Hippocampal volume in subjects at high risk of psychosis: A 5-year longitudinal MRI study

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Word count main text: 3404, Word count abstract: 231, Tables: 2, Figures: 1

Financial Disclosures: The undersigned authors certify that they have no commercial associations that may pose a conflict of interests in connection with the article.

Abstract

Background: The hippocampal formation has been studied extensively in schizophrenic psychoses and alterations in hippocampal anatomy have been consistently reported. Chronic schizophrenia seems to be associated with bilateral hippocampal volume (HV) reduction, while in patients with an at-risk mental state (ARMS) there are contradictory results. This is the first region of interest (ROI) based follow-up MRI study of hippocampal volume comparing ARMS individuals with and without transition to psychosis. The aim was to investigate the timing of HV changes in ARMS in the early phase of psychosis.

Methods: Magnetic resonance imaging data from 18 antipsychotic-naïve individuals with an ARMS were collected within the ***FePsy***-clinic for early detection of psychoses. During follow-up 8 subjects developed psychosis (ARMS-T) and 10 did not (ARMS-NT). Subjects were re-scanned after the onset of psychosis or at the end of the follow-up if they did not develop psychosis.

Results: Across both groups there was a significant decrease in HV over time ($p < 0.05$). There was no significant difference in progression between ARMS-T and ARMS-NT. Antipsychotic medication at follow up was associated with increased HV ($p < 0.05$).

Conclusions: We found a decrease of HV over time in subjects with an ARMS, independently of clinical outcome. Our findings suggest that hippocampal volume alterations accumulate during the transition to psychosis, reflecting brain degeneration, and potentially allow for the accurate early recognition of individuals at risk of developing psychosis.

Keywords

Hippocampus; schizophrenic psychoses; at risk mental state; magnetic resonance imaging; antipsychotics

Background

Over the past decade, research on the prodromal phase of psychosis has exponentially progressed, allowing for preventive therapeutic interventions in clinical psychiatry (Fusar-Poli *et al.,* 2012b). Because it is difficult to predict which subjects with an at-risk mental state (ARMS) will later develop psychosis on the basis of their presenting clinical features, there is a need for cognitive (Fusar-Poli *et al.,* 2012c) and neurobiological markers to identify the individuals at highest risk of developing florid psychosis and those who might benefit most from preventive interventions (Fusar-Poli *et al.,* 2012c). ARMS have about 18%-36% risk of developing psychosis after 6 months to 3 years (Fusar-Poli and Yung, 2012). In recent years, a range of neuroimaging techniques showed alterations in brain structure (Mechelli *et al.*, 2011), function (Fusar-Poli *et al.,* 2007a), and neurochemistry (Howes *et al.*, 2007) in the prodromal phase of psychosis (Borgwardt *et al.*, 2011). These neuroimaging studies have shown that alterations in brain anatomy and neurophysiology found in established psychosis are also present in people with an ARMS (Smieskova *et al.*, 2010). Overall, ARMS subjects show qualitatively similar, but less pronounced, structural brain abnormalities than patients with established schizophrenia. Studies comparing ARMS subjects showed reduced gray matter (GM) in prefrontal, temporal and cingulate regions, insula, and cerebellum in those subjects who develop psychosis (Fusar-Poli *et al.*, 2011a). Interestingly, similar areas were also recently found to be related to the duration of the ARMS (Smieskova *et al.*, 2011)and to schizotypal personality, a subclinical schizophrenia spectrum trait (Ettinger *et al.*, 2011).

The hippocampal formation has been studied extensively in schizophrenic psychoses, and structural and functional changes in hippocampal formation have been reported consistently (Adriano *et al.*, 2011, Shenton *et al.*, 2001, Tamminga *et al.*, 2010). The integrity of the hippocampal formation is important for declarative memory. The significance of hippocampal damage was studied in patients with schizophrenic psychoses

and there is growing evidence for association between dysfunction of the hippocampus and manifestations of schizophrenic psychoses (Heckers, 2001, Olincy *et al.*, 2006, Preston *et al.*, 2005).

