Hippocampal volume and functional connectivity differentiate between cognitively normal individuals with and without subjective memory complaints

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Main Question

Do hippocampal volumetric or functional connectivity measures independently or in combination better differentiate between cognitively normal individuals with and without subjective memory complaints?

Introduction

- Subjective cognitive decline (SCD), specifically subjective memory complaints (SMCs), have been shown to be independent predictors of future cognitive decline and its severity.
- Differences in brain and hippocampal structure (van der Flier et al., 2004; Saykin et al., 2006; Hafkemeijer et al., 2013) and resting-state functional connectivity (rsFC) patterns (Wang et al., 2013; Hafkemeijer et al., 2013; Contreras et al., 2017) have been found between individuals with and without reports of SCD and SMCs.
- MRI studies of SCD and SMCs have largely used either volumetric/structural measures or functional measures, but have not assessed these structural and functional measures in the same set of individuals.
- Detailed examinations of hippocampal resting state functional connectivity patterns with the rest of the brain in SCD and SMCs are also lacking in the literature.
- We examined whether hippocampal subfield volume and hippocampal rsFC strength to the rest of the brain could differentiate between individuals without and with SMCs (SMC- and SMC+, respectively).
- Separate nominal logistic regression models using subfield volumes and rsFC strength were built to determine whether structural or rsFC measures resulted in a better model fit.
- A combined model using both subfield volumes and rsFC strength was built to assess whether both types of measures in combination provided a better model fit.

Participant Information

Participants (n=53) were part of the Health Outreach Program for the Elderly (HOPE) study run through the Boston University Alzheimer's Disease Center. All participants received a consensus diagnosis of cognitively normal based on neuropsychological exams and medical history. All participants completed the Cognitive Change Index (CCI). If a participant's CCI score was 16 or greater on the first 12 items (memory items), he or she was classified as having SMCs. Within a year of completing the memory items on the CCI (mCCI), participants were scanned at the Center for Biomedical Imaging (CBI) at the BU School of Medicine on a 3T Philips Achieva System with a 32-channel head coil.

Measure	SMC- (n=24)	SMC+ (n=29)
Age (years)	72.6 (10.3)	71.8 (6.04)
Sex	9M / 15F	10M / 19F
Education (years)	15.5 (2.67)	16.7 (1.93)
Geriatric Depression Scale (GDS)	0.458 (0.977)	0.964 (1.17)*
mCCI (first 12 memory items)	13.4 (1.10)	23.4 (7.07)**
NAB Short Delay (raw score)	8.79 (2.25)	8.41 (2.23)
NAB Long Delay (raw score)	8.54 (2.17)	8.41 (1.97)
NAB Retention (raw score)	0.986 (0.159)	1.04 (0.255)
Trailmaking Test Part B (time)	73.1 (28.1)	74.8 (25.0)
Mean Relative Displacement	0.191 (0.0902)	0.215 (0.104)

* p < 0.05
** p < 0.0001

Methods

MRI Scanning

- T1W scan parameters: TR / TE = 6.7 / 3.1 ms, voxel size = 0.98 x 0.98 x 1.2 mm, flip angle = 9°.
- T2*W resting-state functional MRI scan parameters: blood oxygenation level-dependent contrast, TR / TE = 3000 / 30 ms, voxel size = 3.31 x 3.31 x 3.31 mm, EPI factor = 59.

Image Processing: Volumetric Variables

- FreeSurfer v6.0 was used to automatically calculate whole hippocampal and subfield volumes.
- Whole hippocampal volume was closely related to subfield volumes. To correct for this, left and right subfield volumes were adjusted for left and right whole hippocampal volume, respectively, using a regression model built from data from all 53 participants. Hippocampal-adjusted subfield volumes were used in all analyses.

Image Processing: Resting-State Functional Connectivity Variables

- Each participants' left and right hippocampus (generated in FreeSurfer v6.0) was divided into head, body and tail using the method described in Greene & Killiany (2012).
- Resting-state functional connectivity (rsFC) strength between the left and right head and body of the hippocampus and 264 regions of interest (ROIs) reported in Power et al. (2011) was calculated, yielding 1056 (264 x 4) rsFC measures. MELODIC v3.14 was run on each participant's resting-state data and noise components were removed using FSL-FIX v1.06. Nonlinear registration with a warp resolution of 2mm was used to coregister each participant's data to the MNI152 2mm atlas. Data were band-pass filtered (0.01-0.1 Hz) and bivariate correlations were run between the average timeseries of each hippocampal and Power ROI in CONN toolbox v18.a running in MATLAB R2017a. R values were converted to Z scores in CONN toolbox.
- To meaningfully reduce the number of rsFC variables, t tests were run to determine which rsFC variables were significantly different between SMC- and SMC+ at the p < 0.05 level.

