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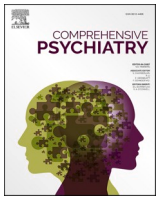

Resting-state functional connectivity and cognitive performance in aging adults with cognitive decline: A data-driven multivariate pattern analysis

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ABSTRACT

Background: Cognitive impairments occur on a continuous spectrum in multiple cognitive domains showing individual variability of the deteriorating patterns; however, often, cognitive domains are studied separately.
Methods: The present study investigated aging individual variations of cognitive abilities and related resting-state functional connectivity (rsFC) using data-driven approach. Cognitive and neuroimaging data were obtained from 62 elderly outpatients with cognitive decline. Principal component analysis (PCA) was conducted on the cognitive data to determine patterns of cognitive performance, then data-driven whole-brain connectome multivariate pattern analysis (MVPA) was applied on the neuroimaging data to discover neural regions associated with the cognitive characteristic.
Results: The first component (PC1) delineated an overall decline in all domains of cognition, and the second component (PC2) represented a compensatory relationship within basic cognitive functions. MVPA indicated rsFC of the cerebellum lobule VIII and insula with the default-mode network, frontoparietal network, and salience network inversely correlated with PC1 scores. Additionally, PC2 score was related to rsFC patterns with temporal pole and occipital cortex.
Conclusions: The featured primary cognitive characteristic depicted the importance of the cerebellum and insula connectivity patterns in of the general cognitive decline. The findings also discovered a secondary characteristic that communicated impaired interactions within the basic cognitive function, which was independent from the impairment severity.

1. Introduction

Decline in cognitive function is a normal process of aging. Even without a diagnosed pathology, older adults often experience declines in several cognitive and neuropsychological aspects, such as memory, reasoning, decision making and abstract thinking [1]. With an aging population, there are growing concern about the impact of cognitive decline on independence and quality of life. Officially, the diagnoses of objective cognitive impairment fall under mild cognitive impairment or dementia, with the latter considered the most severe form of the impairment as the deficit interferes with one's everyday life and independence [2,3]. On the other hand, mild cognitive impairment is characterized by some degree of objective decline, but preserved day-to-day functions and independence [4].

Standardized neuropsychological assessments are routinely carried out to measure one's cognitive abilities of multiple domains. Generally, these comprehensive tests evaluate different domains such as executive function, memory, visuospatial, language, and attention. Although many studies have investigated the neural markers of domain-specific cognitive functions across diagnostic groups, no study has explored the functional connectivity (FC) of domain-combined cognitive performance in aging individuals with concerns of cognitive impairment without a clinical diagnosis. Surveying the relationship between comprehensive cognitive performance levels and resting-state FC (rsFC) pattern may provide a quick and useful barometer to locate a subject on the cognitive impairment spectrum.

There has been a growing interest in using resting-state functional magnetic resonance imaging (rsfMRI) to detect early signs of cognitive pathology [5]. As such, neural markers of mild cognitive impairment and dementia (including Alzheimer's disease) have been extensively

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investigated. Aberrant FC associated with cognitive decline has been consistently shown in various neural systems, including the default mode network (DMN), frontoparietal network (FPN), dorsal attention network and salience network [6–9]. While the majority of studies have conducted group studies of clinically diagnosed patients, they have rarely focused on first-time patients who are suspected of cognitive decline. However, as the severity of cognitive decline lies on a spectrum across multiple domains, especially in the earlier stages [10], it would be imperative to investigate the individual differences of general cognitive skills, and to identify the most critical domains of cognitive functions or to find relationships among multiple cognitive domains during the deteriorating process in the aging population. Examining the neural associations of outpatients with cognitive complaints would offer possible neural markers of subtle cognitive regressions in earlier stages of cognitive impairment.

A growing number of studies on subjective cognitive decline indicates that the memory domain is critical in defining the group, as it has been almost exclusively examined [10]. A neuroimaging study has shown the association of memory severity and rsFC between the occipital and parietal cortices [11]. It has been speculated that the increased connectivity of regions related to visual processing is indicative of dysfunction in visual information processing in early cognitive impairment, and it might follow a compensatory mechanism before the onset of dementia [11]. A deviant rsFC of the DMN has also been regarded as one of the most important neural signatures of cognitive abilities [12–16]. Yet, it remains unclear whether the implicated regions are positively or negatively related to function, as both increased and decreased rsFC have been reported [11–16].

Much of the existing work has taken a priori seed-based and predefined region-of-interest (ROI) analyses. However, mixed results indicate apparent inconsistencies these hypothesis-driven approaches contribute, and that these types of analyses could be neglecting critical rsFC patterns associated with cognitive function. The utility of data-driven multivariate pattern analysis (MVPA) approach to neuroimaging data is starting to be appreciated more. For instance, the unbiased method was used to investigate the neural correlates of scholastic performances in children, and identified an array of neural networks, such as DMN, somatosensory, attention, and FPN to be modulated by the reading abilities [17]. In a clinical context, the data-driven whole-brain analysis has been applied in studying social anxiety disorder, autism spectrum disorder, rapid eye movement sleep behavior disorder, and subjective memory complaints [11,18–20].

