Pre-registration of analysis procedure: PET studies of the glial marker TSPO in psychosis patients - a follow-up meta-analysis using individual participant data

Pontus Plavén-Sigray

September 12, 2019

1) What's the main question being asked or hypothesis being tested in this study?

The study will examine whether patients with psychosis disorder have 1. increased, 2. decreased or 3. unchanged levels of Translocator Protein (TSPO) distribution volume (V_T) in the central nervous system compared to healthy controls.

2) Describe the key dependent variable(s) specifying how they will be measured.

TSPO V_T in three regions of interest (ROIs): hippocampus, temporal cortex (TC) and frontal cortex (FC).

Included studies

This study is a follow-up to an already published individual participant meta-analysis (P. Plavén-Sigray et al. 2018). The aim of the present meta-analysis is to complement the initial study with new data comparing TSPO V_T values between patients with psychosis and healthy controls using second generation TSPO radioligands. Hence, this follow-up study aims to include data from Ottoy et al. (2018) as well as (at the time of writing this document) unpublished data from a study carried out by the Turku PET center.

Data retrieval and quality control

The corresponding authors of the following studies included in the original meta-analysis (P. S. Bloomfield et al. 2015; K. Collste et al. 2017; J. M. Coughlin et al. 2016; Hafizi et al. 2017; Kenk et al. 2015) will be contacted again and asked to contribute with the same data as they did in the original meta-analysis (P. Plavén-Sigray et al. 2018).

The corresponding authors of the new studies will be contacted and asked to share individual participant V_T values from hippocampus, TC and FC, as well as gender, age, TSPO genotype status, medication status, duration of illness and symptom severity scores (such as PANSS or equivalent). When applicable, the data will then be quality controlled by comparing the descriptive statistics of the shared data with those reported in the original articles.

3) How many and which conditions will participants be assigned to?

Two main conditions: Patients with psychosis disorder and healthy controls.

4) Specify exactly which analyses you will conduct to examine the main question/hypothesis.

Statistical model specification

A Bayesian linear mixed effects (LME) model will be specified and run:

- Individual participant ROI V_T values as dependent variable.
- Patient-control group variable as a fixed effect.
- Genotype (HAB or MAB) variable as a covariate (fixed effect)).
- Study as a level 2 random effect (allowing intercepts and slopes to vary).

In addition to the above, we will also run a sepperate analysis adding age and gender as predictors to the model, to examine if controlling for these variables changes the patient-control difference in V_T.

See Appendix - "Specification of Bayesian LME model" for full specification of the statistical model.

Parameter estimation

The effect size of difference between patients and healthy controls (and its 95% credible interval) will be assessed for each ROI using a LME model with a weakly regularizing non-truncated prior distribution over the fixed effect of patient-control status (mean = 0, SD = 10). The reason for this is to provide the field with a robust, accessible and easy to interpret effect size (with credible intervals) for patient-control difference in TSPO V_T.

Hypotheses testing

The statistical model will also be used to evaluate the following hypotheses:

- 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

for each ROI.

The prior on patient-control fixed effect will be a truncated Gaussian distribution with mean = 0 and SD = 0.5, with a lower bound of 0 for H1 and and upper bound of zero for H2. A SD of 0.5 is chosen since it corresponds to a expected medium effect size of the fixed effect (Dienes 2014). The prior over the random effect (Study) will be weakly informative half-Cauchys (scale = 0.707) since the number of groups (both for genotype and for study) is small (Gelman 2006).

For each ROI, Bayes factor will be computed in favor of H1 (there is an increased V_T in patients) compared to the H0 (the fixed effect of patient-control variable is zero). Bayes factor will also be computed in favor of H2 (there is a decreased V_T in patients) compared to H0. Finally, Bayes factor in favor of H1 over H2 will also be computed.

5) Any secondary analyses?

Drug free and medicated patients

If possible, the patient sample will be divided into: patients on medication and patients that are drug free. The same model as specified under "Parameter estimation" will then be run with an additional fixed-effect: medication status. The posterior of this predictor can be extracted and parameter estimation can be performed to conclude how plausible an effect of medication is.

Symptom severity and duration of illness

The association between TSPO V_T values and symptom severity (assessed using e.g. PANSS-Positive, PANSS-Negative and/or PANSS-Total or equivalent measures) will also be examined using the same Bayesian LME model specified under "Statistical model specification" but the patient-control group status fixed-effect will be replaced with symptom severity scores. The association between TSPO V_T values and duration of illness will also be examined using the same Bayesian LME model specified under "Statistical model specification" but the patient-control group status fixed-effect will be replaced with duration of illness measured in months.

Frequentist models

In addition to all Bayesian LME models above, equivalent frequentist versions will also be run. P-values for the fixed-effect of interest (e.g. patient-control status, medication status, duration of illness or symptom severity) will be calculated by testing the improvement in fit from an identical model that does not include the fixed effect of interest (a "null-model"). Alpha will be set to 0.05 for all analyses.

6) Anything else you would like to pre-register? (e.g., data exclusions, variables collected for exploratory purposes, unusual analyses planned?)

All V_T values (dependent variable) will be z-transformed (centered and divided by the SD) within each genotype group, within each study, to account for range differences between different TSPO radioligands used in the studies.

7) Have any data been collected for this study already?

Yes, all data have been collected.

