The interplay between insomnia and Alzheimer's disease on the triple brain network

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INTRODUCTION

Insomnia is a common sleep disorder characterized by perceived difficulties in falling asleep, maintaining sleep, and early waking times [3]. A majority of insomnia symptoms are related to aberrant connectivity within and between the default mode network (DMN), salience network (SN) and central executive network (CEN) [3,6]. These three brain networks, primarily involved in working memory, self-referential processing, and switching between mind-wandering and directed thought, comprise the triple brain network [7].

Insomnia is a significant risk factor for Alzheimer's disease (AD) in the prodromal stage [2], while also being a common comorbidity in the clinical stage [10]. Moreover, much like insomnia, AD is characterized by triple network deficiencies [8]. As such, we hypothesize that **there may be an interaction between the effects of insomnia and Alzheimer's disease pathology within the triple brain network** system.

METHODS

Participants. 320 ADNI [1] subjects: N=178 cognitively normal (CN), N=132 Mild Cognitive Impairment (MCI), N=40 Alzheimer's disease (AD).

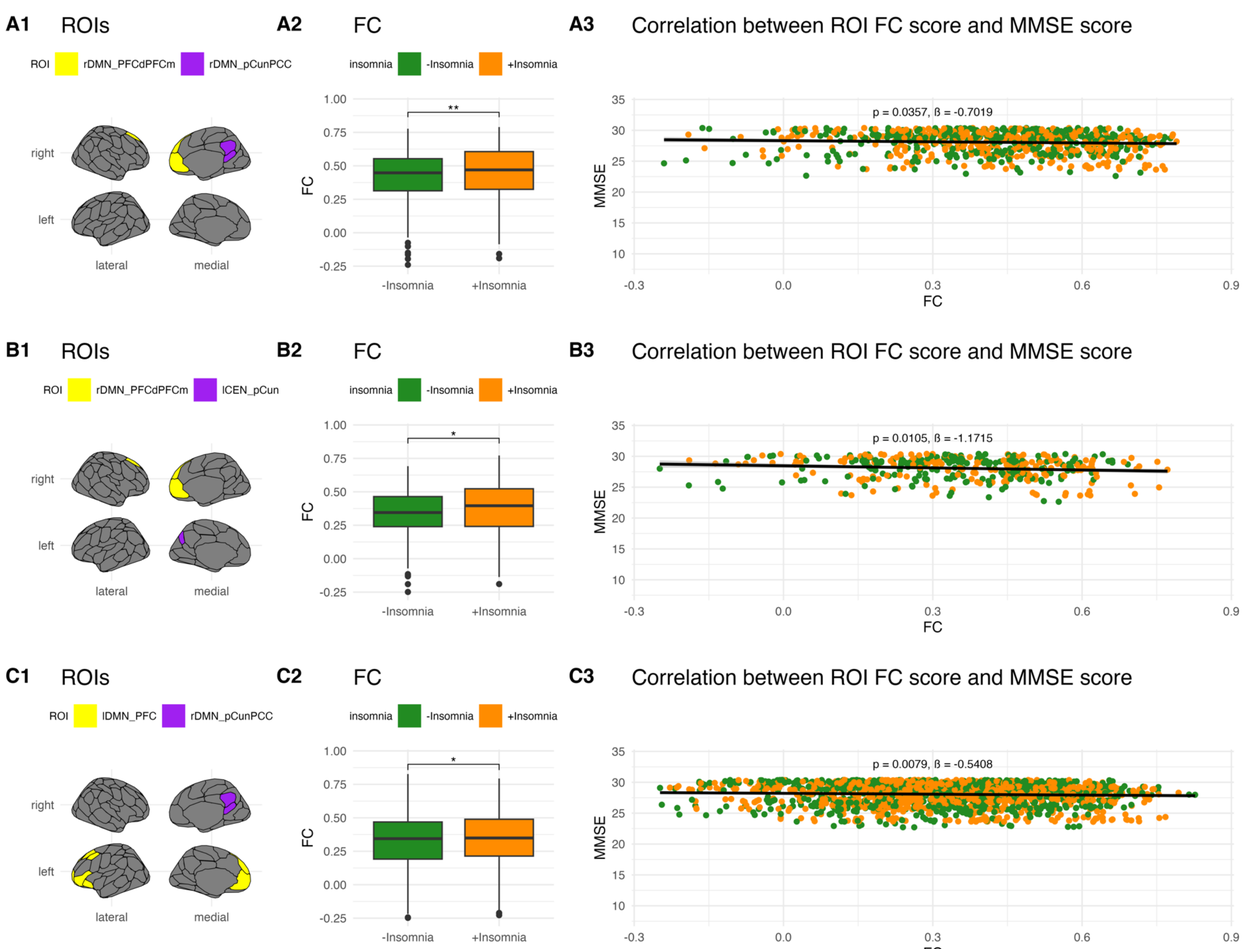
Clinical Variables. 50% of all subjects reported insomnia symptoms on the NPI [4]. All subjects had performed a MMSE. N=58 subjects had CSF biomarker (beta-amyloid, p-tau) data available.

