Brain-wide structural connectivity alterations under the control of Alzheimer risk genes

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Abstract

Background: Alzheimer's disease is the most common form of brain dementia characterized by gradual loss of memory followed by further deterioration of other cognitive function. Large-scale genome-wide association studies have identified and validated more than 20 AD risk genes. However, how these genes are related to the brain-wide breakdown of structural connectivity in AD patients remains unknown.

Methods: We used the genotype and DTI data in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. After constructing the brain network for each subject, we extracted three types of link measures, including fiber anisotropy, fiber length and density. We then performed a targeted genetic association analysis of brain-wide connectivity measures using general linear regression models. Age at scan and gender were included in the regression model as

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covariates. For fair comparison of the genetic effect on different measures, fiber anisotropy, fiber length and density were all normalized with mean as 0 and standard deviation as one. We aim to discover the abnormal brain-wide network alterations under the control of 34 AD risk SNPs identified in previous large-scale genome-wide association studies.

Results: After enforcing the stringent Bonferroni correction, rs10498633 in *SLC24A4* were found to significantly associated with anisotropy, total number and length of fibers, including some connecting brain hemispheres. With a lower level of significance at 5e-6, we observed significant genetic effect of SNPs in *APOE, ABCA7, EPHA1* and *CASS4* on various brain connectivity measures.

Keywords

brain connectivity; imaging genetics association; Alzheimer's disease

Background

Alzheimer's disease is the most common form of brain dementia characterized by gradual loss of memory followed by further deterioration of other cognitive function. It has become one of the leading cause of death and is still increasingly affecting the aging population nationwide[1]. Due to the lack of effective treatment, number of deaths due to Alzheimer's between 2000 and 2014 has significantly increased [1].

Neuroimaging has been a major approach to study AD which allows mapping of structural, functional and molecular AD pathology inside brain [2]. Accumulating evidence from previous studies suggests abnormal imaging patterns in AD patients, such as cortical and subcortical atrophy [3], cortical amyloid deposition[4], grey matter atrophy[5], and functional cortical disconnection [6]. Recently, there is a growing interest in structural brain connectivity captured through diffusion tensor imaging (DTI)in AD. AD patients and those in a mild stage were found to have loss of inter-hemisphere connectivities [7] and increased diffusion anisotropy [8].

On the other hand, genetic factors play an essential role in AD. Results from large-scale twin studies suggests the heritability of AD to reach 70%-80% [9, 10]. *APOE* is the most well-known gene associated with increased AD risk and remains as the risk gene with the greatest known impact. Later, large-scale genome-wide association studies (GWASs) identified and validated twenty novel risk genetic loci [11, 12, 13, 14, 15, 16]. These risk variants have been recently found to differentially regulate brain amyloidosis across different disease stages [17]. However, how they exert effect on the brain-wide breakdown of structural brain connectivity has not been studied yet.

Leveraging the genotype and DTI data in the Alzheimer's Disease Neuroimaging Initiative (ADNI) [18, 19], in this paper, we perform a targeted genetic association analysis of brain-wide connectivity measures to discover the brain network alterations under the control of AD risk SNPs. We focus our analysis on link level measures, including fiber anisotropy, fiber length and density. In addition, to avoid potential bias introduced in imaging processing pipeline, we repeat our imaging processing pipeline and evaluate the reliability of all

connectivity measures. Only high quality measures will be considered for the further imaging genetics association analysis. Using age at scan and gender as covariates, we employ general linear regression models to investigate the association between each pair of candidate SNP and connectivity measure. After enforcing the stringent Bonferroni correction, SNPs rs10498633 in *SLC24A4* were found to be significantly associated with anisotropy, total number and length of fibers including some connecting hemispheres, which is consistent with existing findings. With a lower level of significance at 5e-6, we observed significant genetic effect of SNPs in *APOE, ABCA7, EPHA1* and *CASS4* on various brain connectivity measures.

Methods

ADNI Cohort

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [19, 18]. Involving researchers from more than 50 sites in the USA and Canada, the ADNI is a multi-site study to track the progression of AD in the human brain by collecting longitudinal neuroimaging, biochemical, and genetic biological data. A key aim of the ADNI is to provide the opportunity to combine genetics with multiple types of imaging (e.g. magnetic resonance imaging (MRI) and positron emission tomography (PET)) and clinical data to help investigate mechanisms of the disease. For up-to-date information, see www.adni-info.org. For the proposed brain-wide connectomics genetics association analysis, we downloaded the structural MRI (sMRI) scans, DTI scans, GWAS genotype and demographic data from the ADNI website. Written informed consent was obtained at the time of enrollment and/or genetic sample collection and protocols were approved by each participating study and sites' Institutional Review Board.

