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Lower levels of the glial cell marker TSPO in drug-naïve first episode psychosis patients as measured using PET and [^{11}C]PBR28

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Abstract

Several lines of evidence are indicative of a role for immune activation in the pathophysiology of schizophrenia. Nevertheless, studies using Positron Emission Tomography (PET) and radioligands for the translocator protein (TSPO), a marker for glial activation, have yielded inconsistent results. Whereas early studies using a radioligand with low signal to noise in small samples showed increases in patients, more recent studies with improved methodology has shown no differences or trend-level decreases. Importantly, all patients investigated thus far have been on antipsychotic medication, and since these compounds may dampen immune cell activity, this factor limits the conclusions that can be drawn. Here, we examined 16 drug-naïve, first episode psychosis patients and 16 healthy controls using PET and the TSPO radioligand [^{11}C]PBR28. Gray matter (GM) Volume of Distribution (V_T) derived from a two-tissue compartmental analysis with arterial input function was the main outcome measure. Statistical analyses were performed controlling for both TSPO genotype, which is known to affect [^{11}C]PBR28 binding, and gender. There was a significant reduction of [^{11}C]PBR28 V_T in patients compared to healthy controls in GM as well as in secondary regions of interest. No correlation was observed between GM V_T and clinical or cognitive measures after correction for multiple comparisons. The observed decrease in TSPO binding suggests reduced numbers or altered function of immune cells in brain in early stage schizophrenia.

Introduction

Schizophrenia is a severe mental disorder for which currently available treatment is satisfactory only in a minority of cases. Cognitive impairment, such as memory dysfunction and reduced speed of processing, are present already at an early stage of the disease, and are particularly difficult to ameliorate[1]. The development of new, improved treatment approaches is presently hampered by a lack of understanding of the pathophysiology of the disease.

Genetic and epidemiological data are indicative of an involvement of the immune system in the development of schizophrenia[2,3]. In patients, an on-going immune activation is suggested by studies showing elevation of immune markers in blood and CSF both during long-term illness, as well as in first episode psychosis [4–7]. Using Positron Emission Tomography (PET) and radioligands for the translocator protein 18kDA (TSPO), which in brain is expressed primarily in microglia and astrocytes, it is possible to index brain immune cell activation *in vivo* [8–10]. Initial TSPO PET studies in small samples have shown increased binding in patients with schizophrenia as compared to controls[11,12], however a radioligand with low signal-to-noise ratio was used, as well as an outcome measure generally shown to be less reliable [13]. More recent studies using novel TSPO radioligands have failed to replicate these findings. Although increases in a relative measure of binding was recently reported in schizophrenia patients and ultra-high-risk individuals, there was no absolute TSPO elevation using standard methods of quantification[14]. This observation is in line with results from other studies in patients with long-term illness[15,16], as well as a recent study in patients with recent-onset disease where a trend-level reduction in TSPO was observed[17].

A major limitation of the studies published thus far is that all patients have been on treatment with antipsychotic medication. Importantly, several of these compounds have shown to attenuate blood cytokine levels in patients[18] as well as decrease binding to TSPO in preclinical studies[19]. Though the high-risk individuals investigated by Bloomfield et al[14] were unexposed to antipsychotic medication, on average less than 30% of this group go on to develop a psychotic disorder[20], indicating that the group is heterogeneous and cannot be equated with a prodromal phase of schizophrenia.

The aim of the present study was to overcome the critical drawback of previous investigations by measuring TSPO binding in antipsychotic-naïve, first episode psychotic patients, as compared to age-matched control subjects.

Subjects and methods

Patients and control subjects

The study was approved by the Regional Ethics Committee in Stockholm and the Radiation Safety Committee at the Karolinska University Hospital, Stockholm. Subjects were included after providing written informed consent after receiving a complete description of the study.

Sixteen first-episode psychotic patients (11 male, 5 female, mean age 26.4 (SD 8.4)) were recruited from psychiatric emergency wards and out-patient clinics in Stockholm. At time of investigation all patients were naïve to antipsychotic

treatment and met the diagnostic criteria for Schizophrenia (n=3), Schizophreniform Psychosis (n=4), Psychosis NOS (n=7) or Brief Psychosis (n=2), according to DSM-IV. Exclusion criteria were neurologic or severe somatic illness, current use or history of abuse of illegal drugs (including cannabis) and autism-spectrum disorder. Absence of major brain abnormalities was confirmed using Magnetic Resonance Imaging (MRI). Occasional medication with sedatives and anxiolytics, including benzodiazepines (BZ), were allowed during the course of the study, as well as medication with antidepressants. In cases where diazepam was used, the daily dose was significantly lower than equivalent concentrations of this drug shown to affect TSPO binding according to *in vitro* data[21].

