

Duration of untreated psychosis/illness and brain volume changes in early psychosis

Charlotte Rapp^a, Carlos Canela^a, Erich Studerus, Anna Walter, Jacqueline Aston,
Stefan Borgwardt, Anita Riecher-Rössler*

University of Basel Psychiatric Hospital, Center for Gender Research and Early Detection,
Kornhausgasse 7, CH-4051 Basel, Switzerland

^aShared first authorship

***Corresponding author:**

Prof. A. Riecher-Rössler
University of Basel Psychiatric Hospital
Center for Gender Research and Early Detection
Kornhausgasse 7
CH-4051 Basel, Switzerland
Tel.: +41 61 325 81 61
Fax: +41 61 325 81 60
E-mail: Anita.Riecher@upkbs.ch

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Abstract

The time period during which patients manifest psychotic or unspecific symptoms prior to treatment (duration of untreated psychosis, DUP, and the duration of untreated illness, DUI) has been found to be moderately associated with poor clinical and social outcome. Equivocal evidence exists of an association between DUP/DUI and structural brain abnormalities, such as reduced hippocampus volume (HV), pituitary volume (PV) and grey matter volume (GMV). *Thus, the goal of the present work was to examine if DUP and DUI are associated with abnormalities in HV, PV and GMV.* Using a region of interest (ROI) based approach, we present data of 39 patients from the Basel *FePsy* (*Früherkennung von Psychosen*, early detection of psychosis) study for which information about DUP, DUI and HV, PV and GMV data could be obtained. Twenty-three of them were first episode psychosis (FEP) and 16 at-risk mental state (ARMS) patients who later made the transition to frank psychosis. In unadjusted analyses, we found a significant positive correlation between DUP and PV in FEP patients. However, when adjusted for covariates, we found no significant correlation between DUP or DUI and HV, PV or GMV anymore. There only was a trend for decreasing GMV with increasing DUI in FEP. Our results do not comprehensively support the hypothesis of a “toxic” effect of the pathogenic mechanism underlying untreated psychosis on brain structure. If there is any effect, it might rather occur very early in the disease process, during which patients experience only unspecific symptoms.

Keywords: first episode psychosis, at-risk mental state; grey matter volume, hippocampal volume; pituitary volume

1. Introduction

Patients with psychosis often experience unspecific and psychotic symptoms for long periods before appropriate antipsychotic treatment is initiated (Fusar-Poli et al., 2013). The time period between first self-perceived signs of a change in well-being or unspecific symptoms and treatment is called "duration of untreated illness" (DUI); the time period between the development of the first psychotic symptoms and treatment is called "duration of untreated psychosis" (DUP) (Norman and Malla, 2001). Longer DUP and DUI have been consistently found to be associated with poor clinical and social outcomes, hence the need for early intervention services which create better outcomes in the critical period of the first 2-5 years of the disease (Bangalore et al., 2009; Crumlish et al., 2009; Harris et al., 2005; Keshavan et al., 2003; Marshall et al., 2005; Norman and Malla, 2001; Perkins et al., 2005). It has been hypothesized, that this might be due to a "toxic" effect of ongoing, untreated psychosis, respectively the effect of the untreated pathogenic mechanism underlying psychotic symptoms (Wyatt and Henter, 2001). The investigation if brain volume is affected in the early phases of psychosis has therefore become an important focus of research.

To better understand this possible process, several research groups have investigated the relationship between DUP and different brain structures (Büschen et al., 2011; Crespo-Facorro et al., 2007a; Crespo-Facorro et al., 2007b; Ho et al., 2005; Ho et al., 2003; Hoff et al., 2000; Lappin et al., 2006; Takahashi et al., 2007). The results of these studies were summarized in two systematic reviews (Anderson et al., 2015; Rund, 2014), both finding minimal evidence for the "neurotoxicity" hypothesis. Rund et al. (2014) suggested in his review that there might be a threshold value for a toxic effect of psychosis rather than a linear relationship

between DUP and a neurotoxic effect and that several of the evaluated studies might not have had a long enough DUP to detect a toxic effect of active psychosis (Rund, 2014).

