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The effect of network template from normal subjects in the detection of network impairment

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This study aimed to provide a simple way to approach group differences by independent component analysis when researching functional connectivity changes of resting-state network in brain disorders. We used baseline resting state functional magnetic resonance imaging from the Alzheimer's disease neuroimaging initiative dataset and performed independent component analysis based on different kinds of subject selection, by including two downloaded templates and single-subject independent component analysis method. All conditions were used to calculate the functional connectivity of the default mode network, and to test group differences and evaluate correlation with cognitive measurements and hippocampal volume. The default mode network functional connectivity results most fitting clinical evaluations were from templates based on young healthy subjects and the worst results were from heterogeneous or more severe disease groups or single-subject independent component analysis method. Using independent component analysis network maps derived from normal young subjects to extract all individual functional connectivities provides significant correlations with clinical evaluations.

Key words: functional connectivity, resting-state network, default mode network, Alzheimer's disease, mild cognitive impairment, independent component analysis

INTRODUCTION

Cognitive impairment is the most consistent neurological complication of acquired and degenerative brain disorders. The human brain is currently considered as a network system and cognitive processing is supported by continuous integration of information among brain regions (van den Heuvel and Hulshoff Pol 2010). Exploring the human brain via network approach has been proven as practical to investigate the relation between brain operation and human behavior and to evaluate the disorganization of this process in neurodegenerative diseases (Bullmore and Sporns 2009, Greicius 2008). Resting-state functional magnetic resonance imaging (rfMRI) is capable of measuring the intra-network functional connectivity (FC) during rest (Biswal et al. 1997, Greicius et al. 2003, Lowe et al. 2000) and has already become a popular tool to study cognition and neurological and psychiatric brain disorders (van den Heuvel and Hulshoff Pol 2010).

One of the most commonly used tools to analyze rfMRI data is the independent component analysis (ICA), which is a statistical model-free method and is applicable to process whole-brain voxel-wise data. In this method, hidden sources from observed data are assumed to be linear mixtures of independent sources. Group ICA has been developed to simultaneously evaluate multiple subjects, usually through temporal concatenation approach, and the resultant resting-state networks (RSNs) can be easily selected to compare group differences (van den Heuvel and Hulshoff Pol 2010, Calhoun et al. 2009). Although separate group ICAs for different study groups are sometimes

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performed (Harrison et al. 2008a, 2008b), problems of false-positive group differences may occur (Calhoun et al. 2001, Beckmann et al. 2005). Therefore, in general, all patient and control subjects are included to perform combined group ICA (Calhoun et al. 2009).

RSNs selected from the ICA maps are consistent across healthy subjects (Damoiseaux et al. 2006), but will change in spatial distribution, signal intensity, and internal connection pattern when the brain is diseased (Littow et al. 2015, Hafkemeijer et al. 2012, Wang et al. 2013), suggesting that the patterns of RSNs based on ICA maps resulting from subjects with different characteristics are significantly dissimilar. Nonetheless, these group differences of RSNs might be obscured by performing combined group ICA because the resultant spatial maps are required to be universally present across all subjects in this method, and thereby, the differences across subjects are blurred (Anderson et al. 2011). From the literature review, this problem is mainly handled by clustering single-subject ICA results instead of performing group ICA, such as self-organizing clustering method, bagged clustering method, and group ICA with intrinsic reference, all of which avoid the required assumption of common functional networks across all subjects in group ICA. These methods reflect the individual functional network better and the resultant ICA components are more correlated with individual components than those from traditional group ICA (Anderson et al. 2011, Shi et al. 2015, Esposito et al. 2005). Computing intra-network FC based on these methods may reflect individual network function, but the resultant RSNs are likely composed of partly different brain regions in different subjects and even more different in diseased subjects because the commonness of ICA components across subjects is not included in these new ICA methods.

Increasing evidence suggests that neurodegenerative diseases affect functional networks rather than specific brain regions (Zhou et al. 2012), but the influence of the diseases could impact distinct regions of the networks differently (Damoiseaux et al. 2012, Li et al. 2013, Wang et al. 2015). Therefore, disease-related FC change of original RSNs will result in new but impaired RSNs, showing different spatial distribution, signal intensity, and internal connection pattern (Littow et al. 2015, Hafkemeijer et al. 2012, Wang et al. 2013). Single-subject ICA methods for the analysis of FC will not include the regions decreasingly correlated within original networks, but include new regions increasingly correlated with original networks at the individual level, probably due to compensatory reaction (Damoiseaux et al. 2012, Vemuri et al. 2012, Seidler et al. 2010). Therefore, FC from single-subject ICA methods might not be able to reflect the impaired regions within the original networks and might be affected by new regions outside the original networks. These two conditions will offset each other, raising the possibility of poor reflection of disease-related FC change in the networks. Here, we use RSNs derived from relatively normal subjects as the template to calculate FC for both patients and controls. This method may be able to more precisely reflect the disease-related FC change by including the impaired regions in the original spatial distribution of normal RSNs and excluding the outside compensatory reaction.