Cross-sectional voxel-based morphometry (VBM) studies of ARMS showed reduced gray matter volume in the frontal lobe and medial temporal regions when compared to healthy controls (HC), regardless of outcome (Mechelli *et al.*, 2011). In addition, relative to those subjects who did not develop the illness, those who later became psychotic showed further reduced volumes in particular in the medial and lateral temporal cortex (Borgwardt *et al.*, 2008, Pantelis *et al.*, 2003). Likewise, recent work has suggested that neuroimaging-based multivariate pattern recognition algorithms, such as the support vector machine, can be used to identify ARMS individuals and may have the potential to identify individuals at the highest risk of developing psychosis within this population (Koutsouleris *et al.*, 2011).

Using a region of interest (ROI) approach most of the cross-sectional studies reported gray matter volume reductions in the bilateral hippocampus in first-episode (FE) (Adriano *et al.*, 2011, Phillips *et al.*, 2002) and in chronic schizophrenia (Nelson *et al.*, 1998, Velakoulis *et al.*, 2006) when compared to HC.

There are contradictory results in ARMS: the left HV of individuals with an at-risk mental state with transition to psychosis (ARMS-T) was larger than that of the at-risk mental state without transition to psychosis (ARMS-NT), but no differences were found between the ARMS-T and HC (Velakoulis *et al.*, 2002), whereas subjects who later became psychotic showed reduced gray matter volume in the left parahippocampal gyrus relative to those who did not (Mechelli *et al.*, 2011). However, there have also been a number of ROI studies which did not find any significant difference between ARMS subjects and HC or between ARMS-T and ARMS-NT (Velakoulis *et al.*, 2006, Wood *et al.*, 2005). A recent study of our own group comparing HV across ARMS, FE and HC, found the largest HV in the ARMS group (Buehlmann *et al.*, 2010), and a meta-analysis of VBM studies of

antipsychotic-naïve subjects with an ARMS showed gray matter volume reductions of HV suggesting that vulnerability to psychosis is associated with HV decreases (Fusar-Poli *et al.*, 2011b).

There is one longitudinal VBM study of HV in ARMS with transition to psychosis that showed most extensive changes in the left medial temporal region with a follow-up period of 12 months (Pantelis *et al.*, 2003) and one longitudinal study measuring cortical thickness which showed an increased cortical thinning in the left middle temporal gyrus over time (Ziermans *et al.*, 2011).

This magnetic resonance imaging (MRI) study aimed to investigate the timing of HV changes in ARMS in the early phase of psychosis. To our knowledge there has been no ROI based longitudinal study in an antipsychotic-naïve ARMS population. Based on previous studies we hypothesized that hippocampal volume reductions are associated with an ARMS. Furthermore, we hypothesised a progressive hippocampal volume reduction over time in the ARMS-T but not in the ARMS-NT.

Materials and methods

Participants

The MRI data were collected as part of a research program (Prediction and early detection of schizophrenia – a prospective multilevel approach), that has been described in detail elsewhere (Riecher-Rössler *et al.*, 2007, Riecher-Rössler *et al.*, 2009). Subjects with an ARMS were recruited through the ***FePsy***-clinic, a specialized clinic for the early detection of psychosis at the Department of Psychiatry, University Hospital in Basel, Switzerland.

Following criteria led to exclusion of the study: history of previous psychotic disorder (treated with major tranquilizers for > 3 weeks); symptomatology clearly due to 'organic' disorder or substance abuse according to ICD-10 criteria (except for cannabis

dependency); psychotic symptomatology clearly associated with an affective psychosis or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and IQ less than 70.

