Decoupling of Intrinsic Insula Subregional Connectivity was Associated with Episodic Memory Decline in Amnestic Mild Cognitive Impairment

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Introduction: Neuroimaging techniques have been widely employed to study the potential neural mechanisms underlying amnestic mild cognitive impairment (aMCI) and identify the abnormalities of intrinsic connectivity networks in aMCI patients (1-3). However, little is known about the potential contribution of the insula subregional networks (ISNs) to cognitive performance in aMCI patients. The purpose of this study was to characterize the contribution of ISNs to cognitive performance in aMCI patients.

Methods: Thirty aMCI and 26 age-matched cognitively normal (CN) subjects participated in this Southeast University (Nanjing, China) Institutional Review Board--approved study and completed neuropsychological tests. Consent forms were obtained from each of subject. The intrinsic connectivity of ISNs was measured by the resting-state functional connectivity fMRI approach at a 1.5 T Siemens scanner. Analysis of variance (ANOVA) was used to examine the differential connectivity of ISNs between aMCI and CN groups. Linear regression analysis was used to detect the relationship between the intrinsic connectivity strength of ISNs and cognitive performance in aMCI subjects. Insula subregional volumes also were investigated.

Results: aMCI subjects, when compared to CN subjects, had significantly reduced right posterior insula volumes (**Figure 1**) and cognitive function, and disrupted intrinsic connectivity of ISNs. Specifically, decreased intrinsic connectivity was primarily located in the frontal-parietal network and the cingulo-opercular network, including the anterior prefrontal cortex (aPFC), inferior frontal gyrus, anterior cingulate cortex, operculum, inferior parietal cortex and the precuneus. Increased intrinsic connectivity was primarily situated in the visual-auditory pathway, including the posterior superior temporal gyrus and middle occipital gyrus, which also are involved in memory processes (**Figure 2** and **3**). Conjunction analysis found the overlap regions of the anterior insula networks and posterior insula networks in the bilateral aPFC, left dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC) and anterior temporal pole (aTP). Furthermore, these decoupled intrinsic connectivity strengths were positively correlated with episodic memory scores in aMCI patients (**Figure 4**), but not correlated with executive function, perceptual speed, and working memory ($p > 0.05$).

Discussion and Conclusion: It is well known that the insula is structurally connected with the prefrontal cortex, parietal cortex, temporal lobule, occipital lobe and subcortical regions, including the ventral and dorsal striatum, as well as the thalamus, and functionally implicated in human perception, cognition and attention processing (4). Recently, several groups have begun to investigate the intrinsic functional connectivity of insula subregions in humans and found distinctions of insula subregional networks (5-7). In the current study, aMCI patients exhibited decoupled intrinsic connectivity of the insula subregions related to target regions; the degree of the connectivity strength was positively correlated with episodic memory scores. These findings strongly suggest that the functional integration of the insula subregional networks plays an important role in the memory process. It is suggested that balance the coupling of these neural networks could improve therapeutic strategies in treating memory deficits in aMCI patients.
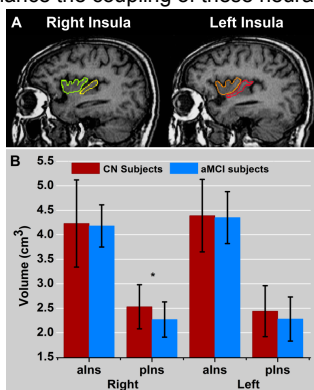

Figure 1. Slice view of insula subregions (**A**) and analysis of insula subregional volume across subjects (**B**). *$p < 0.05$.
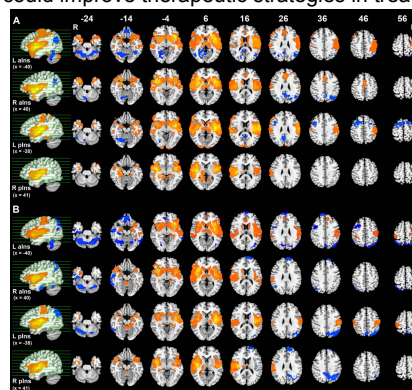

Figure 2. Connectivity pattern of insula subregional networks between CN group (A) and aMCI group (B).
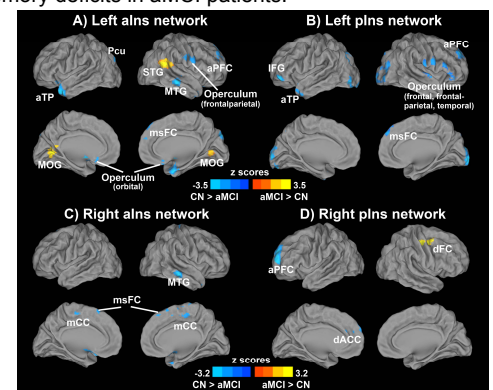

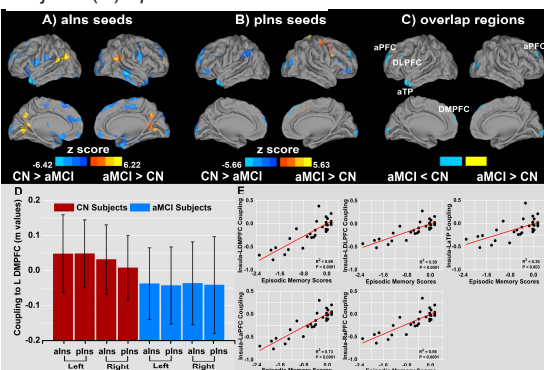**Figure 3.** Differential connectivity in insula subregional networks between CN group and aMCI group.

Figure 4. Group Connectivity Difference of the Anterior Insula (aIns) and Posterior Insula (pIns) Subregional Networks. A) Main effects of aIns network across all subjects; B) Main effects of pIns network across all subjects; C) Overlap regions from the conjunction analysis between A and B; D) Quantitative representation of subregional connectivity of left dorsomedial prefrontal cortex (LDMPFC) from the overlap regions in the CN group and aMCI group. Histogram bars present the mean, and error bars present standard deviation; E) The average connectivity strength in the overlap regions was positively correlated with episodic memory scores in aMCI subjects after controlling the effects of age, education, and gender.

Notes: Episodic memory scores were the composite scores (including Auditory Verbal Memory Test-Delayed Recall and Rey-Osterrieth Complex Figure Test-Immediately Recall scores) and developed in a 2-step process. First, the raw scores of each test for each subject were transformed to *z* scores with reference to the means and standard deviations of each test for all the subjects; Second, the composite scores were calculated by averaging the *z* scores of individual tests in each subject.

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