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Positron Emission Tomography Studies of the Glial Cell Marker Translocator Protein in Patients With Psychosis: A Meta-analysis Using Individual Participant Data

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Abstract

BACKGROUND: Accumulating evidence suggests that the immune system may be an important target for new treatment approaches in schizophrenia. Positron emission tomography and radioligands binding to the translocator protein (TSPO), which is expressed in glial cells in the brain including immune cells, represents a potential method for patient stratification and treatment monitoring. This study examined whether patients with first-episode psychosis and schizophrenia had altered TSPO levels compared with healthy control subjects.

METHODS: PubMed was searched for studies comparing patients with psychosis with healthy control subjects using second-generation TSPO radioligands. The outcome measure was total distribution volume (V_T), an index of TSPO levels, in frontal cortex, temporal cortex, and hippocampus. Bayes factors (BFs) were applied to examine the relative support for higher, lower, or no difference in patients' TSPO levels compared with healthy control subjects.

RESULTS: Five studies, with 75 participants with first-episode psychosis or schizophrenia and 77 healthy control subjects, were included. BFs showed strong support for lower V_T in patients relative to no difference (all BFs > 32), or relative to higher V_T (all BFs > 422), in all brain regions. From the posterior distributions, mean patient–control differences in standardized V_T values were −0.48 for frontal cortex (95% credible interval [CredInt] = −0.88 to 0.09), −0.47 for temporal cortex (CredInt = −0.87 to −0.07), and −0.63 for hippocampus (CredInt = −1.00 to −0.25).

CONCLUSIONS: 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.

Keywords

Immune activation; Meta-analysis; Microglia; Positron emission tomography; Psychosis; Schizophrenia; Translocator protein

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 a positive effect of medication targeting the immune system when used as an 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 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*)-[^{11}C]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*)-[^{11}C]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 (total distribution volume [V_T] obtained using kinetic modeling with metabolite-corrected arterial plasma as input function), higher TSPO expression has so far not been found in patients. In some cases, trend-level (24) or significantly lower (23) TSPO levels were shown.

All previous TSPO PET studies in psychosis have been performed with relatively small sample sizes. In addition, TSPO radioligands display substantial within- and between-subject variability (12,27) even after accounting for the TSPO rs6971 polymorphism that is known to affect radioligand binding in vivo (28–30). This has important implications for sensitivity and the power to detect differences between patients with psychosis and control subjects. Indeed, the power to detect an expected significant medium-sized difference between diagnostic groups (at alpha = .05) has ranged from 23% to 34% in previous designs (22–26). Medication status has also differed both between and within these studies. Because 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 (HCs). A secondary objective was to assess the effects of antipsychotic medication on TSPO levels.

METHODS AND MATERIALS

Preferred Reporting Items for Systematic Reviews and Meta-analyses, Preregistration, and Code Availability

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of IPD (PRISMA-IPD) (32) and according to a study-specific preregistration protocol. The preregistration protocol and all codes 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 IPD from all PET studies that 1) used a second-generation TSPO radioligand, 2) reported V_T values in the central nervous system in subjects with psychosis or schizophrenia as compared with HCs, 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}C]PBR28, [^{18}F]FEPPA, and [^{11}C]DPA713 (22–26). 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 the full list of search terms, see the Supplement). All TSPO PET studies in psychosis or schizophrenia that were not included are listed in Supplemental Table S1 along with a detailed explanation of the selection criteria. Corresponding authors of eligible studies were contacted via e-mail, 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, gender and medication status, Positive and Negative Syndrome Scale (PANSS) scores (or equivalent), and duration of illness. These three ROIs were selected because four of five included studies had reported V_T values from all of them. For the remaining study [Bloomfield *et al.* (22)], unpublished IPD V_T values obtained using the conventional two-tissue compartment model from all three ROIs were provided on request, allowing for consistent pooling. To account for range differences among 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 (PP-S) examined the integrity of the obtained IPD datasets. The data were checked for outliers and inconsistencies with 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 studies.

