Positron Emission Tomography Studies of the Glial Cell Marker TSPO in Psychosis Patients: A Meta-Analysis Using Individual Participant Data

Supplementary Information

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Recruitment of Healthy Controls, Quality Control of Data and Assignment of Subjects Overlapping in the Original Studies

Healthy control subjects were recruited by flyers (1, 2, 3), advertising in newspapers (4), word of mouth (2) and advertising on internet (1, 5). Exclusion criteria for all healthy controls included history of psychiatric disease or other clinically significant medical illness. Fourteen HC subjects from Kenk et al. (1) also served as controls in Hafizi et al. (3). Since different image analysis procedures were used in the two studies, it was not possible to employ a multiple membership model to account for this overlap. Instead, we assigned these 14 subjects to either the Kenk et al. (1) or the Hafizi et al. (3) data set, to make sure that data from the same subject was not used twice in the model. The assignment was performed prior to the inferential analyses, with the purpose of finding the best possible match between the diagnostic groups within both studies. In addition, one HC subject in Kenk et al. (1) had an outlier HIP V_T value (75.55), and a mismatch in the MAB patient group count was found in the Bloomfield et al. (4) data. These inconsistencies were resolved after consultation with the original authors. The final data set from Bloomfield et al. (4) contained two MAB patients, but no MAB HC. These two subjects were excluded from the inferential analyses as standardization (z-scoring) was not meaningful.

Supplementary Table S1. PET TSPO studies in schizophrenia or psychosis not included in the analysis

Study	Did not fulfill selection criteria		
	I	**II**	**III**
van Berckel et al., 2008 (6)	X	X	N/A
Doorduin et al., 2009 (7)	X	X	N/A
Takano et al., 2010 (8)		X	X
van der Doef et al., 2016 (9)	X	X	N/A
Holmes et al., 2016 (10)	X	X	N/A
Di Biase et al., 2017 (11)	X	X	N/A

N/A = not applicable

The selection criteria and their rationale were the following:

I. The use of a second-generation TSPO radioligand

Second generation radioligands show much higher specific binding compared to [^{11}C]PK11195, as has been shown in recent blocking studies (12–14). Low specific binding means lower accuracy and reliability, and therefore loss of sensitivity. Including studies with significantly lower sensitivity would violate one of the basic assumptions of the meta-analysis model, which is that all effects sizes should be drawn from the same underlying distribution.

II. Reporting distribution volume (V_T) values obtained using an arterial input function

Since there is no brain region devoid of TSPO expression, metabolite-corrected arterial plasma measurements of radioligand concentration are necessary for accurate in vivo quantification of binding. When analyzing data obtained using this method, V_T is considered the gold standard outcome measure. Alternative approaches used show either low reliability and precision (such as the use of microparameters for estimating binding potential (15, 16), or ratio approaches (17)). As for criterion I, synthesizing outcomes with very different reliability is in conflict with assumptions underlying the meta-analysis model.

