Meta-analysis of the glial marker TSPO in psychosis revisited: reconciling inconclusive findings of patient-control differences - Result Report

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10/05/2020

Descriptive data

The table below displays the demographic data of the included studies.

Table 1: Descriptive data of all included studies. DOI, duration of illness; HABs, high-affinity binders; HCs, healthy control subjects; MABs, mixed-affinity binders; PANSS-N, PANSS–Negative score; PANSS-P, PANSS–Positive score; Pat, participants with psychosis or schizophrenia.

Diagnostic group	Schizophrenia/ Other*	Age Years Mean (SD)	Count	HABs	MABs	Men	Women	PANSS-P Mean (SD)	PANSS-N Mean (SD)	DOI Months Mean (SD)	Drug free/ Total	Radioligand
Collste et al.												
HC	-	26.38 (8.44)	16	9	7	7	9	-	-	-	-	[11C]PBR28
Pat	4/12	28.50 (8.37)	16	8	8	11	5	20.3 (4.9)	18.1 (7.0)	7.9 (9.6)	16/16	[11C]PBR28
Laurikainen et al.												
HC	-	29.7 (7.45)	15	9	6	5	10	-	-	-	-	[11C]PBR28
Pat	4/9	24.8 (4.00)	13	8	5	7	6	**	**	3.9 (3.4)	2/13	[11C]PBR28
Coughlin et al.												
HC	-	25.36 (4.89)	14	9	5	9	5	-	-	-	-	[11C]DPA173
Pat	12/0	24.33 (3.28)	12	8	4	9	3	13.8 (2.7)	15.8 (4.6)	25.0 (16.3)	2/12	[11C]DPA173
Hafizi et al.												
HC	-	27.17 (9.07)	18	14	4	8	10	-	-	-	-	[18F]FEPPA
Pat	15/4	27.53 (6.78)	19	14	5	12	7	19.2 (3.8)	16.1 (6.1)	33.6 (40.1)	19/19	[18F]FEPPA
Bloomfield et al.												
HC	-	46.21 (13.62)	14	14	0	11	3	-	-	-	-	[11C]PBR28
Pat	12/0	47.00 (9.31)	12	12	0	9	3	17.0 (6.1)	14.1 (4.0)	108.9 (46.7)	0/12	[11C]PBR28
Kenk et al.												
HC	-	54.27 (9.51)	15	10	5	7	8	-	-	-	-	[18F]FEPPA
Pat	16/0	42.50 (14.03)	16	10	6	10	6	19.3 (2.2)	18.6 (5.0)	177.3 (105.7)	0/16	[18F]FEPPA
Ottoy et al.												
HC	-	27.1 (5.69)	15	6	9	15	0	-	-	-	-	[18F]PBR111
Pat	11/0	30.6 (7.65)	11	6	5	11	0	24.3 (5.6)	17.4 (7.3)	62.2 (96.1)	1/11	[18F]PBR111
All												
HC	-	33.5 (13.6)	107	71	36	62	45	-	-	-	-	-
Pat	74/25	32.4 (11.7)	99	66	33	69	30	19.8 (4.9)	16.8 (5.8)	65.9 (87.1)	40/99	-

*For Collste et al. (1) other diagnoses were: 7 schizophreniform disorder, 4 psychosis not otherwise specified, and 1 brief psychosis. For Hafizi et al. (2) other diagnoses were: 3 schizophreniform and 1 delusional disorder. For Laurikainen et al. (3) other diagnoses were: 2 schizophreniform disorder, 4 psychosis not otherwise specified, 2 Major depressive episode, severe with psychotic features and 1 Bipolar disorder, manic episode, severe with psychotic features.

**Laurikainen et al. (3) used the Brief Psychiatric Rating Scale (BPRS) for assessing symptom severity. The BPRS positive mean symptom scale scores were 17.8 (SD = 7.1), and BPRS mean negative symptom scale scores were 17.0 (SD = 6.4) for patients.

Fourteen healthy-control subjects were shared across two of the original studies (2, 4). In this meta-analysis, healthy control subjects from these two studies have been uniquely assigned to either one of the studies, so that no subject's V_T value appears more than once in the statistical models. Assignment was done as to best match the patient groups based on count, genotype, gender, and age.