Our goal of this study was to provide a simple way to enhance the power of ICA to reflect group differences of RSNs. RSNs are relatively stable across healthy subjects (Damoiseaux et al. 2006), and we think only neuronal activities in the spatial maps of normal original RSNs are more likely to reflect the disease-related change. Therefore, using the ICA maps from only healthy subjects to extract FC of RSNs from both controls and patients might be a reasonable and easy way to reflect FC changes of RSNs in disease states. To test our hypothesis, we applied our method to calculate the FC of the extensively studied the default mode network (DMN) (Mevel et al. 2011) in three diagnostic groups: Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy aging.

METHODS

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Inclusion criteria were subjects with baseline fMRI data and preprocessed volumetric 3-dimensional magnetization prepared rapid acquisition gradient echo (3D-MPRAGE) T1-weighted images. Left-handed subjects were excluded. Based on the baseline diagnosis, all subjects were separated into three groups: NL (normal), MCI (mild cognitive impairment), and AD (dementia). Baseline results of six neuropsychological examinations were collected, including four examinations for general cognitive evaluation: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), and modified Alzheimer's Disease Assessment Scale cognitive 13-item scale (ADAS13), and two scores specific for memory function: Memory domain in Everyday Cognition scales (EcogMemory) and a composite score for memory in ADNI dataset (ADNI_MEM). Besides, baseline hippocampal volume (HipV) for each subject was also recorded from the ADNI dataset.

MRI acquisition and analysis

We downloaded raw baseline fMRI data and preprocessed 3D-MPRAGE T1-weighted images from the public ADNI website. The MRI scanners used for the included subjects in this study were all Phillips 3T systems, and according to the ADNI website, the preprocessing procedure in Phillips systems was N3 correction.

All rfMRI data were preprocessed using FSL v5.0.8 (Functional Magnetic Resonance Imaging of the Brain Software Library; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Smith et al. 2004, Woolrich et al. 2009, Jenkinson et al. 2012). The preprocessing steps applied to these datasets included slice timing correction, motion correction, removing non-brain tissue, smoothing, and high-pass temporal filtering to remove low-frequency drifts. After preprocessing procedure, any participant showing a maximum rotation more than 1.5 degree or displacement more than 1.5 mm in any direction was excluded. Then, the preprocessed time series data were registered into a stereotactic space (MNI152 template; Montreal Neurological Institute (MNI), Montreal QC) (Greve and Fischl 2009, Jenkinson and Smith 2001) and we resampled the MNI-space time series data into 4-mm resolution for group ICA analysis to generate intrinsic functional network templates with dimensionality at 20 (Beckmann et al. 2005). We used different subject groups to conduct ICA analysis, including: 1) all subjects, 2) all AD subjects, 3) all MCI subjects, and 4) all NL subjects. For controlling subject number effect and because the AD sample size (27 subjects) was the smallest, we collected two groups with age and gender-matched MCI and NL subjects to form the 5) MCI_27 group and 6) NL_27 group. Another 7) younger normal group (YN) was formed by collecting 22 normal youngest subjects with equal gender number (mean age: 69.1 years, ranging 65.1–73.9 years) from the original NL group. Furthermore, we chose the site with the largest subject number to form 8) a single site population (SS) in order to diminish the effect of heterogeneous data from multi-site database with 23 subjects, including 10 AD subjects, 9 MCI subjects, and 4 NL subjects. One downloaded ICA template was from 9) BrainMap (BM) activation database, analyzed by Smith and others (2009), which was from a 20-component analysis of 29671 subjects, derived from more than 7000 different functional maps. The other downloaded ICA template was from Smith's 20-component analysis result of FMRI data (Smith et al. 2009), composed of 36 healthy young adults (mean age: 28.5 years, ranging 20–35 years; 21 men and 15 women), and this template was considered as the 10) standard template (Smith) for comparison. In addition, we downloaded 11) another group of young and healthy control subjects from a single site of Autism Brain Imaging Data Exchange (ABIDE) project (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino et al. 2014) and the group comprised 28 subjects (mean age: 23.5 years, ranging 18–30 years, 22 men and 6 women). This group had the most similar characteristics to Smith's template, but was analyzed by using our own identical ICA procedure in order to exclude the effect of different analytic method. Last, we performed 12) single-subject ICA for each subject (SICA) (Table I).

Table I. The abbreviations and relevant detailed descriptions of the twelve groups in this study

Group	Detailed description
ABIDE	a downloaded group of young and healthy control subjects from a single site of Autism Brain Imaging Data Exchange (ABIDE) project, analyzed by our protocol
AD	all AD subjects enrolled from ADNI dataset
All	all subjects enrolled from ADNI dataset
BM	a downloaded ICA template from BrainMap (BM) activation database, analyzed by Smith
MCI	all MCI subjects enrolled from ADNI dataset
MCI_27	age and gender-matched subjects with equal subject number to AD group, collected from MCI group
Normal	all normal subjects enrolled from ADNI dataset
Normal_27	age and gender-matched subjects with equal subject number to AD group, collected from Normal group
Smith	a downloaded ICA template from Smith's 20-component analysis result of FMRI data
SS	a single site population with the largest enrolled subject number from the ADNI dataset
YN	22 normal youngest subjects with equal gender number from the original Normal group
SICA	results of single-subject ICA for all subjects enrolled from ADNI dataset

Abbreviations: ABIDE – Autism Brain Imaging Data Exchange, BM – BrainMap, SS – single site population, YN – younger normal, SICA– single subject independent component analysis, ICA – independent component analysis.