After these exclusion criteria were applied, subjects were assessed using the Basel Screening Instrument for Psychosis (BSIP) (Borgwardt *et al.*, 2008), the Brief Psychiatric Rating Scale (BPRS) (Lukoff *et al.*, 1986, Ventura *et al.*, 1993), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989). The BSIP was used to evaluate 'prodromal' symptoms, defined according to DSM-III-R (*American Psychiatric Association*, 1987), occurring in the last 5 years; non-specific 'prodromal' signs (Häfner *et al.*, 1991, Riecher *et al.*, 1991) in the last two years; previous or current psychotic symptoms; psychosocial functioning over the last 5 years; substance dependency; and psychotic disorders among first and second degree relatives (Riecher-Rössler *et al.*, 2006).

The family history of psychosis was obtained using a semi-structured interview from the subject and, whenever possible, a first-degree relative. The frequency of current and previous alcohol use was estimated using a semi-structured interview. To assess the premorbid IQ we used the MWT, an established measure in German-speaking subjects (Lehrl, 1991).

The antipsychotic-naïve ARMS group (n = 18) was defined using criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Phillips *et al.*, 2002, Yung *et al.*, 1998) employed also in previous MRI studies of the ARMS (Borgwardt *et al.*, 2006, Borgwardt *et al.*, 2007b, Garner *et al.*, 2005, Pantelis *et al.*, 2003, Phillips *et al.*, 2002, Velakoulis *et al.*, 2006). Inclusion thus required one or more of the following: (a) "attenuated" psychotic symptoms, (b) brief limited intermittent psychotic symptoms (BLIPS), or (c) a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as a marked decline in social or occupational functioning. Inclusion because of "attenuated" psychotic symptoms required scores of 2 or 3 on the

hallucination item, 3 or 4 on the unusual thought content or 3 or 4 on the suspiciousness items of the BPRS for at least several times a week and persisting for more than 1 week. Inclusion because of BLIPS required scores of 4 or above on the hallucination item, or 5 or above on the unusual thought content, suspiciousness or conceptual disorganization items of the BPRS, with each symptom lasting less than 1 week before resolving spontaneously. This ARMS sample overlaps with the sample, which has been investigated in our cross-sectional study of HVs (Buehlmann *et al.*, 2010).

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the ethics committee of the University of Basel.

Clinical follow-up and transition to psychosis

The ARMS subjects were followed up at monthly intervals during the first year, at 3 month intervals during the second and third year and annually thereafter until transition to frank psychosis or until end of Mai 2007. At each assessment subjects were examined using the BPRS. The criteria for transition to psychosis were those defined by Yung (Yung *et al.*, 1998). In subjects who met these criteria, the diagnosis was determined by a diagnostic interview using ICD-10 research criteria at the time of transition, corroborated by a subsequent assessment at least one year post transition using the Operational Criteria (OPCRIT) checklist for psychotic and affective illness (McGuffin *et al.*, 1991).

Structural MRI

Image acquisition

All patients at baseline were scanned using a SIEMENS 1.5 T scanner at the University Hospital Basel. The first scan was conducted at study intake. Head movement was minimised by foam padding and velcro straps across the forehead and chin. A three-dimensional volumetric spoiled gradient recalled echo sequence generated 170-176

contiguous, 1-mm thick sagittal slices. Imaging parameters were: time-to-echo, 3.04-4 ms; time-to-repetition, 1.9-9.7 ms; flip angle, 12-15; matrix size, 200 × 256; field of view, 25.6 × 25.6 cm matrix; voxel dimensions, 1 × 1 × 1 mm.

Image analysis

Original DICOM data were then converted to Analyze 7.5 format in axial direction coded to ensure blindness of the investigator and patients' confidentiality and finally imported into the image-analysis software AMIRA (Kappos *et al.*, 2006). The boundaries of the hippocampus were identified including the subiculum, cornu ammonis (hippocampus proper), and the dentate gyrus. The amygdala was excluded. The regions of interest were defined on the coronal and sagittal slices, and finally checked on the coronal plane again. Anterior segmentation was achieved by tracing on sagittal slices. The hippocampal volume was traced generally following the protocol of Jack et al. (1989), which has been used by our group before (Buehlmann *et al.*, 2010). All measurements were carried out by a trained and blinded rater (AW). The intra-rater intra-class correlation coefficient at baseline (n = 18) was 0.89 and 0.77 for the right and left HV, respectively, when using manual segmentation in all baseline MRIs that were measured twice within three weeks.

