

Apathy and intrinsic functional connectivity networks in amnesic mild cognitive impairment

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Background: Although several prior works reported that apathy is associated with conversion to Alzheimer's disease in individuals with amnesic mild cognitive impairment (aMCI), effects of apathy on the functional connectivity (FC) of the brain remain unclear. In this study, we assessed the pattern of association between apathy and default mode network (DMN), salience network and central executive network (CEN) in aMCI subjects.

Methods: Fifty subjects with aMCI and 50 controls (CONs) participated in this study. They underwent clinical assessments and magnetic resonance imaging for the structural and resting-state scan. We explored the patterns of association between apathy inventory (IA) total score and the whole-brain voxel-wise FCs of the DMN, salience network and CEN in aMCI subjects.

Results: We observed that the FCs of the DMN were less and those of CEN were more in the aMCI group than the CON group. Total IA score was negatively correlated with FCs of the anterior cingulate within the DMN, and positively correlated with FCs of the middle frontal, inferior frontal, and supramarginal gyrus within the CEN in the aMCI group.

Conclusion: Our findings suggest that distinctive patterns of association between apathy and FCs in the DMN and CEN in the aMCI group might reflect the putative role of functional network change in the development of apathy in aMCI.

Keywords: apathy, amnesic mild cognitive impairment, intrinsic connectivity networks

Introduction

Mild cognitive impairment (MCI) and Alzheimer's disease (AD) are accompanied by a number of neuropsychiatric symptoms, as well as cognitive decline. Among the neuropsychiatric symptoms, apathy is the most frequent symptom, independent of AD severity.¹ Apathy is also prevalent in subjects with MCI,^{2,3} occurring in more than a third of individuals.³ Apathy is defined as a syndrome with diminished motivation, initiative and interest, and blunting of emotions.⁴ Several prior works reported that apathy was associated with progression to AD in amnesic MCI (aMCI) individuals,⁵ executive dysfunction and impairment of activities of daily living.⁶⁻⁸

To date, previous studies attempted to explore the neural substrates of apathy in AD. Studies using different modalities including structural magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) have shown associations among apathy and cortical thinning, white matter integrity change, hypometabolism and hypoperfusion in the orbitofrontal, anterior cingulate and inferior temporal areas in the brains of AD patients.⁹⁻¹⁵ Additionally, several studies showed that the presence of white matter lesions was associated with apathy in aMCI patients.^{16,17} Although strong evidence indicates that apathy is correlated with these specific brain damages that might affect disconnection of the cortico-subcortical network, the direct effects of apathy on the functional connectivity (FC) of the brain remain unclear.

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Resting-state functional MRI (RS-fMRI) has recently been highlighted as a new technique for investigating functional intrinsic connectivity networks (ICNs) without an experimentally determined context in patients with dementia.¹⁸ Functional brain network models are useful to understand the pathophysiology because they consider how neural systems are distributed across the entire brain instead of a specific brain area.¹⁹ To the best of our knowledge, only one study on subjects with MCI has been performed to investigate the relationship between apathy and ICNs.²⁰ This study assessed four different brain networks: the fronto-parietal control network (FPCN; aka central executive network [CEN]), default mode network (DMN), ventral attention network (aka salience network [SN]) and dorsal attention network (DAN), using the neuropsychiatric inventory. The results of the study showed a significant association between increased affective symptoms, in particular, apathy and reduced RS FPCN connectivity. However, they could not show association between apathy and other networks such as the DMN or SN. This might be due to lack of normal distribution of lower apathy score (mean \pm SD; 0.3 ± 1.0) of the study participants. Moreover, as the study only investigated associations between the mean FC of the resting-state network (RSN) and apathy score, it was hard to find out more sophisticated voxel-wise regional FC changes within the large-scale functional networks (DMN, SN, and FPCN) due to apathy of aMCI subjects.

To overcome the limitations of the previous study, we investigated the distinctive patterns of association between apathy severity and the whole-brain voxel-wise FC of the three large-scale ICNs (DMN, SN and CEN) in aMCI subjects with “clinically significant” apathetic symptom. Based on the literature cited, we conceptualized the apathy in aMCI as the behavioral expression of an abnormal RS FC of the brain and hypothesized that apathetic subjects would exhibit aberrant FC changes in the three ICNs.