Meta-analysis and Statistics

The studies included in this meta-analysis recruited participants of two different TSPO affinity types (high-affinity binders and mixed-affinity binders), used different radioligands, and applied different image analysis procedures. To estimate the difference in V_T between diagnostic groups (ΔV_T) while taking this hierarchical structure into account, we constructed and compared four different Bayesian linear mixed-effects (BLME) models of increasing complexity: In model 1 (M1), standardized ROI V_T was specified as the dependent variable, diagnostic group as the fixed effect, and genotype and study as random effects with varying intercepts. Model 2 (M2) was the same as M1 but with varying slopes of the random effect of genotype (i.e., allowing for differences in ΔV_T between high-affinity binders and mixed-affinity binders). Model 3 (M3) was the same as M1 but with varying slopes of the random effect of study (i.e., allowing for differences in ΔV_T between studies). Model 4 (M4) was the same as M1 but with varying slopes for both random effects (i.e., allowing for differences in ΔV_T between genotypes and studies). The model with the best fit to data, as determined by widely applicable information criterion and leave-one-out cross-validation 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 (hypothesis 1 [H1]). For each ROI, we quantified the relative evidence of higher TSPO expression in patients compared with the null hypothesis of no difference (H0). This was done using order-restricted Bayes factor (BF) hypothesis testing (35–37) on ΔV_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 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 with control subjects relative to no difference. Second, 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 with 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, to perform order-restricted hypothesis testing of patient–control differences, the priors over ROI ΔV_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 because this assigns high plausibility to ΔV_T values ranging from 0 to a medium-sized difference (38,39). A medium-sized difference, corresponding to 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 HCs [Cohen's U3 (38)].

A robustness check of the effect of different prior widths on BF was performed by varying the SDs of the half-Gaussian distributions (SDs = 0.2 and 0.8, corresponding to expected

small and large effect sizes of ΔV_T and Cohen's U3 = 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 because 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 HCs. This was done using M3 with a nontruncated, weakly regularizing prior (Gaussian with an SD of 10) over the fixed effect. M3 was selected because it also allowed us to extract the study-specific effects of ROI ΔV_T (random slopes) and the corresponding SDs of these effects (τ). Using these, we produced a forest plot of ROI ΔV_T and examined τ 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 nontruncated Gaussian centered on zero with an SD of 10. The posterior of this predictor was then extracted together with its summary statistics (mean and 95% credible interval [CredInt]) to examine the effect of medication.

We also examined the correlation between ROI V_T values and PANSS-Positive scores, PANSS-Negative scores, and duration of illness using linear effect modeling, allowing the correlations to vary between studies. All data were *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 H1 against H2, i.e., higher TSPO in patients vs. 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 Supplemental 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 February 20, 2017, and resulted in 13 research articles. The articles were read in full by two of the authors (PP-S and SC). Both authors concluded independently that five studies (22–26) fulfilled the inclusion criteria for this meta-analysis (see PRISMA flowchart in Supplemental Figure S3). Each corresponding author provided anonymized individual participant V_T values from FC [three studies (22–24)], dorsolateral prefrontal cortex [two studies (25,26)], TC (all studies), and HIP (all

studies). For all subsequent analyses in this study, the V_T values from FC and dorsolateral prefrontal cortex 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 HCs were included in the statistical analysis. All patients who participated in Kenk *et al.* (26) and Bloomfield *et al.* (22), and all patients except 2 who participated in Coughlin *et al.* (24), were on antipsychotic 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 of lifetime cumulative exposure and 14 were antipsychotic naive at the time of scanning. All patients in Collste *et al.* (23) were antipsychotic naive. 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 HCs, quality control of the data, and assignment of subjects who overlapped in the original studies, see the Supplement. Figure 1 displays the individual participant ROI V_T values from the five studies included in this meta-analysis.

The mean age of all subjects in the patient group was 33.88 years (SD = 12.57), and the mean age of all subjects in the HC group was 35.42 years (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 ($p = .0504$). 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 Methods and Materials. 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

M1 showed a slightly better fit, determined by widely applicable information criterion and leave-one-out cross-validation scores, compared with M2 and M3 (Table 2). Therefore, we used M1 to obtain order-restricted posterior distributions of ROI ΔV_T and subsequently quantified evidence in favor of H0, H1, and H2.