Sixteen control subjects (7 male, 9 female, age 28.5 (8.4)) were recruited by advertisement. They were healthy according to medical history, clinical examination, routine laboratory blood and urine tests as well as a brain MRI examination. The Mini International Neuropsychiatric Interview (MINI) was used to exclude previous or current psychiatric illness. Further exclusion criteria were previous or current use of illegal drugs and first-degree relatives with psychotic illness. None of the control subjects were on any medication at time of the study.

TSPO genotype was assessed in all subjects as described previously[22] using DNA extracted either from whole blood or saliva. There were 8 High Affinity binders (HABs) and 8 Mixed Affinity Binders (MABs) among the patients and 9 HABs and 7 MABs in the control group (Table 1).

Behavioral measures

In patients, psychotic symptoms were assessed using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and the Clinical Global Impression (CGI-S) scale. Cognitive functioning was assessed in all subjects using tests from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)[23,24], which is designed specifically to measure cognition in research on schizophrenia[1]. The cognitive domains assessed were speed of processing (using the tests Category Fluency: Animal Naming, Trail Making Test: Part A (TMT A)), attention/vigilance (Continuous Performance Test- Identical Pairs (CPT-IP), working memory (Wechsler Memory Scale (WMS)®-III: Spatial Span), verbal learning (Hopkins Verbal Learning Test - Revised (HVLT-R)) and visual learning (Brief Visuospatial Memory Test Revised (BVMT-R)). We also performed the Wisconsin Card Sorting Test (WCST) and included categories completed and percent errors as outcome measures.

Magnetic Resonance Imaging

Brain MRI was performed at the MR Centre, Karolinska University Hospital, using a 3-T General Electric Discovery MR750 system (GE, Milwaukee, WI). T2-weighted images were acquired for evaluation regarding pathology by a neuroradiologist, and T1-weighted images were acquired for definition of regions of interest (ROIs).

Positron emission tomography procedures

PET measurements were performed at the PET Centre at

Karolinska University Hospital, Stockholm, using a High Resolution Research Tomograph (HRRT, Siemens Molecular Imaging, Knoxville, TN, USA). Individualized plastic helmets were made for each subject and used together with a head fixation system to minimize movement artifacts. A 6-min transmission scan using a ^{137}Cs source was performed for attenuation correction. [^{11}C]PBR28 was prepared as described previously[25] and injected as a bolus over approximately 10 s into the cubital vein. Emission data was acquired in list mode for up to 91 min, except for one patient (85 min) and two control subjects (77 min). The inclusion of data from these subjects were supported by analyses of a previous dataset[22] where 63 minute 2TCM for GM showed high correlation to that of 91 minutes ($n=12$, $r=0.997$, $p=8\times10^{-13}$). PET images were reconstructed using ordered subset expectation maximization with modeling of the point-spread function, and subsequently corrected for head movement using a frame-by-frame realignment process as described previously[26,27].

An automated blood sampling system (ABSS, Allogg AB, Mariefred, Sweden) was used during the first 5 min of each PET measurement. Discrete arterial blood samples (2–4 mL) were drawn manually at 1, 3, 5, 7, 9, 10.5, 20, 30, 40, 50, 60, 70, 80 and 90 min, except for one patient, for which the samples were drawn at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10.5, 20, 30, 40, 50, 60, 70, 80 and 90 min, and two control subjects with sampling times of 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60 and 72 min. The radioactivity was measured immediately after sampling in a well counter cross-calibrated with the PET system. After centrifugation, 0.7–1.5 mL plasma was pipetted and the radioactivity was measured in the same well counter. The Area Under the Curve (AUC) of the standardized uptake value (SUV)

for the metabolite-corrected plasma curves were calculated for all subjects from 0 to 72 minutes.

