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PII: S0006-3223(18)31298-8
DOI: 10.1016/j.biopsych.2018.02.1171
Reference: BPS 13491

To appear in: Biological Psychiatry

Received Date: 8 December 2017
Revised Date: 13 February 2018
Accepted Date: 20 February 2018


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PET studies of the glial cell marker TSPO in psychosis patients - a meta-analysis using individual participant data

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Short title: Meta-analysis of TSPO in psychosis patients

Keywords: Positron Emission Tomography; psychosis; schizophrenia; translocator protein; microglia; immuneactivation; meta-analysis
Abstract

**Background:** Accumulating evidence suggests that the immune system may be an important target for new treatment approaches in schizophrenia. Positron emission tomography (PET) and radioligands binding to the translocator protein (TSPO), which is expressed in glial cells in brain including immune cells, represents a potential method for patient stratification and treatment monitoring. This study examined if patients with first episode psychosis and schizophrenia had altered TSPO levels compared to healthy control subjects. **Methods:** PubMed was searched for studies comparing patients with psychosis to healthy controls using second-generation TSPO radioligands. The outcome measure was distribution volume ($V_T$), an index of TSPO levels, in frontal cortex (FC), temporal cortex (TC) and hippocampus (HIP). Bayes factors (BF) were applied to examine the relative support for higher, lower or no difference in patients' TSPO levels compared to healthy controls. **Results:** Five studies, with 75 participants with first-episode psychosis or schizophrenia and 77 healthy controls were included. BF showed strong support for lower $V_T$ in patients relative to no difference (all BF>32), or relative to higher $V_T$ (all BF>422), in all brain regions. From the posterior distributions, mean patient-control differences in standardized $V_T$ values were -0.48 for FC (95% credible interval (CredInt)=-0.88 to -0.09), -0.47 for TC (CredInt=-0.87 to -0.07) and -0.63 for HIP (CredInt=-1.00 to -0.25). **Conclusion:** The lower levels of TSPO observed in patients may correspond to altered function or lower density of brain immune cells. Future studies should focus on investigating the underlying biological mechanisms and their relevance for treatment.
Introduction

Genetic, epidemiological and biomolecular data suggest that the immune system is involved in the pathophysiology of schizophrenia (1–3). When translating these findings into clinical trials, initial studies have shown positive effect of medication targeting the immune system when used as add-on treatment to antipsychotics (4–6). To aid further development of this therapeutic approach, tools for directly assessing the status of the brain immune system are needed to allow for patient stratification and monitoring of treatment effects.

Using Positron Emission Tomography (PET), the localization and activation state of central nervous system (CNS) immune response modulators can be assessed with radioligands targeting the 18 kDa translocator protein (TSPO), which is expressed in glial cells (7–9). During the last decade, a handful of TSPO PET studies have been performed in patients with early-stage psychosis or manifest schizophrenia, showing inconclusive results. Early reports using the first-generation TSPO radioligand (R)-[11C]PK11195 showed higher binding in small patient groups (n=7 and n=10) (10, 11), albeit with outcome measures that show low accuracy and reliability (i.e. binding potential estimated from rate constants) (12–14). More recent studies in larger samples using the same radioligand, but without blood sampling for full quantification, did not replicate these findings (15–17). Concerns regarding the low signal to noise ratio of (R)-[11C]PK11195 sparked the development of a series of second-generation TSPO radioligands, showing much greater specific binding (18–21). These tools have subsequently been used to revisit the question of higher levels of TSPO in psychosis (22–26). When employing gold standard outcome measures of binding in
the absence of a reference region (distribution volume, $V_T$, obtained using kinetic modeling with metabolite-corrected arterial plasma as input function), higher TSPO expression have thus far not been found in patients. In some cases, trend-level (24) or significantly lower TSPO levels (23) were shown.

All previous TSPO PET studies in psychosis have been performed with relatively small sample sizes. In addition, TSPO radioligands display a substantial within- and between-subject variability (12, 27), even after accounting for the TSPO rs6971 polymorphism which is known to affect radioligand binding in vivo (28–30). This has important implications for sensitivity and the power to detect differences between psychotic patients and controls. Indeed, the power to detect an expected significant medium-sized difference between diagnostic groups (at alpha=0.05) has ranged from 23% to 34% in previous designs (22–26). Medication status has also differed both between and within these studies. Since antipsychotics have been shown to dampen the immune response, this further limits the conclusions that can be drawn (31). Here, we sought to overcome these limitations and clarify the use of TSPO PET as a biomarker of immune dysfunction in schizophrenia. We conducted an individual participant data (IPD) meta-analysis of all TSPO PET studies performed in psychosis or schizophrenia using second-generation radioligands, where $V_T$ was included as the outcome measure. The primary objective was to evaluate the hypotheses of 1) higher, 2) lower or 3) no difference in $V_T$, between patients and healthy control subjects. A secondary objective was to assess the effects of antipsychotic medication on TSPO levels.
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Materials and Methods

PRISMA, pre-registration and code availability

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD) (32) and according to a study specific pre-registration protocol. The pre-registration protocol and all code used in this study can be found on the public repository https://github.com/pontusps/TSPO_psychosis.