Materials and methods

Study participants

In this study, 50 subjects with aMCI were included. They were recruited through the outpatient geriatric psychiatry clinic of St Vincent’s Hospital from January 2013 to February 2015. All subjects were Korean and right handed. Patients with aMCI met the Petersen’s criteria:²¹ 1) memory complaint, preferably corroborated by an informant; 2) objective memory impairment for age, education, and gender; 3) essentially preserved general cognitive function; 4) largely intact activities of daily living; and 5) not demented. All aMCI patients had an

overall Clinical Dementia Rating²² of 0.5. Objective memory impairment was defined as a performance score of 1.5 SD below the respective age-, education- and gender-specific normative means in at least one of the four episodic memory tests included in the Korean version of Consortium to Establish a Registry for Alzheimer’s disease (CERAD-K) neuropsychological battery, namely the word list memory (WLM), word list recall (WLR), word list recognition (WLRc), and constructional recall (CR) tests.²³

The severity of apathy was assessed using the Apathy Inventory (IA),²⁴ that is based on the neuropsychiatric inventory model.²⁵ Patients who had a score of 4 or more on the total IA scale with clinically significant apathy were included in the aMCI group.²⁴

Study participants who had other neurological or psychiatric conditions were excluded. Fifty healthy control (CON) subjects were recruited within the community through advertisement in a local newspaper. CON subjects were matched to the patients on age, handedness, and level of education.

The study was approved and conducted in accordance with the ethical and safety guidelines set forth by the local Institutional Review Board of the Catholic University of Korea. Written informed consent was obtained from all participants.

MRI acquisition

Imaging data were collected at the Department of Radiology, St Vincent’s Hospital, The Catholic University of Korea, using a 3T Siemens Verio machine and eight-channel Siemens head coil. The parameters of T1-weighted volumetric magnetization-prepared rapid gradient echo scan sequences were TE = 2.5 ms, TR = 1,900 ms, inversion time = 900 ms, FOV = 250 mm, matrix = 256 × 256, and voxel size = 1.0 × 1.0 × 1.0 mm³. RS functional images were collected using a T2* weighting gradient echo sequence with TR = 2,490 ms, TE = 30 ms, matrix = 128 × 128 × 29, and voxel size = 2 × 2 × 3 mm³. One hundred and fifty volumes were acquired over 5 minutes with the instruction “keep your eyes closed and think of nothing in particular”.

Data analysis

In this study, we used a seed-to-voxel analysis method for evaluation of effect of apathy on FC of three ICNs. We produced individual subject seed-to-voxel connectivity maps using the CONN-fMRI Functional Connectivity toolbox v1.5 (<http://www.nitrc.org/projects/conn>). Slice time correction, realignment, normalization, and spatial smoothing were performed for preprocessing of images with a 6 mm kernel, and the images were temporally band-pass filtered ($0.009 < f < 0.08$ Hz).

A component-based noise correction method was used to remove physiological and other noise artifacts.²⁶ These methods involved extraction of the signals from white matter and cerebrospinal fluid regions with movement-related covariates. The seed region of interests (ROIs) consisting of spheres 6 mm in radius centered on Montreal Neurological Institute (MNI) coordinates (Montreal, QC, Canada) were used to identify the corresponding networks in prior studies. Each RSN and its corresponding seed ROI (in MNI coordinates) are as follows: DMN (posterior cingulate cortex: 1, -55, 17), CEN (left and right dorsolateral cortex: -42, 34, 20/44, 36, 20), and SN (left and right frontoinsular cortex: -32, 26, -14/38, 22, -10).

For each subject, the average blood oxygen level-dependent time course of each seed was extracted from the functional echo planar images, and then it was correlated with the time courses of whole-brain voxels, using Pearson correlation analysis. Fisher's *r*-to-*z* transformation of correlation coefficients was conducted for general linear model (GLM) analysis. In the second-level analysis, connectivity maps from all participants were entered into GLM, that was used for measuring the group differences of the FC for each ICN with age, gender, and education as nuisance variables. To examine the relationships between apathy severity and FC of the ICNs in the aMCI group, the total IA scores were correlated with FCs of the DMN, the SN, and the CEN using the GLM. Statistical significance was thresholded at FDR-corrected $P < 0.05$ for multiple-comparison correction.