The primary objective of this study was to discover the patterns of cognitive abilities and rsFC in outpatient aging individuals who are suspected of cognitive decline. First, we aimed to identify unique neuropsychological characteristics of the population by conducting a data-driven principal component analysis (PCA) of the neuropsychological assessment data after controlling for age, gender, and years of education. Subsequently, we examined the unique neural associations with the established cognitive function attributes using a data-driven connectome MVPA after accounting for the other principal components and demographic information. Regarding the cognitive performance profile, we hypothesized that at least one principal component would depict the overall cognitive level that included all domains. As studies have suggested an involvement of various networks across the brain such as attention, DMN, FPN, and salience network, we expected these regions would also correlate with the component solution that described the general cognitive performance level. Then, an exploratory analysis was conducted in order to examine the effects of cognitive decline stage on the rsFC by categorizing the data according to the recommended diagnosis. Deriving a cognitive domain composite score and its neural underpinnings could allow clinicians to comprehensively understand and readily estimate the cognitive impairment severity of the geriatric population, and offer potential neural targets for treatment. Furthermore, because the current investigation employed an agnostic approach for both cognitive and neuroimaging data, we suspected additional component solutions related to some specific cognitive domains would be derived as well.

2. Methods

2.1. Participants and procedure

Data of elderly (over 60 years old) outpatients who visited the Gangnam Severance Hospital Department of Psychiatry from September 2019 to December 2021 with a suspected impairment in cognitive function were considered in the study. When a patient had visited with complaints of cognitive decline (by them or by a guardian), the patient was referred for a full battery neuropsychological assessment and MRI to determine the level of cognitive abilities. The Seoul Neuropsychological Screening Battery Second Edition (SNSB-II) assessment [21], a comprehensive neuropsychological battery assessment of cognitive abilities, was used and was conducted by trained psychologists. The SNSB-II covers five cognitive domains, including attention, frontal and executive functions, language and related functions, memory, and visuospatial functions [21]. For each of the five domains, a domain-specific z-score was computed from raw scores which adjusted for gender, age, and years of education. In addition to the five cognitive domains of neuropsychological assessment, the Mini-Mental State Examination (MMSE) [22], the Geriatric Depression Scale [23,24], and the Global Deterioration Scale (GDS) were also administered [25].

Further, patients who agreed also underwent MRI scanning session, during which functional (resting-state) and structural data were acquired. Typically, the scanning session was scheduled around patients' convenience and on a separate day from the neuropsychological evaluation.

Data of 82 patients with a complete set of the SNSB-II and functional MRI (fMRI) were included in the study. Of the 82 outpatients, data of 20 subjects were excluded for multiple reasons, such as missing MRI data (4 subjects), insufficient number of imaging scans remaining after preprocessing (11 subjects), brain abnormalities upon visual inspection (2 subject), history of brain surgery (1 subject), and/or missing subset score on the full battery neuropsychological assessment (2 subject). Ultimately, 62 outpatient (44 female) data were entered in the analysis. Table 1 presents the demographic and behavioral information for subjects included in the analysis. Of 62 subjects, 47 subjects had scored below 1.5 SD from normative mean, a traditional cutoff criterion that demarcate impairment, on at least one cognitive domain on the neuropsychological evaluation [4,26]. All 62 subjects were given two or higher on the GDS. The diagnostic impressions, or clinical stages of cognitive decline, were determined by trained psychologists according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) guidelines, which holistically assess results from SNSB-II and other tests. However, because the guidelines do not include very mild or subjective cognitive impairment, subjects with some cognitive decline

Table 1
Mean and standard deviation of demographic and behavioral data for participants included in the analysis ($N = 62$).

	Mean ± SD
Age (years)	76.23 ± 6.23
Education (years)	10.64 ± 5.13
SNSB-II cognitive domain (z-scores)	
Attention	−0.56 ± 1.04
Frontal and executive	−1.95 ± 2.38
Language and related functions	−1.43 ± 2.54
Memory	−1.75 ± 1.33
Visuospatial	−1.43 ± 2.1
MMSE	23.18 ± 4.99
Global Deterioration Scale	3.40 ± 0.97
Geriatric Depression Scale	4.60 ± 4.61

Note: M = mean; SD = standard deviation; SNSB=Seoul Neuropsychological Screening Battery; MMSE = Mini-Mental State Examination.

and those on the borderline were categorized as having subjective cognitive decline stage by considering various test results. As per our data, seven patients were recommended as subjective cognitive decline, thirty-nine as mild neurocognitive disorder, and sixteen as major neurocognitive disorder. All subjects had at least one item marked as "abnormal" or "borderline" in the SNSB-II result.

The process of this study was part of a routine clinical process. Thus, the data of this study was retrospectively collected and analyzed. This retrospective study was approved, and informed consent was waived by the Yonsei University Gangnam Severance Hospital Institutional Review Board (Ref ID: 3–2022-0106).

2.2. Neuropsychological data analysis

To reduce the scores of five cognitive domains to more meaningful components, PCA was applied to the obtained z-scores of the SNSB-II for each subject. The PCA decomposition of the cognitive domain scores was implemented using scikit-learn 0.24 in Python 3.9. Components were selected based on the criteria stated by Jolliffe [27], which suggests the cumulative percent variance of the components be >70%, and eigenvalues to be >0.7.

Given that depression is often associated with cognitive impairment, partial correlation analysis was performed between the selected PCA components and the Geriatric Depression Scale scores, after controlling for mean-centered age, education years and gender, to examine whether depressive symptoms are related to the cognitive function profile within the present data. Statistical inferences were set at $p < 0.05$.

2.3. Imaging data analysis

2.3.1. Imaging parameters

Imaging protocol was adapted from UK Biobank brain imaging protocol (https://www.fmrib.ox.ac.uk/ukbiobank/protocol/). Data were acquired on a 3.0 Tesla MR scanner (Syngo, Siemens Medical Solutions) with a 32-channel head coil. For each subject, rsfMRI scans were obtained with multiband acceleration factor of 8 (matrix size, 88 × 88; spatial resolution, 2.4 mm; field of view, 210 mm; repetition time, 0.735 s; number of slices, 64; echo time, 39 ms; flip angle, 52°). The duration of rsfMRI scan was 6 min. Structural T1-weighted images were obtained in the sagittal direction using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence (matrix size, 256 × 256; field of view, 256 mm; number of slices, 208; slice thickness, 1 mm; echo time, 2.01 ms; repetition time, 2 s; flip angle, 8°).