Selection Criteria and Search Strategy

We set out to obtain individual participant data from all PET studies that 1) used a second-generation TSPO radioligand, 2) reported distribution volume ($V_T$) values in the CNS in subjects with psychosis or schizophrenia as compared to healthy controls (HC), and 3) reported TSPO affinity type of all participants. To our knowledge there are currently five published studies reporting such data, using the radioligands $[^{11}\text{C}]$PBR28, $[^{18}\text{F}]$FEPPA and $[^{11}\text{C}]$DPA713 (22–26). In order to ascertain that no relevant studies were omitted from this meta-analysis, we performed a systematic literature search on PubMed. Only articles published after 2004 were included in the search, corresponding to the year when the first report on a second-generation TSPO radioligand was published (33). Search terms included, among others: “psychotic disorder”, “schizophrenia”, “positron emission tomography”, “translocator protein 18 kDa” and “peripheral benzodiazepine receptor” (for full list of search terms see Supplementary Information). All TSPO PET studies in psychosis
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or schizophrenia which were not included are listed in supplementary Table S1, along with a detailed explanation of the selection criteria. Corresponding authors of eligible studies were contacted via email and all agreed to contribute.

**Requested data**

Requested IPD included $V_T$ values from the Frontal Cortex (FC), Temporal Cortex (TC) and Hippocampus (HIP) regions of interest (ROIs), patient-control status, TSPO genotype, age, sex and medication status, Positive And Negative-Syndrome Scale in Schizophrenia (PANSS) scores (or equivalent) and duration of illness. These three ROIs were selected since four out of five included studies had reported $V_T$ from all of them. For the remaining study (Bloomfield et al., 22), unpublished IPD $V_T$ values obtained using the conventional 2TCM from all three ROIs were provided upon request, allowing for consistent pooling. In order to account for range differences between different radioligands used across studies, we z-scored all ROI $V_T$ values within each genotype group of each study.

**Quality control**

The first author (PPS) examined the integrity of the obtained IPD datasets. The data was checked for outliers and inconsistencies to the published data (such as number of participants, means, ranges, and SDs of $V_T$ and age), which were then resolved following discussion with the authors of the relevant study.
Meta-analysis and statistics

The studies included in this meta-analysis recruited participants of two different TSPO affinity types (high-affinity binders, HABs; and mixed-affinity binders, MABs), used different radioligands, and applied different image analysis procedures. In order to estimate the difference in $V_T$ between diagnostic groups ($\Delta V_T$) while taking this hierarchical structure into account, we constructed and compared four different Bayesian linear mixed effect (BLME) models of increasing complexity: M1) standardized ROI $V_T$ was specified as dependent variable, diagnostic group as fixed effect, genotype and study as random effects with varying intercepts; M2) The same as M1 but with varying slopes of the random effect of genotype (i.e. allowing for differences in $\Delta V_T$ between HABs and MABs); M3) The same as M1 but with varying slopes of the random effect of study (i.e. allowing for differences in $\Delta V_T$ between studies); M4) The same as M1 but with varying slopes for both random effects (i.e. allowing for differences in $\Delta V_T$ between genotypes and studies). The model with the best fit to data, as determined by Widely Applicable Information Criterion (WAIC) and Leave-One-Out Cross-validation (LOOC) scores, was selected (34).

Following model selection, we first examined the hypothesis that patients with psychosis or schizophrenia have higher levels of TSPO in the brain (H1). For each ROI we quantified the relative evidence of higher TSPO expression in patients compared to the null-hypothesis of no difference (H0). This was done using order-restricted Bayes Factor (BF) hypothesis testing (35–37) on $\Delta V_T$. BF quantifies the relative evidence, or support, for one hypothesis over another as a ratio of their average likelihoods. A BF $> 10$ is usually considered as
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strong evidence in favor of a hypothesis (and, consequently, BF < 0.1 translates into strong
evidence of the opposite hypothesis) (35). We calculated BF_{H1:H0} to quantify the evidence in
favor of higher ROI $V_T$ in patients compared to controls, relative to no difference. Secondly,
we examined whether patients had lower levels of $V_T$ in the ROI (H2). Again, this was done
by employing an order-restricted BF test of lower $V_T$ in patients (BF_{H2:H0}) over no
difference. Finally, we calculated the support for H2 over H1 (BF_{H2:H1}), signaling the relative
likelihood of lower levels of TSPO in patients compared to higher levels.

For each ROI, H1 and H2 were specified as half-Gaussian (normal) distributions centered on
zero with a standard deviation of 0.5. Hence, in order to perform order-restricted
hypothesis testing of patient-control differences, the priors over ROI $\Delta V_T$ were specified as
half-Gaussians (SD=0.5) with a lower bound of zero for H1, and an upper bound of zero for
H2. The Savage-Dickey Ratio method was then used to calculate BFs. The standard
deviation was set a-priori to 0.5 as this assigns high plausibility to $\Delta V_T$ values ranging from
0 to a medium-sized difference (38, 39). A medium-sized difference, corresponding with a
Cohen’s D of 0.5, was considered a reasonable prediction, based on the precision of the
outcome measure (27). A medium effect size (Cohen’s D = 0.5) group difference in $V_T$ means
that 69% of the patient population would be expected to have a higher (or lower) $V_T$ than
the mean of the population of healthy controls (Cohen’s $U_3$ (38)).