Brain Connectivity Measures

The DTI data was first denoised and corrected for motion and distortion using the approach described in a previous study [20]. Tractography was performed in Camino [21] based on white matter fiber orientation distribution function (ODF). Streamlines were modeled with a multi-tensor modeling approach, where voxels will fit up to two fiber orientations. Second, the sMRI images were registered to the b0 volume of DTI data using the FNIRT toolbox [22] and 278 brain regions of interest (ROIs) were extracted following [23]. The final networks between 278 brain ROIs were constructed using fibers going through white matter and connecting ROIs. In this project, we focus on the link level measures and calculated the fiber anisotropy (FA), length of fibers (LOF) and number of the fibers (NOF) connecting each pair of ROIs. Considering that the number of fibers are partially dependent on the surface area of their connected ROIs, we derived a new measure, the fiber density (FD), for the following association analysis, which is the fraction between number of fibers and the average surface of grey-matter regions *i* and *j*.

Reliability Test

To avoid potential bias introduced in imaging processing pipeline, We further evaluated the reliability of all brain connectivity measures. Since each subject only have one DTI scan in ADNI, we repeated our imaging processing pipeline three times and quantified the reliability

of FA, FD and LOF measures by calculating their intraclass correlation coefficients (ICC) across three runs.

Genotype Data

Genotyping was performed using the Illumina HumanOmni Express BeadChip for all participants included. We first performed standard sample and SNP quality control procedures as described previously [24]. The un-genotyped SNPs were imputed using MACH and minimac in a two-stage procedure following a previous study [25]. The pilot 1 data of the 1000 Genomes Project were used as a reference panels for inferring missing genotypes. Minimac produced the posterior probabilities of the imputed genotypes at un-genotyped marker loci for each individual. To assure the quality of imputation, an r^2 value equal to 0.30 was imposed as the threshold to filter the imputed genotypes. In this project, since we are particularly interested in the brain network alterations under the control of AD, rs429358 in *APOE* and 33 AD risk SNPs used in [17] were included for the association analysis (Table.1).

Brain Connectomics Genetics Association

We performed a targeted genetic association analysis of brain-wide connectivity measures by employing a general linear model (GLM) approach in R. GLMs were developed using age at scan and gender as independent variables. For fair comparison of genetic effect on different measures, FA, LOF and FD measures were normalized to have zero mean and standard deviation as one. Following analysis of brain connectivity to examine the association between candidate SNPs and brainwide connectivity measures, correction for multiple comparisons was enforced using the Bonferroni correction method at a 0.05 level of significance. We also examined the associations showing trend-level significance (uncorrected p   5e-6).

Results

Subject

All the subjects included in this study are participants from the ADNI-2 and ADNI-GO stages. Among all 273 subjects with DTI scans, 214 of them without missing values in sMRI scans, genotype of 34 risk SNPs and demographic information were kept for the association analysis. In total, the study population is consisted of 34 healthy controls (HC), 26 individuals with subjective memory complain (SMC), 59 individuals with early mild cognitive impairment (EMCI), 23 individuals with late MCI (LMCI) and 36 individuals with AD. Shown in Table. 2 is the detailed demographic information for all 214 subjects.

Reliability Test

Among all brain connectivity measures, including FA, LOF and FD, about one third of the measures show inconsistency across three runs with ICC smaller than 0.9. More specifically, 26886 out of 38503 FA measures (69.83%) passed the reliability test with ICC greater than 0.9 [26]. For LOF and FD measures, there are 25644 (66.6%) and 29791 (77.37%) passing the same threshold. Shown in Figure. 1 is the ICC distribution for FA, LOF and FD

respectively. In this paper, we only included those measures with excellent reliability (ICC 0.9) for further analysis.

Genetic effect of AD risk genes on connectivity measures

We identified several significant association between 34 AD risk loci and three types of connectivity measures with excellent reliability (Table. 3). For better interpretation of results, we mapped 278 brain ROIs to Yeo parcellation with seven groups (3rd and 4th columns in Table. 3), including Visual (VIS), Somato-Motor (SM), Dorsal Attention (DA), Ventral Attention (VA), Limbic system (L), Fronto-Parietal (FP), and Default Mode Network (DMN). Shown in Figure. 2(a) is the brain map of Yeo atlas we used in MNI 152 space. We also added subcortical regions (SUBC) and cerebellum (CER) to complement Yeo atlas using the strategy previously described in [27].