Patient–Control Difference in V_T (Primary Aim)

$BF_{H1:H0}$ values in favor of higher V_T in patients (H1) were 0.08 for FC, 0.08 for TC, and 0.06 for HIP. This translates into strong support for the null hypothesis of no difference (H0) relative to higher levels of TSPO in patients. $BF_{H2:H0}$ values in favor of lower V_T in patients (H2) were 32.5 for FC, 34.2 for TC, and 1481.0 for HIP compared with 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 ($BF_{H2:H1}$ values: FC = 422.9; TC = 440.6; HIP = 24524.0). Hence, lower V_T in patients with psychosis, as compared to with HCs, is more than 422 times more likely than higher V_T, conditioned on the data and the models (see Table 3 and Supplemental Figure S1 for all computed BFs).

When varying the widths (SDs = 0.2 and 0.8) of the Gaussian prior distribution on the fixed effect of differences between patients and control subjects, there was still strong support in favor of H2 for all ROIs (all $BF_{H2:H0} > 15$) (see Supplemental 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 Supplemental Table S4).

Estimation of Effect Sizes and Study Heterogeneity

For estimation of effect sizes and study heterogeneity, M3, with an uninformative prior over ΔV_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 ΔV_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 control subjects. 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 with HCs.

For all ROIs, the SDs of the random slopes of studies (τ) were very small (posterior modes < 0.04; posterior means < 0.22) and $I^2 < 15\%$, signifying low study heterogeneity in ΔV_T differences (see Supplemental 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 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 means of the posterior over the difference in standardized V_T due to medication were 0.009 for FC (CredInt = −0.384 to 0.401), −0.013 for TC (CredInt = −0.407 to 0.381), and −0.040 for HIP (CredInt = −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 scores, PANSS-Negative scores, or duration of illness (see Supplemental Figures S5 and S6 and Supplemental Tables S5 and S6).

DISCUSSION

The main finding of this IPD meta-analysis was that patients with schizophrenia and first-episode psychosis showed lower levels of the glial cell marker TSPO compared with HCs. Using BLME modeling, we observed very strong evidence of lower levels of TSPO, measured using V_T, in FC, TC, and HIP, 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 to 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 subjects compared with unmedicated subjects. However, our secondary analysis of the effect of medication status yielded no evidence for such a difference in 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 has demonstrated higher levels of proinflammatory markers, such as cytokines, in cerebrospinal fluid 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 have been hypothesized (48,49). In postmortem studies, higher levels of brain glial cell markers, such as human leukocyte antigen–antigen D related 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 control subjects (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 with HCs. Important caveats when interpreting these studies are that the age of patients and control subjects is generally high and the cause of death in patients is often suicide (52). A recent translational study examined TSPO in an infection-mediated animal model of schizophrenia. Higher levels of proinflammatory cytokines were found in brain regions that also showed lower TSPO expression as measured using immunohistochemistry (55), an observation that paralleled TSPO PET and cerebrospinal fluid 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 (proinflammatory) 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 proinflammatory marker in schizophrenia. Lower levels of TSPO could indicate a compensatory mechanism to a proinflammatory signal (55,60) or altered function of glial cells such as abnormal energy use (61). Because stimulation of TSPO has been 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.

Because 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. 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). Of the studies included in this meta-analysis, one study

reported a significantly higher DVR in patients with schizophrenia 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 with HCs (68). We chose not to include DVR in our analysis. The interpretation of patient–control differences obtained by dividing binding in a target region by that in a reference region is complicated by the possibility that there are 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 nondisplaceable binding 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 in plasma on brain V_T for TSPO radioligands (72), it cannot be ruled out that potential patient–control differences in free radiotracer might contribute to the observed differences in V_T. Of all the original studies included in this meta-analysis that measured free radiotracer (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 HCs across five different studies. The IPD approach offers many advantages over traditional, aggregated meta-analysis (73). In this study specifically, for example, it allowed us to 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 fulfills the precondition of meta-analytical models that outcomes should stem from the 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 current study shows that TSPO levels are lower across several brain regions in patients with first-episode psychosis and schizophrenia compared with HCs, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PP-S and SC conceived of the study, designed the study, wrote the study protocol, supervised the study, and carried out the literature search. PP-S, KC, MGP, JMC, YW, RM, PR, ODH, MV, AHA, and SC aided in the acquisition and quality control of data. PP-S and GJM performed the statistical analyses. PP-S and SC drafted the manuscript. All authors revised the manuscript for intellectual content and approved the final version.