The plasma radioactivity curve for the first 5 minutes was generated by combining the ABSS data with an interpolated curve from the manual samples, and then multiplied with the blood-to-plasma ratio obtained from the plasma samples to create an arterial plasma curve. The time curve for parent fraction of the radioligand was determined using HPLC, fitted using a three-exponential model and multiplied with the plasma curve to generate the arterial input function. To assess the impact of protein binding, the free fraction of radioligand was analyzed using an ultrafiltration method. For additional details on these procedures see[25,28].

Quantification of [^{11}C]PBR28 binding

MR images were realigned, segmented and coregistered to PET images using SPM5 in MATLAB R2007b (Wellcome Trust Centre for Neuroimaging, London, UK; The Mathworks, Natick, MA)[25]. Region of interests (ROIs) were defined using an automated procedure based on the FreeSurfer software (version 5.0.0, http://surfer.nmr.mgh.harvard.edu/), previously validated for PET data analysis[29]. Gray matter (GM) was selected as the primary ROI. In addition, we examined white matter (WM), frontal cortex (FC), temporal cortex (TC) and hippocampus on account of their central interest for research in schizophrenia as well as to enable comparison to previous TSPO PET studies[12,14]. Furthermore, a FreeSurfer whole brain (WB) ROI was created for calculation of Distribution Volume Ratios (DVRs), as described previously[14]. Volumetric data for all ROIs used in the PET

analysis were extracted from FreeSurfer, as well as for the total intracranial volume (ICV).

The main outcome measure of TSPO binding was calculated using the two-tissue compartment model (2TCM) with a metabolite-corrected arterial plasma curve as input function. Binding was expressed as the total volume of distribution (V_T), which corresponds to the ratio between the sum of specific and non-displaceable concentrations of radioligand in the target region to the concentration in plasma at equilibrium. As a secondary analysis to allow for comparison with Bloomfield et al[14], data were analyzed using the 2TCM-1K model which includes an additional irreversible compartment hypothesized to account for endothelial binding in blood vessels[30]. All kinetic analyses were performed using MATLAB R2007b. Finally, DVRs were calculated as the ratio between GM V_T and WB V_T for both 2TCM and 2TCM-1K, to enable additional comparisons with previously published data[14,17].

Statistics

Normality of all demographic data, clinical and cognitive variables, radiochemical data and uptake outcome measures were evaluated using Kolmogorov-Smirnov tests as well as ocular inspection of histograms. Independent-sample two-tailed t-tests were performed to examine potential group differences in demographic data, measurements of cognitive function, radiochemical data, ROI volumes, free fraction of radioligand in plasma as well as differences in plasma SUV AUC values. For variables that were not normally

distributed, a Mann-Whitney U test was performed to examine group differences. Group differences in categorical variables were assessed using a Chi-square test.

Effects of genotype, age and sex on GM V_T were examined using Pearson's correlation and independent sample t-tests (two-tailed). Multivariate ANCOVA with all ROIs as dependent variables was deemed invalid because of high multicollinearity between the outcome measures. For the main statistical analysis, the difference between patients and controls in [^{11}C]PBR28 binding in GM was therefore examined using a univariate ANCOVA: GM V_T derived from the standard 2TCM model was used as dependent variable, group (patients vs. control subjects) as independent variable and gender and genotype as covariates. An analysis was also performed excluding the 5 patients on benzodiazepine treatment. Furthermore, effect sizes for GM binding was estimated for MABs and HABs separately, using partial eta squared values obtained from ANCOVA analyses with gender as covariate.

Secondary, to examine group differences in binding in FC, TC, hippocampus and WM, we performed four additional univariate ANCOVAs, each having sex and genotype as covariates. To allow for comparison with previously published results, the same set of univariate ANCOVAs were performed using regional V_T-values derived from 2TCM-1K, as well as DVR-values based on both 2TCM and 2TCM-1K methods as dependent variables[14] . For the main analysis of GM V_T differences, alpha was set to 0.05.

The relationships between GM V_T and symptom levels (PANSS), global functioning (CGI) and duration of illness were assessed using partial correlation controlling for genotype and gender. For correlations between GM V_T and cognitive measures, age was added as a covariate and the threshold for significance was Bonferroni-corrected for multiple comparisons (alpha=0.05/8=0.00625). All statistical analyses were performed in SPSS 23 (IBM, Armonk, N.Y.) or R (version 3.2.4 "Very Secure Dishes").

