1, List A[a]	8.4	(1.4)	8.7	(2.0)	8.2	(2.2)
Trial 5, List A[a]	13.9	(1.3)	14.3	(1.1)	13.4	(2.0)
Total[b]	61.2	(4.7)	61.3	(7.9)	60.4	(7.3)
Trial A6, Retention[a]	13.3	(1.1)	13.7	(1.8)	13.1	(1.7)
Trial A7, Delayed recall[a]	14.0	(1.1)	13.9	(1.5)	12.8*	(2.1)
List A, Recognition[a]	14.5	(0.7)	14.9	(0.3)	14.1	(1.4)
Volumetry						
Whole-brain volume, cm³	1392	(107)	1391	(134)	1348	(151)
Left hippocampus[c], cm³	3.15	(0.3)	2.93	(0.3)	2.72*	(0.2)
Right hippocampus[c], cm³	3.17	(0.3)	2.95*	(0.3)	2.70*	(0.2)

CTL, Controls; EPS, ultra-high-risk subjects suspected to be in the early prodromal state; GAF, global assessment of functioning; LPS, ultra-high-risk subjects suspected to be in the late prodromal state; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Symptoms Scale; RAVLT, Rey Auditory Verbal Learning Test.

Data are given as means ($\pm$ S.D.).

[a] Maximum possible score, 15.

[b] Maximum possible score, 75.

[c] Unadjusted hippocampal volume.

* Significant difference to controls at Bonferroni-adjusted α level.

Neuropsychological assessment before MRI scanning included the Verbaler Lern- und Merkfähigkeitstest (VLMT; Helmstaedter *et al.* 2001), a German-language analogon of the RAVLT, that consists of five presentations of a 15-word list (Trials 1–5, List A), followed by a free recall trial of a second word list (List B), and a sixth free recall trial of List A (Trial A6, Retention). Delayed recall was examined with a seventh free recall trial after a 30-min interval (Trial A7, Delayed recall). Recognition was tested by asking the respondent to indicate which of 50 words read aloud were from List A and which were not (List A, Recognition). The RAVLT thus provides measures of immediate memory, efficiency of learning, effects of interference, recall following short and long delay periods, and recognition. Schizophrenia patients who have better verbal memory on the RAVLT are likely to perform better on tasks of independent living, underscoring the ecological validity of the RAVLT (Strauss *et al.* 2006). Verbal IQ (VIQ) was determined with the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B; Lehrl, 2005), a German-language analogon of the Spot-the-Word test (STW), that provides a robust estimate of verbal intelligence based upon lexical decisions (Table 2).

MRI protocol

Participants underwent MRI scanning with a 1.5-T MR system (Philips Gryroscan ACS-NT, Philips Medical Systems, Best, The Netherlands) at the Department of Radiology, University of Bonn (EPS subjects, $n=11$; LPS subjects, $n=8$) or with an identical magnet at the Department of Radiology, University of Cologne (EPS subjects, $n=9$; LPS subjects, $n=8$). A T1-weighted 3-dimensional turbo gradient echo (TFE) sequence

generated 150 contiguous, 1-mm sagittal slices. Imaging parameters were time-to-echo, 1.51 ms; time-to-repetition, 25 ms; flip angle, 20°, matrix size, 256 × 256; field of view, 24 × 24 cm matrix; acquisition resolution, 1 × 1.51 × 1 mm; reconstructed resolution, 1 × 1 × 1 mm. Each MR scanner was calibrated fortnightly using the same proprietary phantom to ensure stability and accuracy of measurements. There were no significant differences in brain structural measures between MR scanners (whole-brain volume, $t_{64} = -1.164$, $p = 0.249$; total left hippocampus, $t_{64} = -1.211$, $p = 0.230$; total right hippocampus, $t_{64} = -0.794$, $p = 0.430$). MRI data were analysed using Analyze 7.0 (Mayo Clinic, Rochester, MN, USA). A code was used to ensure confidentiality and blind rating of data. Hippocampal volumes were estimated using a manual tracing technique and defined anatomical criteria (Cook *et al*. 1992). Hippocampal boundaries were defined as posterior (slice with greatest length of continuous fornix); medial (open end of the hippocampal fissure posteriorly, uncal fissure in the hippocampal body and medial aspect of ambient gyrus anteriorly); lateral (temporal horn of lateral ventricle); inferior (white matter inferior to the hippocampus); superior (superior border of hippocampus); and anterior (alveus was used to differentiate hippocampal head from amygdala). Hippocampal length was estimated as the number of slices per hippocampus. One rater (J.L.) performed all hippocampal tracings included in the analyses. The intra-class correlation for intra-rater reliability (J.L.), determined by blindly retracing 20 randomly selected images, was 0.95 and for inter-rater reliability (J.L. and R.H.) was 0.80 in 10 subjects. Hippocampal volumes were divided by whole-brain volumes to correct (normalize) for inter-subject variation in head size (Free *et al*. 1995; but see also Arndt *et al*. 1991). Whole-brain volumes were obtained through an in-house developed algorithm (R.T.) following automated tissue segmentation in Statistical Parametric Mapping (SPM5; Wellcome Trust Centre for Neuroimaging, London, UK).