A robustness check of the effect of different prior widths on BF was performed by varying
the SDs of the half-Gaussian distributions (SD = 0.2 and 0.8 – corresponding to an expected
small and large effect size of $\Delta V_T$, and Cohen’s $U_3 = 58\%$ and $79\%$, respectively) when
testing all hypotheses. For the prior on the SDs of the random effects, half-Cauchy
distributions (with a scale of 0.707) were used. These weakly informative priors were
chosen as the numbers of genotype groups (n=2) and studies (n=5) are small (40).

We also estimated the overall effect size of standardized $V_T$ difference between patients and
HC. This was done using model M3 with a non-truncated, weakly regularizing prior
(Gaussian with a SD of 10) over the fixed effect. M3 was selected since it also allowed us to
extract the study specific effects of ROI $\Delta V_T$ (random slopes), and the corresponding SD of
these effects ($\tau$). Using these we produced a “forest plot” of ROI $\Delta V_T$ and examined $\tau$ as a
measure of study-heterogeneity, in line with the PRISMA-IPD guidelines.

For the secondary aim of analyzing medication effects on $V_T$, we added an additional
predictor, denoting medication status, to the best fitting BLME model. This predictor
quantifies the additional effect of being medicated, after controlling for patient-control
status. For each ROI, the prior distribution over the beta coefficient was a non-truncated
Gaussian centered on zero with a SD of 10. The posterior of this predictor was then
extracted together with its summary statistics (mean and 95% credible intervals
(CredInt95%)) to examine the effect of medication.

We also examined the correlation between ROI $V_T$ values and PANSS-Positive, PANSS-
Negative scores as well as duration of illness (DOI) using linear effect modelling, allowing
the correlations to vary between studies. All data was z-transformed within study (and within genotype for $V_T$).

The primary reason for choosing Bayesian statistical inference is that the BF allows for a direct comparison of the evidence for one hypothesis relative to another hypothesis (such as $H_1$ against $H_2$, i.e. higher TSPO in patients v.s. lower TSPO in patients). Bayesian parameter estimation also allowed us to assess and report the uncertainty around parameters in the model, which guards against overconfidence and overfitting when making inference. For completeness, we also present frequentist equivalents of the best fitting model, showing p-values for patient-control differences in standardized $V_T$ for each ROI in Supplementary Table S2. The Hamiltonian Markov Chain Monte Carlo sampler STAN (41), and the R-packages brms (42) and lme4 (43) were used for the statistical modeling in this meta-analysis.

**Results**

**Study selection and data collection**

The PubMed search was performed on the 20th of February 2017 and resulted in thirteen research articles. The articles were read in full by two authors (PPS and SC). Both authors concluded independently that five studies (22–26) fulfilled the inclusion criteria for this meta-analysis (see PRISMA-flowchart in Supplementary Figure S3). Each corresponding
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author provided anonymized individual participant $V_T$ values from the frontal cortex (three studies (22–24)), dorsolateral prefrontal cortex (DLPFC) (two studies (25, 26)), temporal cortex (all studies) and hippocampus (all studies). For all subsequent analyses in this study, the $V_T$ values from FC and DLPFC were considered to represent the same ROI.

Characteristics of included studies

Table 1 shows demographic information, medication status, PANSS (or equivalent), and duration of illness of all participants included in this meta-analysis. In total, IPD from 75 participants with psychosis or schizophrenia and 77 HC subjects were included in the statistical analysis. All patients that participated in Kenk et al. (26), Bloomfield et al. (22) studies and all patients except two in Coughlin et al. (24) were on anti-psychotic treatment at the time of PET. Of the 19 patients who participated in Hafizi et al. (25), 5 were antipsychotic free with less than 4 weeks lifetime cumulative exposure, and 14 were antipsychotic naïve at the time of scanning. All patients in Collste et al. (23) were antipsychotic naïve. For all studies, exclusion criteria included clinically significant medical comorbidity and substance abuse. In two of the studies benzodiazepines were not allowed (22, 24), whereas in Collste et al. (23), and Kenk et al. (26) the results did not change when removing subjects using benzodiazepines. Based on this information, as well as in vitro data showing effects of only high doses of diazepam on TSPO levels (44), we chose not to include this variable in our analysis. For information on recruitment of healthy control subjects, quality control of the data and assignment of subjects that overlapped in the original
studies see Supplementary Information, Figure 1 displays the individual participant ROI $V_T$ values from the five studies included in this meta-analysis.

The mean age of all subject in the patient group was 33.88 (SD=12.57) and the mean age of the HC group was 35.42 (SD=15.12). This corresponds to a negligible difference in age between diagnostic groups (Cohen’s $d=0.11$). Fisher’s exact test indicated some skewness in gender distribution between the patient and control groups ($p=0.0504$). In order to ascertain that any potential differences in ROI $V_T$ values between diagnostic groups in the main analysis were not driven by gender differences, we included gender as a covariate, and executed an additional set of BLME models, using the same procedure as outlined in the methods. It should be noted that we had no information regarding the menstrual cycle, which could potentially influence the results in female participants, although relationships between TSPO and menstrual cycle hormonal levels have as of yet to be demonstrated.