Preprocessing. T1 MRI and resting state (rs-)fMRI were preprocessed using fMRIprep [5]. Triple network nodes were identified with the Schaefer atlas [9]

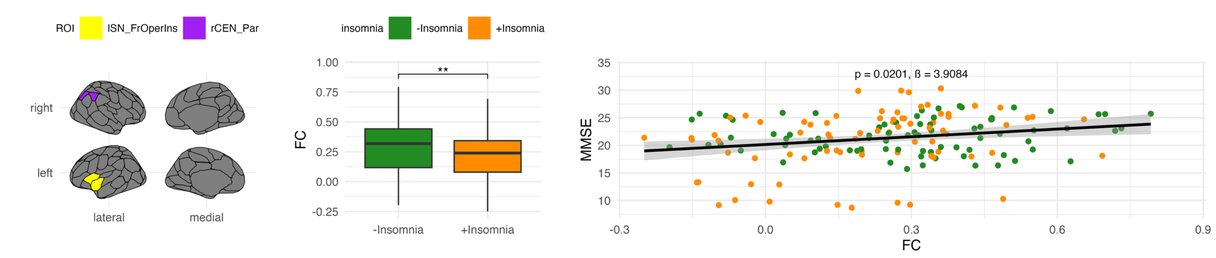
MRI indices. The triple network gray matter volume (GMV) and structural covariance (SC) were obtained to assess (inter-)nodal morphological changes. The degrees centrality (DC) and functional connectivity (FC) were obtained to assess (inter-)nodal functional changes.

Statistical analysis. For each index, pertaining to each (combination of) node(s), we fit a linear regression model, corrected for age and sex, assessing the effect of insomnia symptoms in different diagnostic groups. P<0.05, FDR-corrected.

