Hippocampal-cortical co-morphology networks and their phenotypical correlates in healthy adults and MDD patients

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Introduction

- Human hippocampus is a heterogeneous and plastic brain structure that has been associated with a range of behavioural aspects.
- Hippocampal structural and functional alterations are observed across the most frequent neurocognitive disorders, such as major depressive disorder (MDD)[1-3].
- Our aim is to identify the robust and replicable relationships between hippocampus co-morphology networks and interindividual variability in behavioural phenotype.
- These relationships have been usually addressed with univariate analyses and separately. However, these associations would be more comprehensively and robustly captured by using multivariate approaches like multiblock partial least squares (MB-PLS)[4] with a strict cross-validation framework.
- We here explored how hippocampal-brain co-morphological networks relate to sociodemographic and psychometric variables in healthy and MDD patients.

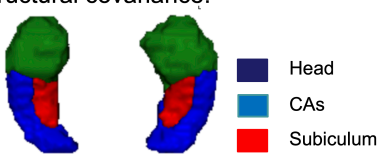
Methods

1) Datasets:

- **HCP Young Adult (HCP-YA):** (S1200), n=1047 (560 females), age (mean ± SD): 28.8 ± 3.7.
- **Rest-MDD:** n=370 (244 females), age (mean ± SD): 33.5 ± 11.8.

Seed data (6 measures):

- Seeds defined as mean grey matter volume (GMV) of bilateral hippocampal subregions based on a tripartite hippocampal parcellation[5] derived from structural covariance.



Behavioural data

HCP-YA : Cognition, Emotion, Sleep, Psychiatric and Life Function, Life outcome (60 measures).

Rest-MDD : Emotion, Insomnia, Body Function, Medication and Life outcome (21 measures)

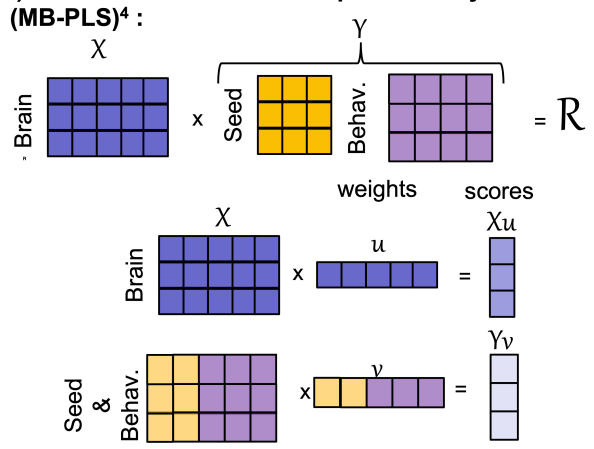
Brain data (232 measures):

- *Grey Matter Volume* (GMV)

2) Processing of brain data:

- GMV: CAT12.5 in HCP-YA;
- Averaged by regions (200 cortical[6], 32 subcortical[7])

3) Multiblock Partial Least Squares Analysis (MB-PLS)[4] :



- X and Y: subjects are in rows, measures are in columns
- MB-PLS finds the weights which maximizing the covariance, R, between X and Y.
- Brain loadings: correlation (X, Xu)
- Behaviour loadings: correlation (Y,vY)
- MB-PLS was applied independently in each cohort.
- Age and gender were regressed out from brain and behaviour.
- For generalizability assessment[8], the data were split into 5 folds (in HCP-YA, splitting was done respecting the family structure).
- The significance of the latent dimensions was assessed with 1000 permutations (also considering the family structure of the data in HCP-YA).

Results

Three dimensions significantly relating interindividual variability in hippocampal subregion's volume, brain GMV and behaviour were identified in both HCP-YA and patients with MDD.

- **First-dimension** (*Range of correlation in the splits: 0.99-1 in HCP-YA and 0.98-0.99 in MDD; p: 0.001*):

It mainly captured overall hippocampal-brain structural covariance with its association to a wide range of behavioural phenotypes. In HCP-YA, the structural covariance pattern of hippocamps is mainly correlated with cognition (e.g., language performance, working memory and fluid intelligence) and life outcome (e.g., education and income). But, in MDD patients the overall hippocampal structural covariance is related to medication and insomnia.

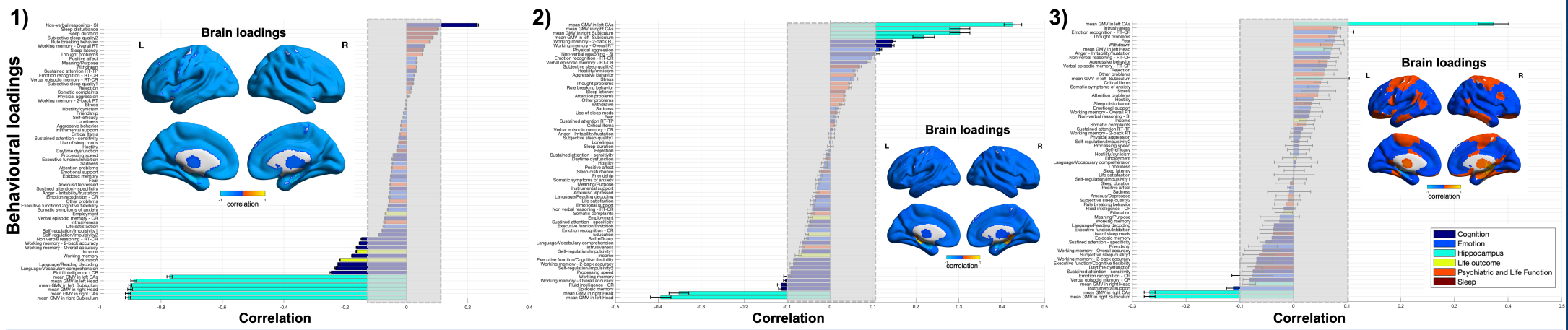
- **Second-dimension** (*0.96-0.98 in HCP-YA and D 0.8-0.9 in MD; p: 0.001*):