**Model selection**

Model M1 showed a slightly better fit, determined by WAIC and LOOC scores, compared to M2 and M3 (Table 2). We therefore used M1 to obtain order-restricted posterior distributions of ROI $dV_T$ and subsequently quantified evidence in favor of H0, H1 and H2.
Patient and control difference in $V_T$ (primary aim)

$BF_{H1:H0}$ in favor of higher $V_T$ in patients (H1) were 0.08 for FC, 0.08 for TC and 0.06 for hippocampus. This translates into strong support for the null-hypotheses of no difference (H0) relative to an higher levels of TSPO in patients. $BF_{H2:H0}$ in favor of lower $V_T$ in patients (H2) were 32.5 for FC, 34.2 for TC and 1481.0 for hippocampus, compared to H0. This signifies very strong evidence for the hypothesis that patients express lower TSPO levels. As a result, there was extremely strong support for H2 over H1 ($BF_{H2:H1}$ FC: 422.9; TC: 440.6; hippocampus: 24524.0). Hence, lower $V_T$ in psychosis patients, as compared to healthy controls, is over 422 times more likely than an higher $V_T$, conditioned on the data and the models (see Table 3 and Supplementary Figure S1 for all computed BFs).

When varying the widths (SD=0.2 and SD=0.8) of the Gaussian prior distribution on the fixed effect of differences between patients and controls, there was still strong support in favor of H2 for all ROIs (all $BF_{H2:H0}>15$, see Supplementary Table S3). The addition of gender as a covariate did not change the qualitative inference for any of the ROIs (all $BF_{H2:H0}>16$, see Supplementary Table S4).
Estimation of effect sizes and study heterogeneity

For estimation of effect sizes and study heterogeneity, model M3, with an uninformative prior over $\Delta V_T$, was used. Figure 2 displays forest plots of the estimated patient-control difference in each study for each ROI. It also shows the posterior distributions of the standardized $\Delta V_T$ across all studies, together with summary statistics (mean and credible intervals). The mean of each ROI’s posterior distribution corresponded to a medium-sized (i.e. Cohen’s $D \approx 0.5$) difference in $V_T$ between patients and controls. When calculating group differences using raw $V_T$ values, subjects with psychosis or schizophrenia had, on average, 15% lower $V_T$ in FC, 14% lower $V_T$ in TC and 24% lower $V_T$ in HIP compared to healthy controls.

For all ROIs, the SDs of the random slopes of studies ($\tau$) were very small (posterior modes $<0.04$; posterior means $<0.22$) and $I^2<15\%$, signifying low study heterogeneity in $\Delta V_T$ differences (see Supplementary Figure S2).

Effect of medication (secondary aim)

We examined the effect of medication on $V_T$, by adding medication-status as an additional predictor to model M1. For all ROIs, the models showed little to no evidence of a medication effect, allocating as much probability to higher $V_T$ as they did to lower $V_T$. The mean of the posterior over the difference in standardized $V_T$ due to medication was 0.009 for FC (CredInt95% -0.384 to 0.401), -0.013 for TC (CredInt95% -0.407 to 0.381) and -0.040 for
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HIP (CredInt95% -0.423 to 0.343), see Figure 3. Thus, no support was found for a difference in TSPO levels between drug-free and medicated patients.

There was little to no evidence for a correlation between regional $V_T$ values and PANSS-Positive, PANSS-Negative scores or DOI (see supplementary Figures S5-S6 and Supplementary Tables S5-S6).

**Discussion**

The main finding of this IPD meta-analysis was that schizophrenia and first-episode psychosis patients showed lower levels of the glial cell marker TSPO compared to healthy control subjects. Using Bayesian linear-mixed-effect modeling, we observed very strong evidence of lower levels of TSPO, measured using $V_T$, in the FC, TC and hippocampus, contrary to the hypothesis of higher TSPO in patients. As such, this study constitutes the most conclusive in vivo investigation of TSPO in psychosis to date.

Antipsychotic medication has been shown to attenuate blood cytokine levels in patients (31) as well as inhibit immune cell activity in vitro (45). Although the effect on TSPO expression in animals is less conclusive (46), these observations suggest that TSPO levels could be lower in medicated compared to unmedicated subjects. However, our secondary analysis of the effect of medication status yielded no evidence for such a difference in...
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radioligand binding between drug-free and medicated patients. This indicates that the observed lower levels of TSPO in patients is not an effect of exposure to antipsychotic treatment.

