Measures of hippocampal structure and functional connectivity differentiate healthy aged subjects with and without reports of subjective cognitive change

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Objective

To examine whether hippocampal subfield volumes and resting-state functional connectivity (rsFC) can differentiate between individuals with and without subjective memory complaints (SMCs).

Introduction

- Subjective cognitive changes, specifically subjective memory complaints (SMC), 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 rsFC (Wang et al., 2013; Hafkemeijer et al., 2013; Contreras et al., 2017) have been found between individuals with and without reports of subjective cognitive change.
- We examined whether hippocampal subfield volumes and hippocampal rsFC to seven major resting-state networks could differentiate individuals with and without SMCs.
- Participants with a Cognitive Change Index (CCI) (Saykin et al., 2006) score of 16 or higher on the first 12 memory items (mCCI) were classified as having SMCs.
- Hippocampal subfield volumes were automatically generated using FreeSurfer v6.0 (beta).
- RsFC between the head and body of the hippocampus to the seven resting-state networks defined in Yeo et al. (2011) was calculated using FSL's dual regression tool.
- The utility of these measures to predict group membership (SMCs vs. no SMCs) was investigated using a nominal logistic regression analysis.
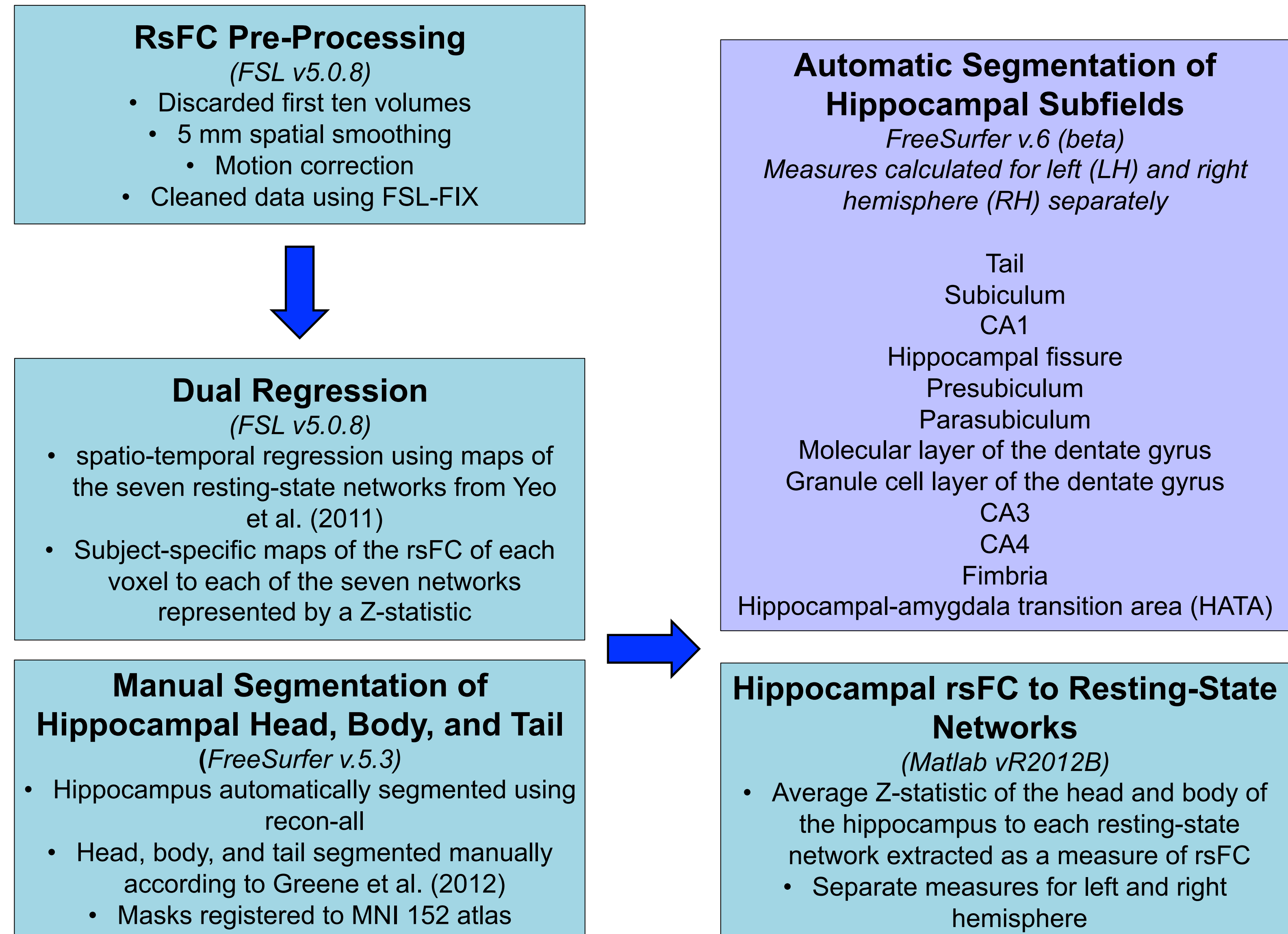
Participant Information