2.3.2. Preprocessing

Acquired imaging data were first converted and organized according to Brain Imaging Dataset Specification format [28]. The first 10 volumes were discarded for magnetic field stabilization. Image preprocessing was performed using fMRIPrep pipeline v21.0.01 [29], a tool based on Nipype v1.6.1 [30,31]. The preprocessing steps included skull-stripping, surface reconstruction, coregistration, motion correction, resampling, normalization, and segmentation. Complete boilerplate of the preprocessing pipeline is available in the Supplementary material. The preprocessed data were then imported to CONN Toolbox (v21a) [32] and were spatially smoothed with a Gaussian kernel of 6 mm full-width at half-maximum. Subjects were excluded from further analysis if the remaining data were <5 min after scrubbing (11 subjects). Moreover, data were temporally band-pass filtered at 0.009–0.08 to remove low-frequency drift.

2.3.3. Multivariate pattern analysis (MVPA)

All statistical analysis of imaging data were conducted with CONN Toolbox. Whole-brain connectome-wide group MVPA was implemented for unbiased, data-driven identification of seed regions for seed-to-voxel analysis. For each subject and voxel in the brain, functional connectivity map between the seed voxel and the rest of the brain was created. Obtained connectivity maps were aggregated to produce a matrix of M (number of subjects) × N (number of voxels in the brain) per seed voxel. The dimension of the matrix was reduced to in terms of lower dimensional component scores that best represent the spatial features using PCA. Then, the three strongest component score sets were retained to yield a M × C (number of components) in order to preserve a conservative ratio of 20:1 subject-to-components [33]. The total variance explained by the three components was 85.38%. In the second-level, an omnibus *F*-test was simultaneously run on the three components for every voxel to identify multivariate patterns of voxels that was uniquely associated with each of the cognitive characteristic scores. The PCA-derived cognitive scores that satisfied the selection criteria were entered into the model with one of the factor scores as a regressor-of-interest, and the others as regressors-of-no-interest, vice versa. In addition, mean-centered age, gender, education years were further included as regressors-of-no-interest. Results were set at a height-level threshold of $p < 0.001$, and a cluster threshold of family-wise error (FWE) corrected $P_{FWE} < 0.01$ to identify significant clusters.

2.3.4. Seed-to-voxel analysis

Then, for each surviving clusters, standard seed-to-voxel *post-hoc* analysis was conducted to identify specific neural couplings that are associated with the respective PCA-derived cognitive scores. The regressor-of-interest, as well as regressors-of-no-interest were identical to those explained in the second-level MVPA analysis. The statistical inferences from the seed-to-voxel analyses were thresholded at a height-level threshold of $p < 0.001$, then $P_{FWE} < 0.01$ with non-parametric (1000 permutations) in order to minimize Type 1 error [34].

2.3.5. Exploratory analysis by clinical stages of cognitive decline

In an exploratory analysis, analysis of covariance (ANCOVA) was conducted on the extracted rsFC strength values from the seed-to-voxel analysis in order to explore the effects of clinical stages of cognitive decline on the functional connectivity. The clinical stages were categorized by the diagnostic impressions given by the trained psychologist (subjective, mild, major cognitive decline). Mean-centered age, gender, and education years were included as controlling variables. Then, any functional coupling showing significant effects with respect to the clinical stages, post-hoc comparisons was performed using independent *t*-test to examine the directionality of the effect. Statistical inferences were set at $p < 0.05$.

3. Results

3.1. Neuropsychological data

PCA on the neuropsychological assessment data produced a two-component solution (PC1 and PC2) that accounted for approximately 76% of the variance. The PC1 negatively loaded on all five cognitive domains, and the PC2 loaded negatively on attention and positively on memory domains. The loadings related to the original neuropsychological scores of PC1 indicated an overall decline in cognitive functions as PC1 scores increase; and those of the PC2 to the original cognitive variables illustrated greater attention impairment and higher memory abilities as PC2 scores increase. The loadings and cumulative percentage of variance explained for each PC is presented in Table 2.

To examine whether depression level is associated with the chosen PCA component, partial correlation was conducted. The results indicated that in this particular dataset, depression level was not correlated with either scores of PC1 ($r = 0.20$, $p > 0.05$) or PC2 ($r = 0.013$, $p > 0.05$).

3.2. Imaging data

3.2.1. Multivariate pattern analysis

Seed regions whose rsFC patterns uniquely correlated with each

Table 2
Principal Component Analysis (PCA) loadings for cognitive function domains.

Cognitive domains Components (%†)	PC1 (61%)	PC2 (76%)	PC3 (86%)	PC4 (94%)	PC5 (100%)
Attention	***−0.653***	***−0.729***	0.002	0.133	−0.200
Frontal and executive	***−0.855***	0.042	0.273	0.260	0.375
Language and related functions	***−0.816***	−0.066	−0.459	−0.312	0.197
Memory	***−0.777***	***0.448***	−0.258	0.283	−0.257
Visuospatial	***−0.812***	0.180	0.418	−0.338	−0.186

Note. PC=Principal Component. Selected principal components with loadings > 0.4 are represented in bold and italics.
† Cumulative percentage of variance explained.

PCA-derived cognitive score were identified after controlling for the other PC score, age, gender, and years of education. Significant seed clusters from whole-brain connectome MVPA are displayed in Fig. 1. MVPA revealed two regions, the right cerebellum lobule VIII (Lobule VIII) and right insula, to be associated with PC1 (Fig. 1A). In addition, it had found the right temporal pole (TP) and left occipital gyrus to be related to PC2 (Fig. 1B).

