Introduction

Cognitive fluctuations, a core feature of Dementia with Lewy Bodies, recently have been described in Alzheimer’s disease, and are associated with worse clinical dementia rating and neuropsychological performance.\(^1\) Fluctuations may represent fragmentation of wakefulness, and demonstrate the instability of mechanisms separating sleep-wake states in neurodegenerative disease.

Functional cortical networks characterized by correlated BOLD activity are preserved during wake and light sleep in controls, suggesting these networks maintain connectivity independent of state.\(^2\) However, many studies have shown that connectivity in these networks changes in cognitive pathology, reflecting abnormalities in cognitive processes.

We compared functional networks in subjects with mild or uncertain Alzheimer’s Disease with cognitive fluctuations, to those without fluctuations, as well as to healthy controls, to assess whether cognitive fluctuations are associated with abnormalities in functional networks. Additionally, we assessed brain volumes using automated segmentation, and other sleep-wake problems using questionnaires.

Methods

Subjects: age ≥60 were drawn retrospectively from a longitudinal study of memory and aging at the Washington University Alzheimer Disease Research Center. Subjects were divided into three groups by Cognitive Impairment Rating (CDR): 0, 0.5-1, >1. Subjects with informant answers of 1-10, all answered by an informant for each subject.

The Volumetric Data

Fluctuators were compared to a “positive control” group of CDR 0.5 to 1 (Dementia of Alzheimer Type or Mild Cognitive Impairment) and no fluctuations, (DAT-MCI), and to Controls with CDR 0 and no fluctuations. Demographics were similar in all groups, except a greater proportion of fluctuators were male. Overall alertness (out of 10) was decreased in the fluctuator group compared to the other groups (*p < 0.005). A greater proportion of fluctuators reported sleep symptoms on the Mayo Sleep Questionnaire.

Results

Volumetric analysis

Connectivity maps (2≤p≤0.05) to key Dorsal Attentional Network (dATTN) and Default Mode Network (DMN) for all three groups are shown. There was weakened connectivity in all groups compared to prior reports in young adults, likely due to small sample size, as well as possible effects of normal aging. Fluctuators had decreased connectivity and less variance in dATTN and DMN, than both control groups. Cross-network anticorrelation (green) was present but not as pronounced as expected.

Conclusions

Cognitive fluctuations are present in a subset of patients with early Dementia of Alzheimer Type or Mild Cognitive Impairment. In this study, those with fluctuations had decreased daytime alertness and increased frequency of other sleep symptoms. Cognitive fluctuations are associated with changes in the correlation between components of cognitive networks. In this pilot study, there was decreased connectivity in both default mode and dorsal attention networks in the group with fluctuations. Moreover, there was decreased anti-correlation between the two networks tested. These results did not reach statistical significance due to small sample size.

Volumetric analysis showed differences between subjects with fluctuations and those without fluctuations. Significantly, the hippocampus, an area which typically shows atrophy early in the course of DAT, was not atrophied in the fluctuators. This suggests that fluctuations indicate a subset of individuals with DAT, whose course of degeneration may be distinct from typical DAT.

Further studies with larger groups, evaluation of other cognitive networks such as executive control, and control for changes due to normal aging, are necessary to definitively determine the functional and anatomical abnormalities that give rise to cognitive fluctuations.

References

3. Boeve et al. AAN 2009 abstract

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