Results

Patient and control groups did not differ significantly in age, sex distribution, BMI or genotype distribution (Table 1). Duration of illness was 7.9 (9.6) months and total PANSS score 77.4 (18.3). None of the patients had been exposed to antipsychotic medication at time of investigation. Nine patients received anxiolytics or sedatives, of which five patients received benzodiazepines; (diazepam (5 mg/day) in one case and oxazepam (10-30 mg/d) in four cases) (suppl Table 1). One patient was prescribed paroxetin 20 mg/d. Two of the patients and none of the controls were cigarette smokers. Regional brain volumes did not differ significantly between patients and controls (Table 2) also after normalizing with ICV (ST2), therefore correction for partial volume effects was not performed for analyses of [^{11}C]PBR28 binding.

Group effects on regional [^{11}C]PBR28 binding

There was a significant effect of both genotype and sex on GM V_T (t=3.5, df=30, p=0.001 and t=2.1, df=30, p=0.043 respectively) whereas no correlation was

observed between age and GM V_T (r=-0.09, p =0.62). Hence, only sex and genotype was included as covariates in the ANCOVA. A decrease in [^{11}C]PBR28 GM V_T was observed in patients as compared to controls, with a significant effect of group obtained in the ANCOVA analysis (F=6.19, df=1,28, p=0.019). The decrease was more prominent in HAB patients, with an effect size of 0.38 (partial eta square) compared to 0.02 for the MAB subgroup (Figure 1). The effect remained when excluding the 5 patients on benzodiazepine treatment (F=6.71, df=1,23, p=0.016). In the regional analysis, significant group effects were observed for FC (F=6.08, df=1,28, p=0.020), TC (F=6.51, df=1,28, p=0.016) and hippocampus (F=5.49 , df=1,28, p=0.026), but not for WM (F=1.54, df=1,28, p=0.23) (ST3). There was also a significant effect of group for GM V_T derived using 2TCM-1k (F=6.66, df=1,28, p=0.015), whereas no difference was found when analyzing DVR values calculated either using 2TCM or 2TCM-1K V_T (ST3). No statistically significant difference between patients and control subjects was observed for plasma AUC (mean = 6.84 x 10^4 (SD = 2.7 x 10^4) vs. 6.35 x 10^4 (2.2 x 10^4); t=-0.56, df=30, p = 0.58) or free fraction (8.2 (3.1) vs. 9.0 (2.8); t=-0.74, df=30, p = 0.46).

Correlations between [^{11}C]PBR28 binding and behavioral measures

In patients, there was no significant association between GM V_T and either positive, negative, general or total PANSS scores, CGI or duration of psychosis. The patients performed more poorly than controls in all the cognitive outcome measures (Table 1). However, there were no significant correlations between GM V_T and cognitive performance in patients after correction for multiple comparisons (Table 3).

Discussion

The results of the present study are novel in two important respects. First, this is to our knowledge the only study thus far to investigate TSPO binding in drug-naïve patients with psychosis. The finding of reduced TSPO levels suggests that the lack of increases, or even trend-level decreases in V_T reported in recent studies employing novel TSPO radioligands[14,15,17] is not explained by the effects of antipsychotic medication. Second, patients had a mean duration of illness of less than eight months which is significantly shorter than in previous studies, including the average of 2.2 years reported in a recently published report in recent-onset schizophrenia[17]. Hence, the results imply that there is no TSPO elevation also in very early stages of disease. Instead, first episode psychosis patients may even be characterized by having decreased glial cell activation.

TSPO is present in myeloid and astrocytic cells throughout the whole brain, also at physiological conditions[31,32]. Therefore, quantification of radioligand binding to TSPO requires a metabolite corrected plasma input function as reference. To reduce the variability induced by plasma measurements, relative outcome measures of binding such as SUV ratio (SUVR) or DVR have been suggested instead of the widely used V_T values[33]. In the study by Bloomfield et al, a non-significant reduction of around 10% in regional V_T was found in patients and ultra-high-risk individuals, whereas V_T values normalized to whole brain binding showed an apparent increase in both groups[14]. However, the normalization approach has been criticized[34] . Importantly, the WB values used for the