The whole brain volume (WBV) was measured to correct for differences in head size as previously described (Borgwardt *et al.*, 2007a, Borgwardt *et al.*, 2007b, Haller *et al.*, 2009)

Statistical analysis

Statistical Analyses were performed using the R environment for statistical (R Development Core Team, 2012). Clinical and demographic differences between groups were examined with Fisher's exact test and Welch's two-sample t-test. HV changes over time were analyzed by using a linear mixed effects model that included a random intercept factor for the subjects and fixed effects for time, hemisphere, age, medication, WBV (at

baseline) and time by hemisphere interaction. Due to the small sample size, significance tests of the fixed effects parameters in linear mixed effects models were based on 10,000 Markov Chain Monte Carlo (MCMC) simulations using the pvals.fnc function in the languageR package (Baayen, 2011).

Results

Demographic and clinical data

During follow-up, 8 out of 18 ARMS individuals made the transition to psychosis (ARMS-T) and 10 did not (ARMS-NT). Those subjects who developed psychosis during the follow-up period were scanned again after its onset (1178 ± 501 days). The other subjects were scanned at the end of the follow-up period (1541 ± 224 days) (Table 1).

INSERT TABLE 1 HERE

There were no significant differences between ARMS-T and ARMS-NT regarding sex, age, education at baseline, and interscan-interval. There was a trend towards higher BPRS and SANS scores at baseline in ARMS-T compared to the ARMS-NT (Table 1). All patients were antipsychotic-naïve at the time of baseline. At the time of follow-up scan, 5 of the ARMS-T patients were treated with antipsychotics (three with olanzapine, one with risperidone, one with perphenazine) because these patients had to be treated for clinical and ethical reasons. The time lag between the transition and the second scan was 988 days on average. All ARMS-NT subjects were still antipsychotic-naïve at follow-up.

Hippocampal volume change during follow-up

There was a significant negative main effect of time ($p < 0.05$) but no significant time by hemisphere interaction, suggesting that HV decreased over time in the combined ARMS-T + ARMS-NT sample and that HV changes across time did not differ between hemispheres. A model that additionally included group (ARMS-T vs. ARMS-NT) and the time by group interaction as independent variables did not reveal statistically significant group and group by time interaction effects, i.e. no differences between ARMS-T and ARMS-NT subjects Table 2, Figure 1).

INSERT TABLE 2 AND FIGURE 1 HERE

Effects of whole brain volume, age, hemisphere, and antipsychotics on HV

We found a significant effect of WBV ($p = 0.0004$) but no effect of age on HV. We did not consider gender as a fixed effect because we found a strong effect of WBV on HV and adding sex as a fixed effect did not change our results. There was a trend for smaller HV on the left side compared to the right side ($p < 0.1$). The mixed effects model revealed that – independent of time and all other covariates in the model – antipsychotic medication, which was present in 5 ARMS-T patients at the second scan, was associated with increased HV ($p < 0.05$).

Correlational analyses with clinical psychopathology

In a next step, we tested whether HV was associated with the severity of psychopathological symptoms. We found no significant correlation between HV and SANS or BPRS at baseline. These results also did not change when we corrected for WBV.

Discussion

Our first hypothesis that ARMS group as a whole would show progressive hippocampal volume reduction was confirmed. We found a reduction of manually traced HV over time in antipsychotic-naïve ARMS, independently of clinical outcome. Interestingly, we found that medication with antipsychotics in the ARMS-T after transition to psychosis was associated with larger HV.

Our results are in line with a previous longitudinal VBM study in ARMS with transition to psychosis giving evidence for progressive gray-matter volume reduction in the left medial temporal lobe over a follow-up period 12 months (Borgwardt *et al.*, 2008, Pantelis *et al.*, 2003). Likewise, Ziermans et al. (2011) demonstrated an increased cortical thinning in the left middle temporal gyrus in an adolescent ARMS groups over a follow-up period of 2 years. Our findings support studies that suggest that hippocampal volume reduction is a marker of illness rather than a marker of risk (Velakoulis *et al.*, 2006).