One of the key regions to be investigated is the hippocampus, which is involved in memory functions and complex behaviors, including stress responses (Small et al., 2011), and has been proposed to be important in the development of schizophrenia (Antonova et al., 2004; Heckers and Konradi, 2002; Koolschijn et al., 2010; Phillips et al., 2002). It is among the most consistently reported abnormal brain regions in schizophrenia (Adriano et al., 2012) and highly interconnected with other regions of the brain. There is some evidence suggesting a change of the hippocampal volume (HV) during the early stages of a psychotic disorder. HV has been found to be decreased in patients with first episode psychosis (FEP) and patients with an at-risk mental state (ARMS) for psychosis (e.g. Buehlmann et al., 2010; Dean et al., 2016; Wood et al., 2010) compared to healthy controls (HC) (Adriano et al., 2012) .

Although it might be inferred from these findings that there is a time period at the beginning of the disease in which HV changes, it is yet unknown whether and when such changes actually occur. According to the “neurotoxicity” hypothesis, HV changes would be expected to increase the longer untreated symptoms persist. Nonetheless, to our knowledge no clear association between DUP and HV has been found up to now (Ho et al., 2005).

Another region that has been investigated recently and which seems to be affected in the early stages of the disease is the pituitary volume (PV) (Büschen et al., 2011). A recent meta-analysis of studies investigating the volumes of the pituitary in patients with schizophrenia, FEP, schizotypal disorder or ARMS and healthy controls found

a trend for larger PVs in both ARMS patients with later transition to psychosis and FEP patients compared to HC (Nordholm et al., 2013). Whether there is an association between the duration of untreated symptoms and volume changes in the pituitary is still unclear due to inconsistent results.

Several studies have also found volumetric changes of various grey matter regions in early stages of psychosis and ARMS (Borgwardt et al., 2007; Borgwardt et al., 2008; Chua et al., 2007; de Castro-Manglano et al., 2011; Witthaus et al., 2009).

Investigations on the correlation between DUP and grey matter volume (GMV) changes have yielded equivocal results (Ho et al., 2003; Hoff et al., 2000; Lappin et al., 2006; Malla et al., 2011; Penttila et al., 2010; Takahashi et al., 2007).

Studies investigating a possible correlation of DUI and GMV abnormalities found similar equivocal results. Bangalore et al. found a significant inverse correlation between DUI and the volume of some grey matter regions (Bangalore et al., 2009), Velakoulis et al. found right medial temporal, medial cerebellar and bilateral anterior cingulate GMV changes, and white matter volume loss in the right posterior limb of the internal capsule associated with a longer DUI (Velakoulis et al., 2002), whereas Hoff et al. (2000) could not find a significant correlation between changes in GMV and DUI. In line with the hypothesis of a “neurotoxicity” of untreated psychosis, it might be surmised that the longer untreated psychotic processes/symptoms persist, the more pronounced structural alterations of HV, PV and GMV could be.

The objective of the present study was to investigate a possible correlation between DUP/DUI and different structural brain abnormalities (HV, PV and GMV) that have been found to be affected in early stages of psychosis. On the basis of previous longitudinal studies of DUP and other volume abnormalities in early stages of

psychosis, we tested the hypothesis that a longer DUP or DUI would be associated with a decrease in HV, PV and GMV. This is the first study to look at the relationship between all three brain parts, HV, PV and GMV, and DUP/DUI in the same study. Additionally, in contrast to most other studies, this study mainly includes antipsychotic-free subjects, which is highly relevant due to the fact that antipsychotic treatment itself can lead to brain structural changes (Vita et al., 2015).

2. Methods

2.1. Participants

This study was part of the *FePsy* (*Früherkennung von Psychosen*; early detection of psychosis) study (Riecher-Rössler et al., 2007), a multi-domain study on the early detection of psychosis. Subjects with an ARMS or FEP were recruited from a service area covering about 200,000 inhabitants in and around Basel, Switzerland, into the study via the *FePsy* Clinic at the University Hospital Basel, which was set up specifically to identify, assess and treat individuals in the early stages of psychosis. The study design and criteria for identification of ARMS and FEP subjects have been described in detail previously (Riecher-Rössler et al., 2007).