Stepwise Nominal Logistic Regression Models

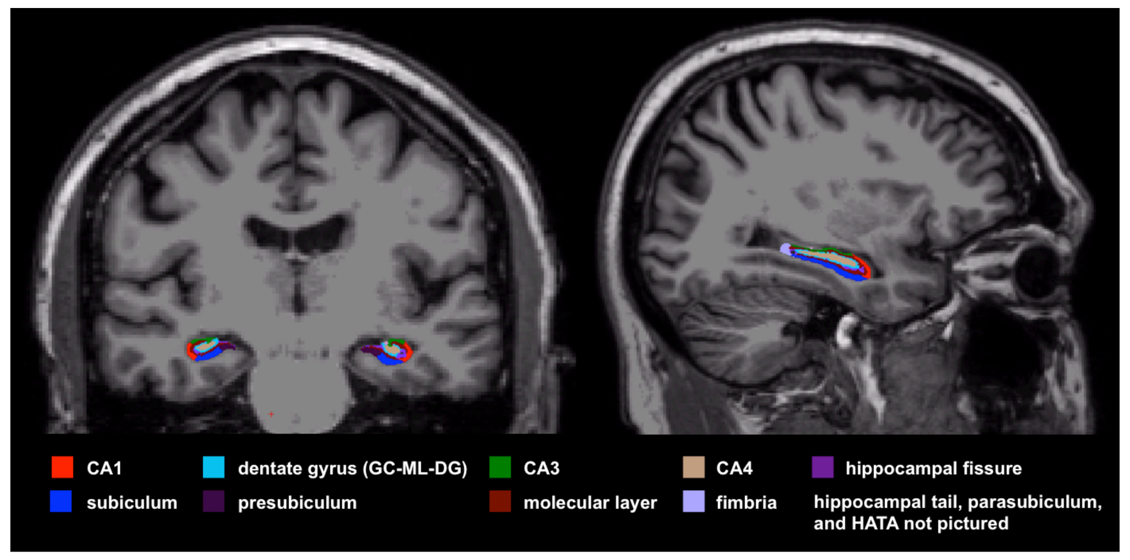
- Collinearity amongst subfield volumes and the reduced set of rsFC variables was assessed. Adjusted subfield volumes with a correlation of 0.7 or greater with other subfield volumes were noted and one variable in each of these correlations was removed. RsFC variables with a correlation of 0.6 or greater with other rsFC variables were noted and one variable in each of these correlations was removed. This resulted in a set of 19 adjusted subfield volumes and 33 rsFC variables.
- In JMP Pro v13, stepwise variable selection was used to select subfield volumes and rsFC variables for separate nominal logistic regression models. A p-value threshold of 0.25 to enter and exit the analysis was set with mixed direction and the combine rule. Separate subfield volume and rsFC models were built. The variables selected for these models were then entered into another stepwise variable selection to build a combined subfield and rsFC model using the same parameters.
- The effects of mCCI score and neuropsychological assessment battery (NAB) memory scores on subfield and rsFC model variables were assessed.