normalization procedure were around 20% lower both for the UHR and patient groups as compared to controls, a difference which in patients appeared to be driven by significant decreases in white matter. Moreover, DVR values were obtained using WB as a covariate in the statistical analysis rather than dividing the region of interest by WB. Since a high degree of correlation is expected between WB and GM regions, this method may reduce variability significantly, resulting in increased effect sizes. In the present study, the observed reduction of GM TSPO in patients did not remain when using whole brain–normalized V_T (DVR, ratio method) as outcome measure. The effect of using DVR instead of V_T was thus in the same direction as for Bloomfield et al. The lack of significant increases in our case may be explained by the statistical DVR procedure as well as the use of different WB templates, which could influence WB V_T values. Finally, we observed no group difference in the metabolite-corrected input function or free plasma fraction of radioligand in our data, providing support for the validity of our primary outcome measures[35].

Evidence for a heightened immune response in schizophrenia patients comes primarily from biomolecular studies, showing increases in pro-inflammatory markers both in long-term illness and in early psychosis[4–7]. With regard to the role of brain immune cells, some post-mortem studies have shown increased levels of microglia in patients, however no differences or even decreases have also been reported[36]. For instance, two autoradiography studies assessing TSPO have yielded contrasting results, reporting reductions in [^{3}H]PK11195 and increases in [^{3}H]PBR28 binding respectively[37,38]. Whereas initial *in vivo* PET studies using [^{11}C]PK11195 in small samples have shown increased TSPO

binding in antipsychotic drug treated schizophrenia patients, this finding has not been replicated using more recently developed TSPO radioligands with higher sensitivity. Importantly, preclinical studies combining PET with post-mortem immunohistochemistry have shown a close correspondence between TSPO levels and glial cell markers[8,9]. Consequently, although the high variability observed in human TSPO PET studies may limit the sensitivity[15,25,37], a plausible interpretation of both *in vitro* and *in vivo* TSPO studies across different disease stages is that glial up-regulation is not a robust feature of schizophrenia.

Our findings of reduced TSPO levels in drug-naive patients with psychosis is congruent with the numerically lower V_T values reported in antipsychotic drug treated patients with long-term schizophrenia[14,15], as well as the trend-level reductions shown in recent-onset patients[17]. It may be hypothesized that reduced glial activation in early stage psychosis reflects a failure of the immune system to adapt to other pathological processes associated with being in a psychotic state, thus promoting the development of the disorder. Importantly, both microglia and astrocytes also have neuroprotective and pro-inflammatory roles in the brain[39], and the immune hypothesis in schizophrenia may thus be thought of as an imbalance rather than a one-dimensional activation. A limitation is that TSPO radioligands cannot differentiate between pro- and antiinflammatory cell phenotypes, and there is thus a need for immune cell markers with improved functional specificity. This view is corroborated by the lack of significant correlations between TSPO V_T values and symptom levels or cognitive functioning observed in our study as well as in previous reports[15,17].

In the present study the decrease in TSPO binding was more prominent in the group of HAB individuals. Although the lack of statistical power limits the conclusions that can be drawn when examining the genetic groups separately, this effect may partly be explained by the higher ratio of specific to non-displaceable binding in HABs compared to MABs[31,40]. This pattern needs confirmation in larger samples or as part of a meta-analysis.

An alternative hypothesis that allows for reconciliation of the lack of TSPO elevation at least with genetic and epidemiological data[2,3] is that pro-inflammatory microglial activation exerts its major influence preceding the onset of manifest disease. For instance, both human and animal research has suggested a link between immune activation and excessive synaptic pruning[41,42], which may correspond to the cortical thinning observed already in early stages of schizophrenia[43]. Consequently, although all patients in the present study were examined during their first psychotic episode, it may be speculated that this was still too late to detect a hypothesized increase in immune cell activation.

Conclusion

In this study we found a decrease in TSPO binding in antipsychotic-naïve first episode psychosis patients compared to control subjects, indicating lower number or altered function of immune cells in brain in early stage schizophrenia. Further studies combining molecular and structural brain imaging with detailed characterization of pro- and antiinflammatory immune markers over time are needed to clarify the role of the immune system during the different disease stages of the disorder.