Using fslcc utility in FSL to compare with Smith's template, the DMN was then identified visually from the ICA components with higher correlation for further FC analysis. FC was calculated by measuring the internal correlation among the four major portions of the DMN, including 1) the posterior cingulate cortex and precuneus, 2) anterior cingulate cortex and ventral medial prefrontal cortex, 3) right temporoparietal junction, and 4) left temporoparietal junction (Utevsky et al. 2014, Mars et al. 2012). For the DMN in all 11 group ICA results, we used a z value of 3.7 (representing p<0.0001) as a threshold to divide the DMN into several clusters. After the visualization check, 4 clusters fitting in the abovementioned 4 core regions of the DMN were extracted for further FC calculation. Individual FC in the DMN was then evaluated by calculating the correlation among mean time courses of the resultant 4 core clusters in each of these 11 group ICA results. The same method of extracting FC of the DMN was also applied on our single-subject ICA results to measure individual FC of the DMN.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) program, version 20 (SPSS Inc. Chicago, IL, USA). After test of homogeneity of variance for age, gender, and years of schooling among the three diagnostic groups, NL, MCI, and AD, the one-way analysis of variance (ANOVA) with post-hoc test using Scheffe's method to observe group differences in FC of the DMN from all 12 different ICA results. Cohen's effect size with 95% confidence interval for these between-group comparisons was also calculated. In addition, partial correlation was used to observe the association between FC of the DMN and 1) MMSE, 2) MOCA, 3) CDR-SB, 4) ADAS13, 5) EcogMemory, 6) ADNI_MEM, and 7) HipV, after controlling for age, gender, and years of schooling. The threshold for statistical significance was a p value of less than 0.05.

RESULTS

Subjects

The initial selection of subjects from the ADNI database, searching for baseline visits with brain fMRI data and preprocessed T1WI images, resulted in 173 subjects. Among them, 28 subjects were excluded for the following reasons: 11 left-handed, 5 failing to transform fMRI data

Table II. The between-group comparison of DMN FC among the three diagnostic groups: NL, MCI, AD

	NL *vs.* MCI (p value) (Cohen's d effect size, [CI 95%])	NL *vs.* AD (p value) (Cohen's d effect size, [CI 95%])	MCI *vs.* AD (p value) (Cohen's d effect size, [CI 95%])
ABIDE	NL>MCI (p=0.324) (0.29, [−0.08 to 0.66])	NL>AD (p=0.041)* (0.61, [0.11 to 1.09])	MCI>AD (p=0.337) (0.33, [−0.11 to 0.78])
AD	NL>MCI (p=0.197) (0.36, [−0.02 to 0.73])	NL>AD (p=0.116) (0.47, [−0.02 to 0.94])	MCI>AD (p=0.765) (0.16, [−0.28 to 0.60])
All	NL>MCI (p=0.203) (0.36, [−0.01 to 0.73])	NL>AD (p=0.080) (0.52, [0.03 to 0.99])	MCI>AD (p=0.646) (0.21, [−0.24 to 0.65])
BM	NL>MCI (p=0.555) (0.21, [−0.17 to 0.58])	NL>AD (p=0.922) (0.10, [−0.38 to 0.57])	MCI<AD (p=0.893) (−0.12, [−0.56 to 0.32])
MCI	NL>MCI (p=0.561) (0.22, [−0.15 to 0.59])	NL>AD (p=0.095) (0.49, [0.00 to 0.97])	MCI>AD (p=0.352) (0.33, [−0.12 to 0.77])
MCI_27	NL>MCI (p=0.623) (0.19, [−0.18 to 0.56])	NL>AD (p=0.110) (0.50, [0.01 to 0.98])	MCI>AD (p=0.348) (0.33, [0.11 to 0.78])
Normal	NL>MCI (p=0.071) (0.47, [0.09 to 0.84])	NL>AD (p=0.018)* (0.66, [0.16 to 1.13])	MCI>AD (p=0.520) (0.25, [−0.19 to 0.69])
Normal_27	NL>MCI (p=0.116) (0.42, [0.04 to 0.79])	NL>AD (p=0.030)* (0.60, [0.11 to 1.08])	MCI>AD (p=0.526) (0.25, [−0.20 to 0.69])
Smith	NL>MCI (p=0.289) (0.31, [−0.06 to 0.68])	NL>AD (p=0.010)* (0.69, [0.20 to 1.18])	MCI>AD (p=0.141) (0.45, [0.00 to 0.89])
SS	NL>MCI (p=0.210) (0.36, [−0.02 to 0.73])	NL>AD (p=0.103) (0.48, [−0.01 to 0.96])	MCI>AD (p=0.714) (0.19, [−0.26 to 0.63])
YN	NL>MCI (p=0.052) (0.49, [0.11 to 0.86])	NL>AD (p=0.013)* (0.68, [0.19 to 1.16])	MCI>AD (p=0.512) (0.26, [−0.19 to 0.70])
SICA	NL>MCI (p=0.387) (0.28, [−0.09 to 0.65])	NL>AD (p=0.332) (0.36, [−0.12 to 0.84])	MCI>AD (p=0.906) (0.09, [−0.35 to 0.54])