Currently, the stress-vulnerability model is commonly accepted in psychotic disorders (van Os *et al.*, 2010). The decrease of HV might reflect hippocampal sensitivity to stress due to the fact that being in an ARMS is accompanied by a higher level of stress, and the vulnerability of the hippocampus to various hormones induced by stressful experiences has been demonstrated (McEwen, 1999). The most likely mechanism by which stress suppresses adult neurogenesis in the hippocampus is via activation of the hypothalamic–pituitary–adrenal (HPA) axis and subsequent elevation of glucocorticoid levels (Phillips *et al.*, 2006). Furthermore the hippocampus itself dampens the activity of HPA axis, so impaired functioning of the hippocampus could lead to further activation of the HPA axis and to elevated levels of cortisol. A cross-sectional study found no relationship between plasma cortisol levels and HVs (Thompson et al. 2007).

Contrary to our second hypothesis, we were not able to demonstrate a progressive decrease of HV in ARMS-T compared to ARMS-NT. This is in line with an own VBM study (Borgwardt *et al.*, 2008) and previous ROI studies that found normal hippocampal volumes

in patients with first-episode psychosis and no differences between the ARMS-T and HC (Velakoulis *et al.*, 2006). Our results might be due to fact that we did not split the patients with transition to psychosis into subgroups that potentially differ in their HV reduction.

We report no difference in HVs between ARMS-T and ARMS-NT which has been shown in two previous large volumetric MRI studies (Velakoulis *et al.*, 2006, Wood *et al.*, 2005) and also in a small sample by our own group (Bühlmann et al. 2009). There is only one early cross-sectional study with contradictory results which reported smaller HVs in ARMS-T compared to ARMS-NT (Phillips *et al.*, 2002) and differing results may be explained by the smaller sample size.

Our finding of a left laterality of hippocampus is consistent with previous neuroimaging reports from a sample of which the here presented sample is part of (Buehlmann *et al.*, 2010) and is in line with most (Velakoulis *et al.*, 1999, Velakoulis *et al.*, 2006), but not all previous studies (Hurlemann et al., 2008).

There are many mechanisms that can lead to medial temporal volume changes including medication use. Thus, another explanation might be that progressive HV decrease in ARMS-T is masked by the enlarging effect of antipsychotics, which were only present in the ARMS-T group at the time of the second scan (Borgwardt *et al.*, 2010). The here presented data suggest that antipsychotic medication may reduce hippocampal volume loss. Certainly, the observed medication effect must be interpreted with caution because it is only based on five patients. Reduced HV loss has been shown for first generation antipsychotics (Lieberman *et al.*, 2001) or for both first and second generation antipsychotics (Wood *et al.*, 2001), including quetiapine in preclinical studies (Bi *et al.*, 2009, Park *et al.*, 2006). Due to the small sample size and because 4 out of 5 patients were treated with atypical antipsychotics, we could not differentiate typical from atypical antipsychotics. However, comparing treatment with haloperidol to clozapine**,** there was no difference in hippocampal volume (Arango *et al.*, 2003) and data regarding the effects of

typical and atypical antipsychotic medications in general on hippocampal volume are equivocal (Velakoulis *et al.*, 2006).

Contrary to that, atypical antipsychotics showed significant increase in left hippocampal volume as compared to the typical antipsychotics (McClure *et al.*, 2006) and atypical antipsychotics rather than haloperidol may protect against hippocampal volume reduction (Chakos *et al.*, 2005). Consistently, schizophrenia patients treated with antipsychotics showed gray matter volumetric reductions in medial temporal regions (Smieskova *et al.*, 2009) and has been demonstrated in a large longitudinal study (Ho *et al.*, 2011), but to differentiate the contribution of the medication and the psychosis itself was not clearly possible.