3.2.2. *Post-hoc seed-to-voxel analysis*

Post-hoc seed-to-voxel analysis using the MVPA-derived clusters for each principal component are illustrated in Fig. 2 and Table 3. For the right Lobule VIII as a seed (Fig. 2A-1), results revealed significant rsFC with the left dorsolateral prefrontal cortex (DLPFC), bilateral precuneus/post cingulate cortex (PCC), left superior parietal lobule (SPL), right angular gyrus (AG), left cerebellum lobule VII (Lobule VII), and bilateral cerebellum Crus I/II (Crus I/II). All connectivity strengths between these clusters and PC1 score were identified to be inversely correlated. The PC1 score was negatively correlated with the right insula-based rsFC with the left DLPFC, left temporal cortex, and a large cluster encompassing bilateral temporal cortex/precentral gyrus (PreCG)/postcentral gyrus (PostCG)/SPL/anterior cingulate cortex (ACC)/supramarginal gyrus (SMG); whereas, the first principal component score was positively related to the connectivity strength between the right insula and the right PCC/retrosplenial (Fig. 2A-2).

Moreover, PC2 score was positively correlated with the right TP-based rsFC with the bilateral dorsal PFC, right parietal cortex, right temporoparietal junction (TPJ)/posterior middle temporal gyrus (pMTG), bilateral AG, left Crus II and Lobule VII, and left Crus I/II (Fig. 2B-1). Regarding the left occipital cortex as the seed, its FC with bilateral precuneus/PCC, left AG, and right Crus I/II were positively correlated with the individual variability of the PC2 score (Fig. 2B-2).

3.2.3. *Effects of clinical stages of cognitive decline*

The effects of clinical stages of cognitive decline on the seed-based rsFC strengths were explored using ANCOVA. Results revealed that all rsFC of seed ROIs related to the PC1 scores showed significant differences with respect to the impairment stages (Fig. 3). Specifically, for the right Lobule VIII seed, its connectivity with the left DLPFC showed significant clinical stage differences ($F_{2,56} = 10.75$, $p < 0.001$; subjective > mild > major). In addition, all of rsFC pairs between the seed Lobule VIII and bilateral precuneus/PCC ($F_{2,56} = 11.26$, $p < 0.001$; subjective > mild > major), left SPL ($F_{2,56} = 11.25$, $p < 0.001$; subjective > mild > major), right AG ($F_{2,56} = 12.81$, $p < 0.001$; subjective > mild and major), left Lobule VII ($F_{2,56} = 11.97$, $p < 0.001$; subjective > mild > major), and bilateral Crus I/II ($F_{2,56} = 18.29$, $p < 0.001$; subjective > mild > major) showed significant clinical stage of cognitive decline effect. For the seed right insula, its rsFC pairs between the seed and left DLPFC ($F_{2,56} = 6.36$, $p = 0.003$; subjective > mild and major), left temporal cortex ($F_{2,56} = 8.80$, $p < 0.001$; subjective > mild > major), a large cluster of bilateral temporal cortex/ PreCG/PostCG/SPL/ACC/SMG ($F_{2,56} = 7.52$, $p = 0.001$; subjective > mild > major), and right PCC/retrosplenial ($F_{2,56} = 6.50$, $p = 0.003$; major > mild > subjective) also showed significant effect of clinical stage. On the other hand, none of the rsFC pairs related to PC2 scores showed significant effect of clinical stage of cognitive decline.

4. Discussion

The present investigation took a data-driven and unbiased approach to elucidate connectivity patterns associated with the individual variability of the cognitive functions in aging adults with suspected cognitive impairment. As the average depression score was <5 and was not correlated with any of the PC scores, it was taken that depressive symptoms did not have a great influence on the cognitive decline [23,24]. To the best of our knowledge, it is the first study to have taken a data-driven approach to extract the core underlying characteristics of neuropsychological data and associate with rsFC patterns. The study found two component solutions from the neuropsychological data and

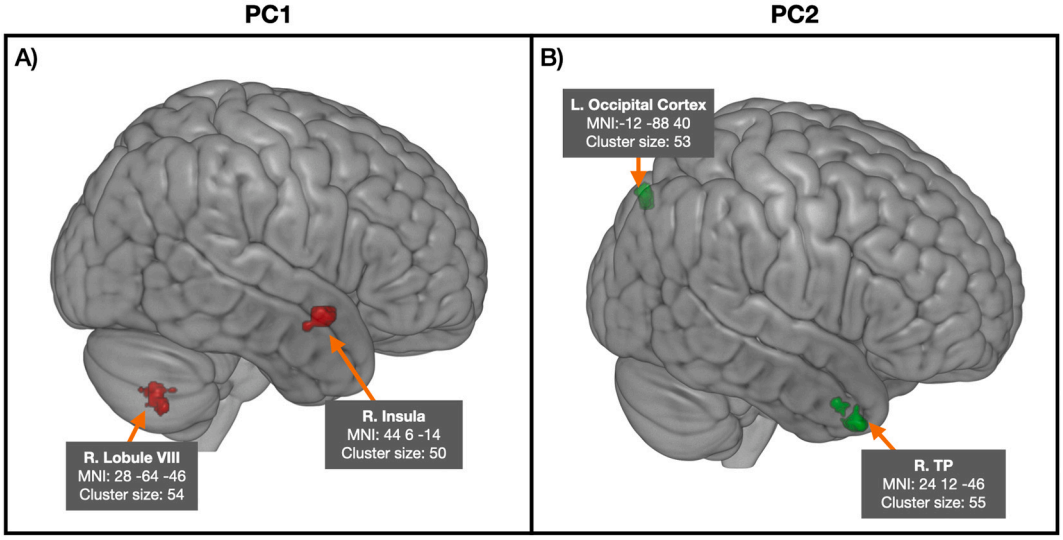

Fig. 1. An illustration of neural regions significantly associated with the neuropsychological assessment data. Data-driven connectome multivariate pattern analysis (MVPA) was conducted to identify neural clusters, where resting-state functional connectivity patterns uniquely associated with A) PC1 scores and, B) PC2 scores derived from principal component analysis of cognitive data. Abbreviations: PC, principal component; R, right; L, left; TP, temporal pole.