It reflects more specifically different covariance pattern for hippocampal head and hippocampal body-tail associated respectively to working and episodic memory performance in HCP-YA. However, in MDD patients, this dimension reflects more specifically covariance between hippocampal head subregion and a network of somatomotor, dorsal attention and limbic regions, in turn mainly correlating with emotion.

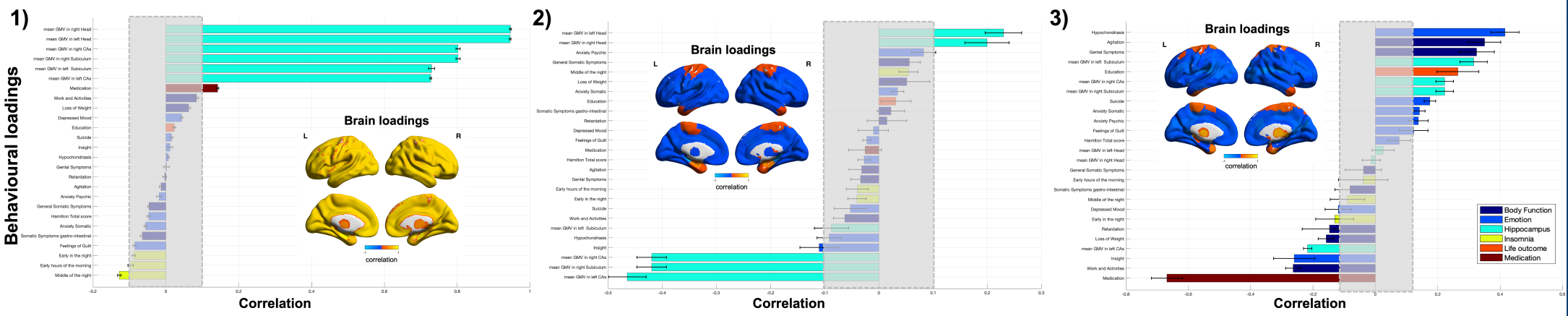
- **Last dimension** (*0.61-0.68 in HCP-YA and 0.54-0.66 in MDD ; p: 0.001*):

This dimension strikingly distinguished right and left hippocampal body-tail subregions as two extreme poles associated with positive behaviour and GMV in dorso-attentional network VS negative behaviour, respectively. But in MDD patients, this dimension mainly identified medication VS symptoms as two extreme poles associated mainly with hippocampal body-tail.

Latent dimensions in HCP-YA



Latent dimensions in MDD



Discussion

- Employing a multivariate approach here provided new insights into relevant dimensions of hippocampal-brain co-morphology and their associations to behavioural phenotype in healthy adults and patients with MDD.
- One dimension captured the structural covariance network of head subregions related to both working memory performance and variability in life style in HCP-YA.
- The above-mentioned dimension in MDD patients reflects more specifically covariance between the hippocampal head subregion and a network of somatomotor, and dorsal/ventral attention that are often functionally impaired in MDD[9].
- Finally, while hippocampal asymmetry with regards to behaviour functions and inter-individual variability has been often assumed, it was clearly captured as a relevant dimension of covariance here in HCP-YA.
- The relationship between individual GMV in the right hippocampus and positive behaviour revealed here should be further explored in future studies as it could contribute to a better understanding of vulnerability and behaviour phenotype in neurological and psychiatric diseases.

References: **1. Kharabian Masouleh 2020**, "Characterizing the gradients of structural covariance in the human hippocampus", Neuroimage; **2. Weissman 2020,** "Reduced hippocampal and amygdala volume as a mechanism underlying stress sensitization to depression following childhood trauma.", Depression and Anxiety; **3. Santos 2018,** "Global hippocampal atrophy in major depressive disorder: a meta-analysis of magnetic resonance imaging studies.", Trends in psychiatry and psychotherapy; **4. McIntosh 2004,** "Partial least squares analysis of neuroimaging data: applications and advances.", Neuroimage; **5. Plachti 2020,** "Hippocampus co-atrophy pattern in dementia deviates from covariance patterns across the lifespan.", Brain; **6. Schaefer 2018,** "Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI", Cereb Cortex; **7. Tian 2020,** "Topographic organization of the human subcortex unveiled with functional connectivity gradients", Nature Neuroscience; **8. Mihalik 2020,** "Multiple Holdouts With Stability: Improving the Generalizability of Machine Learning Analyses of Brain-Behavior Relationships." Biological Psychiatry; **9. Liu 2020,** "Altered Resting-State Functional Connectivity of Multiple Networks and Disrupted Correlation With Executive Function in Major Depressive Disorder", Frontiers in Neurology.

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