III. Reporting TSPO affinity type of all participants

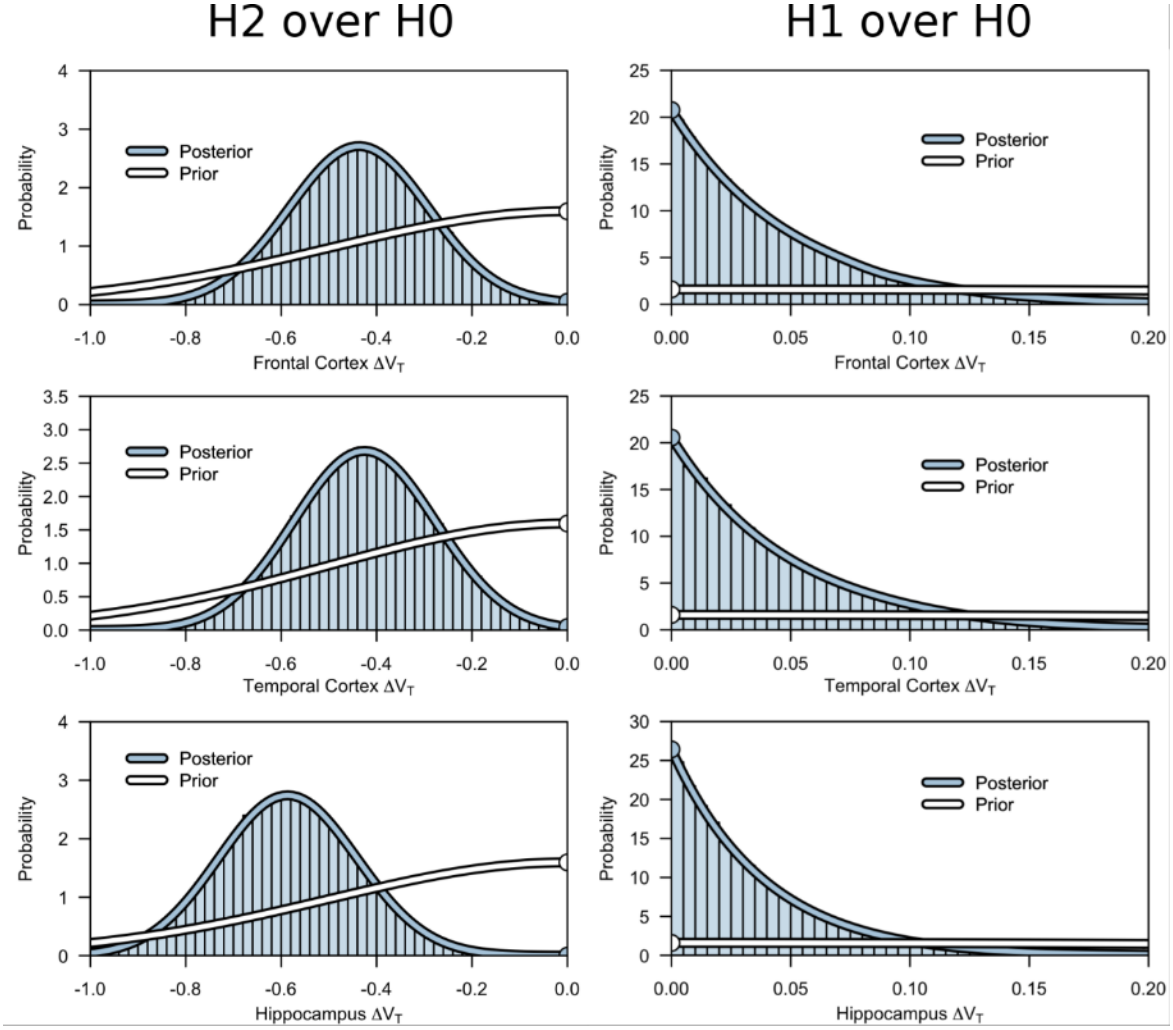
All second generation TSPO radioligands have shown to be sensitive for TSPO genotype (18–20), a factor which therefore has to be taken into account in the analysis.

Supplementary Table S2. Hypothesis testing - p-values

Frequentist version of model M1 showing maximum likelihood estimates of psychosis patient and healthy control differences in standardized (z-scored) V_T (an estimate of TSPO levels) values.