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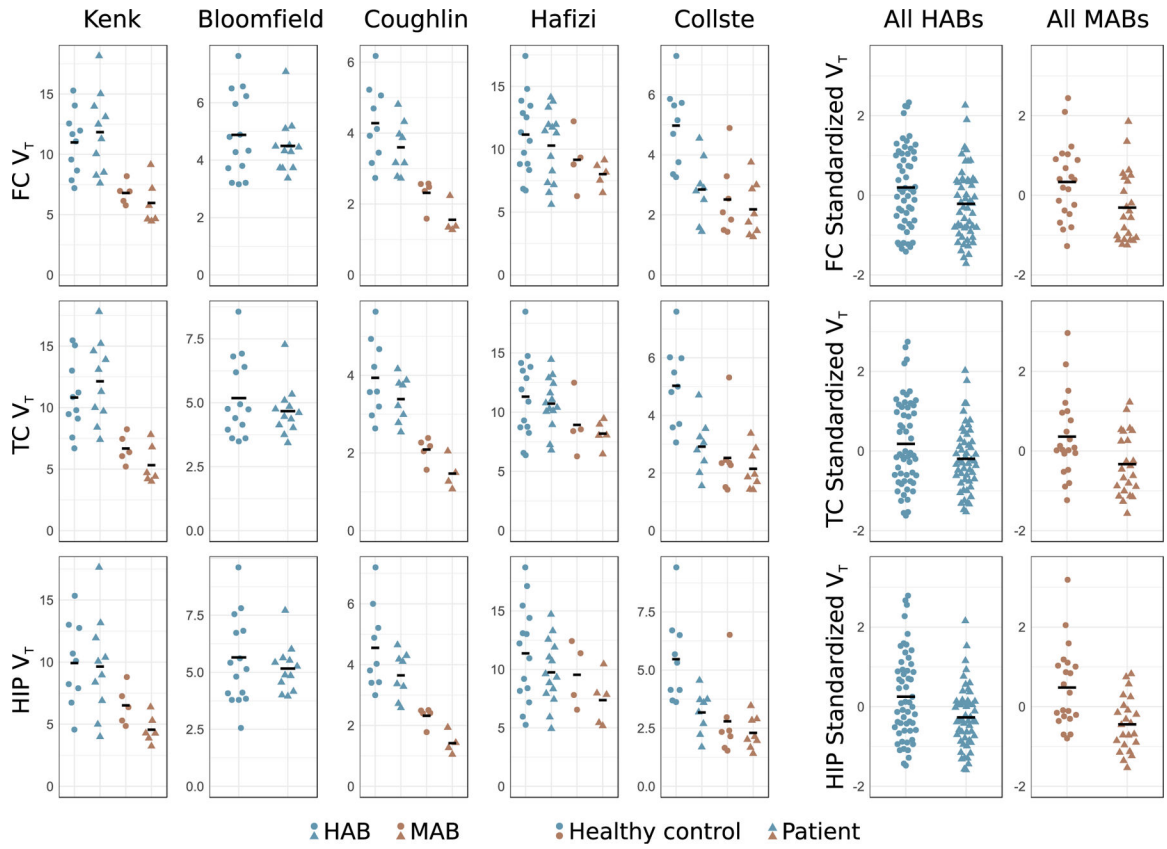

Figure 1.