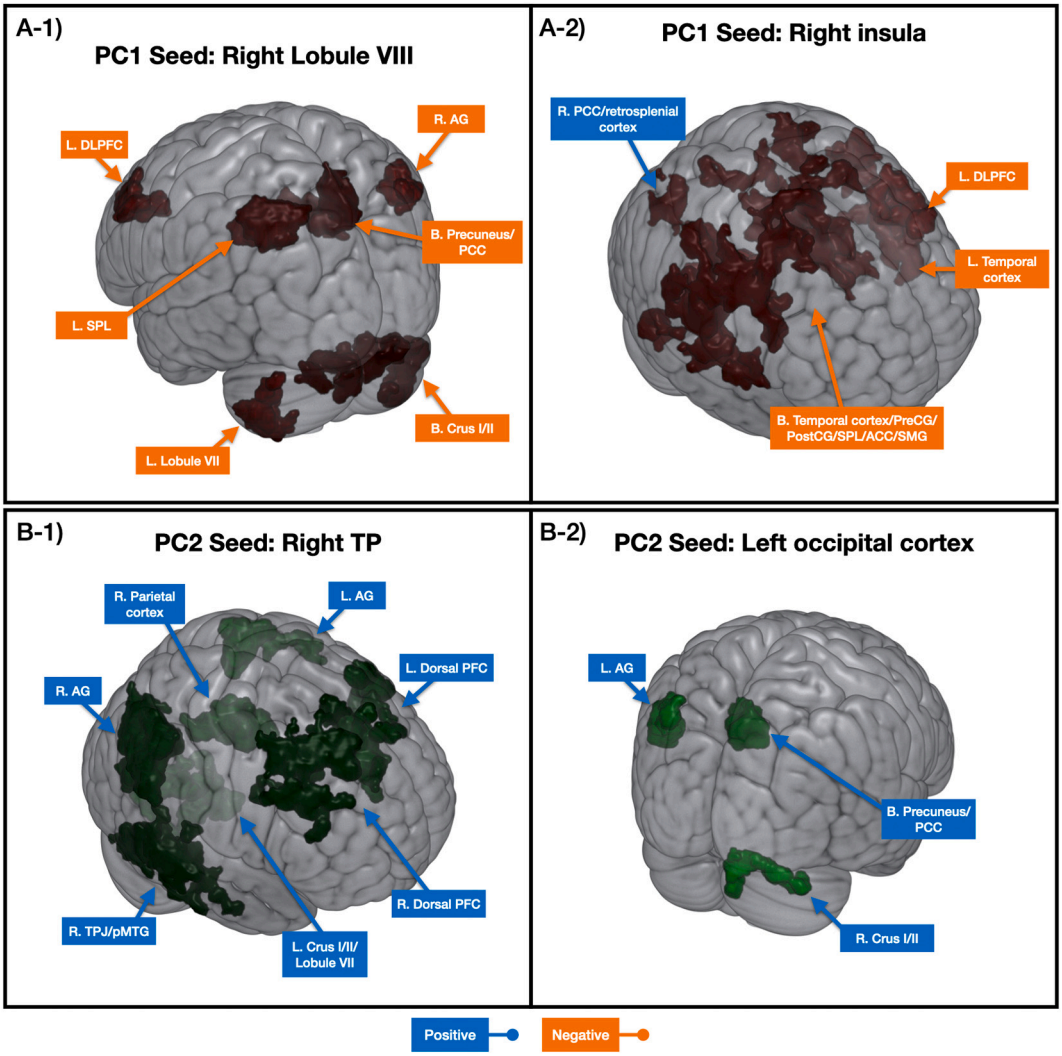

Fig. 2. An illustration of *post-hoc* seed-to-voxel analysis results. *Post-hoc* seed-to-voxel analysis indicated that resting-state functional connectivity of several regions with A-1) the right cerebellum lobule VIII, and A-2) the right insula correlated with the PC1 scores. In addition, the individual variability of PC2 scores was correlated with functional connectivity strengths between MVPA-derived seed clusters, B-1) the right TP and B-2) left occipital cortex. Positive correlation between functional connectivity strength and component score is displayed in blue, and negative correlation is displayed in orange. Abbreviations: PC, principal component; R, right; L, left; B, bilateral; AG, angular gyrus; DLPFC, dorsolateral prefrontal cortex; PCC, posterior cingulate cortex; SPL, superior parietal lobule; PreCG, precentral gyrus; PostCG, postcentral gyrus; ACC, anterior cingulate cortex; SMG, supramarginal gyrus; TP, temporal pole; TPJ, temporoparietal junction; pMTG, posterior middle temporal gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

discovered several critical neural regions associated with each cognitive function profile using a data-driven connectome MVPA.