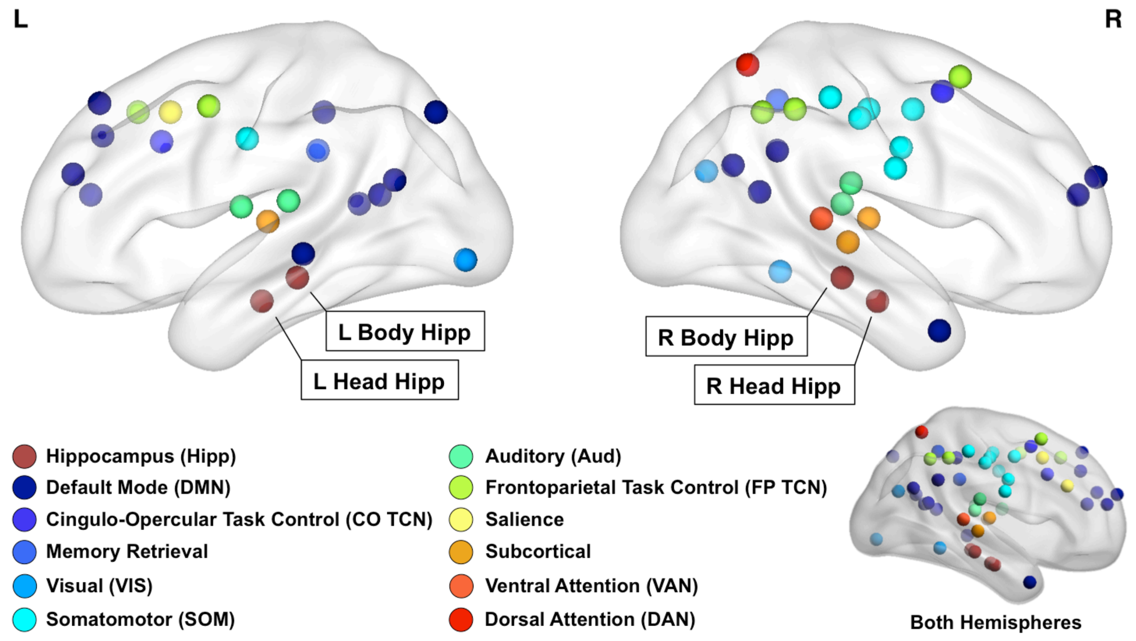
Logistic Regression Models

Model: Hippocampal Subfield Volumes
R^2 = 0.265
p = 0.0017
All variables in model significant (FDR-corrected p < 0.05)
Right presubiculum (smaller in SMC+)
Left subiculum (larger in SMC+)
Left CA1 (smaller in SMC+)
Left GC-ML-DG (larger in SMC+)
Left presubiculum (larger in SMC+)
17/24 SMC- classified accurately
23/29 SMC+ classified accurately

Model: Hippocampal rsFC Strength
R^2 = 0.490
p < 0.0001
5/7 variables in model significant (* = FDR-corrected p < 0.05)
R body hipp – L paracingulate gyrus (FP TCN) *
L head hipp – R lingual gyrus (VIS) *
R head hipp – R precentral gyrus (SOM) *
R body hipp – R precuneus (DMN) *
R body hipp – R precuneus (Memory Retrieval) *
R body hipp – R insula (Aud)
R body hipp – R paracingulate gyrus (DMN)
18/24 SMC- classified accurately
26/29 SMC+ classified accurately