ANOVA with Scheffe's *post-hoc* results. No group difference in age, gender, and years of schooling. Abbreviations: DMN – default mode network, FC – functional connectivity, NL – normal, MCI – mild cognitive impairment, AD – Alzheimer's disease, ABIDE – Autism Brain Imaging Data Exchange, BM – BrainMap, SS – single site population, YN – younger normal, SICA – single subject independent component analysis, CI – confidence interval; * p<0.05.

to a 4D image, 2 with marked motion artifact, and 10 with imaging distortion. The resultant 145 subjects were divided into three groups based on the baseline diagnosis: NL group: 46 subjects (including 20 men) with mean age 74.04±5.67 years (ranging 65.1–85.6 years) and mean years of schooling 16.78±2.11 years (ranging 12–20 years), MCI group: 72 subjects (including 36 men) with mean age 71.33±7.61 years (ranging 55.5–88.6 years) and mean years of schooling 15.94±2.67 years (ranging 11–20 years), and AD group: 27 subjects (including 14 men) with mean age 72.68±7.44 years (ranging 55.9–86.5 years) and mean years of schooling 15.63±2.69 years (ranging 12–20 years). These three groups did not differ in terms of age, gender, and years of schooling.

Group differences of FC in DMN

Among the three diagnostic groups, all 12 templates did not show significant FC differences between NL and MCI groups or between MCI and AD groups. However, significantly higher FC in the NL group than the AD group was found in 5 results: ABIDE (p=0.041), Normal (p=0.018), Normal_27 (p=0.030), Smith (p=0.010), and YN (p=0.013). The results of p values and Cohen's d effect sizes for all the between-group comparisons were listed in Table II. All the effect sizes in the comparison between NL and MCI and between MCI and AD were below 0.50. The effect sizes in the comparison between NL and AD ranged from 0.10 to 0.69 and the top five conditions with at least effect size of 0.60 were compatible with the significant results: ABIDE (d=0.61), Normal (d=0.66), Normal_27 (d=0.60), Smith (d=0.69), and YN (d=0.68).

Correlation between FC of DMN and neuropsychological examinations or HipV

In MMSE, there was no significant correlation. In MOCA, a positive correlation was found in ABIDE (r=0.204, p=0.023), AD (r=0.182, p=0.043), All (r=0.206, p=0.022), MCI (r=0.180, p=0.045), Normal (r=0.219, p=0.014), Normal_27 (r=0.211, p=0.018), Smith (r=0.223, p=0.013), and YN (r=0.233, p=0.009). In CDR-SB, a negative correlation was noted in ABIDE (r=−0.196, p=0.029), Smith (r=−0.252, p=0.005), and YN (r=−0.195, p=0.030). In ADAS13,

Table III. Partial correlation between the DMN FC and neuropsychiatric evaluations or HipV

r (p value)	MMSE	MOCA	CDRSB	ADAS13	EcogMemory	ADNI_MEM	HipV
ABIDE	x	0.204 (0.023)	−0.196 (0.029)	x	−0.177 (0.049)	0.182 (0.043)	0.262 (0.003)
AD	x	0.182 (0.043)	x	x	x	x	x
All	x	0.206 (0.022)	x	x	x	x	0.182 (0.043)
BM	x	x	x	x	x	x	x
MCI	x	0.180 (0.045)	x	x	x	x	x
MCI_27	x	x	x	x	x	x	x
Normal	x	0.219 (0.014)	x	x	x	x	0.229 (0.011)
Normal_27	x	0.211 (0.018)	x	x	x	x	0.216 (0.016)
Smith	x	0.223 (0.013)	−0.252 (0.005)	−0.180 (0.046)	−0.203 (0.024)	0.202 (0.024)	0.301 (0.001)
SS	x	x	x	x	x	x	x
YN	x	0.233 (0.009)	−0.195 (0.030)	x	x	0.178 (0.048)	0.252 (0.005)
SICA	x	x	x	x	x	x	x

Partial correlation results controlling age, gender and years of schooling. Abbreviations: DMN – default mode network, FC – functional connectivity, HipV – hippocampal volume, MMSE – mini-mental state examination, MOCA – Montreal cognitive assessment, CDRSB – Clinical Dementia Rating Scale Sum of Boxes, ADAS13 – modified Alzheimer's Disease Assessment Scale cognitive 13-item scale, EcogMemory – Memory domain in Everyday Cognition scales, ADNI_MEM – a composite score for memory in ADNI dataset, MCI – mild cognitive impairment, AD – Alzheimer's disease, ABIDE – Autism Brain Imaging Data Exchange, BM – BrainMap, SS – single site population, YN – younger normal, SICA – single subject independent component analysis.

a negative correlation was found in Smith (r=−0.180, p=0.046). In EcogMemory, a negative correlation was noted in ABIDE (r=−0.177, p=0.049) and Smith (r=−0.203, p=0.024). In ADNI_MEM, a positive correlation was found in ABIDE (r=0.182, p=0.043), Smith (r=0.202, p=0.024), and YN (r=0.178, p=0.048). The correlation between HipV and FC of the DMN was also evaluated and six results were found to be positively correlated with HipV, including ABIDE (r=0.262, p=0.003), All (r=0.182, p=0.043), Normal (r=0.229, p=0.011), Normal_27 (r=0.216, p=0.016), Smith (r=0.301, p=0.001) and YN (r=0.252, p=0.005) (Table III).