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Conflict of Interest

LFA is an employee of AstraZeneca and affiliated with KI. SC has received grant support from AstraZeneca as co-investigator, and has served as a one-off speaker for Roche and Otsuka Pharmaceuticals. SE has received grant support from AstraZeneca as principal investigator, has served as a one-off speaker for Roche pharmaceuticals and participated in workshops organized by Otsuka Pharmaceuticals. All authors report no conflict of interest in relation to the work described.

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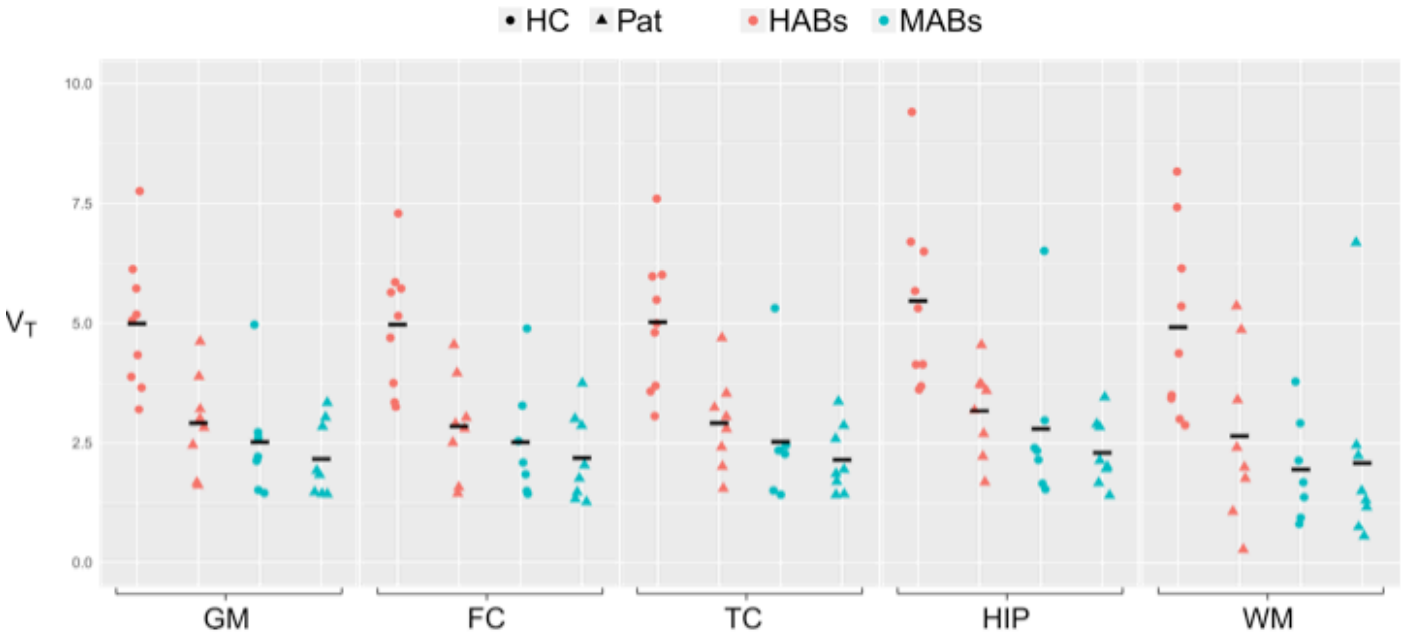

Figure 1. Regional V_T values in first episode psychosis patients (Pat) and healthy control subjects (HC) estimated using 2TCM. HAB = High Affinity Binder; MAB = Mixed Affinity Binder; GM = Grey Matter; FC = Frontal Cortex; TC = Temporal Cortex; HIP = Hippocampus; WM = White Matter.

Table 1. Demographic, radiochemical and clinical data for first episode psychosis patients and control subjects.