The study sample overlaps with previous samples reported on from the *FePsy* study (Borgwardt et al., 2006; Buehlmann et al., 2010; Büschlen et al., 2011; Riecher-Rössler et al., 2007; Walter et al., 2012b; Walter et al., 2014). The study was approved by the Ethics Committee of Basel, Switzerland (EKBB) and written informed consent was obtained from the participants.

In this study, we present data of 39 patients from the Basel *FePsy* study for which information about DUP, DUI and region of interest (ROI) data could be obtained.

Twenty-three patients were identified as FEP patients and 16 as ARMS individuals who later made the transition to frank psychosis (ARMS-T). The service is fully responsible for all ARMS and FEP patients of a catchment area (Kanton Basel-Stadt). Our study sample did not significantly differ from all patients of our service in the respective period regarding sociodemographic characteristics.

Screening procedure

For screening purposes and measuring the severity of (pre-)psychotic phenomena, we used the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008). Individuals were assessed and classified as individuals with an ARMS, FEP or “not at risk for psychosis” (other psychiatric diseases). All assessments were conducted by experienced psychiatrists/psychologists who underwent regular training.

Inclusion criteria

We included FEP patients and ARMS individuals who later made the transition to frank psychosis (ARMS-T) according to the PACE (Personal Assessment and Crisis Evaluation) criteria proposed by Yung et al. (1998) (Yung et al., 1998) which have also been employed in previous MRI studies of patients with an ARMS (Borgwardt et al., 2006; Garner et al., 2005; Pantelis et al., 2003; Velakoulis et al., 2006).

Exclusion criteria

Patients aged below 18 years with insufficient knowledge of German, IQ below 70, a previous episode of schizophrenic psychosis (treated with antipsychotics for more than 3 weeks), a psychosis due to organic reasons or substance dependency and

psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder were excluded from the study.

2.2. Acquisition and analysis of MRI data

All participants received MRI within an average 25 days after entering into our early detection service.

Since this study is a part of the *FePsy* project, the acquisition of the presented MRI data has already been described elsewhere (Buehlmann et al., 2010; Büschlen et al., 2011).

Briefly, a SIEMENS (Erlangen, Germany) MAGNETOM VISION 1.5 T scanner was used at the University Hospital Basel to scan all subjects at the inclusion to the study, i.e. when they first presented with prodromal or psychotic symptoms. Foam padding and velcro straps were used to minimize head movement. A three-dimensional volumetric spoiled gradient recalled echo sequence generated 176 contiguous, 1 mm thick sagittal slices. Imaging parameters were: time-to-echo, 4 ms; time-to-repetition, 9.7 ms; flip angle, 12; matrix size, 200×256; field of view, 25.6×25.6 cm matrix; voxel dimensions, 1.28×1×1 mm.

A detailed description of the measuring processes of the regions of interest (ROI) and GMV used in this sample has been published elsewhere (Harris et al., 2005; Phillips et al., 2002). In summary, a ROI approach was used to measure HV and PV manually by a single tracer with a mouse-driven cursor, using the interactive public domain software program AMIRA which displays all three planes simultaneously (Kappos et al., 2006). All measurements of HV and PV were carried out by a trained and blinded rater (AW). The intra-rater intra-class correlation coefficient and inter-

rater reliability have been reported in our previously published studies (Walter et al., 2012a; Walter et al., 2014). To assess GMV, a voxel-based morphometry, using the fully automated software SIENAX (www.fmrib.ox.ac.uk/fsl), allowed us to estimate the whole brain volumes from a single image, normalized for skull size (Smith et al., 2007) . After stripping non-brain tissue, the software estimates the scaling between the subject's image and standard space using the brain and skull images. It then runs tissue segmentation to estimate the volume of brain tissue and multiplies this by the estimated scaling factor to reduce head-size-related variability between subjects (Smith et al., 2002).

2.3. DUP and DUI

DUI was defined as the time period between first self-perceived signs of a change in well-being and first contact with our specialized early detection service. DUP was defined as the time period between the appearance of the first positive psychotic symptom and first contact with our specialized early detection service. DUP was only assessed in FEP patients because it was almost zero in our ARMS-T patients due to our close follow-up during the at-risk mental state and prompt treatment at transition.