Region	Estimate	SE	df*	*t*-value	*p*
FC	-0.48	0.15	150.00	-3.12	0.00218
TC	-0.47	0.15	150.00	-3.03	0.00291
HIP	-0.64	0.15	149.00	-4.26	0.00004

FC = frontal cortex; TC = temporal cortex; HIP = hippocampus; SE = standard error; df = degrees of freedom
*df calculated using Satterthwaite approximation



Supplementary Figure S1. Hypothesis testing - posteriors

Prior and posterior distributions of Bayes factor hypothesis tests of psychosis patient-control differences in standardized (z-transformed) V_T values (an estimate of TSPO levels). The Savage-Dickey-Ratio was used to compute the Bayes factors. For all tests, the prior distribution was a truncated Gaussian centered at 0 with a SD of 0.5. The SD was chosen since this corresponds to an expected difference of a medium effect size between patients and controls. In the left panel, the hypothesis of a decreased V_T in patients as compared to healthy controls (H2), over the hypothesis of no change (H0) is shown. In the right panel, the hypothesis of an increased V_T in patients as compared to healthy controls (H1), over the hypothesis of no change (H0) is shown.

Supplementary Table S3. Hypothesis testing - Bayes factors robustness check.

In order to examine how much the Bayes factors were affected by different priors, we varied the widths of the half-Gaussian distribution on patient-control difference in standardized brain V_T (an estimate of TSPO levels) values, using the best fitting model (M1). SDs of 0.2 and 0.8 were chosen as these correspond to approximately small and large expected effect sizes respectively.

Region	Large (SD=0.8)		Small (SD=0.2)			
	H0:H2	**H2:H0**	**H0:H2**	**H2:H0**	**H0:H1**	**H1:H0**
FC	0.035	28.736	0.050	19.993	5.064	0.197
TC	0.042	23.762	0.062	16.008	5.305	0.189
HIP	0.001	831.085	0.005	210.730	6.804	0.147

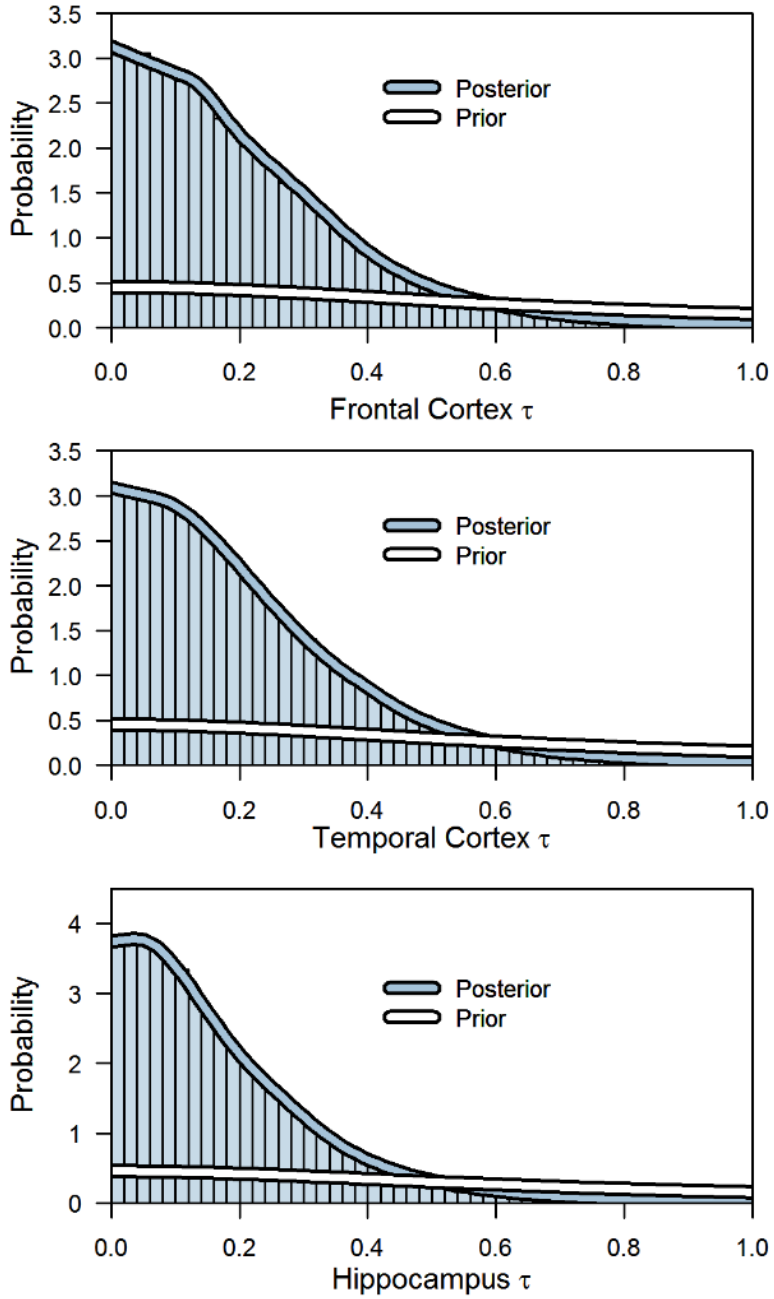
H0:H1: Bayes factor denoting evidence in favor of H0 over H1; H1:H0: evidence in favor of H1 over H0; H0:H2: evidence in favor of H0 over H2; H2:H0: evidence in favor of H2 over H0