Participants were part of the Health Outreach Program for the Elderly (HOPE) study run through the Boston University Alzheimer's Disease Center (BU-ADC). 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 CCI, 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.

	Controls (N = 19)	SMC (N = 13)
Age (years)	73.5 (9.97)	72.2 (7.61)
Education (years)	15.3 (2.86)	17.5 (1.61)*
Sex	8 M, 11 F	5 M, 8 F
mCCI score	13.2 (1.1)	23 (7.58)*
Mean relative motion during rsfMRI (mm)	0.193 (0.094)	0.158 (0.071)

$p < 0.05$

Methods

MRI Scan Parameters
T1-Weighted: TR = 6.78 ms, TE = 3.14 ms, voxel size = 1 x 1 x 1.2 mm
Resting-state fMRI (rsfMRI): Participants fixated on a white dot on a black screen and were asked to stay awake and let their minds wander as BOLD fMRI data with the following parameters was acquired: TR = 3000 ms, TE = 30 ms, 10 mins (200 dynamics), voxel size = 3.31 x 3.31 x 3.31 mm
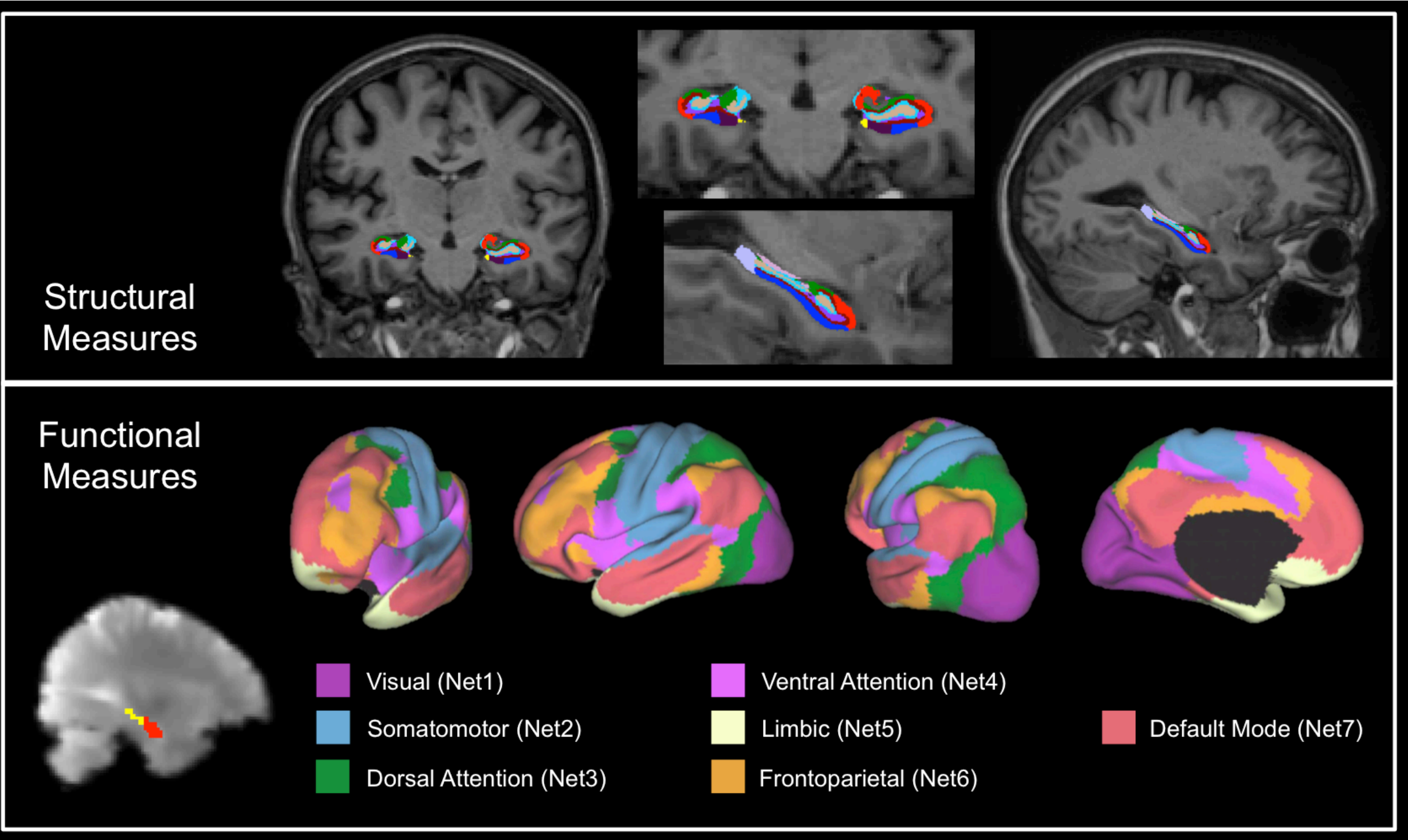
RsFC Pre-Processing
(FSL v5.0.8)
- Discarded first ten volumes
  - 5 mm spatial smoothing
  - Motion correction
- Cleaned data using FSL-FIX

