Replication Recipe (Brandt et al., 2013): Pre-Registration

Yoon et al., 2022 - “Abnormal tau in amyloid PET negative individuals”

The Nature of the Effect

Description

Verbal description of the effect I am trying to replicate

I am trying to replicate the examination of older adults with evidence of tauopathy without amyloid-beta (A-T+) and compare them to A-T- and A+T+ groups.

Firstly, I will check if A-T+ group displays similar differences in demographics to the other two groups (i.e., age, education, APOE e4, cognitive function) as in the original paper (Table 1; Yoon et al. 2022).

Secondly, I will investigate if amyloid-beta negative tau positive (A-T+) older adults have intermediate tau levels in Braak 1, Braak 34, Braak 56, and metatemporal ROI when compared to A-T- and A+T+ while adjusting for age, sex, and clinical diagnosis (Fig 1; Yoon et al. 2022).

Thirdly, I will see if the tau deposition follows similar patterns between the groups as in the original paper (Fig 3; Yoon et al. 2022).

Replication Importance

It is important to replicate this effect because

The authors of the original work have attempted to characterize older adults according to ATN criteria with a focus on A-T+ subjects to create a better understanding of this subgroup of subjects. It is important to try to create more definitions for these subgroups which are very heterogeneous to gain a better understanding of how to treat them later.

This replication is important to validate their study findings on an independent dataset to confirm whether the effects are valid.

Effect Size

The effect size of the effect I am trying to replicate is

Unfortunately, the original study did not report the effect sizes in their paper, but only the significance levels via p-values of the statistical tests. Therefore, I can only describe the comparison differences via the direction of the effect and the significance level.

Demographics analysis (Table 1):

- A-T+ was older than A-T- ($p<0.05$).

- No gender differences.
- A-T+ had more education years than A+T+ ($p<0.05$).
- Percentage of APOE e4 carriers in A-T+ was similar with A-T- ($p>0.05$) but lower than in A+T+ ($p<0.05$).
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Main analysis (Fig 1):

- Tau levels between all three groups for all four ROIs in the original paper were statistically significant where the differences where following A-T- < A-T+ < A+T+ formula ($p < 0.001$; ANCOVA after adjusting for age, sex, diagnosis with Bonferroni correction).

Additional analysis (Fig 3):

- Qualitatively compared to the A-T+ group, the A+T+ group shows a more widespread distribution of tau deposition extending to parietal, frontal, and occipital lobes, but similar patterns showing amygdala, temporal and orbitofrontal lobes.

Confidence Interval
The confidence interval of the original effect is

N/A

Sample Size
The sample size of the original effect is

n (A-T-) = 316
n (A-T+) = 63
n (A-T+) = 182

Original Study Conducted
Where was the original study conducted? (e.g., lab, in the field, online)

The study was conducted with the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.

Region
What country/region was the original study conducted in?

63 sites in US and Canada

Original Sample Size
What kind of sample did the original study use? (e.g., student, Mturk, representative)

Observational cohort of older adults with and without Alzheimer's disease pathology.

Original Data Collection
Was the original study conducted with paper-and-pencil surveys, on a computer, or something else?

The study used already collected data from different medical centers.

Designing the Replication Study

Original Materials Available

Are the original materials for the study available from the author?

- **no**

Assumptions

I know that assumptions (e.g., about the meaning of the stimuli) in the original study will also hold in my replication because

Due to the nature of medical data and similar population and study design of the replication dataset, the results should not vary too much.

Data Collection Location

Location of the experimenter during data collection

Region Skåne Memory Clinic, Sweden

Knowledge of Experimental Condition

Experimenter knowledge of participant experimental condition

N/A

Knowledge of Hypotheses

Experimenter knowledge of overall hypotheses

N/A

Sample Size Target

My target sample size is

Aim to use all individuals from the BioFINDER-2 cohort that fit the inclusion/exclusion criteria defined in the original study.
Initial sample size estimate is 1249 participants (A-T- = 415; A-T+ = 183; A+T+ = 562). This is not considering having an MRI scan or CSF measures.

Sample Size Rationale

The rationale for my sample size is

An attempt to get a larger sample size than the original study but trying to follow most of the inclusion/exclusion criteria of the original study’s protocol.