DUI was determined by using the Basel Interview for Psychosis (BIP) (Riecher-Rössler et al., 2015; Riecher-Rössler et al., 2007), a structured and specifically developed interview for the early detection of psychosis, allowing an exact description of the onset of all symptoms. The DUP was assessed using the Basel Screening Interview for Psychosis (BSIP) (Riecher-Rössler et al., 2008).

Both DUP and DUI were assessed according to the patient's subjective response but also by using other available information resources (e.g. information from family members, medical histories).

Psychopathology measures

Positive symptoms were assessed with the 4 items: hallucinations, suspiciousness, unusual thought content, and conceptual disorganization of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993). Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983).

2.4. Statistical analysis of clinical and demographic data

Statistical analyses were performed using the R environment for statistical computing (R Development Core Team, 2012). Due to a strong positive skew, both DUP and DUI were anchored at 1 and then log transformed. Two tailed *t*-tests for the continuous and Fisher's Exact or χ^2 tests for the categorical variables were used in order to compare groups for demographic and clinical data ($p < 0.05$).

Associations of brain structural volumes with DUP and DUI were analyzed using linear regression and mixed effects (LME) models, in which log transformed DUP or DUI served as outcome variables and brain structural volumes as predictors. Linear regression models were used for PV and whole brain GMV and LME models for HV. LME models were used in the latter case to account for repeated measures resulting from assessing HV at both the left and right hemispheres. The within subject factor hemisphere and the interaction between hemisphere and DUI/DUP was therefore included in all LME models. The random effect structure of the LME models consisted of a random intercept per subject.

All models included age and gender as covariates. Models with PV and HV as outcome variables additionally included whole brain volume as covariate.

Furthermore, models with DUI included group (ARMS-T vs. FEP) and group x DUI

interaction terms and in case of HV group x hemisphere and group x hemisphere x DUI interaction terms. All continuous variables were z-transformed before entering the models to get fully standardized regression coefficients for continuous variables and y-standardized regression coefficients for binary variables.

3. Results

In this paper we present data of 39 individuals (23 FEP, 16 ARMS-T) screened between 01.03.2000 and 29.2.2004, in whom the MRI scans were completed. The sociodemographic, clinical characteristics and diagnoses of the sample are presented in Table 1. As was to be expected, the BPRS score was higher in FEP than in ARMS-T patients ($p = 0.024$), while the SANS score did not differ significantly between the two groups ($p = 0.648$).

The median DUP (only assessed in FEP) was 3.7 months (mean: 11.3; SD: 16.6).

The median DUI for the total sample was 36 months (mean: 52.5; SD: 59.1), 51 months (mean: 47.9; SD: 37.7) for ARMS-T and 27 months (mean: 55.8; SD: 71.6) for FEP.

ARMS-T patients had significantly bigger left HV than FEP patients ($p = 0.020$).

There were no significant differences between the ARMS-T and FEP groups in the right HV, PV, and GMV.

Table 2 displays regression coefficients and p -values of the models testing associations between DUP and brain structural volumes in FEP patients. DUP was not significantly associated with HV, PV and GMV in FEP patients when adjusted for confounders (age, sex, whole brain volume). However, when the model was only

adjusted for whole brain volume, there was a positive relationship between DUP and PV ($p = 0.042$).

Four (25%) of the ARMS-T patients and 9 (39%) of the FEP patients were taking antipsychotics at the time of MRI assessment. Additionally, one ARMS-T patient had been taking antipsychotics before but not during the MRI assessment. All other patients were antipsychotic-naïve. Since according to our inclusion criteria patients were only allowed to have taken antipsychotics for up to three weeks at the time of inclusion, all patients were treated for a relatively short period of time. Moreover, patients were exclusively treated with low to moderate doses of either olanzapine or risperidone.