A wealth of data have demonstrated higher levels of pro-inflammatory markers, such as cytokines, in CSF and plasma in patients across disease stages of schizophrenia (3, 47). In the brain, these signaling molecules are mainly released by microglia and astrocytes, which have key roles in the immune response (9). Therefore, increases in numbers or activity of these cells in schizophrenia has been hypothesized (48, 49). In post-mortem studies, higher levels of brain glial cell markers, such as HLA-DR and CD11b, have been observed in patients, although results have been mixed (50–52). With regard to astrocyte markers, there is no evidence of any overall differences between patients and controls (51, 52). In the case of TSPO, which is expressed in microglia and astrocytes among other cells (8, 9, 53), autoradiographic studies have reported both higher (28) and lower (54) binding in patients as compared to healthy controls. Important caveats when interpreting these studies, are that the age of patients and control subjects is generally high, and in patients the cause of death is often suicide (52). A recent translational study examined TSPO in an infection-mediated animal model of schizophrenia. Higher levels of pro-inflammatory cytokines were found in brain regions which also showed lower TSPO expression as measured using immunohistochemistry (55), an observation that paralleled TSPO PET and CSF data in patients (24). Importantly, microglia and astrocytes have been found to exist in both pro- and anti-inflammatory states (56, 57), which cannot be differentiated by TSPO.
Indeed, very recent in vitro data suggest that M1 (pro-inflammatory) macrophages and microglia may show lower TSPO expression in humans (58,59). The above discussed literature, together with the results of our study, challenges the utility of TSPO as an exclusively pro-inflammatory marker in schizophrenia. Lower levels of TSPO could indicate a compensatory mechanism to a pro-inflammatory signal (55, 60), or altered function of glial cells such as abnormal energy utilization (61). Since stimulation of TSPO has shown to attenuate microglial activation in response to neuroinflammatory challenges (62–64), lower TSPO in psychosis could also indicate an inherent weaker anti-inflammatory response. These hypotheses all need to be addressed in future studies.

Since there is no brain region devoid of TSPO expression (65, 66), metabolite-corrected arterial plasma measurements of radioligand concentration are necessary for accurate in vivo quantification of binding. In order to overcome variability that may be associated with the arterial measurements (27, 67), relative measures of binding, such as distribution volume ratios (DVRs), have been proposed (22). Out of the studies included in this meta-analysis, one reported a significant higher DVR in schizophrenia patients and people at clinical risk for psychosis (22) whereas three studies showed no difference in schizophrenia (23–25). More recently, one study found no evidence of higher DVR in high risk individuals compared to healthy controls (68). We chose not to include DVR in our analysis. The interpretation of patient-control differences obtained by dividing binding in a target region with that of a reference region are complicated by the possibility that there could be alterations in specific binding in the reference region as well. In addition, the reliability of
DVR for TSPO radioligands has been found to be low (69). Given the lack of a true reference region, $V_T$ is the most suitable outcome for TSPO quantification, under the assumption that non-displaceable binding ($V_{ND}$) does not differ between groups. Apart from glial cells, TSPO is also expressed in perivascular and endothelial cells (55, 70), and under certain conditions also neurons (71). Further research is needed to evaluate the contribution of these components to the observation of lower levels of $V_T$ in schizophrenia. Finally, while there is as yet no published evidence showing an effect of the fraction of free radiotracer ($f_P$) in plasma on brain $V_T$ for TSPO radioligands (72), it cannot be ruled out that potential patient-control differences in $f_P$ might contribute to the observed differences in $V_T$. Of all the original studies included in this meta-analysis that measured $f_P$ (22-24), none found a significant difference between groups, suggesting that this factor did not have a major influence on the results.

In this IPD meta-analysis, the hierarchal statistical models allowed us to investigate the difference in TSPO levels between patients with psychosis and healthy controls across five different studies. The IPD approach offers many advantages over traditional, aggregated meta-analysis (73). In this study specifically, it allowed us to e.g. examine the effect of medication, investigate correlations between $V_T$ and clinical measures, and control for potential cofounders such as gender, all of which would not have been possible if effect sizes had only been extracted from literature. By including only studies employing second-generation radiotracers, and reporting the standard outcome measure $V_T$, the analysis fulfils the pre-condition of meta-analytical models that outcomes should stem from the
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same underlying distribution of effects. Synthesizing data in this way, we were able to overcome the critical limitation of small sample sizes in the individual reports. Despite this, the total number of included subjects did not allow for investigations of specific subgroups, such as different disease stages.

**Conclusions**

The present study shows that TSPO levels are lower across several brain regions in patients with first-episode psychosis and schizophrenia compared to healthy controls, suggesting an altered function, or reduced density of immune and glial cells. Further work is needed to assess the exact biological meaning of these changes, using both clinical and translational studies.

**Acknowledgement**

We thank Yong Du, Ph.D., and Sina Hafizi, M.D., Ph.D., for helpful comments on the manuscript. The pre-registration study- and analysis protocol together with all analysis code can be found at https://github.com/pontusps/TSPO_psychosis.

Dr Cervenka reports funds from the Swedish Research Council (523-2014-3467) and Stockholm County Council. Dr Collste reports funding from PRIMA Barn- och Vuxenpsykiatri AB. Dr Howes reports funds from Research Council-UK (no. MC-A656-
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5QD30), Maudsley Charity (no. 666), Brain and Behavior Research Foundation, and Wellcome Trust (no. 094849/Z/10/Z), and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. Dr Ashok reports funding from the Medical Research Council and King’s College London. Dr Pomper reports funding from US DoD (GW130098). Dr Mizrahi reports funding from the National Institutes of Health (NIH) R01 grant MH100043. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest

Dr Cervenka has received grant support from AstraZeneca as a co-investigator, and has served as a one-off speaker for Otsuka-Lundbeck. Dr Cervenka’s spouse is an employee of Swedish Orphan Biovitrum. Dr Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Dr Mizrahi has received a one-time speaking fee from Otsuka-Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.
Author contributions

Plavén-Sigray and Cervenka conceived of the study, design the study, wrote the study protocol and supervised the study. Plavén-Sigray and Cervenka carried out the literature search. Plavén-Sigray, Collste, Pompers, Coughlin, Wang, Mizrahi, Rusjan, Howes, Veronese, Ashok and Cervenka aided in the acquisition and quality control of data. Plavén-Sigray and Matheson performed the statistical analyses. Plavén-Sigray and Cervenka drafted the manuscript. All authors revised the manuscript for intellectual content and approved of the final version.