Table 1 Demographic and clinical characteristics of the study participants

| | CON group (N=50) | aMCI group (N=50) | P-value |
|-------------------------------|---------------------|----------------------|---------|
| Age (\pm SD) (years) | 71.2 \pm 4.3 | 72.1 \pm 3.8 | NS |
| Education (\pm SD) (years) | 9.4 \pm 3.1 | 9.0 \pm 4.2 | NS |
| Gender (M:F) | 22:28 | 23:27 | NS |
| CDR (\pm SD) | 0 | 0.5 | |
| CERAD-K battery (\pm SD) | | | |
| VF | 13.3 \pm 3.9 | 13.2 \pm 3.9 | NS |
| BNT | 12.7 \pm 2.1 | 11.8 \pm 2.3 | NS |
| MMSE | 28.4 \pm 1.5 | 24.4 \pm 3.3 | <0.0001 |
| WLM | 18.5 \pm 4.5 | 7.0 \pm 3.4 | <0.0001 |
| CP | 9.4 \pm 1.5 | 9.2 \pm 1.9 | NS |
| WLR | 7.7 \pm 1.8 | 2.3 \pm 1.8 | <0.0001 |
| WLRc | 9.9 \pm 1.2 | 3.5 \pm 1.7 | <0.0001 |
| CR | 6.7 \pm 2.9 | 3.2 \pm 2.9 | <0.0001 |
| IA score (SD) | 0 | 9.3 \pm 2.2 | <0.0001 |

Abbreviations: aMCI, amnesic mild cognitive impairment; BNT, 15-item Boston Naming Test; CDR, Clinical Dementia Rating; CERAD-K, Korean version of Consortium to Establish a Registry for Alzheimer's Disease; CON, control; CP, constructional praxis; CR, constructional recall; F, female; IA, apathy inventory; M, male; MMSE, Mini Mental Status Examination; NS, nonsignificant; SD, standard deviation; VF, verbal fluency; WLM, word list memory; WLR, word list recall; WLRc, word list recognition.

Results

Baseline demographic and clinical data

Table 1 shows the baseline demographic data of the two subject groups. The Kolmogorov-Smirnov test showed that all variables including total IA scores and CERAD-K neuropsychological test scores were normally distributed. There were no significant differences in gender, age or education between the aMCI and CON groups. Compared with the CON group, the aMCI group showed significantly poorer performances in the Mini Mental Status Examination, WLM, WLR, WLRc, and CR in CERAD-K neuropsychological battery ($P < 0.05$).

Group differences in FC

Figure 1 shows the statistical map representing the DMN, SN, and CEN determined across all subjects.

Group analysis showed lower FC in the DMN in the aMCI group compared to the CON group in the anterior cingulate cortex and posterior cingulate. In the SN, there were no significant differences between the aMCI and the CON groups in the FCs. The FC in the left middle temporal gyrus and right supramarginal gyrus was significantly higher within the CEN in the aMCI group compared to the CON group (Table 2 and Figure 2; FDR-corrected $P < 0.05$).

Figure 2 shows the results of the analysis of correlation between the FCs of the DMN, SN, and CEN and the total IA score in the aMCI group. In the DMN, the FC of the anterior cingulate was negatively correlated with total IA score. In the CEN, the FCs of the middle frontal, inferior frontal, and supramarginal gyrus were positively correlated with the total IA score (Table 2; FDR-corrected $P < 0.05$). There was no significant difference between the FC of the SN and the total IA score in the aMCI group.

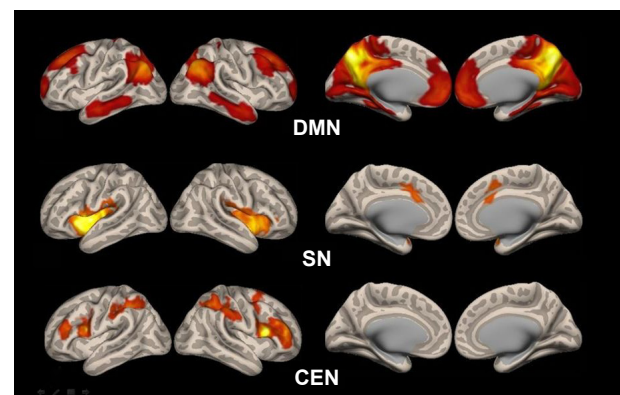


Figure 1 Statistical map representing the DMN, SN, and CEN determined across all subjects.