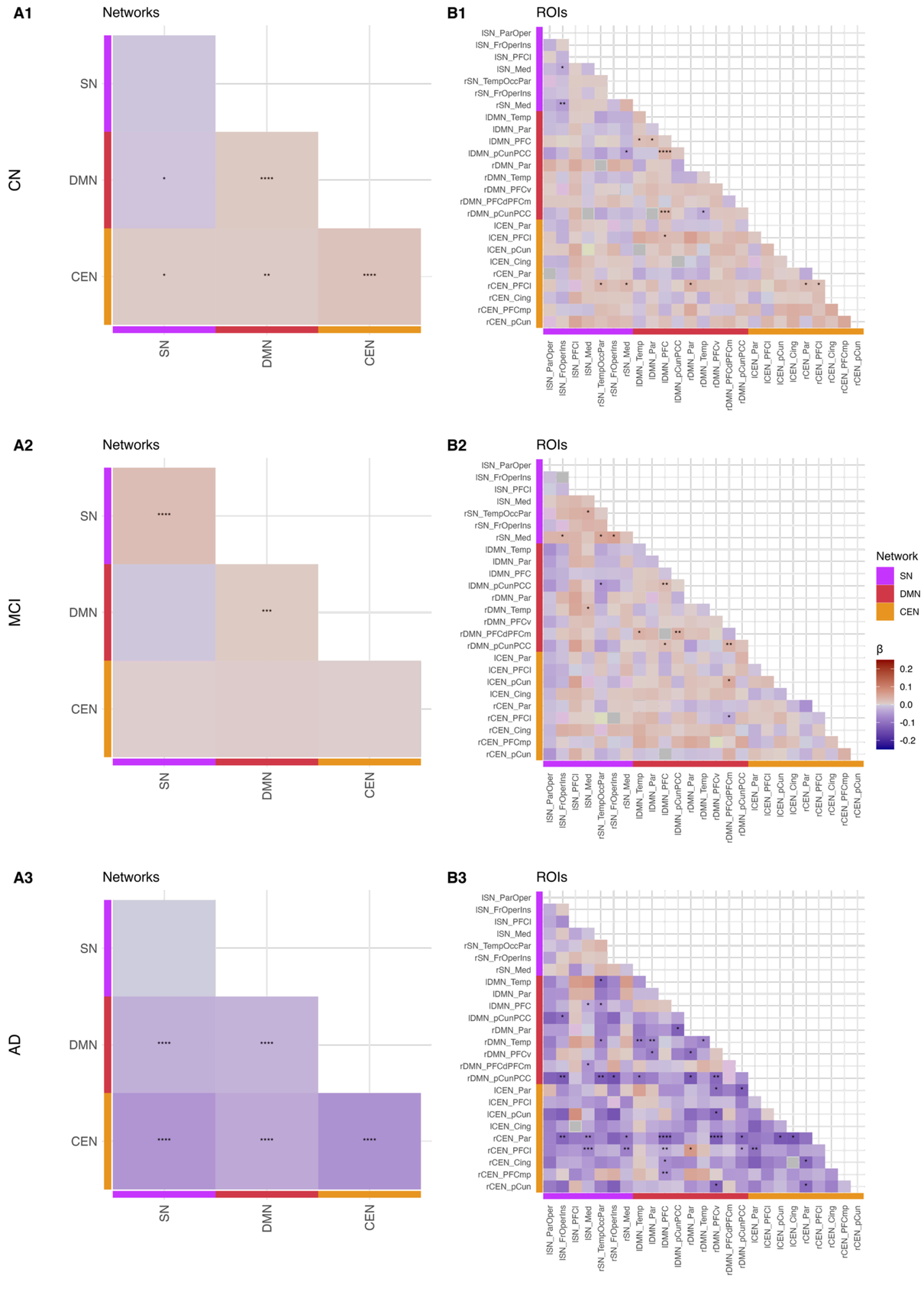
MMSE: MCI



MMSE: AD



FC: All groups



RESULTS

There were no significant changes in GMV, SC, and DC across all groups. CN and MCI individuals displayed patterns of hyperconnectivity in the DMN, SN and CEN. In contrast, AD individuals displayed patterns of hypoconnectivity across the DMN and CEN. Intra-DMN hyperconnectivity in CN and MCI and CEN hypoconnectivity in AD were primarily associated with decreased a MMSE score. These connectivity alterations were not associated with significant change in CSF biomarker burden.

CONCLUSION

- Insomnia symptoms modify the effect of AD on triple network FC
- Prodromal stages (CN, MCI) are associated with classical markers of hyperarousal, including intra-DMN hyperconnectivity.
- Clinical stages (AD) are associated with markers of emotional dysregulation and post-insomnia anxiety
- Comorbidities with anxiety and depression may underlie a heightened sensitivity to the affective symptoms of insomnia in AD.

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