Data analysis

Differences in age, sex, VIQ, RAVLT performance, and whole-brain volumes were assessed by a multivariate analysis of variance (ANOVA) defined by a three-level (CTL, EPS, LPS) between-subjects group factor. Differences in hippocampal volumes were assessed by a repeated-measures ANOVA defined by a three-level (CTL, EPS, LPS) between-subjects group factor and a two-level (left and right hippocampal volumes) within-subjects laterality factor, followed by two-tailed two-sample *post-hoc* t tests to determine the source of significance. As no consensus has evolved on the validity of ratio measures in MRI volumetric studies, group comparisons were calculated on whole-brain volume adjusted (first analysis) and unadjusted hippocampal volumes (second analysis) (Arndt *et al*. 1991; Free *et al*. 1995). The assigned 0.05 α level was Bonferroni-corrected to account for an inflation of the type I error rate attributable to multiple *post-hoc* testing. Effect sizes were quantified by calculating the values of Cohen's *d*. Associations among brain structural, neuropsychological, and psychopathological measures were assessed using Pearson correlations.

Results

As shown in Table 2, groups did not significantly differ with respect to age ($F_{2,63} = 1.819$, $p = 0.171$), sex ($F_{2,63} = 0.337$, $p = 0.715$), VIQ ($F_{2,63} = 0.296$, $p = 0.745$), and whole-brain volume ($F_{2,63} = 0.698$, $p = 0.501$). However, there was a significant between-group difference in RAVLT delayed recall ($F_{2,63} = 4.009$, $p = 0.023$), produced by a 9.2% lower performance in LPS subjects relative to CTL subjects ($t_{44} = 2.723$, $p = 0.009$, $d = 0.86$). Groups significantly differed in corrected hippocampal volumes ($F_{2,63} = 20.006$, $p < 0.0001$); however, these differences did not vary between left and right hippocampus ($F_{2,63} = 0.004$, $p = 0.673$). We detected bilateral hippocampal volume reductions of 7.7% in EPS subjects (left hippocampus, $t_{48} = 3.227$, $p = 0.002$, $d = 0.95$; right hippocampus, $t_{48} = 3.404$, $p = 0.001$, $d = 1.00$) and 11.9% in LPS subjects (left hippocampus, $t_{48} = 5.174$, $p < 0.0001$, $d = 1.64$; right hippocampus, $t_{48} = 5.977$, $p < 0.0001$, $d = 1.89$) relative to CTL subjects. These results were largely confirmed when uncorrected hippocampal volumes, and whole-brain volumes as covariate, were entered into a second analysis ($F_{2,62} = 20.627$, $p < 0.0001$). We identified hippocampal volume decreases of 7.7% in EPS subjects (right hippocampus, $t_{48} = 2.637$, $p = 0.011$, $d = 0.78$) and 14.8% in LPS subjects (left hippocampus, $t_{44} = 6.562$, $p < 0.0001$, $d = 2.08$; right hippocampus, $t_{44} = 6.190$, $p < 0.0001$, $d = 1.96$) relative to CTL subjects (Fig. 1). To ensure that these results were not due to differences in hippocampal length (defined by the number of slices traced per hippocampus), subsidiary analyses were carried out on hippocampal length, covarying for whole-brain volume. However, there were no significant between-group differences in left hippocampal length ($F_{2,62} = 0.201$, $p = 0.819$) nor in right hippocampal length ($F_{2,62} = 0.222$, $p = 0.802$). As expected, LPS subjects had higher PANSS negative ($F_{1,27} = 14.993$, $p = 0.001$) and PANSS positive scores ($F_{1,27} = 10.469$, $p = 0.003$) compared to EPS subjects, but there were no differences in PANSS total scores ($F_{1,27} = 1.731$, $p = 0.199$), MADRS scores ($F_{1,27} = 0.694$,