Dual Regression
(FSL v5.0.8)
- spatio-temporal regression using maps of the seven resting-state networks from Yeo et al. (2011)
- Subject-specific maps of the rsFC of each voxel to each of the seven networks represented by a Z-statistic

Manual Segmentation of Hippocampal Head, Body, and Tail
(FreeSurfer v.5.3)
- Hippocampus automatically segmented using recon-all
- Head, body, and tail segmented manually according to Greene et al. (2012)
  - Masks registered to MNI 152 atlas

Automatic Segmentation of Hippocampal Subfields
FreeSurfer v.6 (beta)
Measures calculated for left (LH) and right hemisphere (RH) separately

Tail
Subiculum
CA1
Hippocampal fissure
Presubiculum
Parasubiculum
Molecular layer of the dentate gyrus
Granule cell layer of the dentate gyrus
CA3
CA4
Fimbria
Hippocampal-amygdala transition area (HATA)

Hippocampal rsFC to Resting-State Networks
(Matlab vR2012B)
- Average Z-statistic of the head and body of the hippocampus to each resting-state network extracted as a measure of rsFC
  - Separate measures for left and right hemisphere

Statistics: Two-Sample T-Tests
(JMP Pro v.12)
Between-group tests of systematic differences in hippocampal measures

Prediction Models: Discriminant Function Analysis (DFA)
(JMP Pro v.12)
- For data reduction purposes
- Entered volumetric and rsFC hippocampal measures in a stepwise fashion
- RH and LH whole hippocampal volumes included as variables
- Identified the minimum number of variables needed to achieve 100% group classification