Abbreviations: CEN, central executive network; DMN, default mode network; SN, salience network.

Table 2 Whole-brain voxel-wise FC analysis results

| Region | L/R | Cluster | P-value ^a | MNI coordinate (x, y, z) | | |
|--|-----|---------|----------------------|--------------------------|-----|-----|
| Group differences | | | | | | |
| Default mode network | | | | | | |
| CON > aMCI | | | | | | |
| Anterior cingulate | R | 287 | 0.02 | 2 | 20 | -12 |
| Posterior cingulate | L | 283 | 0.01 | -6 | -42 | 26 |
| Posterior cingulate | R | 164 | 0.01 | 12 | -38 | 30 |
| Central executive network | | | | | | |
| CON < aMCI | | | | | | |
| Supramarginal gyrus | R | 558 | 0.02 | 72 | -42 | -4 |
| Middle temporal gyrus | L | 376 | 0.02 | -52 | -34 | 6 |
| Total IA score-aMCI FC correlations | | | | | | |
| Default mode network | | | | | | |
| Anterior cingulate | L | 382 | 0.02 | -2 | 36 | 18 |
| Central executive network | | | | | | |
| Inferior frontal gyrus pars opercularis | L | 478 | 0.01 | -52 | 16 | 22 |
| Inferior frontal gyrus pars opercularis | R | 97 | 0.01 | 50 | 30 | 14 |
| Supramarginal gyrus | L | 109 | 0.01 | -58 | -22 | 40 |
| Middle frontal gyrus | R | 109 | 0.03 | 46 | 6 | 32 |
| Frontal pole | L | 106 | 0.02 | -40 | 36 | 4 |

Note: ^aFDR-corrected P-values for the multiple comparisons.

Abbreviations: aMCI, amnesic mild cognitive impairment; CON, control; FC, functional connectivity; FDR, false discovery rate; IA, apathy inventory; L, left; MNI, Montreal Neurological Institute; R, right.

Discussion

Although this study is not the first RS-fMRI study on the apathy in aMCI, it is the first study to elaborate the relationships between apathy severity and FCs of the large-scale ICNs such as the DMN, the SN, and the CEN.

In this study, we found that the FCs of the DMN were lower and those of the CEN were higher in the aMCI group than in the CON group, that were partially in line with the previous studies. DMN's activity during rest is necessary for memory consolidation.²⁷ Additionally, amyloid deposition,

one of the hallmark pathologies of AD, is found initially and most prominently in DMN hubs.²⁸⁻³⁰ For these reasons, the DMN is the most frequently studied network in dementia. Loss of FC in the DMN is a well-established finding in AD patients, but it is inconsistent in MCI patients. Our findings showing a decreased FC in the DMN of MCI patients are consistent with previous studies.³¹⁻³⁴ However, the changes of the DMN in MCI patients remain controversial. A previous study showed the selective disruption of the DMN in MCI patients, indicating both decreased and increased DMN connectivity.¹¹ Moreover, the most recent study on MCI patients presented increased DMN connectivity.³⁵ Gardini et al explained that increased FC of the DMN in aMCI subjects may reflect a maladaptive mechanism that would represent the damaged brain's attempt to cope with regional atrophy or amyloid deposition in these areas.³⁶ Based on the current uncertainty inherent in the clinical concept of MCI,^{37,38} controversial changes of DMN in aMCI patients may be due to the heterogeneity of the aMCI population between the studies.

Besides the DMN, SN and CEN play important roles in cognitive processing.³⁹ The SN plays a crucial role in switching between the CEN and the DMN.⁴⁰ Once a salient event is detected, the SN initiates the appropriate transient control signals to engage the CEN to mediate attention, working memory, and executive control, all while disengaging the

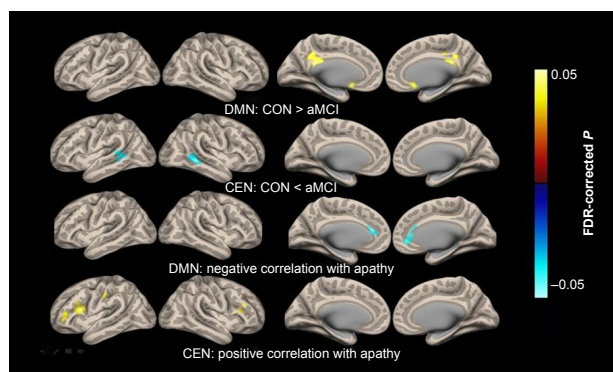


Figure 2 Analysis of correlation between the FCs of the DMN, SN, and CEN and the total IA score in the aMCI group.