8) Appendix

Specification of Bayesian LME model:

$$y_i \sim N(\mu_i, \sigma)$$
$$Model:\ \mu_i = \beta_0 + \beta_1 x_i + \beta_{2,3,4,...} x_i + w_{0k} + w_{1k} x_i$$
$$\begin{pmatrix} w_{0k} \\ w_{1k} \end{pmatrix} \sim MV\ Normal\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} {\sigma_{w0}}^2 & \rho_w \sigma_{w0} \sigma_{w1} \\ \rho_w \sigma_{w0} \sigma_{w1} & {\sigma_{w1}}^2 \end{pmatrix} \right)$$
$$\sigma \sim Student's\, t(3, 0, 10) T(0, \infty)$$
$$\beta_0 \sim Student's\, t(3, 0, 10)$$
$$\beta_1 \sim Normal(0, 0.5) T(0, \infty)^{\mathrm{A}} \ \vee \ \beta_1 \sim N(0, 0.5) T(\infty, 0)^{\mathrm{B}}$$
$$\beta_{2,3,4,...} \sim Normal(0, 1)$$
$$\sigma_{u_0}, \sigma_{w_0} \sim Cauchy(0, \sqrt{(}2)/2) T(0, \infty)$$
$$\sigma_{u_1}, \sigma_{w_1} \sim Cauchy(0, \sqrt{(}2)/2) T(0, \infty)$$
$$\rho_u, \rho_w \sim Uniform(-1, 1)$$
$$i \in \{Subject_1, Subject_2, Subject_3 ...\}$$
$$x_i \in \{Patient, Control\}$$
$$j \in \{HAB, MAB\}$$
$$k \in \{Study_1, Study_2, Study_3, ...\}$$

where y_i is ROI V_T for subject i, $beta_1$ is the fixed effect for diagnostic group (ΔV_T), $beta_{2,3,4,...}$ are the covariates to be included (such as sex, age and genotype status), w_{0k} and w_{1k} are the intercept and slope for Study k. A corresponds to $H1$ and B corresponds to $H2$.

Please note that priors on random effects and co-variates are not final! These may be changed after having run the model with all data included in order to facilitate model convergence.

References

Bloomfield, Peter S., Sudhakar Selvaraj, Mattia Veronese, Gaia Rizzo, Alessandra Bertoldo, David R. Owen, Michael A.P. P Bloomfield, et al. 2015. "Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [11C] PBR28 PET brain imaging study." *American Journal of Psychiatry* 173 (1). Am Psychiatric Assoc: 44–52. doi:10.1176/appi.ajp.2015.14101358.

Collste, K, P Plavén-Sigray, H Fatouros-Bergman, P Victorsson, M Schain, A Forsberg, N Amini, et al. 2017. "Lower levels of the glial cell marker TSPO in drug-naive first-episode psychosis patients as measured using PET and [11C]PBR28." *Molecular Psychiatry* 22 (6). Nature Publishing Group: 850–56. doi:10.1038/mp.2016.247.

Coughlin, J M, Y Wang, E B Ambinder, R E Ward, I Minn, M Vranesic, P K Kim, et al. 2016. "In vivo markers of inflammatory response in recent-onset schizophrenia : a combined study using [11 C] DPA-713 PET and analysis of CSF and plasma." *Translational Psychiatry* 6 (4). Nature Publishing Group.

Dienes, Zoltan. 2014. "Using Bayes to get the most out of non-significant results." *Frontiers in Psychology* 5. Frontiers: 781.

Gelman, Andrew. 2006. "Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper)." *Bayesian Analysis* 1 (3). International Society for Bayesian Analysis: 515–34.

Hafizi, Sina, Huai Hsuan Tseng, Naren Rao, Thiviya Selvanathan, Miran Kenk, Richard P. Bazinet, Ivonne Suridjan, et al. 2017. "Imaging microglial activation in untreated first-episode psychosis: A PET study with [18F]FEPPA." *American Journal of Psychiatry* 174 (2): 118–24. doi:10.1176/appi.ajp.2016.16020171.

Kenk, Miran, Thiviya Selvanathan, Naren Rao, Ivonne Suridjan, Pablo Rusjan, Gary Remington, Jeffrey H Meyer, Alan A Wilson, Sylvain Houle, and Romina Mizrahi. 2015. "Imaging neuroinflammation in gray and white matter in schizophrenia: an in-vivo PET study with [18F]-FEPPA." *Schizophrenia Bulletin* 41 (1). MPRC: 85–93.

Ottoy, Julie, Livia De Picker, Jeroen Verhaeghe, Steven Deleye, Lauren Kosten, Bernard Sabbe, Violette Coppens, Maarten Timmers, Luc Van Nueten, and Sarah Ceyssens. 2018. "[18F] PBR111 PET Imaging in Healthy Controls and Schizophrenia: Test–Retest Reproducibility and Quantification of Neuroinflammation." *Journal of Nuclear Medicine*. Soc Nuclear Med, jnumed–117.

Plavén-Sigray, Pontus, Granville J Matheson, Karin Collste, Abhishekh H Ashok, Jennifer M Coughlin, Oliver D Howes, Romina Mizrahi, Martin G Pomper, Pablo Rusjan, and Mattia Veronese. 2018. "Positron Emission Tomography Studies of the Glial Cell Marker Translocator Protein in Patients With Psychosis: A Meta-analysis Using Individual Participant Data." *Biological Psychiatry* 84 (6). Elsevier: 433–42.