Documenting Differences between the Original and Replication Study

Instruction Similarities
The similarities/differences in the instructions are

- **Close**

Measure Similarities
The similarities/differences in the measures are

- **Close**

Stimuli Similarities
The similarities/differences in the stimuli are

- **N/A**

Procedure Similarities
The similarities/differences in the procedure are

- **Close**

Location Similarities
The similarities/differences in the location (e.g., lab vs. online; alone vs. in groups) are

- **Close**

Remuneration Similarities
The similarities/difference in remuneration are

- **Unclear**

Participant Similarities
The similarities/differences between participant populations are

- **Close**

Difference Influencing Effects
What differences between the original study and your study might be expected to influence the size and/or direction of the effect?

The differences could arise from the fact that the original study used 8F-Florbetaben (FBB) or 18F-Florbetapir (FBP) PET for defining amyloid positivity in participants whereas the replication study is using Flutemetamol PET (or CSF Ab42/40 ratio if PET imaging was not available).

In addition to that, the tau-PET tracer used in the original study is 18F-Flortaucipir (FTP) PET, whereas in the replication study the [18F]RO948 tracer is used which is more sensitive for detecting tau pathology.

Data processing pipelines for PET and MRI images vary between the original and replication studies.

Stimuli Similarities

I have taken the following steps to test whether the differences listed in the previous question will influence the outcome of my replication attempt

N/A

Analysis and Replication Evaluation

Exclusion Criteria

My exclusion criteria are (e.g., handling outliers, removing participants from analysis)

Inclusion criteria of the replication follows the same procedure as in the original paper with minor differences.
- Diagnosis either healthy, subjective cognitive decline (SCD), mild cognitive impairment (MCI), or Alzheimer's disease (AD).
- No underlying etiology (e.g., brain tumors, genetic disorders)
- Age over 50 years
- PET (both amyloid and tau) scans acquired
- Have measured Apolipoprotein E genotype
- (optional) Have CSF measures (p-tau181, Ab42, Ab42/40 ratio)
- (optional) Have structural MRI scan for hippocampal volume

Analysis Plan

My analysis plan is (justify differences from the original)

First, I will (1) group participants into three groups – A-T-, A-T+, and A+T+. After that, I will conduct three different analyses – (2) group demographics comparison, (3) tau levels comparison, and (4) tau deposition topography and asymmetry.

(1) Grouping of the participants to A-T-, A-T+, and A+T+ groups:
- Apply all the beforementioned inclusion/exclusion criteria for select subjects for the study
- Amyloid positivity defined by 18F-flutemetamol PET with a composite cut-off of 1.033 and non-partial volume corrected or in case of no available PET, defined by CSF Ab42/40 ratio

    - This varies from the original study as we are using a different PET tracer which has different established cut-off for amyloid positivity
- Tau positivity will be defined by either exceeding threshold SUVRs at Cho I/II regions (same as in the original study, i.e., Braak 1) or Cho III/IV (partial overlap of regions with the original study's used Braak 34) with cut-offs of 1.379 and 1.357, respectively
    - This varies from the original study as we are using a different PET tracer which has different established cut-offs for Cho regions that are overlapping with the original study's used Braak regions

(2) Demographics analysis comparing differences between the groups:
- ANOVA or Kruskal-Wallis tests for 'age' and 'education'
- Chi-square for 'sex' and 'APOEe4 status'
- ANCOVA (adjusting age, sex, education) test for 'MMSE' and 'mPACC'
- ANCOVA (adjusting age, sex, diagnosis) test for 'hippocampal volume' and available amyloid PET (centiloid) and CSF variables (p-tau 181, Ab42, Ab42/40, Ab42/p-tau, p-tau/Ab40)
    - In case of unavailability of some CSF measures, will consider using alternate measures (e.g. another p-tau or plasma measures)

(3) Tau levels comparison between the groups:
- ANCOVA (adjusting age, sex, diagnosis) for Braak1 SUVR, Braak34 SUVR, Braak56 SUVR, and metatemporal ROI SUVR

(4) Tau deposition topography and hemispheric asymmetry:
- Count the ROIs that had the highest SUVR level per subject and plot a histogram and brain surface plot to have a qualitative overview of the group differences.
    - Could attempt to quantify this comparison with Chi-square tests of the distribution between groups (not done in the original study)
- Calculate asymmetry index of all ROIs and plot a forest plot for qualitative overview

Successful Replication

A successful replication is defined as

Partially replicated study findings would be optimal considering some methodologically different procedures between the original and the replication studies (i.e., different PET tracers).
The main aim would be to successfully replicate same direction differences between the groups in tau levels in the regions of interest (see analysis 3 in previous section). We would also expect to see similar demographics differences between the groups.