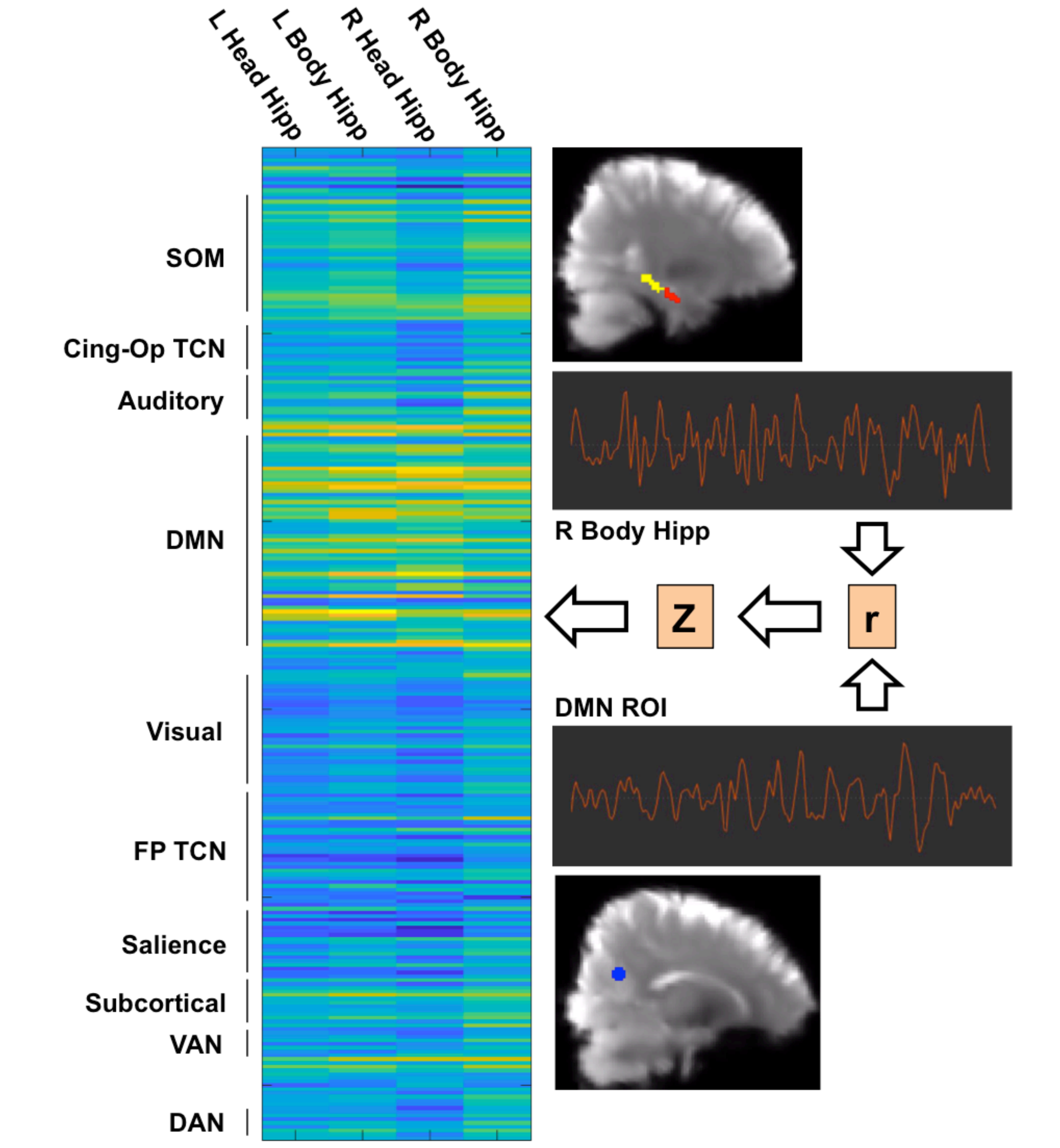
Hippocampal Measures





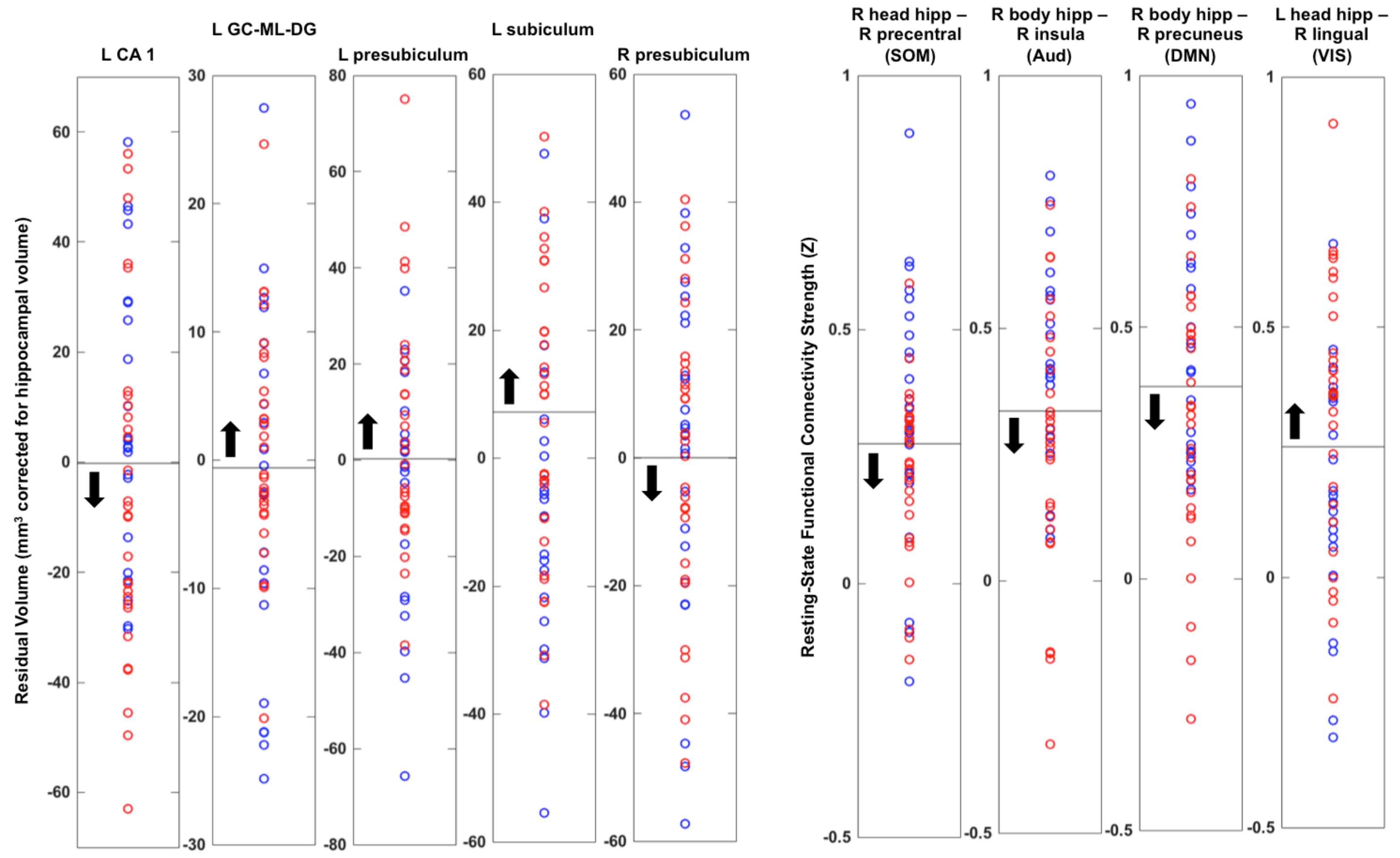
Hippocampal rsFC Strength to x Number of ROIs in the Following Networks Differed between SMC– and SMC+ at p < 0.05 (displayed in above figure)