Supplementary Table S4. Hypothesis testing - Bayes factors with gender as covariate

Bayes factors of hypothesis testing for the difference in standardized brain V_T (an estimate of TSPO levels) between patients and controls, using the best fitting model (M1), while covarying for gender.

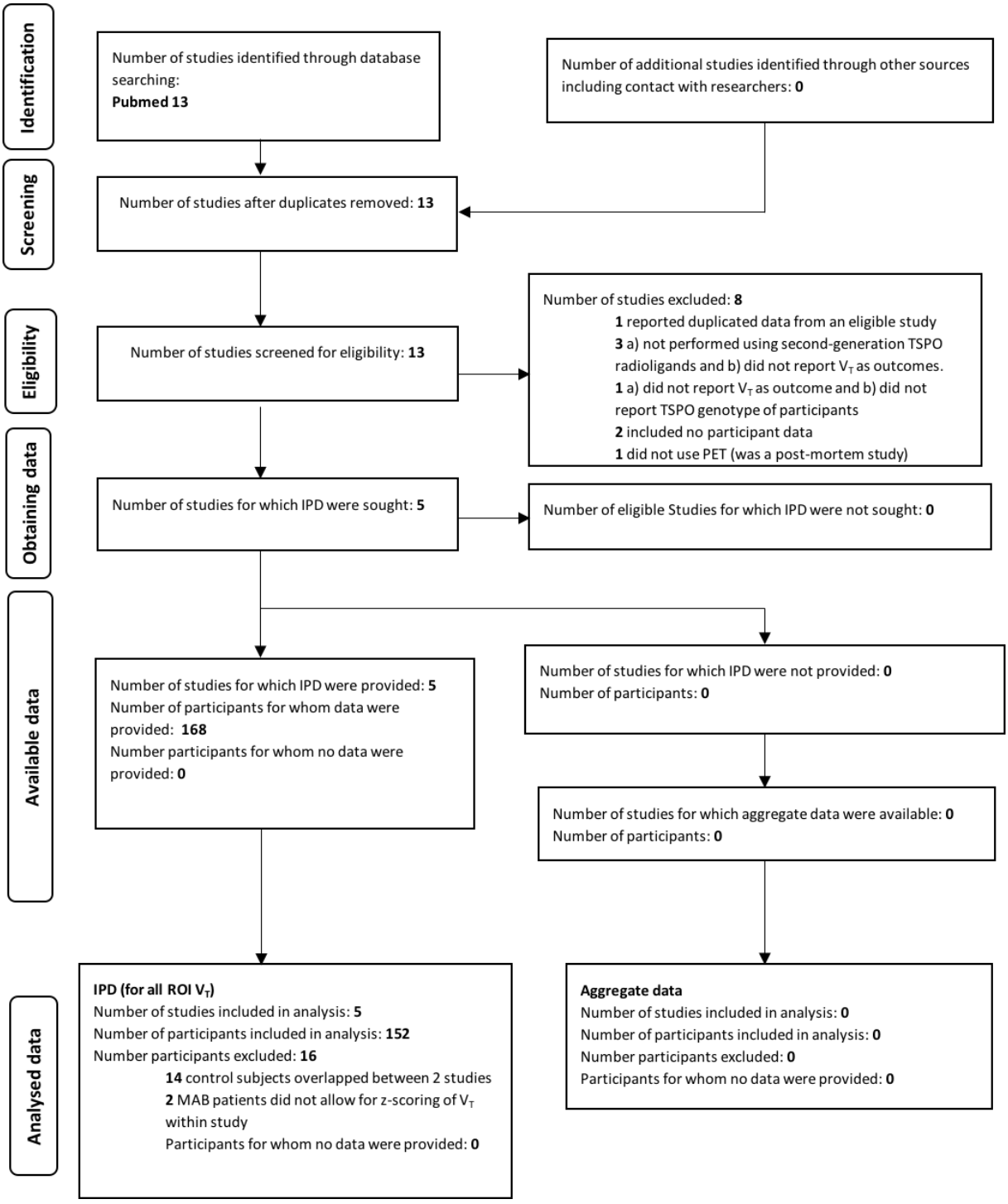
Region	H0:H1	H1:H0	H0:H2	H2:H0	H1:H2	H2:H1
FC	12.338	0.081	0.053	18.859	0.004	232.670
TC	4.960	0.202	0.062	16.105	0.013	79.883
HIP	10.557	0.095	0.001	675.455	<0.001	7130.563