One of the challenges in interpreting neuropsychological assessments is the lack of a composite score that represents a global level of cognitive abilities. To capture both group characteristics and individual differences from multidimensional cognitive domains, we utilized PCA and obtained two orthogonal factors. In essence, the PC1 depicted the general cognitive abilities, where higher component score indicated more severe decline in cognitive functions. This characterization of cognitive deterioration occurring simultaneously in all cognitive domains was as expected, which encourages more studies to comprehensively examine all cognitive domains as a whole.

In connection to the PC1 score, connectome MVPA analysis identified the right Lobule VIII and right insula as seed regions. Specifically, the analysis revealed that rsFC between the right Lobule VIII and several regions, including the bilateral Crus I/II, left Lobule VII, members of the FPN (left DLPFC) as well as the DMN (bilateral precuneus/PCC, left SPL and right AG) to be negatively associated with the global cognitive function component score. While traditionally associated with motor, balance, and automation, the cerebellum is also believed to be engaged in a spectrum of processes, such as cognitive, emotional, task-negative, and attention [35–37]. It is generally taken that the Lobule VIII plays a significant role in motor and sensorimotor functions, while Lobule VII and Crus I/II are involved in higher cognitive, affective, and default-mode processing [36–39]. The involvement of the Lobule VIII in coordinating movements during goal-directed behaviors and integrating goal-relevant information may be an echo of previous theories that propose that action control is necessary for cognitive and abstract processing [40,41]. The observed negative correlation between FC strengths within the cerebellum and PC1 potentially underscores the importance of motor and non-motor communication in maintaining high cognitive performance level.

Given its extensive connections to various cortical areas, the cerebellum is deemed to play a modulatory role in the execution of tasks following input from the cerebral cortex [41–43]. Consequently, damaged cerebellum has been tied with cognitive impairments and various neuropsychiatric diseases, especially in the aging population [44–48]. This negative relationship between the PC1 score and rsFC

Table 3
Post-hoc seed-to-voxel functional connectivity analysis.

Component	Seed	Target	HEM	Cluster Size	X	Y	Z	Direction	r
PC1	Right cerebelllum lobule VIII	DLPFC	L	394	−52	30	28	Negative	−0.614
		Precuneus/PCC	B	1106	−4	−34	42	Negative	−0.625
		SPL	L	830	−38	−70	50	Negative	−0.578
		AG	R	317	44	−58	52	Negative	−0.551
		Lobule VII	L	403	−48	−64	−46	Negative	−0.66
		Crus I/II	B	2259	44	−74	−34	Negative	−0.674
	Right insula	DLPFC	L	397	−46	24	32	Negative	−0.641
		Temporal cortex	L	1125	−68	−16	6	Negative	−0.624
		Temporal cortex/PreCG/PostCG/SPL/ACC/SMG	B	7361	64	−20	2	Negative	−0.687
		PCC/retrosplenial cortex	R	395	32	−50	12	Positive	0.623
		Dorsal PFC	R	1467	20	28	50	Positive	0.702
		Dorsal PFC	L	1210	−8	26	42	Positive	0.716
		Parietal cortex	R	765	6	−28	34	Positive	0.632
	Right temporal pole	TPJ/pMTG	R	1656	70	−42	0	Positive	0.712
		AG	R	1431	44	−54	56	Positive	0.647
PC2	AG	AG	L	464	−32	−54	42	Positive	0.628
		Crus II/Lobule VII	L	469	−34	−72	−48	Positive	0.657
		Crus I/II	L	440	−8	−88	−32	Positive	0.692
		Precuneus/PCC	B	900	0	−64	40	Positive	0.589
	Left occipital cortex	AG	L	523	−42	−66	28	Positive	0.573
		Crus I/II	R	371	32	−66	−36	Positive	0.599

Note. HEM = hemisphere; PC = principal component; PCC = posterior cingulate cortex; SPL = superior parietal lobule; DLPFC = dorsolateral prefrontal cortex; PreCG = precentral gyrus; PostCG = postcentral gyrus; ACC = anterior cingulate cortex; SMG = supramarginal gyrus; TPJ = temporoparietal junction; pMTG = poserior middle temporal gyrus; PFC = prefrontal cortex; AG = angular gyrus; R = right; L = left; B = bilateral.

patterns of the cerebellum with the DMN and FPN seems to resonate previous work that had shown the association between disrupted cortico-cerebellum rsFC and cognitive impairments in mild cognitive disorder and Alzheimer's disease patients [49].

The DMN is known to be involved in introspection and memory processes and its engagement during rest is considered critical for maintaining psychological well-being [50]. The associations with reduced DMN and cognitive decline in dementia patients, and Alzheimer's disease progression severity have been established [6,51]. On the contrary, the FPN is a control system involved with working memory, attention, decision-making, self-control [52,53], and it is a foundation for a swift and flexible control of other neural regions [54,55]. As a pivotal hub for cognitive flexibility, the FPN is believed to contribute to the overall cognitive functioning [56]. From the results from the exploratory analysis, we also saw that the cerebellum-based couplings are significantly decreased as cognitive impairment stages worsen. Consequently, our data not only reaffirm the significance of the DMN and FPN, but also suggest that the cerebellum serves as a pivotal node for overall cognitive health, potentially by allowing greater efficiency. These findings convey the cerebellum as a vital neural marker of overall cognitive abilities, and offer an architecture of cerebellum-cerebrum network, which remained unclear [57].

Studies indicate the insula to be responsible for cognition and processing of internal signals, such as emotion and interoception [58–60]. As part of the salience network, the insula is believed to contribute to cognitive functioning by appropriate allocation of cognitive resources for efficient switching between the FPN and DMN [61]. These networks have been proposed as core networks of the neurocognition, and dysfunctions of these networks have often been linked to neuropsychiatric disorders [52,62,63]. Analogously, our study also found the connectivity between the insula and sensory regions, such as the temporal cortex, SPL, PreCG and PostCG, to positively vary with cognitive abilities. Generally, the connectivity between the insula and vital regions for multisensory input processing has been attributed to the integration of external and internal information [64–66]. Together, our results suggest an association of greater multisensory integration and higher overall cognitive abilities.