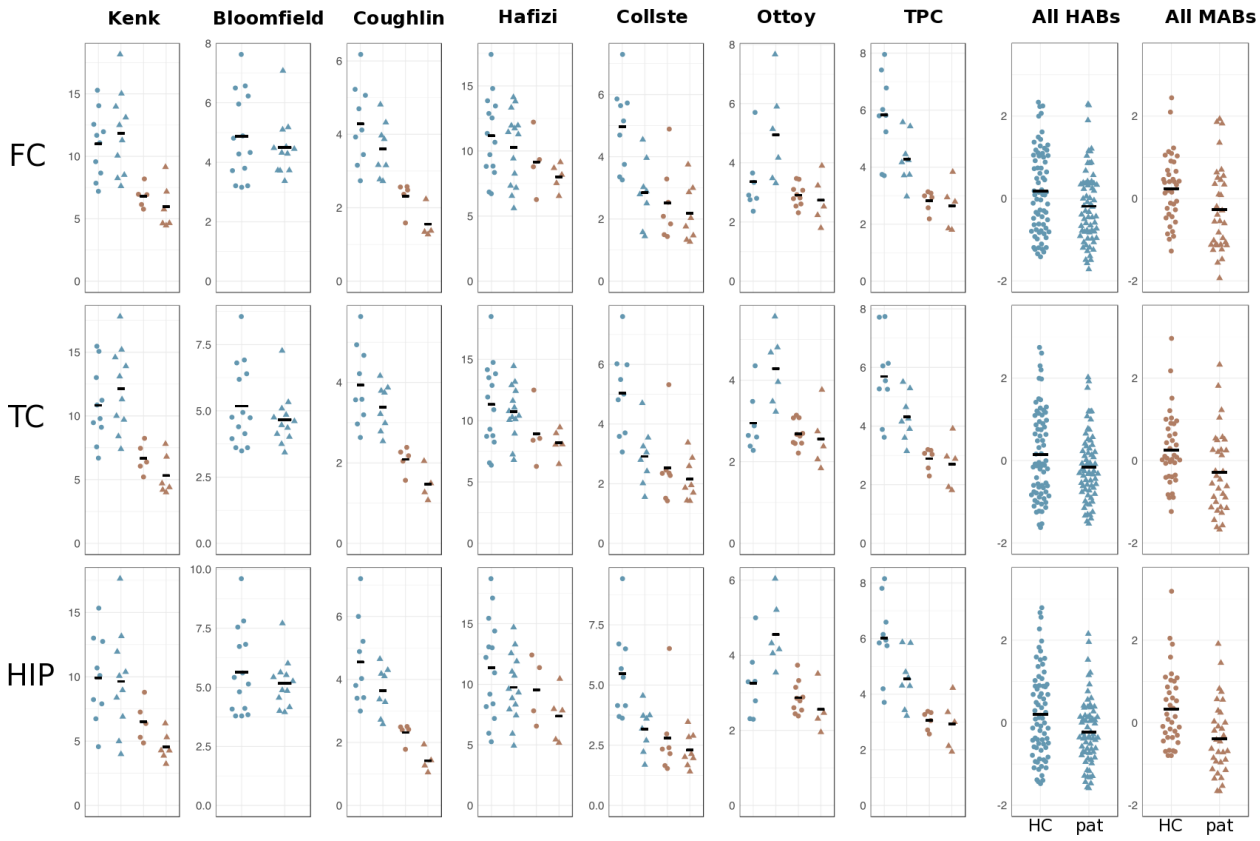

Figure 1: Individual participant data showing translocator protein levels (estimated using VT) in participants with first-episode psychosis or schizophrenia and healthy control subjects, from all seven included studies, from frontal cortex (FC), temporal cortex (TC), and hippocampus (HIP). The black bars denote the group means. For each region, subjects' VT 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.

Figure 1 shows the rae VT data from all included studies. The the right most panel data for all HABs and MABs have been pooled. VT values have been z-scored (mean set to 0 and SD set to 1) within each genotype group to allow for visualization.

Hypotheses testing

Three hypotheses were examined:

- H0: No difference in V_T between patients and controls
- H1: Patients have higher V_T as compared to controls
- H2: Patients have lower V_T as compared to controls

Frequentist stats

Results from LME model including only genotype as covariate:

Table 2: Association between VT and Patient-Control status

Region	Estimate	SE	t	df	p
FC	-0.41	0.13	-3.11	205	0.0022
TC	-0.38	0.13	-2.85	205	0.0048
HIP	-0.53	0.13	-4.02	203	0.0001

Results from LME model including genotype as covariate and age and sex as additional predictors:

Table 3: Association between VT and Patient-Control status while controlling for age and sex.