References


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18. Fujita M, Kobayashi M, Ikawa M, Gunn RN, Rabiner EA, Owen DR et al. (2017): Comparison of four 11C-labeled PET ligands to quantify translocator protein 18 kDa (TSP0) in human brain: (R)-PK11195, PBR28, DPA-713, and ER176—based on recent publications that measured specific-to-non-displaceable ratios. EJNMMI Research. 7: 84.


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56. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L et al. (2017): Neurotoxic reactive astrocytes are induced by activated microglia. *Nature.*


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Figure Captions

Figure 1. Individual participant raw data showing TSPO levels (estimated using $V_T$) in participants with first episode psychosis or schizophrenia and healthy controls, from all five included studies, from frontal cortex (FC), temporal cortex (TC) and hippocampus (HIP). The black bars denote the group means. For each region, subjects’ $V_T$ values have been z-scored within study, and within genotype, in order to produce the pooled plots of all HABs and MABs. For this reason, HABs and MABs have the same mean (set to zero) in the right-hand panels.

Figure 2. Standardized difference in TSPO levels (estimated using $V_T$) between patients with psychosis disorder and healthy controls. The posterior distribution for each study-specific $\Delta V_T$ estimate (random slopes) from the linear mixed model are presented. 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 patient-control mean difference in raw data (together with its 95% CI), without performing linear mixed effects modeling. Hence, the difference between the dot and the cross displays the model shrinkage towards the mean. The overall $\Delta V_T$ estimate suggests that patients with schizophrenia or first episode psychosis have lower levels of TSPO, compared to healthy controls.

Figure 3. Posterior distributions over the differences in standardized brain TSPO levels (estimated using $V_T$) values between patients and controls, and the additional effect of medication status (being medicated with anti-psychotics or not at the time of PET). The posterior distributions of medication effect are centred on zero and suggest that anti-psychotic treatment does not affect brain $V_T$, after differences between psychosis or schizophrenia patients and controls have been accounted for.
Table 1. Descriptive characteristics of included data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic group</th>
<th>Schizophrenia/ Other</th>
<th>Age Mean</th>
<th>Age SD</th>
<th>Count</th>
<th>HABs</th>
<th>MABs</th>
<th>Males</th>
<th>Females</th>
<th>PANSS-T Mean</th>
<th>PANSS-P Mean</th>
<th>PANSS-N Mean</th>
<th>DOI Mean (Months)</th>
<th>Drugfree/ Total</th>
<th>Radioligand</th>
<th>Original Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield et al.</td>
<td>HC</td>
<td>-</td>
<td>46.21</td>
<td>13.62</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>11</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[18F]FEPPA</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>pat</td>
<td>12/0</td>
<td>47.00</td>
<td>9.31</td>
<td>12</td>
<td>12</td>
<td>0†</td>
<td>9</td>
<td>3</td>
<td>63.7 (18.1)</td>
<td>17.0 (6.1)</td>
<td>14.1 (4.0)</td>
<td>108.9 (46.7)</td>
<td>0/12</td>
<td>[18F]PBR28</td>
<td></td>
</tr>
<tr>
<td>Colste et al.</td>
<td>HC</td>
<td>-</td>
<td>26.38</td>
<td>8.44</td>
<td>16</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[18F]PBR28</td>
<td>↓ pat</td>
</tr>
<tr>
<td></td>
<td>pat</td>
<td>4/12**</td>
<td>28.50</td>
<td>8.37</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>5</td>
<td>77.4 (18.3)</td>
<td>20.3 (4.9)</td>
<td>18.1 (7.0)</td>
<td>7.9 (9.6)</td>
<td>2/16</td>
<td>[18F]PDA173</td>
<td>N.S.</td>
</tr>
<tr>
<td>Coughlin et al.</td>
<td>HC</td>
<td>-</td>
<td>25.36</td>
<td>4.89</td>
<td>14</td>
<td>9</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>pat</td>
<td>12/0</td>
<td>24.33</td>
<td>3.28</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>-</td>
<td>13.8 (2.7)††</td>
<td>15.8 (4.6)††</td>
<td>25.0 (16.3)</td>
<td>19/19</td>
<td>[18F]FEPPA</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hafizi et al.</td>
<td>HC</td>
<td>-</td>
<td>27.17</td>
<td>9.07</td>
<td>18</td>
<td>14</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[18F]FEPPA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pat</td>
<td>15/4***</td>
<td>27.53</td>
<td>6.78</td>
<td>19</td>
<td>14</td>
<td>5</td>
<td>12</td>
<td>7</td>
<td>68.6 (13.0)</td>
<td>19.2 (3.8)</td>
<td>16.1 (6.1)</td>
<td>33.6 (40.1)</td>
<td>19/19</td>
<td>[18F]FEPPA</td>
<td>N.S.</td>
</tr>
<tr>
<td>Kenk et al.</td>
<td>HC</td>
<td>-</td>
<td>54.27</td>
<td>9.51</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[18F]FEPPA</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>pat</td>
<td>16/0</td>
<td>42.50</td>
<td>14.05</td>
<td>16</td>
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<td>6</td>
<td>10</td>
<td>6</td>
<td>70.2 (9.7)</td>
<td>19.3 (2.2)</td>
<td>18.6 (5.0)</td>
<td>177.3 (105.7)</td>
<td>0/16</td>
<td>[18F]FEPPA</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>HC</td>
<td>-</td>
<td>35.42</td>
<td>15.12</td>
<td>77</td>
<td>56</td>
<td>21</td>
<td>42</td>
<td>35</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>pat</td>
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<td>33.86</td>
<td>12.57</td>
<td>75</td>
<td>52</td>
<td>23</td>
<td>51</td>
<td>24</td>
<td>-</td>
<td>18.2 (4.2)</td>
<td>16.6 (5.5)</td>
<td>72.1 (57.2)</td>
<td>37/77</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HC = healthy controls; pat = participants with psychosis or schizophrenia; HABs = high-affinity binders; MABs = medium-affinity binders; PANSS-T = Positive and Negative Syndrome Scale – Total score; PANSS-P = PANSS – Positive score; PANSS-N = PANSS – Negative score; DOI = duration of illness; DUP = duration of untreated psychosis; Drug-free = drug-naive patients (n=30) or patients not medicated with anti-psychotics at the time of the PET examinations (n=7); N.S. = non-significant; ↓pat = lower V1 in subjects with psychosis.