Several reports have recognized the aberrant rsFC between the insula and DLPFC as one of the sources of cognitive dysfunctions [67,68]. Additionally, cognitively demanding tasks typically engage the salience network and FPN and disengage the DMN [63,69]. Even when the impairment stage was taken into consideration, rsFC patterns of the insula with FPN became more out-of-sync in the more severe stages. Similarly, the anticorrelation between the insula and DMN was significant greater in the subjective decline stage than other stages, which was to be expected [70,71]. As the insula allows for efficient inter-network switching and allocation of cognitive resources, our findings could be signifying an association between higher overall cognitive abilities and the inverse FC patterns seen among these networks. Collectively, the rsFC patterns associated with the primary characteristic propose potential neural markers for therapeutic interventions for cognitive impairment.

Attention and memory are basic cognitive domains that tend to exhibit the steepest decline in aging adults and impairments typically occur simultaneously [72,73]. The second cognitive profile, PC2, which loaded negatively on the attention and positively on the memory domain, depicted an association of greater memory deficit and higher attention function. These basic cognitive functions are interdependent. Meaning that because the capacity of memory is limited, attention must be involved for an optimal selection of stimulus during encoding [74]. Yet, this unexpected characterization of our cognitive data is presenting a more nuanced interplay between the inability to select task-relevant information and memory deficits. Moreover, such basic cognitive function scores uniquely correlated with the rsFC patterns of the TP and occipital cortex. Notably, none of the significant couplings were related to the stages of cognitive decline, possibly suggesting that this secondary characteristic is not necessarily dependent on the progression of impairment. The TP is a complex structure that is involved in a number of cognitive functions [75]. Among them, earlier works paint the anterior portion as a hub for semantic cognition, a function crucial when generating appropriate actions [76–78]. Previously, damaged TP has been identified as a key feature in semantic dementia patients [79]. Our results also demonstrated significant rsFC between the TP and regions often implicated in semantic processing, such as the AG, TPJ/pMTG, parietal cortex, and prefrontal cortex [76–78]. As a secondary feature of the cognitive impairment, results with PC2 seem to suggest that semantic processing is involved to preserve attention or memory function when the other is impaired.

The occipital cortex, a visual center, is also employed during memory demands. It is speculated that abnormal engagement of this cortex might