H0:H1: Bayes factor denoting evidence in favor of H0 over H1; H1:H0: evidence in favor of H1 over H0;
H0:H2: evidence in favor of H0 over H2; H2:H0: evidence in favor of H2 over H0;
H1:H2: evidence in favor of H1 over H2; H2:H1: evidence in favor of H2 over H1

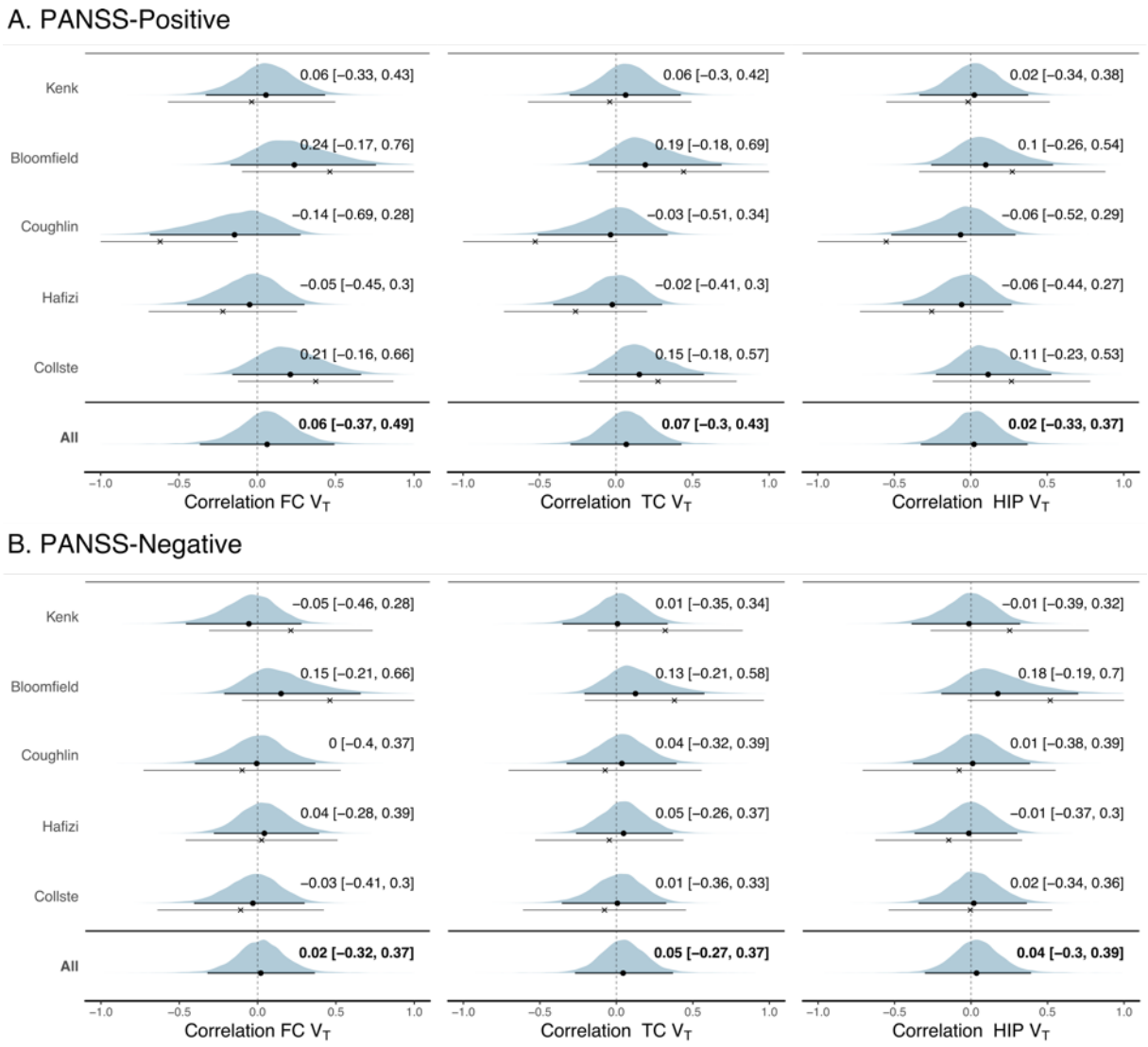


Supplementary Figure S2. Study heterogeneity - Posteriors over tau

Prior and posterior distribution of the standard deviation (τ) of study slopes from model M3, for each ROI. The study-slopes are the study-specific differences in standardized brain V_T (an estimate of TSPO levels) values between patient and controls. As such, τ is an estimate of the study-heterogeneity. The prior distribution of τ was a half-Cauchy, centered at zero with a scale of 0.707. The posterior distributions of τ for all regions used in this meta-analysis suggest low study heterogeneity.



Supplementary Figure S3. PRISMA IPD Flowchart



Supplementary Figure S4. Forest plot of LME relationship between regional V_T values and PANSS-Positive (A) and PANSS-Negative (B).