For FA measure, after enforcing the stringent Bonferroni correction based on the total number of FA measures and risk SNPs, the genetic effect of rs10498633 in *SLC24A4* achieved brain-wide significance and showed association with the anisotropy of fibers connecting Ventral Attention and Subcortical, Ventral Attention and Cerebellum, and within Default Mode Network respectively. rs10498633 in *SLC24A4* is also found to be significantly associated with the length and density of fibers connecting Cerebellum and Somato-Motor, Ventral Attention and Cerebellum, Ventral Attention and Subcortical, and within Default Mode Network etc. After lowering the level of significance to 5e-6 (uncorrected), other SNPs such as rs11771145 and rs10498633 are found to be nominally associated with the fibers connecting Cerebellum and Somato-Motor, Dorsal Attention and Somato-Motor respectively. In addition, rs17125944 in *FERMT2* is associated with the internal connectivity anisotropy inside Default Mode Network with a nominal significance. rs429358 in top AD risk gene *APOE* only shows nominal significance of association with the density of fibers between Subcortical and Cerebellum.

Shown in the top panel of Figure. 2(b) is the heatmap of association results between rs10498633 and three types of connectivity measures. Each row and column were reordered based on Yeo atlas. The bottom panel is the corresponding brain connectivity map showing only links with ICC 0.9 and uncorrected p *leq* 5e-6. Links in the bottom panel are corresponding to the dots in the top panel. Different node colors in the brain connectivity map indicate the Yeo group information of each ROI. Among all the fibers affected by those risk genes, we observed that some of them associated with rs10498633 connect two hemispheres. This is consistent with previous findings that AD patients show loss of inter-hemispheric connectivity. Figure. 2(c)-(e) are example brain maps of three associations with nominal significance.

Discussion

To the best of our knowledge, this is the first comprehensive analysis to test the association of the top AD risk variants with brain connectivity measures. By performing a targeted genetic association of brain-wide connectivity, we were able to replicate the previous findings such as abnormal inter-hemispheric connectivity patterns and fiber anisotropy in AD. rs10498633 in *SLC24A4* consistently shows significant genetic effect on all three type

of brain connectivity measures, including some inter-hemispheric connectivity which is a known abnormal pattern in AD patients.

SLC24A4 encodes a member of the potassium-dependent sodium/calcium exchanger protein family. It has been previously reported to have significant association with gray matter density and brain metabolism [28]. According to the Allen Human Brain Atlas (AHBA) (www.brain-map.org), *SLC24A4* is highly expressed in part of the cerebellum and some subcortical regions, including Amygdala, Puta-men, etc. Results of a large-scale eQTL analysis (www.braineac.org) show that rs10498633 is an eQTL in Thalamas, Putamen and white matter. Taken together, these evidence gives strong support to our connectomics-genetics findings. It also suggests potential role of rs10498633 in regulating the brain connectivity by mediating the expression of certain genes including *SLC24A4*.

Conclusion

We performed a targeted genetic association analysis of brain-wide connectivity measures to investigate the effect of AD risk genes on brain networks. We identified several significant genetics-connectomics associations. Particularly, rs10498633 in *SLC24A4* shows significant genetic effect on the anisotropy, length and density of fibers, some of which connect two hemispheres. Since rs10498633 is an eQTL locus in multiple brain regions, the regulation role of rs10498633 in brain network may be achieved by mediating the expression of certain genes including *SLC24A4*.