MOCA and HipV showed relatively more significant correlations with the twelve ICA results and the scatterplots with fitted regression lines and associated R-squared values in significant correlations were created for these two measurements respectively (Figs 1 and 2). The R-squared values ranged from 0.035 to 0.062 in MOCA and from 0.016 to 0.072 in HipV. Though not shown, the R-squared values in the significant correlations of the rest 5 measurements were in similar ranges.

DISCUSSION

Among the twelve ICA results, significantly higher FC of the DMN in NL than AD with relatively higher effect size was demonstrated only in the ICA results from normal subjects, including young and old normal subject groups, suggesting using ICA templates from normal subjects was better to demonstrate FC difference of the DMN between normal subjects and patients with Alzheimer's disease. In this study, we used seven measurements to evaluate the twelve ICA results. These seven measurements were known to be able to reflect the effect of Alzheimer's disease on patients, including 4 general cognitive measurements, 2 specific memory function measurements, and HipV. Among the twelve ICA results, the stronger correlation results were all from the ICA results from young healthy adults. On the contrary, the weaker results were from heterogeneous conditions, diseased groups, and single-subject ICA method. Therefore, using ICA templates from young healthy subjects to extract FC of DMN was more likely to enhance the correlation between FC change of DMN and clinical measurements.

Among all ICA results, significantly higher FC in NL than AD was demonstrated in the ABIDE, Normal, Normal_27, Smith, and YN groups. There was no condition showing significant difference between NL and MCI or between MCI and AD. MCI condition is recognized as the transitional zone between normal aging and AD, and although not fulfilling the criteria for AD, MCI subjects have significant cognitive deficits and are of higher risk for AD (Mueller et al. 2005). In the research field of DMN in MCI, insignificant difference of FC between normal and MCI subjects or between MCI and AD subjects has been demonstrated but FC of MCI group is numerically in between those of normal and AD groups (Binnewijzend et al. 2012). The phenomenon of ambiguous but intermediate status of FC in MCI and increased FC in normal than AD groups is compatible with our findings and is considered as a reasonable FC result. This phenomenon might be due to the heterogeneous regional FC changes in the DMN, including both increased and decreased FC, in MCI status (Qi et al. 2010, Cha et al. 2013) and these bidirectional changes will increase the variation of FC of the DMN as a whole. Besides, using Cohen's d effect size to evaluate these between-group comparisons, the comparisons between NL and MCI and between MCI and AD show a d value below 0.50, suggesting at most small effect in these comparisons (Cohen 1988).

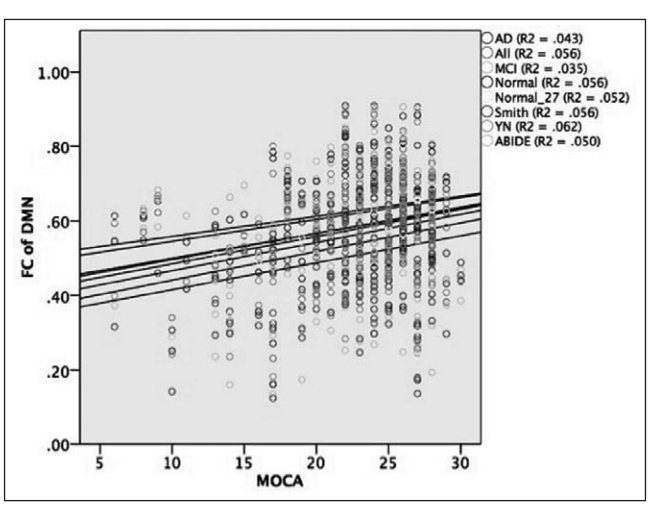

Fig. 1. Scatterplots with fitted regression lines and associated R-squared values in significant correlations between FC of DMN and MOCA.

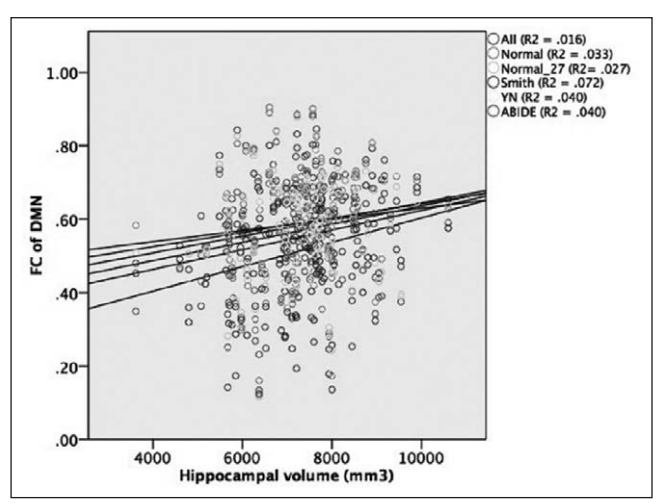

Fig. 2. Scatterplots with fitted regression lines and associated R-squared values in significant correlations between FC of DMN and hippocampal volume.