Table 3. *Pearson correlations between neuropsychological and brain structural measures*

Hippocampus[a]	CTL		EPS		LPS	
	Left	Right	Left	Right	Left	Right
RAVLT						
Trial 1, List A	0.256	0.190	0.314	0.335	0.222	0.393
Trial 5, List A	0.256	0.114	−0.025	−0.073	0.430	0.467
Total	0.071	0.047	0.170	0.177	0.101	0.221
Trial A6, Retention	0.119	0.207	0.020	−0.022	0.471	0.625
Trial A7, Delayed recall	0.229	0.307	0.095	0.082	0.606	0.680*
List A, Recognition	−0.035	−0.042	−0.239	−0.176	0.252	0.270
Volumetry						
Whole-brain volume, cm³	0.711*	0.855*	0.836*	0.845*	0.561	0.595

CTL, Controls; EPS, ultra-high-risk subjects suspected to be in the early prodromal state; LPS, ultra-high-risk subjects suspected to be in the late prodromal state; RAVLT, Rey Auditory Verbal Learning Test.

[a] Unadjusted hippocampal volume.

* Significant at Bonferroni-adjusted α level.
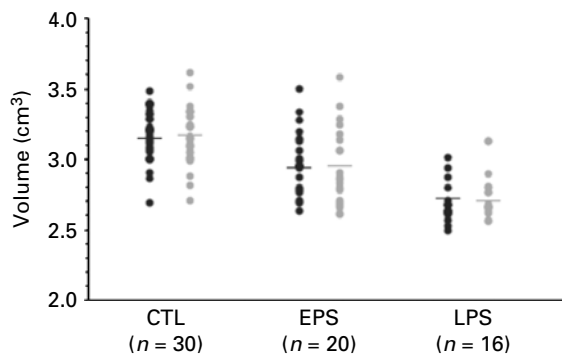

Fig. 1. Left (first column, black symbols) and right (second column, grey symbols) unadjusted hippocampal volumes for each subject group. CTL, Controls; EPS, ultra-high-risk subjects suspected to be in the early prodromal state; LPS, ultra-high-risk subjects suspected to be in the late prodromal state.

$p=0.412$), and hippocampal volumes, whether corrected for whole-brain volume (left hippocampus, $F_{1,34}=1.781$, $p=0.191$; right hippocampus, $F_{1,34}=2.802$, $p=0.103$) or not (left hippocampus, $F_{1,33}=2.320$, $p=0.137$; right hippocampus, $F_{1,33}=2.971$, $p=0.094$). Table 3 presents Pearson correlations between RAVLT subscores and anatomical measures. Within the LPS group, smaller right hippocampal volume correlated significantly with lower RAVLT delayed recall ($r=0.680$, $p=0.004$). No further associations among neuropsychological, psychopathological, and brain structural measures were present. In addition, there was no greater neuropsychological or hippocampal volume deficit in converters ($n=8$) relative to the majority of subjects ($n=28$) who remained at-risk at follow-up.

Discussion

This study was designed to examine brain–behaviour relationships in the ARMS, i.e. before the onset of schizophrenia and without the potential confounds of illness chronicity and antipsychotic drug action.

Consistent with our *a priori* hypothesis, anatomical measures revealed 9.6% reductions of MRI hippocampal volumes across EPS and LPS subjects, with mean weighted effect sizes of 1.26 on the left side and 1.40 on the right side. These results are in line with recent meta-analyses that document 8% smaller hippocampi in first-episode schizophrenia patients, with effect sizes ranging from −0.06 to 1.21 on the left side and from 0.10 to 1.32 on the right side (Steen *et al.* 2006; Vita *et al.* 2006; Vita & de Peri, 2007). In LPS subjects but not in EPS subjects, a 9.2% deficit in RAVLT delayed recall was correlated with reduced MRI hippocampal volumes, suggesting progressive and interrelated structural-functional pathology of the hippocampus, as prodromal symptoms and behaviours accumulate, and the level of risk for psychosis increases.