Table 3 displays the results of the models testing associations between DUI and brain structural volumes in FEP and ARMS-T patients combined. DUI was not significantly associated with PV and HV and – as indicated by non-significant interaction terms – the effect of DUI was not moderated by group (FEP vs. ARMS-T) or hemisphere (left vs. right) in these volumes. For whole brain volume, there was a significant interaction between group and DUI ($p = 0.027$), indicating different associations between DUI and whole brain volumes in ARMS-T and FEP patients. We therefore performed separate regression models for ARMS-T and FEP patients and found that there was a trend for decreased gray matter volume with increasing DUI in FEP ($p = 0.093$) but not in ARMS-T patients. When the model was calculated without adjusting for confounders, the results did not change significantly.

4. Discussion

Using an ROI-based approach we investigated associations between PV, HV, GMV and DUP/DUI. To our knowledge, our study is one of the first to investigate the effect of DUI/DUP on HV, PV and GMV in the same patients. Our study did not find associations between DUP/DUI and brain volume which confirms findings of many earlier studies.

In accordance with other studies (Ho et al., 2005; Takahashi et al., 2007) we found that HV was neither significantly associated with DUP nor with DUI. Penttilä et al. (Penttila et al., 2010) found a correlation between DUP and the right HV that we could not replicate. One possible explanation for this discrepancy is that in their study the MRI was taken many years after the ending of DUP (mean duration between onset of treatment and MRI scan of more than 10 years), whereas in our study the MRI was conducted at baseline (i.e. immediately before treatment initiation). Thus, it is possible that a longer DUP might affect the right HV only at a later stage of the illness.

In the unadjusted analysis, there was a significant positive correlation between DUP and PV. However, we found no association between DUP/DUI and PV when adjusted for covariates. An increased PV has been found in the prodromal phase (Garner et al., 2005; Pariante et al., 2005; Pariante et al., 2004) and the early stages of psychotic disease (Büschen et al., 2011; Walter et al., 2014). From our results it is not clear whether the duration of untreated psychosis plays a role for this increase.

Consistent with other studies (Ho et al., 2003; Lappin et al., 2006; Penttila et al., 2010) we found no correlation between GMV and DUP. The correlation between

DUP and GMV Malla et al. (Malla et al., 2011) found might have been due to the inclusion of patients with affective psychosis. An analysis of only those individuals with schizophrenia found no correlation with DUP in that study either.

Although our results could not reveal a statistically significant correlation between DUI and GMV in both groups, we found a statistical trend for a negative correlation between DUI and GMV in the FEP group. This could suggest a possible negative association of untreated, very early, non-specific psychiatric symptoms with GMV in FEP, which is somewhat in accordance with a meta-analysis investigating the relationship between DUI and different GMV areas (Anderson et al., 2015). However, from our results, no causal conclusions can be drawn.

HV, PV and GMV have been found to be altered in the early stages of the illness (Büschen et al., 2011; Koolschijn et al., 2010; Pantelis et al., 2003), thus raising the question whether there might be a damaging impact of the prodromal phase or early untreated psychosis on said structures. In the last decade, most studies have investigated the time period when psychotic symptoms are already apparent (DUP) and yielded equivocal results. Generally, such studies were conducted with small samples and therefore were underpowered to reliably detect small effects. Thus, the replication of known results becomes an important aim in this field of research. Only few research groups have expanded their focus and included the prodromal stage (DUI), such as we did in our study.

Different mechanisms causing the neurotoxic effect of psychosis have been suggested: e.g. glutamatergic excitotoxicity (de la Fuente-Sandoval et al., 2011),

elevated dopamine levels (Keshavan et al., 1998) or persistent catecholaminergic activity (Bangalore et al., 2009).

Another possible reason for volume changes in the first stages of psychosis might be hormonal abnormalities, which have consistently been reported (Riecher-Rössler et al., 2013; Walker et al., 2008). Increased levels of cortisol have been found in some patients with increased risk for psychosis (Walker et al., 2013); such higher levels seem to be associated with reduced HV (Mondelli et al., 2010).

Higher prolactin levels have also been found in antipsychotic-naïve patients with schizophrenia (Garcia-Rizo et al., 2012), FEP (Riecher-Rössler et al., 2013) and ARMS (Aston et al., 2010; Ittig et al., 2016). Since a higher prolactin production is known to be associated with an enlargement of the PV (MacMaster et al., 2007), a higher prolactin secretion might explain why increased PV have been found during the prodromal phase (Riecher-Rössler et al., 2013).