Seven comparisons between NL and AD have medium effect, including ABIDE, All, MCI_27, Normal, Normal_27, Smith, and YN and of which, the top five comparisons with an effect size of at least 0.60 are using ABIDE, Normal, Normal_27, Smith, and YN ICA templates, compatible with significant results. Among the three diagnostic groups, better FC results came from only templates based on old or young normal subjects. From this standpoint, FC of the DMN by using ICA results from relatively normal healthy groups are more likely to significantly show reasonable findings, which might be obscured by using ICA results from diseased or heterogeneous condition subjects or single-subject ICA method.

Furthermore, we chose 4 general cognitive measurements, 2 specific memory function measurements, and HipV to evaluate correlations between these measurements, or HipV with FC of the DMN in order to validate the ICA results in the twelve conditions. MMSE is a commonly used reliable test to measure cognitive impairment and a higher score indicate a healthier condition (Pangman et al. 2000). However, in our study, no condition showed any correlation with MMSE scores. Different regional FC correlation of the DMN with MMSE has been noted and is probably lower the significant correlation of average FC in the whole DMN in our study (Cha et al. 2013). MOCA is another validated tool for the detection of cognitive impairment in MCI and early AD and a higher score indicates a healthier condition (Nasreddine et al. 2005). Significantly positive correlations existed between MOCA scores and most DMN FC results, including those from the ABIDE, AD, All, MCI, Normal, Normal_27, Smith, and YN groups. No correlation was found in results from the BM, MCI_27, and SS groups. CDR-SB score is useful to stage the severity of AD and MCI, with a higher score indicating more severe symptoms (O'Bryant et al. 2008). Negative correlation between FC of the DMN and CDR-SB scores was present in the results from the ABIDE, Smith, and YN groups. ADAS13 is used to evaluate cognitive function including a variety of cognitive domains and a higher score reflects more cognitive impairment (Mohs et al. 1997). Negative correlation between ADAS13 and FC of the DMN was found in the result from Smith group. Except for MMSE, better correlation results were from the Smith template in the other three general neuropsychiatric evaluations, closely followed by the ABIDE and YN groups. The other results merely showed one or no fitting correlation.

Moreover, memory impairment is one of the main symptoms of AD, which also exists in MCI, and is the earliest manifestation of AD (Association 2000, Salmon 2012). Results of two specific memory evaluations were collected from ADNI website, including EcogMemory and ADNI_MEM, which is a composite score for memory function from the ADNI neuropsychological battery using modern psychometric methods. EcogMemory is one of the six domain-specific factors included in the measurement of Everyday Cognition (Ecog) and is a useful tool to evaluate everyday memory function in the elderly. A higher EcogMemory score is suggestive of worse daily function (Farias et al. 2008). There were two conditions showing negative correlations with the EcogMemory score, including ABIDE and Smith. ADNI_MEM has been tested for the power to predict progression from MCI to AD and shows equal or better results as compared with many other scores, such as longitudinal Rey Auditory Verbal Learning Test, AD Assessment Schedule – Cognition, MMSE, and CDR-SB. In addition, ADNI_MEM is suggested for analyzing the strength of associations between imaging and memory and a higher score represents better memory performance (Crane et al. 2012). In this study, only the ABIDE, Smith and YN conditions showed positive correlations with ADNI_MEM. For these two memory specific measurements, only the ICA results from the ABIDE group and Smith's template show good correlation, followed by the YN group. Furthermore, smaller HipV in patients with AD and MCI as compared with healthy controls has been validated in many studies (den Heijer et al. 2010). Therefore, we also used HipV to evaluate the quality of ICA results in the eleven conditions. There were 6 conditions showing positive correlations between FC of the DMN and HipV, including ABIDE, All, Normal, Normal_27, Smith, and YN. Considering all six clinical evaluation scores and HipV, the best two ICA results fitting 5 to 6 kinds of measurements were the Smith template and the ABIDE group, followed by the YN group, which fitted 4 kinds of measurements. Three groups, All, Normal, and Normal_27 groups, fitted 2 measurements. The AD and MCI groups only fitted one measurement and the BM, MCI_27, SS, and SICA results fitted no measurement. Thus, the best results came from the Smith's and ABIDE group templates, both derived from young and healthy adults, while the worst results come from the heterogeneous condition, diseased groups, and single-subject ICA method. The SS group was purely from a single site but showed one of the worst results, suggesting that single site data do not have the strength to properly reflect clinical measurements and the unsatisfactory result might be primarily due to the heterogeneous condition of this single site population. The correlation result from single-subject ICA also showed one of the worst results. This phenomenon might be partly due to the different spatial distribution of the individual DMN, which is likely affected by diseases, and to the change in the spatial distribution results from the decreased and increased regional FC of the whole brain to the original healthy DMN, which might mutually offset. Therefore, though the single-subject ICA method is better to reflect