As a neuropsychological measure of verbal learning and memory, the RAVLT is thought to be supported by a widely distributed neural circuitry including frontotemporal subregions (Fletcher *et al.* 1997). A key function of this circuitry is to bind verbal items into specific episodes that can be later retrieved and consciously recollected (Squire *et al.* 2004). For the LPS subjects in this study, their specific deficit in RAVLT delayed recall could then reflect disturbances of episodic encoding- and/or retrieval-related frontotemporal functioning. Recent evidence of abnormal hippocampal responses during associative encoding

of arbitrary information in first-episode schizophrenia patients (Achim *et al.* 2007) as well as reports of preserved retrieval-induced forgetting in patients with chronic schizophrenia (Nestor *et al.* 2007) suggest diminished encoding efficiency in the hippocampus as a potential underlying pathomechanism. However, we cannot rule out that impaired RAVLT delayed recall in LPS subjects is primarily caused by a failure to retrieve, among competing, interfering alternatives, and to bring into consciousness, an intact representation of the original learning episode (Boyer *et al.* 2007).

Together with related findings in schizophrenia patients (Kuroki *et al.* 2006; Nestor *et al.* 2007) and non-psychotic first- and second-degree relatives of schizophrenia patients (Lymer *et al.* 2006), our results propose a link between psychometric measures of verbal learning and memory and the degree of integrity and volume of the hippocampus. However, the structural-functional correlations calculated in this study are based upon rather small subsets of EPS and LPS subjects, and thus the derived empirical relationship is best viewed as preliminary and exploratory. Moreover, we cannot exclude the confounding influence of heterogeneity in MRI acquisition due to the use of two MR scanners.

The observation that hippocampal pathology varies as a function of risk for psychosis may conflict with concepts of schizophrenia as a static encephalopathy. Substantial support for a progressive degenerative pathology comes from longitudinal morphometric studies which revealed an increase in frontotemporal grey-matter volume reduction in ultra-high-risk subjects whose illness proceeded from the ARMS to first-episode psychosis (Pantelis *et al.* 2003). Moreover, evidence from molecular neuroimaging studies suggests neurochemical abnormalities in ultra-high-risk subjects that accumulate with increasing risk for psychosis (Hurlemann *et al.* 2008; see also Fusar-Poli *et al.* 2007). Furthermore, there is evidence for continued and interrelated changes in brain structural and bioelectrical indices after onset of schizophrenia (Salisbury *et al.* 2007). In light of these findings, dynamic models of emerging schizophrenia have been conceptualized, wherein an early (pre- or perinatal) static lesion is thought to synergistically interact with later progressive frontotemporal grey-matter lesion to express the disorder (Pantelis *et al.* 2003; Salisbury *et al.* 2007). The underlying biological mechanisms are not clear. However, post-mortem histological findings suggest that smaller hippocampi in schizophrenia patients do not necessarily result from decreases in total cell number (Heckers & Konradi, 2002; Walker *et al.* 2002; Hurlemann *et al.* 2005) but could reflect a dendritic/synaptic pathology of the hippocampus (Feinberg, 1983; McGlashan & Hoffmann, 2000). While our findings of impaired verbal learning and memory in LPS but not in EPS subjects would be compatible with a dendritic/synaptic hippocampal degeneration near psychosis onset, a progressive and interrelated reduction of hippocampal volume and function within the same individuals over time remains to be documented by future prospective longitudinal studies.

In portraying the ARMS as a period of progressive and interrelated structural-functional hippocampal pathology, our results may contribute to the validation of a diagnostic distinction between EPS and LPS subjects (Hafner *et al.* 2004) and to the clarification of declarative episodic memory deficits in the ARMS. Such clarification is critical for therapeutic efforts to forestall illness progression and prevent cognitive decline from increasing. As impaired declarative episodic memory in schizophrenia is significantly associated with poorer social and vocational competences (Green, 1996; Niendam *et al.* 2006), cognitive dysfunctioning in the ARMS has become a prime target for the development of preventive treatments. Specifically, cognitive remediation programmes may be able to capitalize on encoding and retrieval strategies to enhance declarative episodic memory in LPS subjects. In summary, our data implicate progressive and interrelated structural-functional pathology of the hippocampus as an index of increased risk for schizophrenia.

Declaration of Interest

Acknowledgements

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