MegaEntropy-Psilocybin NRU (#103872)

Created: 08/02/2022 06:42 AM (PT)
Public: 08/03/2022 04:51 AM (PT)

Author(s)
Drummond McCulloch (Neurobiology Research Unit, Rigshospitalet, Copenhagen) - drummond.mcculloch@nru.dk
Anders Stevnhoved-Olsen (Neurobiology Research Unit, Rigshospitalet, Copenhagen) - anders.s.olsen@nru.dk
Patrick Fisher (Neurobiology Research Unit, Rigshospitalet, Copenhagen) - patrick.fisher@nru.dk

1) Have any data been collected for this study already?
It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in this study?
Psilocybin administration will be associated with changes in various measures of entropy, derived from resting-state blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI, rs-fMRI), described in previous studies. The magnitude of this change in BOLD entropy measures will be associated with plasma psilocin level, estimated 5-HT2A receptor occupancy, and subjective drug intensity.

3) Describe the key dependent variable(s) specifying how they will be measured.
Plasma psilocin level (PPL) / 5-HT2AR occupancy – Intravenous blood samples are drawn following each rs-fMRI scan. The concentration of free, unconjugated psilocin in plasma is measured using liquid chromatography / mass spectrometry and a validated method at the Department of Forensic Medicine at Copenhagen University Hospital (Rigshospitalet). Based on the occupancy curve described in 10.1038/s41386-019-0324-9 these PPL values will be converted to estimated 5-HT2A receptor occupancy values. Subjective drug intensity (SDI) – Following each rs-fMRI scan (and otherwise at ~20 min intervals), participants are verbally asked and verbally respond to the question: "On a scale from 0 to 10, how intense is your experience right now?" (Translated from Danish)

4) How many and which conditions will participants be assigned to?
Participants completed a single-blind, crossover study design. On each intervention day, participants received either 20 mg ketanserin or ~0.3 mg/kg psilocybin in a randomised order, 3-4 weeks apart. Both drugs were administered peroral. On both intervention days, participants completed multiple rs-fMRI scan sessions (length: 10 mins) on one of two different MR scanners. Prior to drug administration, participants completed a single rs-fMRI scan session. Participants completed approximately three rs-fMRI scans between 40 and 180 minutes post-drug. Participants completed an additional rs-fMRI scan session at ~300 minutes post-drug following psilocybin administration. A blood sample for PPL quantification and an assessment of SDI was acquired after every rs-fMRI scan session.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
We will evaluate whether we replicate similar effects of acute psilocybin administration on BOLD entropy measures described previously. We will compute BOLD entropy measures as previously described (below) on our own rs-fMRI data acquired in 28 participants before and following intervention with psilocybin and ketanserin. We will calculate BOLD entropy measures for each rs-fMRI session. BOLD entropy measures will be computed following an SPM/Conn-based pre-processing and denoising of rs-fMRI data. Our default SPM-based preprocessing pipeline, includes 1) slice-timing correction (except multiband data), 2) motion correction, 3) bias field unwarping, 4) coregistration, 5) normalization into MNI152 standard space, and 6) smoothing (5mm FWHM). If we are not able to sufficiently replicate an entropy measure reported in a study that applied a different pre-processing pipeline, we may attempt to more closely replicate the previously reported pre-processing pipeline to assess it as a potential source of the discrepant outcome. We will use CONN to denoise rs-fMRI time series, including regressing out the first five principal components from voxelwise WM and CSF time series and their first derivatives (aCompCor), motion parameters (and first derivative) and volumes flagged by ART (default settings). We will apply a bandpass filter to the time series. Denoised time series will be used for subsequent analyses and quantifications. As relevant, region-to-region connectivity measures will be calculated in CONN, using Fisher's r-to-z transformation of the Pearson's correlation coefficient between time series. Regions will be defined by the same atlas applied in the original manuscript. For certain BOLD entropy measures derived from voxel-wise signals, we will also employ the same post-preprocessing steps as in the original manuscript, e.g., voxel-wise filtering. Cerebellar regions in certain atlases were removed from analyses as they were outside of the FoV of the scan. BOLD entropy metrics are described in: DOI: 10.3389/fnhum.2014.00020, 10.1002/hbm.2256, 10.1002/hbm.22833,10.1002/hbm.23234,10.1038/s41598-017-06854-0, 0.1038/s41598-020-59282-y,10.1016/j.neuroimage.2020.117049,10.1073/pnas.1921475117, 10.1101/2021.05.14.444193. Once a BOLD entropy measure is calculated for each scan, the association between these values and PPL, estimated 5-HT2AR Occupancy, or SDI are calculated using a mixed effects model with subject ID as a random variable. As an approximation of previous studies that compared pre-drug and post-drug scans, we will perform comparisons between pre-drug and the scan with the highest PPL level. Secondly, we will investigate the extent to which each of the above entropy metrics are intercorrelated. Covariates will be determined based on maximum likelihood estimation.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Scans will be excluded that: Have >50% of volumes flagged by ART for excessive signal variation or movement. Were stopped prematurely. Had technical failures during data collection Have missing BOLD signal that prohibits analysis.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.

Data was acquired in 28 healthy participants. Data collection is complete.

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

Secondary hypotheses: Entropy measures described by Singleton 2021 and Kringelbach 2020 will be highly correlated. Entropy measures described by Viol 2017 and Lebedev 2015 will be highly correlated. All entropy measures will be at least moderately correlated. There will be a drug x time interaction effect on BOLD entropy (drugs = psilocybin or ketanserin).

We believe that this is a valid pre-registration because although we have collected this data, it has not been analysed in this way. 15 of these sessions are reported in 10.1016/j.euroneuro.2021.06.001 but use an entirely different analysis framework.