		Controls (N=16)	Patients (N=16)	chi-square	t-value[2]	df	Mann-whitney U value	p-value
Age		26.4 (8.4)	28.5 (8.4)				106.5	0.415
Gender	Male/Female	7/9	11/5	2.032		1		0.154
Genotype	HAB/MAB	9/7	8/8	0.125		1		0.723
Descriptive statistics	BMI	21.9 (1.9)	22.9 (4.8)		-0,722*	19.8		0.479
	Education years	14.9 (2.2)	13.6 (3.3)		1.278	25		0.213
Nicotine-user	Yes/No	0/16	2/14	NA[3]				
PET measures	Injected mass tracer (µg)	0.68 (0.57)	0.66 (0.32)		0.166	30		0.870
	Specific radioactivity (GBq/µmol)	313.8 (213.4)	276.4 (170.8)				120.5	0.777
	Injected radioactivity (MBq)	403.9 (52.5)	402.1 (69.5)		0.083	30		0.934
Duration of illness (months)[1]			7.9 (9.6)					
PANSS[1]	Positive		20.3 (4.9)					
	Negative		18.1 (7.0)					
	General		39.1 (10.8)					
	Total		77.4 (18.3)					
Level of functioning[1]	CGI		4.6 (1.2)					
		(N=16)	**(N=15)**					
Cognitive measurements								
MATRICS	TMT	22.6 (4.6)	35.5 (14.4)				36	$8.65*10^{-4}$
	HVLT-R	28.4 (2.3)	21.2 (5.8)				26	$1.65*10^{-4}$
	WMS-III-SS	19.0 (2.2)	14.8 (3.4)				32.5	$4.90*10^{-4}$
	BVMT-R	29.0 (5.4)	19.1 (6.6)		4.581	29		$8.10*10^{-5}$
	Fluency	25.6 (6.7)	18.8 (4.2)		3.368	29		0.002
			(N=14)					
	CPT-IP	2.9 (0.4)	2.0 (0.4)		5.316	28		$1.20*10^{-5}$
		(N=15)	**(N=13)**					
WCST	PctErrors	14.6 (7.5)	33.3 (18.2)				27.5	0.00123
	CatCompl	5.9 (0.3)	4.5 (2.1)				64	0.0315

Averages and standard deviations are reported as Mean (SD). PANSS=Positive and Negative Symptom Scale in Schizophrenia; CGI=Clinical Global Impression (1-6); WCST=Wisconsin Card Sorting Test; TMT=Trail Making Test: Part A; HVLT-R=Hopkins Verbal Learning Test - Revised; WMS-III-SS=Wechsler Memory Scale III: Spatial Span; BVMT-R=Brief Visuospatial Memory Test Revised; CPT-IP=Contiunous Performance Test-Identical Pairs; WCST=Wisconsin Card Sortin Test; PctErrors=Percent errors; CatCompl=Categories completed. *Equality of variance not assumed, Welch's Independent sample t-test was performed. 1. Ratings only exist for patient group 2. In the case of equality of variance Welch's t-test was performed. 3. Expected cell counts too low to perform a chi-square test.

Table 2. Comparison of measured ROI volumes between first episode patients with psychosis and healthy control subjects.

	Controls (N=16)		**Patients (N=16)**			
Region	*Mean*	*SD*	*Mean*	*SD*	*t-value*	*p-value*
Whole Brain	1230.7	130.8	1256.0	126.2	-0.6	0.582
Grey Matter	738.7	61.7	739.1	71.8	-0.015	0.988
Frontal Cortex	153.7	12.3	156.1	18.5	-0.431	0.670
Temporal Cortex	110.5	7.5	111.8	13.1	-0.357	0.723
Hippocampus	8.8	0.8	8.7	0.7	0.255	0.801

SD=Standard deviation. All volumes expressed in cm^3. *p*-value as determined using an independent sample t-test.

Table 3. Partial correlations between GM V_T and clinical and cognitive variables in patients with first episode psychosis.

		r	df	p-value
Duration of Illness (months)[1]		0.035	12	0.91
PANSS[1]	Positive	0.45	12	0.11
	Negative	0.10	12	0.73
	General	0.29	12	0.31
	Total	0.35	12	0.22
Level of functioning[1]	CGI	0.41	12	0.14
Cognitive measures [2,3]				
MATRICS (N=15)	TMT	-0.41	10	0.19
	HVLT_R	0.70	10	0.012
	WMS_III_SS	-0.082	10	0.80
	BVMT_R	0.21	10	0.52
	Fluency	0.016	10	0.96
(N=14)	CPT_IP	-0.15	9	0.66
WCST (N=13)	PctErrors	-0.049	8	0.89
	CatCompl	0.016	8	0.97

r=partial correlation coefficient. 1. Controlling for TSPO genotype and gender. 2. Controlling for TSPO genotype, gender and age. 3. Bonferroni corrected alpha-value=0.00625.