Region	Estimate	SE	t	df	p
Patient-Control status					
FC	-0.37	0.13	-2.82	203	0.0053
TC	-0.34	0.13	-2.60	203	0.0101
HIP	-0.50	0.13	-3.79	201	0.0002
Age					
FC	0.00	0.07	-0.06	203	0.9488
TC	-0.01	0.07	-0.11	203	0.9120
HIP	-0.03	0.07	-0.38	201	0.7080
Sex					
FC	-0.37	0.14	-2.70	203	0.0076
TC	-0.31	0.14	-2.24	203	0.0259
HIP	-0.28	0.14	-2.08	201	0.0392

When controlling for sex and age, patient-control status remain a significant predictor for VT in all three regions. Hence, lower VT in patients does not appear to be explained by either of these two variables. VT is significantly lower in males compared to females.

Bayes factor

The Bayes Factors show that there is strong evidence in data for the hypothesis that patients have lower VT than HC in all three regions, compared to patients having higher VT than HC.

Table 4: BF10 - Higher in patients v.s. no difference; BF20 - Lower in patients v.s. no difference; BF12 - Higher in patients v.s. lower in patients

Region	BF10	BF01	BF20	BF02	BF12	BF21
FC	0.13	7.73	8.28	0.12	0.02	64.01
TC	0.16	6.39	5.03	0.20	0.03	32.11
HIP	0.16	6.26	24.12	0.04	0.01	150.98

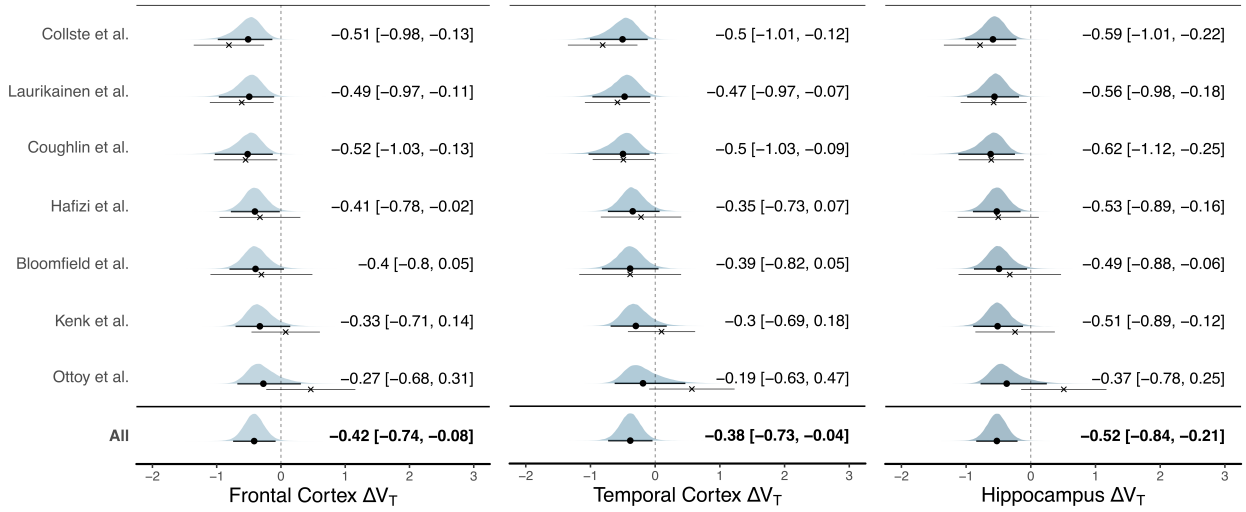

Figure 2: Estimated standardized difference in VT using a Bayesian linear effects model, with study as random effect. The black circle denotes the posterior mean, and the thick line denotes the 95% credible interval of the estimated random slopes (study specific effects); these are also presented in text next to the plots. The cross denotes the patient–control mean difference in raw data (together with its 95 percent confidence interval) without performing linear mixed-effects modeling. Hence, the difference between the dot and the cross displays the model shrinkage towards the mean.