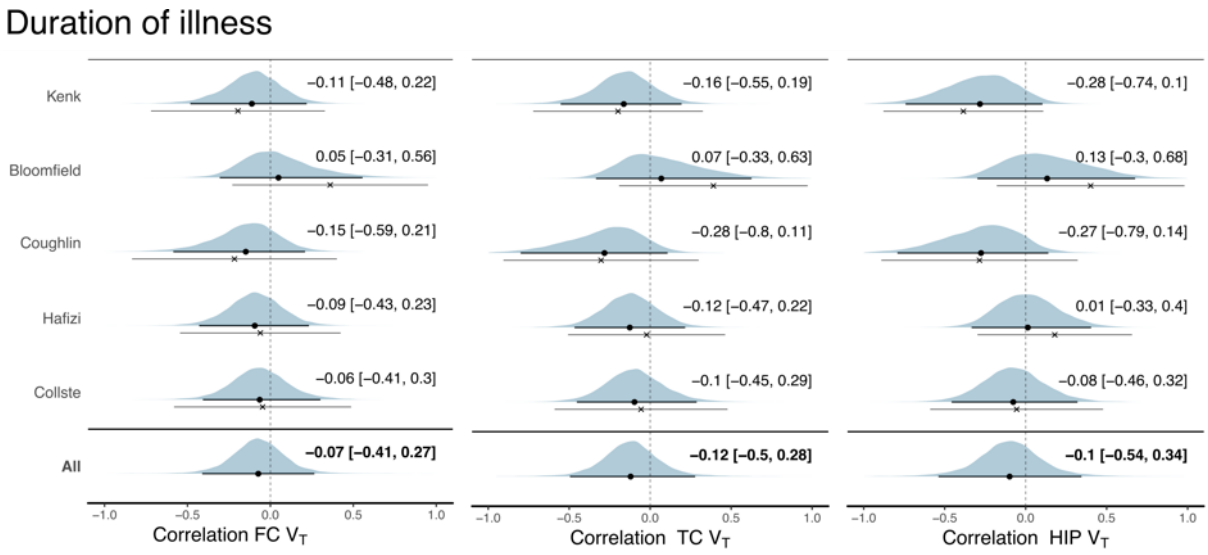
Forest-plot of posteriors of correlations between regional V_T (an estimate of TSPO levels) and Positive And Negative Syndrome Scale (PANSS) Positive and Negative scores. A random effect model, allowing for study specific correlations to vary have been used (akin the design of model M3 for the main article). A weakly regularizing prior, ranging from -1 to 1, was specified for the beta coefficient. The black circle denotes the posterior mean, and the thick line the 95% credible interval, which are also presented in text next to the plots. The cross denotes the V_T-PANSS correlation using raw data (together with its 95% CI), without performing linear mixed effects modelling. Hence, the difference between the dot and the cross displays the model shrinkage towards the mean. SAPS and SANS scores from the study by Coughlin et al. have been converted to PANSS scores using van Erp et al (21). The Figure show that there is little to no evidence for a correlation between regional V_T and PANSS scores.

Supplementary Table S5. Regional V_T values correlated with PANSS p-values

Maximum likelihood estimates from LME model of correlation between regional V_T and PANSS-Positive and PANSS-Negative scores in psychosis patients.

Scale	Region	Estimate	SE	*t-value*	*p*
PANSS-Positive	FC	0.06	0.15	0.42	0.70
	TC	0.07	0.12	0.56	0.61
	HIP	0.02	0.11	0.18	0.86
PANSS-Negative	FC	0.02	0.11	0.15	0.88
	TC	0.04	0.11	0.37	0.71
	HIP	0.03	0.11	0.24	0.81

FC = frontal cortex; TC = temporal cortex; HIP = hippocampus; SE = standard error



Supplementary Figure S5. Forest plot of LME relationship between regional V_T values and duration of illness.

Forest-plot of posteriors of correlations between regional V_T (an estimate of TSPO levels) and duration of illness (DOI). A random effect model, allowing for study specific correlations to vary have been used (akin the design of model M3 for the main article). A weakly regularizing prior, ranging from -1 to 1, was specified for the beta coefficient. The black circle denotes the posterior mean, and the thick line the 95% credible interval, which are also presented in text next to the plots. The cross denotes the V_T-DOI correlation using raw data (together with its 95% CI), without performing linear mixed effects modelling. Hence, the difference between the dot and the cross displays the model shrinkage towards the mean. The figure show that there is little to no evidence for a correlation between regional V_T and DOI.

Supplementary Table S6. Regional V_T and duration of illness p-values

Maximum likelihood estimates from LME model of correlation between regional V_T and duration of illness scores in psychosis patients.

Region	Estimate	SE	*t-value*	*p*
FC	-0.08	0.11	-0.69	0.49
TC	-0.12	0.11	-1.08	0.28
HIP	-0.10	0.14	-0.69	0.52

FC = frontal cortex; TC = temporal cortex; HIP = hippocampus; SE = standard error

Supplemental References

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