Acknowledgements

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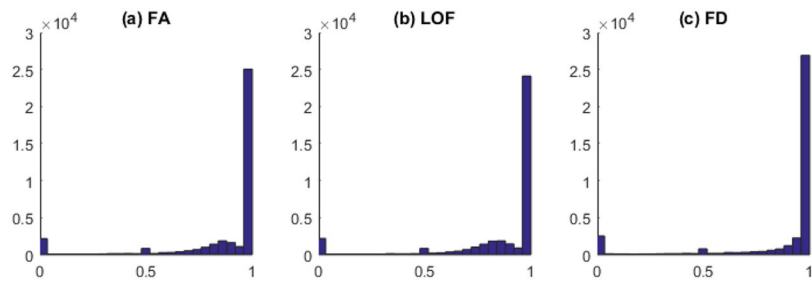
Figure 1. ICC distribution for all measures
(a) Fiber anisotropy, (b) Length of fibers, (c) Fiber density.
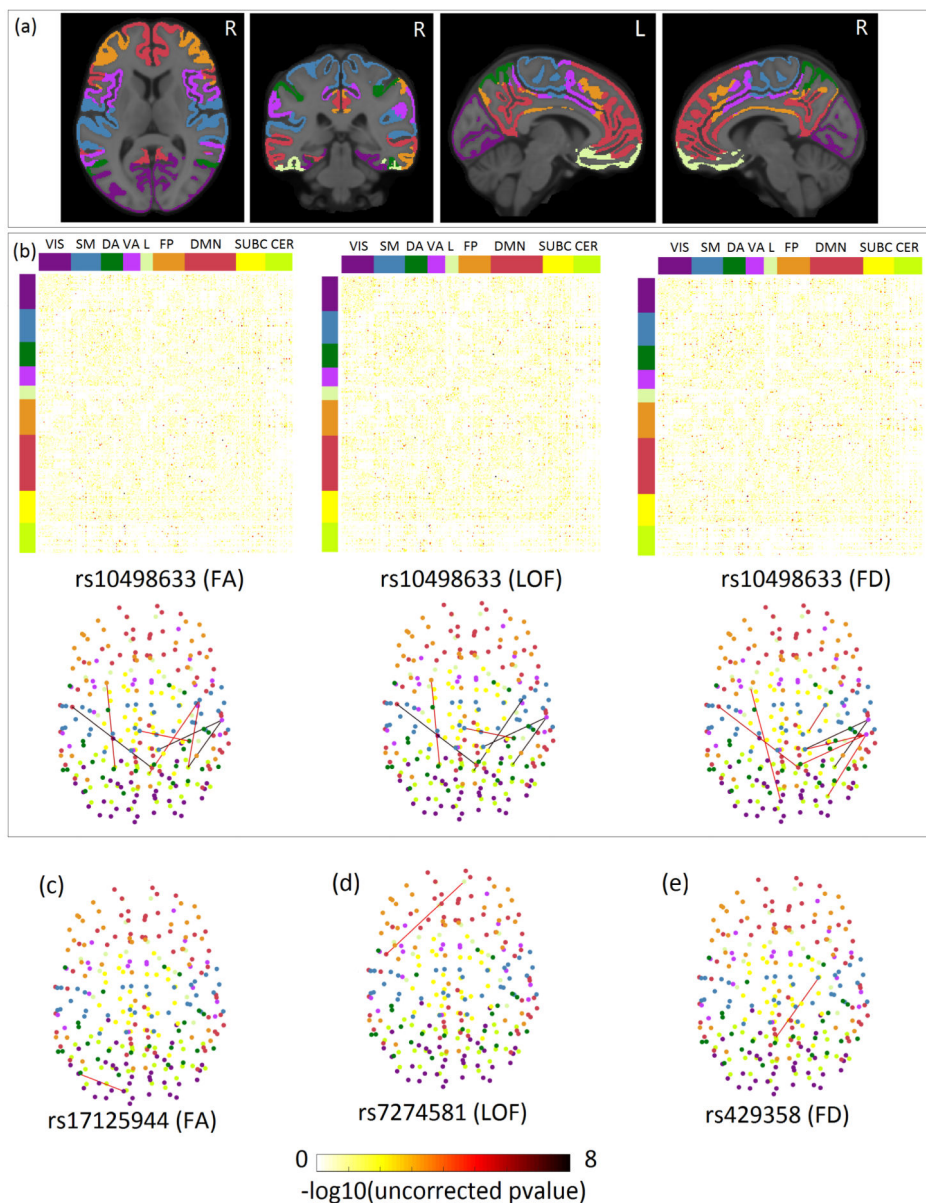
Figure 2. Heatmap of all SNP-connectivity associations and brain map of selected connectivities with uncorrected p 5e-6.