*The 14 HC subjects shared across the Kenk et al. and Hafizi et al. studies have been uniquely assigned to either one of the studies. Assignment was done as to best match the patient groups based on count, genotype, gender and age.

**Other diagnoses: 7 schizophreniform disorder, 4 psychosis NOS, 1 brief psychosis

***Other diagnoses: 3 schizophreniform and 1 delusional disorder

† The 2 MAB subjects from the patient-group were excluded from the hierarchal inferential analyses since z-scoring within genotype was not meaningful

††PANSS – P score converted from SAPS score, and PANSS – N score converted from SANS score, using van Erp et al. (73)
Table 2. Model fits for four different Bayesian linear mixed effect models examining the difference in TSPO binding (estimated using $V_T$) between patients with psychosis and healthy controls. A null model (0) without patient-control status as predictor is included as a baseline comparison. Lower dLOOC and dWAIC values indicate better model fit.

<table>
<thead>
<tr>
<th>Region</th>
<th>Model</th>
<th>dLOOC</th>
<th>dWAIC</th>
<th>Akaike Weights* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex</td>
<td>0</td>
<td>7.6</td>
<td>7.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.8</td>
<td>0.8</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.1</td>
<td>1.1</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.9</td>
<td>1.9</td>
<td>14</td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>0</td>
<td>7.1</td>
<td>7.1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>35</td>
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<td></td>
<td>2</td>
<td>0.6</td>
<td>0.6</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.6</td>
<td>1.6</td>
<td>16</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0</td>
<td>15.3</td>
<td>15.4</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.4</td>
<td>0.4</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.3</td>
<td>1.2</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.7</td>
<td>1.6</td>
<td>16</td>
</tr>
</tbody>
</table>

dLOOC = distance to best fitting model calculated using Leave-One-Out Cross-Validation; dWAIC = distance to best fitting model calculated using Widely Applicable Information Criteria
*Weights calculated using LOOC scores
Table 3. Bayes factors of hypothesis testing of the difference in standardized brain TSPO binding (estimated using $V_T$) between patients and controls, using the best fitting model (M1).

<table>
<thead>
<tr>
<th>Region</th>
<th>H0:H1</th>
<th>H1:H0</th>
<th>H0:H2</th>
<th>H2:H0</th>
<th>H1:H2</th>
<th>H2:H1</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>13.0</td>
<td>0.08</td>
<td>0.03</td>
<td>32.5</td>
<td>0.002</td>
<td>422.9</td>
</tr>
<tr>
<td>TC</td>
<td>12.9</td>
<td>0.08</td>
<td>0.03</td>
<td>34.2</td>
<td>0.002</td>
<td>440.6</td>
</tr>
<tr>
<td>HIP</td>
<td>16.6</td>
<td>0.06</td>
<td>0.001</td>
<td>1481.0</td>
<td>&lt;0.001</td>
<td>24524.0</td>
</tr>
</tbody>
</table>

FC = frontal cortex; TC = temporal cortex; HIP = hippocampus; 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.
Frontal Cortex $\Delta V_T$