It has been hypothesized that the psychological distress during prodromal states and emerging psychosis might lead to hyperprolactinemia (Riecher-Rössler et al., 2013) and hypercortisolism, which in turn might cause structural changes in PV and HV. In line with the hypothesis of a “neurotoxicity” of untreated psychosis, it might be surmised that the longer such processes/symptoms and psychological distress persist, the more pronounced structural alterations of HV and PV could be.

Investigations focusing on DUP/DUI and reduced cognitive functioning as another possible “toxic” effect have yielded similarly equivocal results regarding the “neurotoxicity” hypothesis (Rapp et al., 2013). Other factors (i.e. social decline,

substance abuse, etc.) might be responsible for the worse outcome associated with longer DUI/DUP (Broussard et al., 2013).

Besides a “general” neurotoxicity hypothesis, it seems important to maintain that this “toxic” process might also only occur in a subgroup of psychosis patients.

Furthermore, first episode psychosis might be in a too early phase of the disease to detect this phenomenon.

In general, the comparability across studies may be reduced due to different anatomic ROI definitions, biases in voxel-based morphometry (Fusar-Poli et al., 2013), and different MRI acquisition parameters (e.g. different slice thickness). Another methodological problem are the different definitions and measurements of DUP and DUI in different studies (Polari et al., 2011), which make comparisons difficult, as does the inclusion of different patient groups (e.g. affective psychosis, etc.) since some brain volume anomalies might be connected to other symptoms (i.e. depressive symptoms) (Koolschijn et al., 2010). It has also been suggested that defining DUP just as a period of time might not be enough when investigating a possible toxicity of a pathogenic mechanism underlying psychosis, since this definition of DUP makes no difference between individuals who experience continuous symptoms during DUP and others who suffer symptoms for short periods with long intervals before treatment. It is also possible that some individuals with a faster progression of the disease suffer greater structural brain changes but are hospitalized or treated sooner, resulting in a shorter DUP. Additionally, patients that have a reduced GMV might suffer from cognitive deficits that hinders them to get access to fast treatment.

4.1. Limitations

As this study has a cross-sectional design, no causal relationships but only correlational relationships can be established. On the other hand longitudinal studies on this topic seem hardly feasible, as individuals usually do not seek help immediately when first symptoms occur. Also, our sample only comprises 39 patients, so that small effects cannot be detected. This study examined whole grey matter volume and hippocampus but did not examine other important cortical areas (frontal regions, superior temporal gyrus, etc). Other potentially influencing factors on brain volumes apart from the disease could not be controlled for. Since the number of tested brain volumes were relatively small and since we had limited power, we did not want to further reduce power by performing correction for multiple testing.

4.2. Conclusions

We found a significant positive correlation between DUP and PV in FEP patients. However, when adjusted for covariates, we found no significant correlation between DUP or DUI and HV, PV or GMV anymore. There only was a trend for decreasing GMV with increasing DUI in FEP. Our results do therefore not comprehensively support the hypothesis of a “toxic” effect of the pathogenic mechanism underlying untreated psychosis on brain structure. If there is any effect, it might rather occur very early in the disease process, during which patients experience only unspecific symptoms (during DUI).

Conflict of interest: none of the authors have any conflicts of interests to declare.