23/57 DMN	4/57 Aud	3/57 VIS	1/57 VAN
8/57 SOM	3/57 Memory Retrieval	3/57 Subcortical	1/57 DAN
6/57 FP TCN	3/57 CO TCN	2/57 Salience	



Left: Functional connectivity matrix from one participant. Warmer colors (yellow) represent stronger interactions at rest and cooler colors (deep blue) represent weaker interactions at rest. Columns correspond to hippocampal ROIs and rows correspond to Power ROIs. Rows containing ROIs that correspond to well-known brain networks are shown on the left. **Right:** (top) Hippocampal head (red) and body (yellow) ROIs from one participant and (bottom) a DMN ROI (blue). Examples of average timeseries from a right hippocampal body ROI and a DMN ROI are shown. Bivariate correlations between pairs of hippocampal and Power ROI timeseries such as these were performed; r values were converted to Z scores and were used to form a connectivity matrix for each participant.

Combined Model: Hippocampal Subfield Volumes and rsFC Strength
R^2 = 0.746
p < 0.0001
All variables in model significant (FDR-corrected p < 0.05)
Right presubiculum
Left subiculum
R body hipp – R precuneus (DMN)
Left presubiculum
L head hipp – R lingual gyrus (VIS)
Left CA1
R head hipp – R precentral gyrus (SOM)
Left GC-ML-DG
R body hipp – R insula (Aud)
22/24 SMC- classified accurately
27/29 SMC+ classified accurately



Significant Effect of mCCI (subjective)
R head hipp – R precentral gyrus (SOM) *
R body hipp – R insula (Aud) *
R body hipp – R paracingulate gyrus (DMN) **
R body hipp – R precuneus (Memory Retrieval) *
R body hipp – L paracingulate gyrus (FP TCN) *

Significant Effect of NAB (objective)
L GC-ML-DG (NAB Long Delay) *
R head hipp – R precentral gyrus (SOM) (NAB Retention) *
* p < 0.05, ** p < 0.01, All inverse effects

SMC +
SMC –
chance of being SMC+ is 75%
chance of being SMC+ is greater than 75%

Summary

- RsFC strength between the hippocampus and many regions in the default mode network was reduced in SMC+ compared to SMC-. RsFC strength between the left head of the hippocampus and right lingual gyrus was the only rsFC variable that was stronger in SMC+ compared to SMC-.
- RsFC strength between the right body of the hippocampus and several brain networks was reduced in SMC+ compared to SMC- (39/57 rsFC variables).
- The hippocampal subfield volume and hippocampal rsFC strength models were both significant, but the rsFC strength model had a better fit and accurately classified more participants than the subfield volume model.
- The combined model that included both hippocampal subfield volume and rsFC strength variables had a better fit than both separate models and accurately classified most participants.
- MCCI score (a subjective memory measure) had an effect on 5/7 rsFC model variables compared to NAB Retention score (an objective memory measure), which had an effect on 1/7 rsFC model variables. MCCI did not have an effect on any subfield volume variables and NAB Retention score had an effect on 1 subfield volume (left GC-ML-DG).
- These findings support the presence of neurobiological differences between cognitively normal individuals with and without SMCs.
- Hippocampal subfield volume and hippocampal rsFC patterns likely capture different features underlying SMCs – with rsFC strength between right hippocampus and frontoparietal regions reflecting the degree of SMCs reported.