Individual participant raw data showing translocator protein levels (estimated using total distribution volume [V_T]) in participants with first-episode psychosis or schizophrenia and healthy control subjects, 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 high-affinity binders (HABs) and mixed-affinity binders (MABs). For this reason, HABs and MABs have the same mean (set to zero) in the right-hand panels. Included studies: Bloomfield *et al.* (22); Collste *et al.* (23); Coughlin *et al.* (24); Hafizi *et al.* (25); Kenk *et al.* (26).

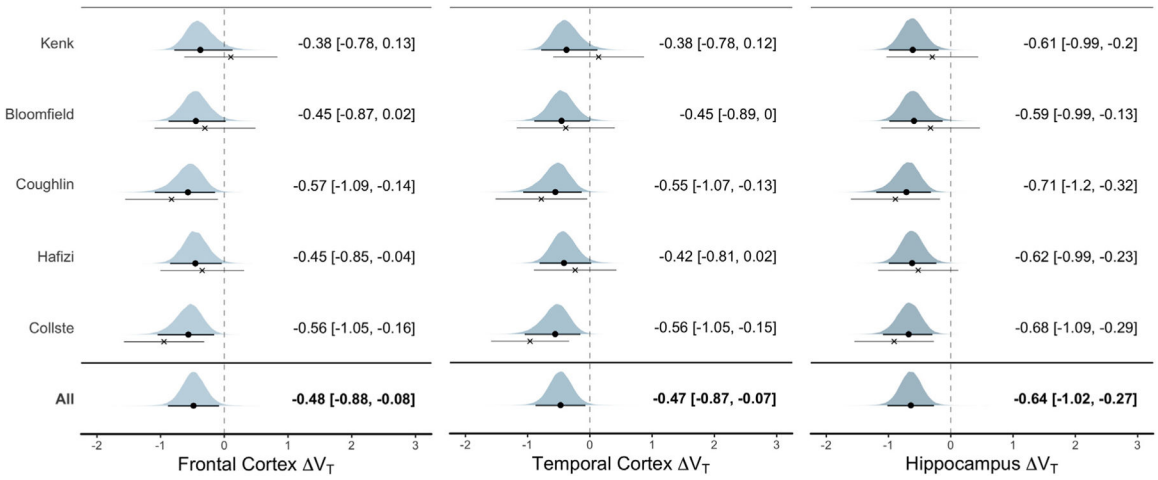

Figure 2.

Standardized difference in translocator protein levels (estimated using total distribution volume [V_T]) between patients with psychosis and healthy control subjects. The posterior distribution for each study-specific difference in V_T (ΔV_T) estimate (random slopes) from the linear mixed model is presented. The black circle denotes the posterior mean, and the thick line denotes the 95% credible interval; these are also presented in text next to the plots. The cross denotes the patient–control mean difference in raw data (together with its 95% credible interval) without performing linear mixed-effects modeling. Hence, the difference between the dot and the cross displays the model shrinkage toward the mean. The overall ΔV_T estimate suggests that patients with schizophrenia or first-episode psychosis have lower levels of translocator protein compared with healthy control subjects. Included studies: Bloomfield *et al.* (22); Collste *et al.* (23); Coughlin *et al.* (24); Hafizi *et al.* (25); Kenk *et al.* (26).