Temporal Cortex $\Delta V_T$

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

Supplementary Information

Search Strategy for PubMed

((("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields])) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]) OR ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields])) OR "psychotic disorders"[All Fields] OR ("psychotic"[All Fields] AND "disorder"[All Fields]) OR "psychotic disorder"[All Fields]) OR ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields])) AND ((translocator[All Fields] AND ("proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields]))) OR (translocator[All Fields] AND ("antigens, cd59"[MeSH Terms] OR ("antigens"[All Fields] AND "cd59"[All Fields])) OR "cd59 antigens"[All Fields] OR "protein 18"[All Fields]) AND kDa[All Fields]) OR TSPO[All Fields] OR (peripheral[All Fields] AND ("receptors, gaba-a"[MeSH Terms] OR ("receptors"[All Fields] AND "gaba-a"[All Fields]) OR "gaba-a receptors"[All Fields] OR ("benzodiazepine[All Fields] AND "receptor"[All Fields])) OR "benzodiazepine receptor"[All Fields])) OR PBR[All Fields]) AND (("positron-emission tomography"[MeSH Terms] OR ("positron-emission"[All Fields] AND "tomography"[All Fields]) OR "positron-emission tomography"[All Fields] OR ("positron"[All Fields] AND "emission"[All Fields] AND "tomography"[All Fields]) OR "positron emission tomography"[All Fields]) OR PET[All Fields]) AND 2004/01/01[EDAT] : 2017/02/20[EDAT]
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 Vₚ 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Did not fulfill selection criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>van Berckel et al., 2008 (6)</td>
<td>X</td>
</tr>
<tr>
<td>Doorduin et al., 2009 (7)</td>
<td>X</td>
</tr>
<tr>
<td>Takano et al., 2010 (8)</td>
<td>X</td>
</tr>
<tr>
<td>van der Doef et al., 2016 (9)</td>
<td>X</td>
</tr>
<tr>
<td>Holmes et al., 2016 (10)</td>
<td>X</td>
</tr>
<tr>
<td>Di Biase et al., 2017 (11)</td>
<td>X</td>
</tr>
</tbody>
</table>

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 (VT) 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, VT 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.

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimate</th>
<th>SE</th>
<th>df*</th>
<th>t-value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>-0.48</td>
<td>0.15</td>
<td>150.00</td>
<td>-3.12</td>
<td>0.00218</td>
</tr>
<tr>
<td>TC</td>
<td>-0.47</td>
<td>0.15</td>
<td>150.00</td>
<td>-3.03</td>
<td>0.00291</td>
</tr>
<tr>
<td>HIP</td>
<td>-0.64</td>
<td>0.15</td>
<td>149.00</td>
<td>-4.26</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Region</th>
<th>Large (SD=0.8) H0:H2</th>
<th>Large (SD=0.8) H2:H0</th>
<th>Small (SD=0.2) H0:H2</th>
<th>Small (SD=0.2) H2:H0</th>
<th>Small (SD=0.2) H0:H1</th>
<th>Small (SD=0.2) H1:H0</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>0.035</td>
<td>28.736</td>
<td>0.050</td>
<td>19.993</td>
<td>5.064</td>
<td>0.197</td>
</tr>
<tr>
<td>TC</td>
<td>0.042</td>
<td>23.762</td>
<td>0.062</td>
<td>16.008</td>
<td>5.305</td>
<td>0.189</td>
</tr>
<tr>
<td>HIP</td>
<td>0.001</td>
<td>831.085</td>
<td>0.005</td>
<td>210.730</td>
<td>6.804</td>
<td>0.147</td>
</tr>
</tbody>
</table>

\( H0:H1 \): 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.

<table>
<thead>
<tr>
<th>Region</th>
<th>H0:H1</th>
<th>H1:H0</th>
<th>H0:H2</th>
<th>H2:H0</th>
<th>H1:H2</th>
<th>H2:H1</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>12.338</td>
<td>0.081</td>
<td>0.053</td>
<td>18.859</td>
<td>0.004</td>
<td>232.670</td>
</tr>
<tr>
<td>TC</td>
<td>4.960</td>
<td>0.202</td>
<td>0.062</td>
<td>16.105</td>
<td>0.013</td>
<td>79.883</td>
</tr>
<tr>
<td>HIP</td>
<td>10.557</td>
<td>0.095</td>
<td>0.001</td>
<td>675.455</td>
<td>&lt;0.001</td>
<td>7130.563</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Region</th>
<th>Estimate</th>
<th>SE</th>
<th>$t$-value</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS-Positive</td>
<td>FC</td>
<td>0.06</td>
<td>0.15</td>
<td>0.42</td>
<td>0.70</td>
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<tr>
<td></td>
<td>TC</td>
<td>0.07</td>
<td>0.12</td>
<td>0.56</td>
<td>0.61</td>
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<tr>
<td></td>
<td>HIP</td>
<td>0.02</td>
<td>0.11</td>
<td>0.18</td>
<td>0.86</td>
</tr>
<tr>
<td>PANSS-Negative</td>
<td>FC</td>
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<td>0.11</td>
<td>0.15</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>0.04</td>
<td>0.11</td>
<td>0.37</td>
<td>0.71</td>
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<tr>
<td></td>
<td>HIP</td>
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<td>0.11</td>
<td>0.24</td>
<td>0.81</td>
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</table>

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.

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.49</td>
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<td>TC</td>
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<td>-0.69</td>
<td>0.52</td>
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</tbody>
</table>

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


DPA-713 has much greater specific binding to translocator protein 18 kDa (TSPO) in human brain than 11C-(R)-PK11195. *J Cereb Blood Flow Metab.* 0: 0271678X17699223.