The presented study is the second longitudinal study regarding HV in ARMS and the first with a follow-up period beyond 12 months. With an average follow-up duration of approximately five years, we can be quite sure that we did not miss a transition to psychosis because transition to psychosis is likely to happen within the first three years of clinical presentation (Fusar-Poli *et al.*, 2012a).

We did not find a correlation between psychopathology and hippocampal volume which is in contrast to other results, which showed significant inverse correlations between left hippocampus and negative symptoms, and left anterior and posterior hippocampus volumes and positive and negative symptoms, respectively (Rajarethinam *et al.*, 2001). Another group also demonstrated significant correlation between reduced scores on neuropsychological measures of declarative-episodic memory and reduced hippocampal volumes (Kuroki *et al.*, 2006).

The lack of significant differences between ARMS-T and ARMS-NT in the present study may be driven by the relatively small sample size of this high risk population, which is very difficult to collect and to follow up on. Moreover, ARMS individuals may present

with other non-psychotic features such as anxiety and depression that might also contribute to enhance the heterogeneity within the group leading to limited statistical power.

Furthermore, we did not quantify cumulative medication with antipsychotics or for other medication than antipsychotics even though several of our ARMS patients who had additionally depressive symptoms were treated with antidepressants, and a stimulation of neurogenesis in the hippocampus by antidepressants has been suggested by others (Krishnan and Nestler, 2008, Santarelli *et al.*, 2003). Moreover, an antipsychotic effect of antidepressants by improving mood, reducing the faulty appraisal of prodromal symptoms, and modulating the individual's response to environmental stressors has been hypothesized (Fusar-Poli *et al.*, 2007b).

Conclusions

This is the first longitudinal long-term MRI study of hippocampal volume in antipsychotic-naïve ARMS patients suggesting a role of reduced HV in early psychosis.

Our findings suggest that hippocampal volume alterations accumulate during the transition to psychosis potentially allowing for the accurate early recognition of individuals at risk of developing psychosis.

Declaration of interest

The undersigned authors certify that they have no commercial associations that may pose a conflict of interests in connection with the article.

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Table 1. Sociodemographic and Clinical Sample description by group

	ARMS-NT (n = 10, w/m = 5/5)	ARMS-T (n = 8, w/m = 8/2)	p
Age at baseline scan (years)	25.54 (6.00)	25.83 (7.56)	0.7[2]
Education (years)	11.60 (3.43)	10.69 (1.65)	0.713[2]
BPRS total score at baseline	36.20 (4.78)	43.88 (10.18)	0.079[2]
SANS total score at baseline	13.62 (10.82)	34.32 (26.58)	0.069[2]
Inter-scan interval t0-tx (days)	1541 (224)	1178 (501)	0.089[2]
Time between transition and 2nd scan (days)	-	988 (688)	

Data are mean (SD) unless otherwise stated.

SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1989); BPRS = Brief Psychiatric Rating Scale (Lukoff *et al.*, 1986).