Prediction Models: Nominal Logistic Regression Analysis
(JMP Pro v.12)
Explored the set of 12 predictive variables selected from the stepwise DFA, which achieved 100% classification
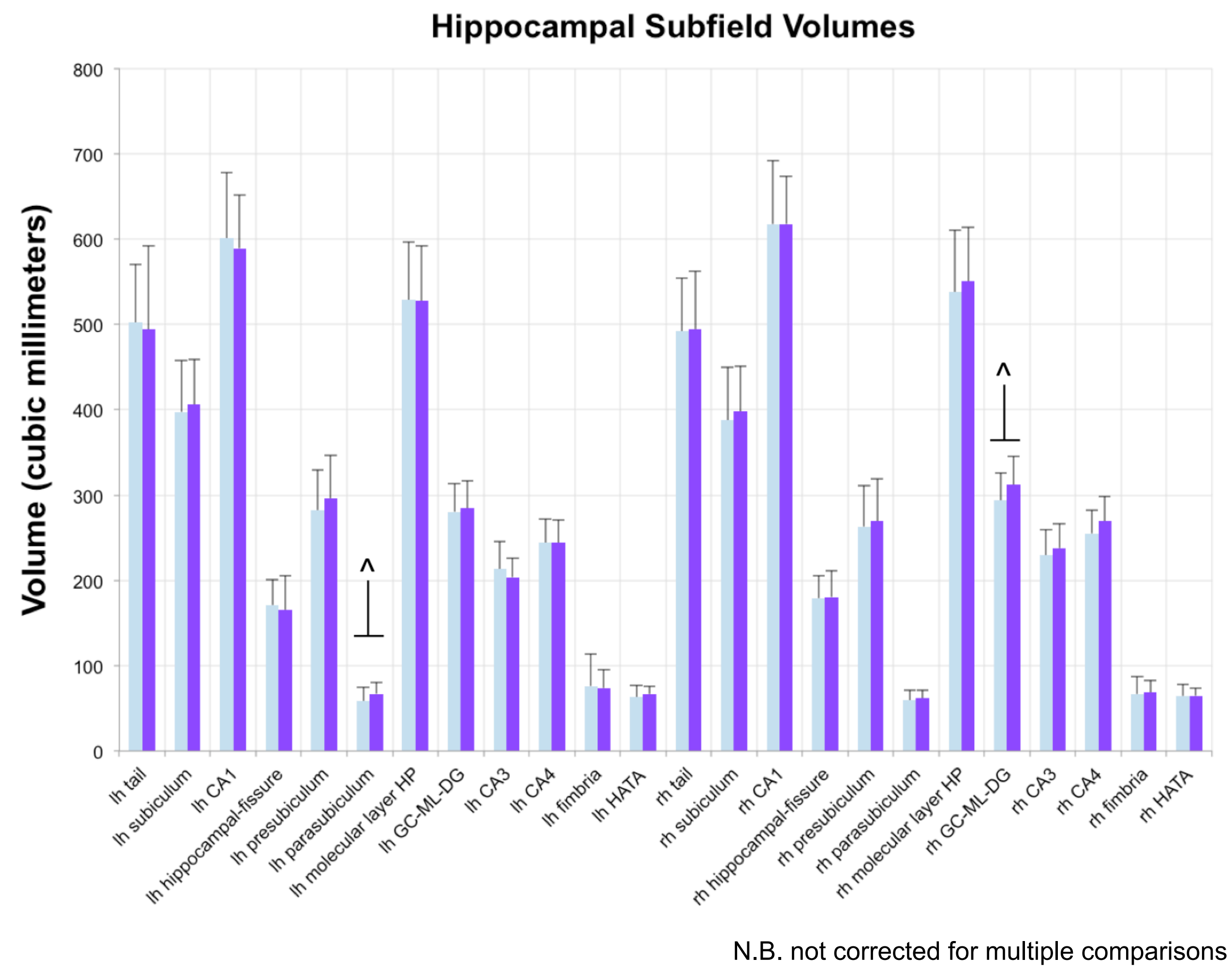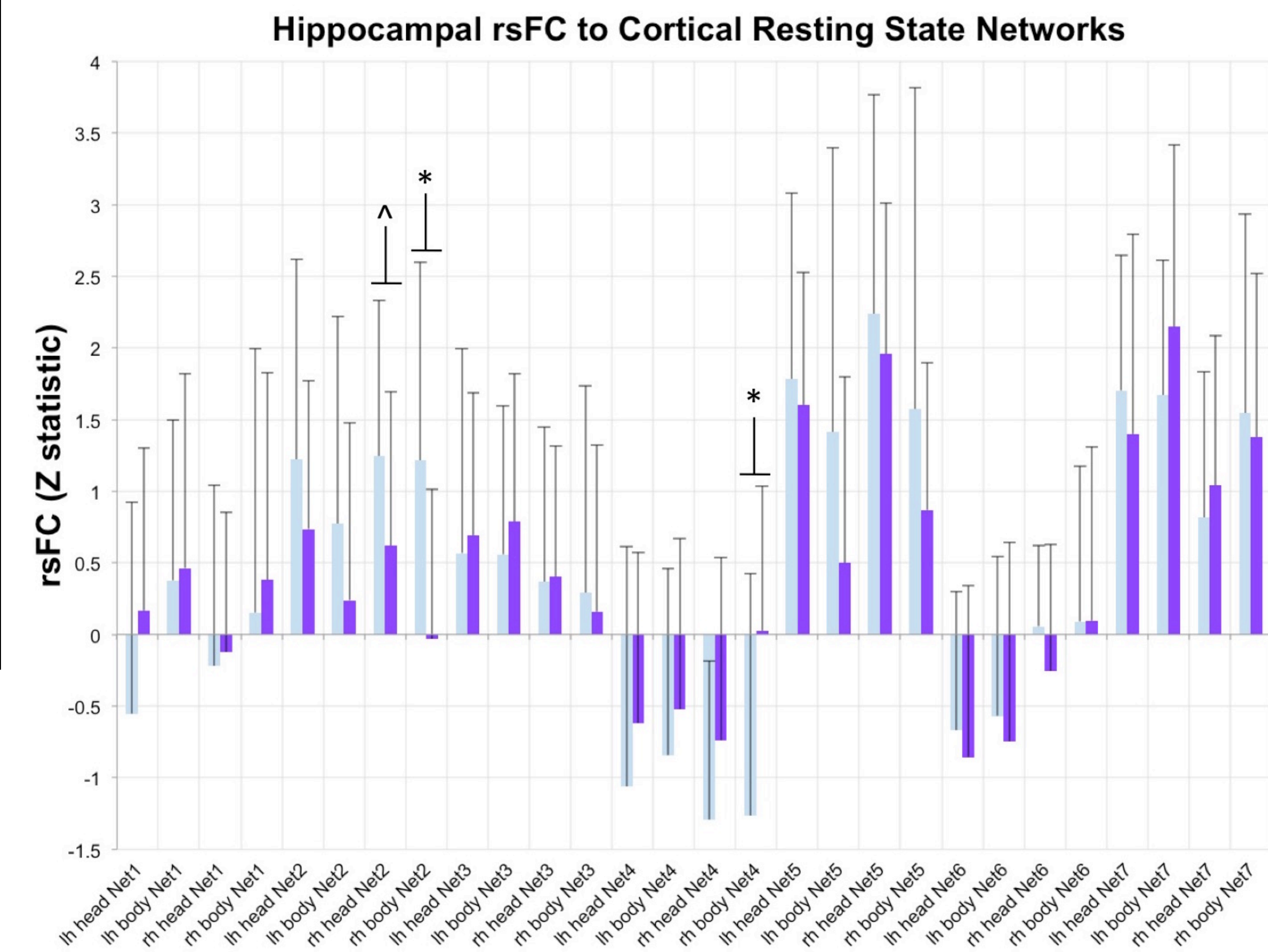
Hippocampal Measures