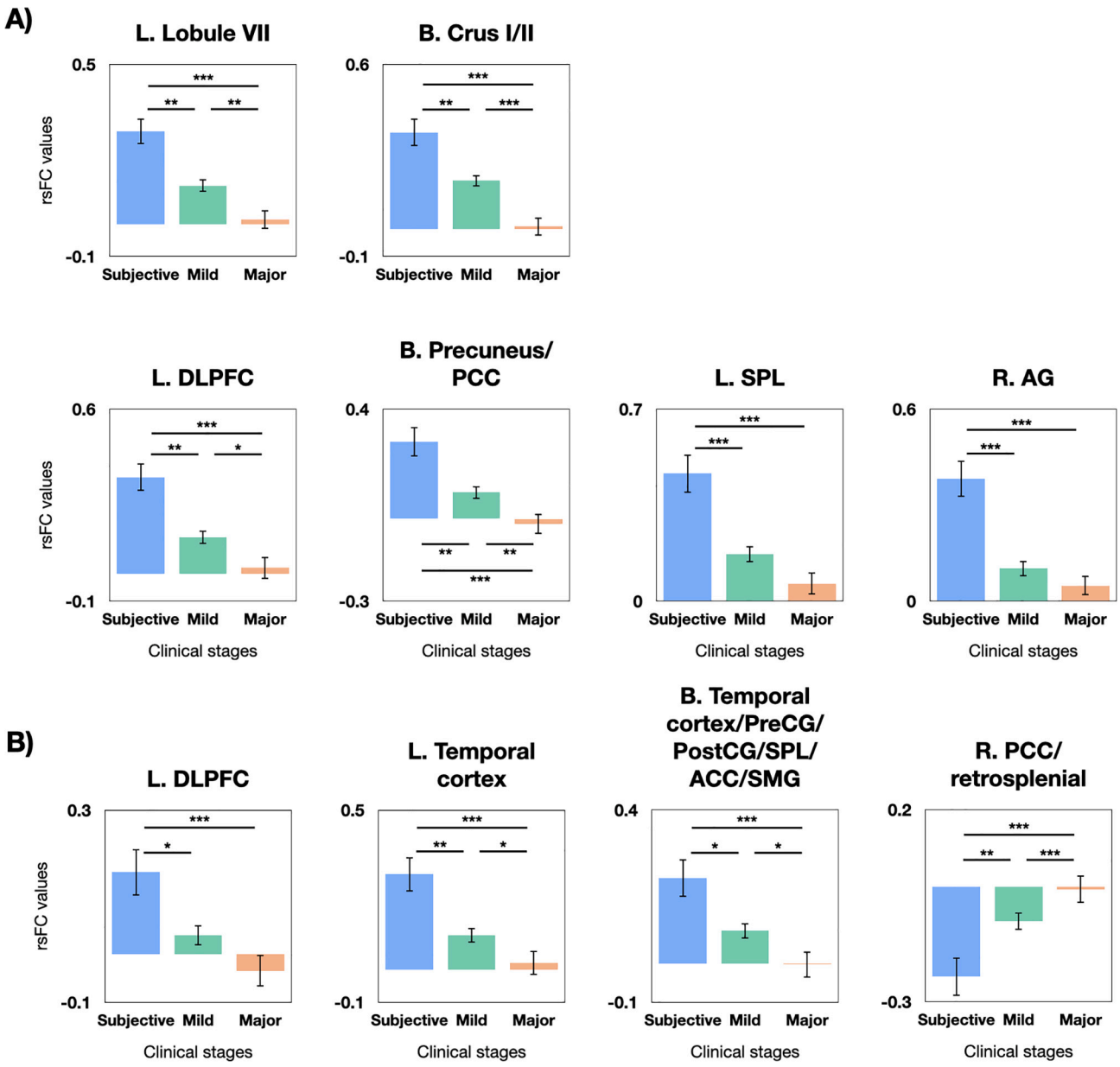

Fig. 3. Effect of clinical stages of cognitive decline. The bar graphs display adjusted-mean (accounted for age, gender, and years of education) and standard error of functional connectivity values for each clinical stage of cognitive decline. Exploratory analysis revealed significant effects of clinical stage (subjective, mild, major) in all resting-state functional connections with seed regions associated with PC1 scores: A) the right cerebellum lobule VIII, and B) right insula. However, cognitive decline stage effect was not found in any of the functional couplings related to PC2 scores (not shown). Abbreviations: R, right; L, left; B, bilateral; DLPFC, dorsolateral prefrontal cortex; PCC, posterior cingulate cortex; SPL, superior parietal lobule; AG, angular gyrus; Lobule VII, cerebellum lobule VII; Crus I/II, cerebellum crus I/II; PreCG, precentral gyrus; PostCG, postcentral gyrus; ACC, anterior cingulate cortex; SMG, supramarginal gyrus.

be overcompensating for cognitive regression in early cognitive impairment [11], and its abnormalities seem to correlate with the semantic memory impairment severity [80]. As a core structure of DMN, reduced FC with the precuneus/PCC has been repeatedly shown in both aging adults and patients with Alzheimer's disease [6,81]. However, studies have also implicated greater occipital-DMN anticorrelation with better attentional control [82]. Likewise, the altered connectivity of these networks at rest could be reflecting increased resources for memory, perhaps due to the decreased or ineffective attentional control. The AG is an integrative hub that is associated with a variety of functions including semantic cognition, attention, comprehension, and mental imagery [83–85]. The functional coupling between the AG and occipital cortex has been characterized in cognitively impaired individuals [86]. Our findings hint that the hyperconnectivity with the visual cortex at rest could be related to an overcompensation due to suboptimal attention in order to preserve memory function in aging adults. The lack of impairment stage effect in any of the connections related to the secondary characteristics of aging adults with cognitive decline could be highlighting the neural correlates of the impaired interaction between attention and memory functions, regardless of the impairment progression.

There are a few limitations that should be acknowledged. One potential limitation is that the current analysis did not include any structural information, such as cortical thickness or local concentration of neural tissues using voxel-based morphometry. The impact of these structural correlates on cognitive performance in patients with neurodegenerative disorders has been established through several studies [87–89]. Second, as the MRI and neuropsychological assessment data

were acquired near their first visit without any other examinations, no comprehensive diagnosis was directly taken into the analysis; however, we have conducted an exploratory analysis to show the effects of clinical stages of cognitive decline. Third, medication information or other minor medical or psychological illnesses were not accounted. Though, as the data were obtained near the beginning of treatment, medication may not have posed a significant threat to the quality of data. Fourth, due to several technical issues, the MRI acquisition protocol did not include a fieldmap or single band reference sequence for distortion correction. While distortion correction on rsfMRI appears to improve the detection of low-frequency signals, we believe that the implementation of a sub-second temporal resolution and multiband acquisition protocol, as well as the state-of-the-art preprocessing pipeline, fMRIPrep, mitigate the possible issues. Fifth, although subjects could have been exposed to SNSB-II assessment at another facility, which could introduce practice effects, it was only administered on those who had not been tested at least for a year. Lastly, given that cross-sectional research design limits the ability to investigate cognitive or neural changes over time [90], our results and interpretations should not be used to understand the long-term trends of the cognitive decline patients.

5. Conclusion

In conclusion, the present investigation employed data-driven approaches on both cognitive and neuroimaging data to derive key characteristics of aging adults with cognitive decline. The primary characteristic identified was the overall cognitive function, while the secondary characteristic indicated intricate interactions between attention and memory domains. Neuroimaging data reflected the Lobule VIII and insula as hub regions linked to the abilities of all cognitive domains. Further analysis of the rsFC patterns underlined efficiency and multisensory information processing to be particularly related to the domain-combined cognitive functions. While attention and memory decline occur simultaneously, the secondary attribute revealed a nuanced relationship demonstrating inefficient interaction within the basic cognitive function that is associated with neural regions involved in semantic and sensory processing. Collectively, findings not only presented critical hub regions related to general cognitive decline but also shed light on the complex nature of attention and memory functions that exists in aging adults with cognitive decline.

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Author contributions

JO conceptualized the study, HEK, JO, JHS, and JYP curated data. HEK collected and analyzed the data. JO, JJK, and JYP provided validation of the analysis. HEK drafted the original manuscript, figures, and tables under the supervision of JO, JJK, and JHS. JO edited and revised the manuscript. All authors approved the final manuscript.

CRediT authorship contribution statement

Hesun Erin Kim: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Visualization. **Jae-Jin Kim:** Data curation, Resources, Supervision, Validation. **Jeong-Ho Seok:** Data curation, Resources, Supervision, Validation. **Jin Young Park:** Data curation, Resources, Supervision, Validation. **Jooyoung Oh:** Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2023.152445.

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