Abbreviations: aMCI, amnesic mild cognitive impairment; CEN, central executive network; CON, control; DMN, default mode network; FCs, functional connectivities; FDR, false discovery rate; IA, apathy inventory; SN, salience network.

DMN.⁴¹ Negative correlations (anticorrelations) between the DMN and the CEN or SN support the reciprocal relationship between these ICNs.^{41,42} Other RS-fMRI studies explained that the greater FCs of the CEN and SN might be due to a compensatory mechanism associated with DMN impairments.^{31,43} Therefore, the results that showed decreased FCs of the DMN and increased FCs of the CEN in the aMCI group could be interpreted by the DMN impairment associated with disease progression and aberrant hyperactivity of CEN associated with a compensatory process.

We also found that total IA score of the aMCI group was negatively correlated with the FC of the anterior cingulate within the DMN and positively correlated with the FC of the middle frontal, inferior frontal, and supramarginal gyrus within the CEN in the aMCI group. Apathy is a complex syndrome with lack of initiation, lack of interest, and reduced emotional responsiveness⁴ due to direct or indirect involvement of the prefrontal lobes.⁴⁴ Neural substrates associated with apathy were found in several studies in AD spectrum disorders. An SPECT imaging study found that apathy was negatively correlated with perfusion in the right anterior cingulate cortex, right middle orbitofrontal gyrus, and left superior dorsolateral prefrontal cortex.⁹ An MRI study using voxel-based morphometry found that apathy was associated with atrophy of the anterior cingulate, ventrolateral orbitofrontal cortex, and left insula in AD.⁴⁵ Other studies using MRI with diffusion tensor imaging have shown relationships between increased white matter abnormalities and apathy in MCI and AD.^{15,17,46} A recent study found that the presence of lesions in the anterior thalamic radiations was associated with the severity of apathy in aMCI.¹⁶ These studies confirmed the evidence of white matter disconnection associated with apathy and support the view that alterations in the neural mechanisms of apathy occur in the early course of AD. Furthermore, a recent RS-fMRI study revealed that a decreased FPCN was associated with greater apathy in MCI.²⁰ Our findings build upon previous work by suggesting FC changes in the three ICNs for individuals with aMCI who have greater apathy. Also, our result of association between apathy and anterior cingulate coincided with many existing reports in AD.^{3,46–48} The anterior cingulate is one of the important anatomical structures involved in motivation. The meso-cortico-limbic pathway is a dopaminergic network from the ventral tegmentum⁴⁹ to the different anterior cortical regions (frontal and parietal) connecting via the anterior cingulate.⁵⁰ Therefore, the disruption of connections between the anterior cingulate and other cortical and subcortical regions would lead to the mechanism of apathy.⁵¹

The present study has several limitations. First, all presented data are cross-sectional in nature. Further longitudinal studies will be needed to clarify the large-scale functional network changes underlying apathy in the AD progression. Second, as we recruited ICNs that were most similar to the previously identified networks template, other networks of interest such as the DAN could not be observed. Third, we did not account for use of psychotropic medications such as antidepressants, cholinesterase inhibitors, dopamine agonists or stimulants such as methylphenidate or modafinil that reportedly help patients with apathy. Despite these limitations, this study showed that apathy is associated with an alteration of large-scale functional brain networks, that included not only the intra-networks but also inter-networks of the DMN, SN, and CEN. Additionally, we included a relatively large number of subjects compared with the studies previously reported.

Conclusion

We showed altered FCs of the DMN and CEN and distinctive patterns of correlations between apathy and FCs in the DMN and CEN in the aMCI group. These results might reflect putative role of functional network change in the development of apathy in aMCI. Additional large and longitudinal studies will help further elucidate the underlying neurobiological mechanism of apathy in AD progression.

Acknowledgment

This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT, and Future Planning (NRF-2015R1C1A1A02036578).

Disclosure

The authors report no conflicts of interest in this work.

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