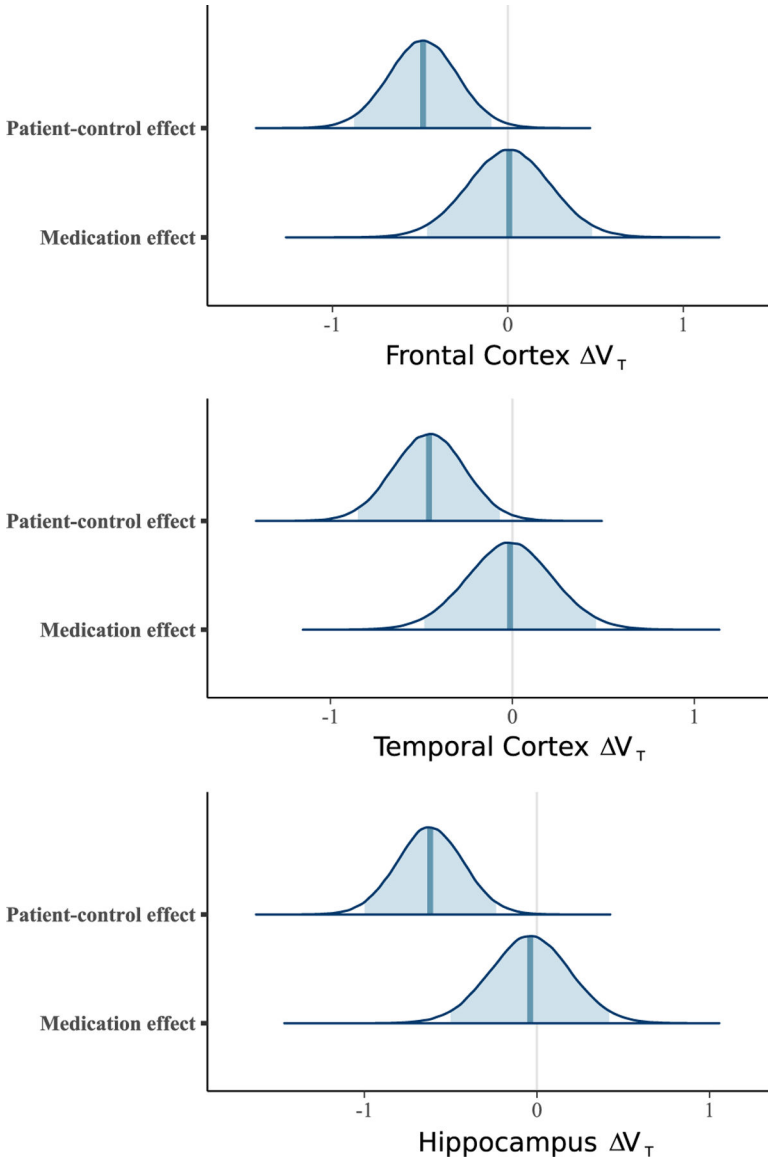

Figure 3.

Posterior distributions over the differences in standardized brain translocator protein levels (estimated using total distribution volume [V_T]) between patients and control subjects and the additional effect of medication status (being medicated with antipsychotics or not at the time of positron emission tomography). The posterior distributions of medication effect are centered on zero and suggest that antipsychotic treatment does not affect brain V_T after accounting for differences between patients with psychosis or schizophrenia and control subjects. ΔV_T, difference in V_T.

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Table 1.

Descriptive Characteristics of Included Data

Study	Diagnostic Group	Schizophrenia/ Other	Age, Mean (SD), Years	Count	HABs	MABs	Men	Women	PANSS-T, Mean (SD)	PANSS-P, Mean (SD)	PANSS-N, Mean (SD)	DOI Mean (SD), Months	Drug Free[a]/ Total	Radioligand	Original Result
Bloomfield *et al.* (22)	HCs	–	46.21 (13.62)	14	14	0	11	3	–	–	–	–	–	[^{11}C]PBR28	N.S.
	Pat	12/0	47.00 (9.31)	12	12	0[b]	9	3	63.7 (18.1)	17.0 (6.1)	14.1 (4.0)	108.9 (46.7)	0/12		
Collste *et al.* (23)	HCs	–	26.38 (8.44)	16	9	7	7	9	–	–	–	–	–	[^{11}C]PBR28	↓Pat
	Pat	4/12[d]	28.50 (8.37)	16	8	8	11	5	77.4 (18.3)	20.3 (4.9)	18.1 (7.0)	7.9 (9.6)	16/16		
Coughlin *et al.* (24)	HCs	–	25.36 (4.89)	14	9	5	9	5	–	–	–	–	–	[^{11}C]DPA173	N.S.
	Pat	12/0	24.33 (3.28)	12	8	4	9	3	–	13.8 (2.7)[c]	15.8 (4.6)[c]	25.0 (16.3)	2/12		
Hafizi *et al.* (25)[e]	HCs	–	27.17 (9.07)	18	14	4	8	10	–	–	–	–	–	[^{18}F]FEPPA	N.S.
	Pat	15/4[f]	27.53 (6.78)	19	14	5	12	7	68.6 (13.0)	19.2 (3.8)	16.1 (6.1)	33.6 (40.1)	19/19		
Kenk *et al.* (26)[e]	HCs	–	54.27 (9.51)	15	10	5	7	8	–	–	–	–	–	[^{18}F]FEPPA	N.S.
	Pat	16/0	42.50 (14.03)	16	10	6	10	6	70.2 (9.7)	19.3 (2.2)	18.6 (5.0)	177.3 (105.7)	0/16		
All	HCs	–	35.42 (15.12)	77	56	21	42	35	–	–	–	–	–	–	–
	Pat	59/16	33.88 (12.57)	75	52	23	51	24	–	18.2 (4.2)	16.6 (5.5)	72.1 (57.2)	37/77		