Structural Measures

Functional Measures

Visual (Net1)   Ventral Attention (Net4)   Default Mode (Net7)
Somatomotor (Net2)   Limbic (Net5)
Dorsal Attention (Net3)   Frontoparietal (Net6)

Nominal Logistic Regression

Model Significant	p = 0.0008
R^2	0.70
Misclassification Rate	0.094 (3/32 misclassified, 2 Controls & 1 SMC)
Number of variables in Model	10

Variables in Model	Significance
rsFC: RH body hipp - somatomotor network	< 0.0001
Volume: RH granule cell layer of the dentate gyrus	0.0002
Volume: RH CA 1	0.0021
rsFC: LH body hipp - default mode network	0.0116
rsFC: RH head hipp - dorsal attention network	0.0144
rsFC: LH body hipp - ventral attention network	n.s.
Volume: LH HATA	n.s.
rsFC: RH body hipp – dorsal attention network	n.s.
Volume: RH fimbria	n.s.
rsFC: RH body hipp – default mode network	n.s.

N.B. Neither the left nor right whole hippocampal volume was chosen by the DFA

Results

Control   SMC   ^ p < 0.07   * p < 0.01

Hippocampal rsFC to Cortical Resting State Networks

Hippocampal Subfield Volumes

N.B. not corrected for multiple comparisons

Summary

- The final nominal logistic regression model was significant with a low misclassification rate (0.094).
- 2 controls and 1 SMC were misclassified as SMCs and control, respectively.
- Both rsFC and volumetric hippocampal measures were significant predictors in the model suggesting that both are important to capturing the difference between controls and SMCs .
- Most measures that differentiated between controls and SMCs in the DFA and entered into the nominal logistic regression analysis were right hippocampal measures.
- Whole hippocampal volume was not selected as a predictor in the DFA, suggesting that more detailed functional and structural measures are necessary to differentiate between controls and SMCs.
- SMCs were educated for a longer period of time than controls.
- These findings support the view that SMCs may represent one of the earliest clinical features of non-normal aging and reflect alterations in hippocampal morphometry and connectivity.