Table 1: Demographic and clinical sample characteristics

	Combined N=39	ARMS-T N=16	FEP N=23	p-value
Gender:				0.734
Women	11 (28.2%)	5 (31.2%)	6 (26.1%)	
Men	28 (71.8%)	11 (68.8%)	17 (73.9%)	
Age	27.1 (6.4)	26.8 (6.6)	27.2 (6.5)	0.848
Years of education	10.3 (2.8)	10.7 (2.2)	10.0 (3.2)	0.464
BPRS total score	46.8 (11.9)	41.8 (9.4)	50.5 (12.4)	0.024
SANS total score	32.0 (18.8)	30.3 (18.4)	33.1 (19.5)	0.648
Diagnoses ¹				
Paranoid Schizophrenia		2 (12.5%)	15 (65.2%)	
Undifferentiated Schizophrenia		2 (12.5%)	1 (4.3%)	
Acute transient psychotic disorder		2 (12.5%)	4 (17.4%)	
Schizoaffective disorder		2 (12.5%)	2 (8.7%)	
Depression with psychotic symptoms		2 (12.5%)		
Missing diagnosis		6 (37.5%)	1 (4.3%)	
Duration of untreated psychosis [months]	11.3 (16.6)		11.3 (16.6)	
Duration of untreated illness [months]	52.5 (59.1)	47.9 (37.7)	55.8 (71.6)	0.665
Hippocampus right volume [mm ³]	3162 (235)	3194 (216)	3140 (249)	0.470
Hippocampus left volume [mm ³]	2841 (256)	2956 (251)	2761 (232)	0.020
Pituitary volume [mm ³]	537 (106)	541 (119)	535 (98.5)	0.860
Grey matter volume [cm ³]	681 (55.8)	680 (57.5)	681 (55.9)	0.983
Antipsychotic-naive	25 (64.1%)	11 (68.8%)	14 (60.9%)	0.869
Antipsychotics currently	13 (33.3%)	4 (25.0%)	9 (39.1%)	0.565
Chlorpromazine equivalent dose [mg]	250 (153)	262 (149)	244 (163)	0.851

FEP = First episode psychosis; ARMS-T = Patients with an at-risk mental state for psychosis and later transition to psychosis. Categorical variables are presented as absolute numbers and percentages in parenthesis and were compared with Chi-square or Fisher's Exact tests. Continuous variables are presented with means and standard deviations in parentheses and were compared with Welch's two sample t-tests.

¹ Diagnoses in ARMS-T after transition to psychosis

Table 2: Hippocampus, pituitary, and grey matter volumes regressed on duration of untreated psychosis (DUP) and other covariates in first episode psychosis (FEP) patients

Term	Hippocampus		Pituitary		Grey matter	
	Coef	<i>p</i> -value	Coef	<i>p</i> -value	Coef	<i>p</i> -value
DUP (log)	0.016	0.937	0.393	0.073	-0.107	0.530
DUP (log) x Hemisphere	0.096	0.577				
Age	-0.277	0.224	-0.056	0.805	-0.488	0.012*
Hemisphere	0.262	0.128				
Sex	-0.229	0.728	0.002	0.997	1.424	0.002**
Whole brain volume	0.365	0.185	0.259	0.350		

Coef = regression coefficient; DUP = duration of untreated psychosis. Dummy coding of binary variables: Sex: men=-0.5, women=0.5; Hemisphere: left=-0.5, right=0.5. All independent and dependent variables except binary variables were z-transformed before model fitting.

Table 3: Hippocampus, pituitary, and grey matter volumes regressed on duration of untreated illness (DUI) and other covariates in first episode psychosis (FEP) and prodromal (ARMS-T) patients combined

Term	Hippocampus		Pituitary		Grey matter	
	Coef	<i>p</i> -value	Coef	<i>p</i> -value	Coef	<i>p</i> -value
DUI (log)	-0.073	0.689	0.118	0.499	0.039	0.813
DUI (log) x Group	0.147	0.701	0.079	0.829	-0.741	0.027*
DUI (log) x Group x Hemisphere	0.184	0.460				
DUI (log) x Hemisphere	-0.012	0.923				
Age	-0.229	0.152	0.027	0.859	-0.268	0.065
Group	-0.494	0.127	-0.125	0.683	-0.046	0.871
Group x Hemisphere	0.560	0.016*				
Hemisphere	-0.020	0.861				
Sex	0.028	0.941	-1.058	0.007**	0.772	0.019*
Whole brain volume	0.170	0.356	0.244	0.171		

Coef = regression coefficient; DUP = duration of untreated psychosis. Dummy coding of binary variables: Sex: men=-0.5, women=0.5; Hemisphere: left=-0.5, right=0.5; Group: ARMS-T=-0.5, FEP=0.5. All independent and dependent variables except binary variables were z-transformed before model fitting.

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