[1]Fisher's Exact test

[2]Welch Two Sample t test

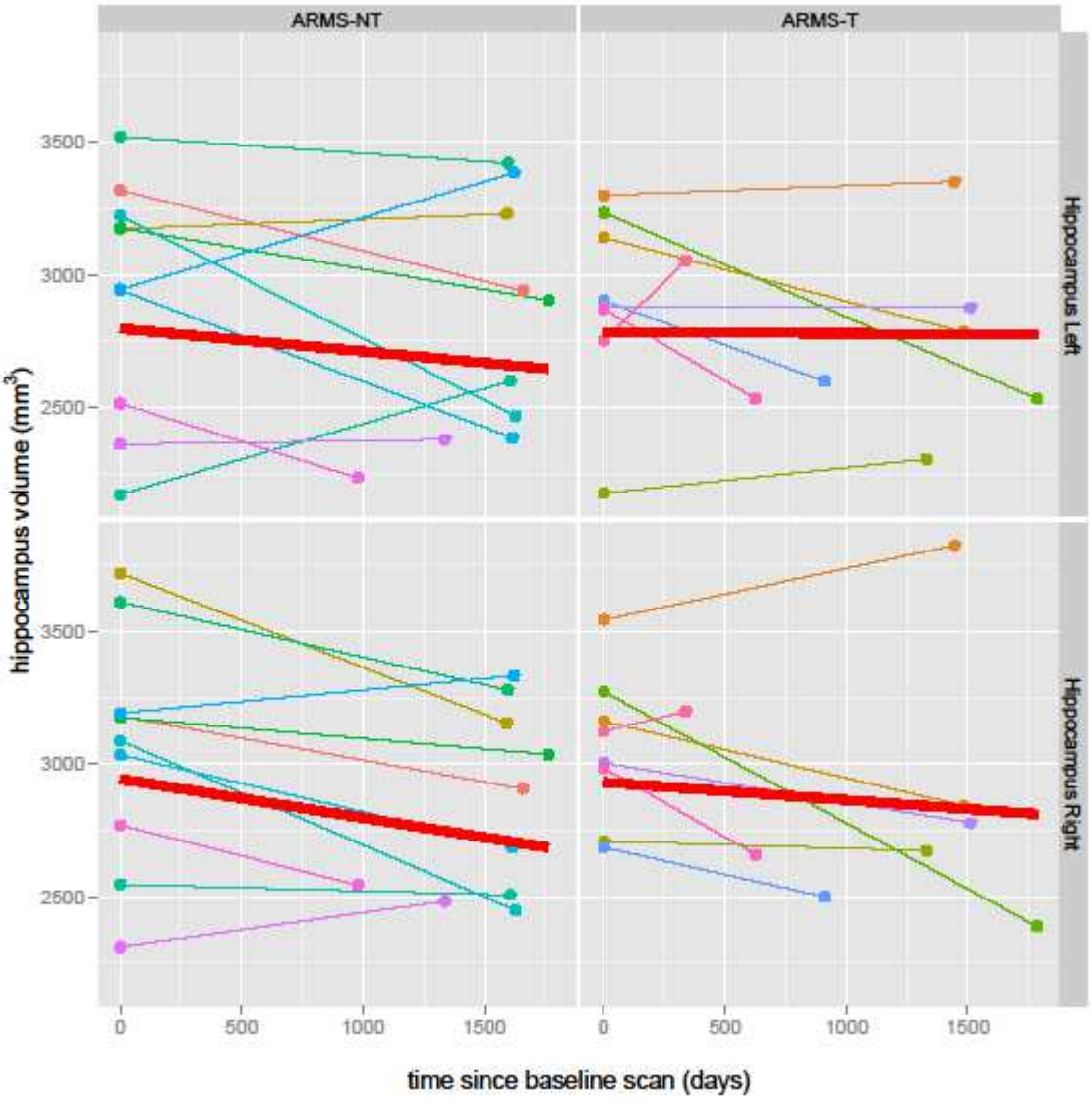
Table 2. Hippocampal and Whole Brain Volume by Group HV

		ARMS-NT (n = 10)	ARMS-T (n = 8)	p
Baseline	Right HV	3.062 (0.43)	3.060 (0.284)	0.992[1]
	Left HV	2.934 (0.444)	2.906 (0.354)	0.886[1]
	Whole brain volume	1310 (122)	1318 (112)	0.883[1]
Follow-up	Right HV	2.837 (0.346)	2.858 (0.460)	0.919[1]
	Left HV	2.794 (0.442)	2.754 (0.335)	0.829[1]
	Whole brain volume	1264 (122)	1281 (106)	0.756[1]

Data are presented as mean ml (SD).

[1]Welch Two Sample t test

Figure 1. Volume changes of the hippocampus (left and right side) in patients with an ARMS without transition (ARMS-NT) and with transition to psychosis (ARMS-T).



Values of baseline and follow-up scans in each subject are connected with a straight line. The thick red lines are the model predicted hippocampus volumes for different time points, patients groups, and hemispheres, when the other covariates are held at their mean values.