current individual FC of the DMN (Anderson et al. 2011, Shi et al. 2015, Esposito et al. 2005), this method might not be able to detect the influence of impaired regions of DMN and to diminish the effect of compensatory regions on the DMN (Damoiseaux et al. 2012, Vemuri et al. 2012, Seidler et al. 2010). Instead, our method, using a DMN template from young and normal subjects to extract FC of the DMN for all subjects, is likely to solve this problem and truly demonstrate a much better clinical correlation than the single-subject ICA method. In addition, the overall correlation results from the Normal and Normal_27 groups were slightly worse than the results from the ABIDE, Smith, and YN groups, among which, the YN group was worse than the ABIDE group and Smith template. The possible explanation is that although the subjects in the NL group from the ADNI dataset have relatively preserved cognitive function, they are aging and the aging process can alter RSNs even though less severely than diseased conditions (Huang et al. 2015, Onoda et al. 2012, Geerligs et al. 2015, Agosta et al. 2012, Campbell et al. 2015). Therefore, the DMN is still impaired in elder normal subjects, causing relatively poor correlation results.

There are several limitations in this study. One is that we performed ICA for subjects from the ADNI dataset and ABIDE project subjects and downloaded the templates from BM and Smith's studies. Therefore, those downloaded templates might be based on ICA using different parameter settings from ours, even though all are analyzed at the same dimensionality of 20. In addition, fMRI data from the ADNI, ABIDE, BM, and FMRI could be with different scan protocols, which might affect the imaging quality and imaging results. The solution to these limitations is to use the same group ICA setting to analyze subjects from single MRI scanner with identical scan protocols, with subjects who are young healthy adults, normal elderly, and diseased participants. All the resultant ICA templates from different groups can be applied on identical subject groups with clinical cognitive evaluations to test which result has better power to reflect clinical conditions. Furthermore, the R-squared values in the linear regression analysis of significant correlations between FC of DMN and the seven measurements are quite low, suggesting marked variability of the data, but this phenomenon is not uncommon in studying human behavior.

CONCLUSION

By using group differences among three diagnostic groups and using correlation evaluation with 4 global cognitive measurements, 2 memory specific measurements, and HipV, the best results fitting clinical evaluations were the FC results of the DMN template derived from young healthy subjects. Results from relatively young normal elders intermediately fit the clinical evaluations and the worst results were from heterogeneous or more severe disease groups and single-subject ICA method. The overall findings suggest that the diseased condition or even aging process will alter the DMN and some significant correlations with clinical evaluations might be obscured by using the DMN derived from ICA results with source subjects who are diseased or aging, as compared with the ICA results from young and healthy adults. The single-subject ICA method is able to reflect individual DMN condition but is of low power to reflect disease influence on the DMN. Accordingly, testing a new imaging analysis method, such as using different ICA maps, on a well-evaluated subject group might also be helpful in order to reduce the possibility of false negative or false positive results.

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REFERENCES

Agosta F, Pievani M, Geroldi C, Copetti M, Frisoni GB, Filippi M (2012) Resting state fMRI in Alzheimer's disease: beyond the default mode network. Neurobiol Aging 33: 1564–1578.

Anderson A, Bramen J, Douglas PK, Lenartowicz A, Cho A, Culbertson C (2011) Large sample group independent component analysis of functional magnetic resonance imaging using anatomical atlas-based reduction and bootstrapped clustering. Int J Imaging Syst Technol 21: 223–231.

Association AP (2000) Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR (4th ed.). American Psychiatric Association, Washington, DC, USA.

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360: 1001–1013.

Binnewijzend MA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N (2012) Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 33: 2018–2028.

Biswal BB, Van Kylen J, Hyde JS (1997) Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed 10: 165–170.

Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10: 186–198.

Calhoun VD, Adali T, Pearlson GD, Pekar JJ (2001) Spatial and temporal independent component analysis of functional MRI data containing a pair of task-related waveforms. Hum Brain Mapp 13: 43–53.

Calhoun VD, Liu J, Adali T (2009) A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. Neuroimage 45(1 Suppl): S163–S172.

Campbell MC, Koller JM, Snyder AZ, Buddhala C, Kotzbauer PT, Perlmutter JS (2015) CSF proteins and resting-state functional connectivity in Parkinson disease. Neurology 84: 2413–2421.

Cha J, Jo HJ, Kim HJ, Seo SW, Kim HS, Yoon U (2013) Functional alteration patterns of default mode networks: comparisons of normal aging, amnestic mild cognitive impairment and Alzheimer's disease. Eur J Neurosci 37: 1916–1924.

Cohen J (1988) Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Lawrence Earlbaum Associates, Hillsdale, NJ, USA.

Crane PK, Carle A, Gibbons LE, Insel P, Mackin RS, Gross A (2012) Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Brain Imaging Behav 6: 502–516.

Damoiseaux JS, Prater KE, Miller BL, Greicius MD (2012) Functional connectivity tracks clinical deterioration in Alzheimer's disease. Neurobiol Aging 33: 828.e19–30.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM (2006) Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103: 13848–13853.

den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP (2010) A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. Brain 133(Pt 4): 1163–1172.

Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K (2014) The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 19: 659–667.

Esposito F, Scarabino T, Hyvarinen A, Himberg J, Formisano E, Comani S (2005) Independent component analysis of fMRI group studies by self-organizing clustering. Neuroimage 25: 193–205.

Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K (2008) The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology 22: 531–544.

Geerligs L, Renken RJ, Saliasi E, Maurits NM, Lorist MM (2015) A brain-wide study of age-related changes in functional connectivity. Cereb Cortex 25: 1987–1999.

Greicius M (2008) Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol 21: 424–430.

Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100: 253–258.

Greve DN, Fischl B (2009) Accurate and robust brain image alignment using boundary-based registration. Neuroimage 48: 63–72.

Hafkemeijer A, van der Grond J, Rombouts SA (2012) Imaging the default mode network in aging and dementia. Biochim Biophys Acta 1822: 431–441.

Harrison BJ, Pujol J, López-Solà M, Hernández-Ribas R, Deus J, Ortiz H (2008a) Consistency and functional specialization in the default mode brain network. Proc Natl Acad Sci U S A 105: 9781–9786.

Harrison BJ, Pujol J, Ortiz H, Fornito A, Pantelis C, Yucel M (2008b) Modulation of brain resting-state networks by sad mood induction. PLoS One 3: e1794.

Huang CC, Hsieh WJ, Lee PL, Peng LN, Liu LK, Lee WJ (2015) Age-related changes in resting-state networks of a large sample size of healthy elderly. CNS Neurosci Ther 21: 817–825.

Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) FSL. Neuroimage 62: 782–790.

Jenkinson M, Smith S (2001) A global optimisation method for robust affine registration of brain images. Med Image Anal 5: 143–156.

Li B, Liu L, Friston KJ, Shen H, Wang L, Zeng LL (2013) A treatment-resistant default mode subnetwork in major depression. Biol Psychiatry 74: 48–54.

Littow H, Huossa V, Karjalainen S, Jääskeläinen E, Haapea M, Miettunen J (2015) Aberrant functional connectivity in the default mode and central executive networks in subjects with schizophrenia – a whole-brain resting-state ICA study. Front Psychiatry 6: 26.

Lowe MJ, Dzemidzic M, Lurito JT, Mathews VP, Phillips MD (2000) Correlations in low-frequency BOLD fluctuations reflect cortico-cortical connections. Neuroimage 12: 582–587.

Mars RB, Neubert FX, Noonan MP, Sallet J, Toni I, Rushworth MF (2012) On the relationship between the "default mode network" and the "social brain". Front Hum Neurosci 6: 189.

Mevel K, Chetelat G, Eustache F, Desgranges B (2011) The default mode network in healthy aging and Alzheimer's disease. Int J Alzheimers Dis 2011: 535816.

Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M (1997) Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 11(Suppl 2): S13–S21.

Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L (2005) The Alzheimer's disease neuroimaging initiative. Neuroimaging Clin N Am 15(4): 869–877, xi–xii.

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53: 695–699.

O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ (2008) Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol 65: 1091–1095.

Onoda K, Ishihara M, Yamaguchi S (2012) Decreased functional connectivity by aging is associated with cognitive decline. J Cogn Neurosci 24: 2186–2198.

Pangman VC, Sloan J, Guse L (2000) An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. Appl Nurs Res 13: 209–213.

Qi Z, Wu X, Wang Z, Zhang N, Dong H, Yao L (2010) Impairment and compensation coexist in amnestic MCI default mode network. Neuroimage 50: 48–55.

Salmon DP (2012) Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. Curr Top Behav Neurosci 10: 187–212.

Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT (2010) Motor control and aging: links to age-related brain structural, functional, and biochemical effects. Neurosci Biobehav Rev 34: 721–733.

Shi Y, Zeng W, Wang N, Chen D (2015) A novel fMRI group data analysis method based on data-driven reference extracting from group subjects. Comput Methods Programs Biomed 122: 362–371.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE (2009) Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 106: 13040–13045.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Suppl 1): S208–S219.

Utevsky AV, Smith DV, Huettel SA (2014) Precuneus is a functional core of the default-mode network. J Neurosci 34: 932–940.

van den Heuvel MP, Hulshoff Pol HE (2010) Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 20: 519–534.

Vemuri P, Jones DT, Jack CR Jr (2012) Resting state functional MRI in Alzheimer's Disease. Alzheimers Res Ther 4: 2.

Wang H, Zeng LL, Chen Y, Yin H, Tan Q, Hu D (2015) Evidence of a dissociation pattern in default mode subnetwork functional connectivity in schizophrenia. Sci Rep 5: 14655.

Wang L, Li H, Liang Y, Zhang J, Li X, Shu N (2013) Amnestic mild cognitive impairment: topological reorganization of the default-mode network. Radiology 268: 501–514.

Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T (2009) Bayesian analysis of neuroimaging data in FSL. Neuroimage 45(1 Suppl): S173–S186.

Zhou J, Gennatas ED, Kramer JH, Miller BL, Seeley WW (2012) Predicting regional neurodegeneration from the healthy brain functional connectome. Neuron 73: 1216–1227.