(a) Brain map of Yeo parcellation with 7 groups in MNI 152 space. (b) Top panel: Heatmap showing the association of rs10498633 in *SLC24A4* with three different types of connectivity measures. Rows and columns are reordered to form 7 groups corresponding to Yeo parcellation. Top and side colorbasr indicate the corresponding Yeo parcellation of each ROI. The last two groups, subcortical (SUBC) and Cerebellum (CER), are added to complement the Yeo atlas. (c) Brain map of the association between rs17125944 and FA measures. (d) Brain map of the association between rs7274581 and LOF measures. (e) Brain map of the association between rs429358 and FD measures. All the links in the brain connectivity map share the same colormap with the dots in the heatmap. Yeo parcellation in

(a), top and side colorbars in (b), and all the nodes in the brain connectivity map share the same color scheme.

Table 1

34 AD risk loci included in the brain-wide connectomics genetics association.

SNP	Gene	MAF	SNP	Gene	MAF
rs3752246	ABCA7	0.17	rs6701713	CR1	0.25
rs3764650	ABCA7	0.2	rs11767557	EPHA1	0.2
rs4147929	ABCA7	0.18	rs11771145	EPHA1	0.43
rs6733839	BIN1	0.39	rs17125944	FERMT2	0.11
rs744373	BIN1	0.36	rs35349669	INPP5D	0.21
rs7561528	BIN1	0.2	rs190982	MEF2C	0.22
rs7274581	CASS4	0.09	rs610932	MS4A6A	0.45
rs9349407	CD2AP	0.19	rs983392	MS4A6A	0.23
rs10948363	CD2AP	0.19	rs2718058	NME8	0.34
rs3865444	CD33	0.21	rs3851179	PICALM	0.31
rs10838725	CELF1	0.26	rs10792832	PICALM	0.31
rs11136000	CLU	0.38	rs561655	PICALM	0.34
rs1532278	CLU	0.26	rs28834970	PTK2B	0.32
rs9331896	CLU	0.38	rs10498633	SLC24A4/RIN3	0.15
rs12034383	CR1	0.41	rs1131497	SORL1	0.37
rs3818361	CR1	0.25	rs1476679	ZCWPW1	0.21
rs6656401	CR1	0.07	rs429358	APOE	0.15

Table 2

Demographic information of all participants.

	HC	SMC	EMCI	LMCI	AD
Number	34	26	59	23	36
Gender(M/F)	19/15	18/8	34/25	16/7	22/14
Age(Mean±std)	72.97±5.94	73.5±5.22	72.9±7.59	71.39±8.1	75.06±8.94

Table 3

Significant associations between AD risk SNPs and brain connectivity measures.

Data Type	SNP	ROI1	ROI2	Beta	p(uncorrected)	ICC
	rs10498633	DMN	DMN	0.89	1.44E-08	1.00
	rs10498633	VA	CER	0.88	1.68E-08	1.00
	rs10498633	VA	SUBC	0.88	1.73E-08	1.00
	rs10498633	CER	FP	0.76	1.52E-06	1.00
Fiber Anisotropy	rs10498633	CER	SM	0.75	2.08E-06	1.00
	rs10498633	CER	SM	0.75	2.72E-06	1.00
	rs11771145	CER	SM	0.58	4.08E-06	1.00
	rs17125944	VS	VS	0.48	4.35E-06	0.92
	rs10498633	DA	SM	0.72	4.89E-06	1.00
	rs10498633	CER	SM	0.90	8.73E-09	1.00
	rs10498633	DMN	DMN	0.90	9.06E-09	1.00
	rs10498633	VA	CER	0.88	1.68E-08	1.00
Length of Fibers	rs10498633	VA	SUBC	0.88	1.68E-08	1.00
	rs10498633	DA	SM	0.76	1.54E-06	1.00
	rs10498633	CER	FP	0.75	2.56E-06	1.00
	rs7274581	L	DMN	0.53	4.49E-06	1.00
	rs10498633	VA	CER	0.88	1.76E-08	1.00
	rs10498633	VA	SUBC	0.88	2.20E-08	1.00
	rs4147929	SUBC	CER	0.68	1.04E-06	1.00
	rs10498633	SM	SUBC	0.77	1.40E-06	0.95
	rs10498633	DMN	DMN	0.76	1.48E-06	1.00
Fiber Density	rs429358	SUBC	CER	0.64	2.71E-06	1.00
	rs10498633	VA	CER	0.74	3.37E-06	1.00
	rs10498633	VA	CER	0.74	3.62E-06	1.00
	rs10498633	VA	SUBC	0.73	4.15E-06	1.00
	rs10498633	VS	L	0.73	4.56E-06	1.00