DOI, duration of illness; HABs, high-affinity binders; HCs, healthy control subjects; MABs, medium-affinity binders; N.S., nonsignificant; PANSS-N, PANSS–Negative score; PANSS-P, PANSS–Positive score; PANSS-T, Positive and Negative Syndrome Scale–Total score; Pat, participants with psychosis or schizophrenia; ↓Pat, lower total distribution volume in subjects with psychosis.

[a]Drug-naive patients (n = 30) or patients not medicated with antipsychotics at the time of the positron emission tomography examinations (n = 7).

[b]The 2 MAB subjects from the patient group were excluded from the hierarchal inferential analyses because Z-scoring within genotype was not meaningful.

[c] PANSS-P score converted from Scale for the Assessment of Positive Symptoms score, and PANSS-N score converted from Scale for the Assessment of Negative Symptoms score, using van Erp *et al.* (74).

[d] Other diagnoses: 7 schizophreniform disorder, 4 psychosis not otherwise specified, and 1 brief psychosis.

[e] The 14 HCs shared across the Kenk *et al.* (26) and Hafizi *et al.* (25) 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.

[f] Other diagnoses: 3 schizophreniform and 1 delusional disorder.

Table 2.

Model Fits for Four Different Bayesian Linear Mixed-Effects Models Examining the Difference in TSPO Binding (Estimated Using V_T) Between Patients With Psychosis and Healthy Control Subjects

Region	Model	dLOOC	dWAIC	Akaike Weight[a] (%)
Frontal Cortex	0	7.6	7.6	1
	1	0	0	38
	2	0.8	0.8	26
	3	1.1	1.1	22
	4	1.9	1.9	14
Temporal Cortex	0	7.1	7.1	1
	1	0	0	35
	2	0.6	0.6	26
	3	0.9	0.9	22
	4	1.6	1.6	16
Hippocampus	0	15.3	15.4	< 1
	1	0	0	36
	2	0.4	0.4	29
	3	1.3	1.2	19
	4	1.7	1.6	16

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.

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; TSPO, translocator protein; V_T, total distribution volume.

[a]Weights calculated using LOOC scores.

Table 3.

Bayes Factors (BF) of Hypothesis Testing of the Difference in Standardized Brain TSPO Binding (Estimated Using V_T) Between Patients and Control Subjects Using the Best-Fitting Model (M1)

Region	H0:H1	H1:H0	H0:H2	H2:H0	H1:H2	H2:H1
FC	13.0	0.08	0.03	32.5	0.002	422.9
TC	12.9	0.08	0.03	34.2	0.002	440.6
HIP	16.6	0.06	0.001	1481.0	< 0.001	24524.0

FC, frontal cortex; H0, null hypothesis; H1, hypothesis 1; H2, hypothesis 2; H0:H1, BF denoting evidence in favor of H0 over H1; H1:H0, BF denoting evidence in favor of H1 over H0; H0:H2, BF denoting evidence in favor of H0 over H2; H2:H0, BF denoting evidence in favor of H2 over H0; H1:H2, BF denoting evidence in favor of H1 over H2; H2:H1, BF denoting evidence in favor of H2 over H1; HIP, hippocampus; M1, Model 1; TC, temporal cortex; TSPO, translocator protein; V_T, total distribution volume.