Parameter estimation

Figure 2 shows the meta-analytic estimate of on overall patient-control difference in VT. The overall effect suggest that patients have lower VT in all three regions compared to controls. The posterior distributions are centered around what is commonly interpreted as a "medium" sized effect. The 95% credible intervals does however indicate that the uncertainty of the overall effect range from a negligible effect (i.e. a Cohen's D close to 0) to a large effect (i.e. a Cohen's D close to 1).

Secondary analyses

Effect of medication

When adding anti-psychotic medication-status (medicated or non-medicated) as predictor, it shows no significant association to VT in any of the three regions. Patient-control status also remains a significant predictor of VT.

Table 5: Association between VT and medication status.

Region	Estimate	SE	t	df	p
Patient-control status					
FC	-0.37	0.13	-2.82	203	0.0053
TC	-0.34	0.13	-2.60	203	0.0101
HIP	-0.50	0.13	-3.79	201	0.0002
medication status					
FC	0.10	0.20	0.50	204	0.6151
TC	0.08	0.20	0.43	204	0.6658
HIP	0.08	0.19	0.41	202	0.6822

Symptom severity

Association between VT and PANSS-Positive (or equivalent) and PANSS-Negative (or equivalent) in all three regions.

Table 6: Association between VT and symptom severity

Region	Estimate	SE	t	df	p
PANSS-Positive					
FC	0.05	0.09	0.55	110.00	0.5844
TC	0.05	0.09	0.61	102.67	0.5437
HIP	0.01	0.08	0.06	104.88	0.9490
PANSS-Negative					
FC	-0.01	0.09	-0.09	110.00	0.9259
TC	0.02	0.09	0.18	102.49	0.8610
HIP	-0.01	0.08	-0.11	104.75	0.9104

There is no significant association between VT and PANSS-Positive or PANSS-Negative scores in any of the three regions.

Duration of illness

Table 7: Association between VT and duration of illness

Region	Estimate	SE	t	df	p
FC	0.06	0.10	0.64	96.00	0.5269
TC	0.05	0.09	0.51	10.45	0.6212
HIP	0.01	0.09	0.15	95.00	0.8824

There is no significant association between VT and duration of illness in any of the three regions.

Exploratory analyses

The following analyses were not part of the pre-registration, and performed after seeing the results of the analyses above.

Age-Group interaction effect

Results from LME model including genotype as covariate and a patient-control status v.s. age interaction effect:

Table 8: Association between VT and age-group interaction effect.

Region	Estimate	SE	t	df	p
Patient-Control status					
FC	-0.37	0.13	-2.81	202	0.0054
TC	-0.34	0.13	-2.59	202	0.0103
HIP	-0.50	0.13	-3.79	200	0.0002
Patient-Control status Age interaction					
FC	0.06	0.13	0.46	202	0.6438
TC	0.00	0.14	0.03	202	0.9723
HIP	-0.04	0.13	-0.31	200	0.7600

The patient-control status to age-interaction was not significant, indicating no differential age effect on patients' and controls' VT values in any of the three regions of interest.

Sex-Group interaction effect

Results from LME model including genotype as covariate and a patient-control status v.s. sex interaction effect:

Table 9: Association between VT and sex-group interaction effect.

Region	Estimate	SE	t	df	p
Patient-Control status					
FC	-0.50	0.22	-2.27	203	0.0243
TC	-0.52	0.22	-2.31	203	0.0218
HIP	-0.79	0.22	-3.60	201	0.0004
Patient-Control status Sex interaction					
FC	0.20	0.28	0.74	203	0.4594
TC	0.27	0.28	0.96	203	0.3398
HIP	0.45	0.27	1.66	201	0.0981

The patient-control status to sex-interaction was not significant, indicating no differential sex effect on patients' and controls' VT values in any of the three regions of interest.

References

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3. Laurikainen H, Vuorela A, Toivonen A, Reinert-Hartwall L, Trontti K, Lindgren M *et al.* (2020): Elevated serum chemokine CCL22 levels in first-episode psychosis: associations with symptoms, peripheral immune state and in vivo brain glial cell function. *Translational psychiatry.* In press.

4. Kenk M, Selvanathan T, Rao N, Suridjan I, Rusjan P, Remington G *et al.* (2015): Imaging neuroinflammation in gray and white matter in schizophrenia: an in-vivo PET study with [18F]-FEPPA. *Schizophrenia bulletin.* 41: 85–93.