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

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Abstract: Alzheimer's disease is the most common form of brain dementia characterised by gradual loss of memory. Large-scale genome-wide association studies (GWASs) have identified some AD risk genes, but their relationship with the brain-wide network breakdown in AD remains unknown. Using the genotype and diffusion tensor imaging (DTI) data in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, we performed a targeted genetic association analysis of three types of link measures, including fibre anisotropy, fibre length and density. For fair comparison, all link measures were normalised with zero mean and unit standard deviation. We focused on 34 AD risk SNPs identified in previous GWAS studies. After Bonferroni correction, rs10498633 in SLC24A4 was found to be significantly associated with anisotropy, total number and length of fibres. rs429358 in top AD risk gene APOE showed nominal significance of association with the density of fibres between subcortical and cerebellum regions.

Keywords: brain connectivity; imaging genetics association; Alzheimer's disease.

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1 Background

Alzheimer's disease is the most common form of brain dementia characterised 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 ageing population nationwide (Association et al., 2017). Due to the lack of effective treatment, number of

deaths due to Alzheimer's between 2000 and 2014 has significantly increased (Association et al., 2017).

Neuroimaging has been a major approach to study AD which allows mapping of structural, functional and molecular AD pathology inside brain (Teipel et al., 2015). Accumulating evidence from previous studies suggests abnormal imaging patterns in AD patients, such as cortical and subcortical atrophy (Fox and Schott, 2004), cortical amyloid deposition (Villemagne et al., 2011), grey matter atrophy (Thompson et al., 2003), and functional cortical disconnection (Pievani et al., 2011). 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 (Wang et al., 2015) and increased diffusion anisotropy (Douaud et al., 2011).

On the other hand, genetic factors play an essential role in AD. Results from large-scale twin studies suggest the heritability of AD to reach 70–80% (Wingo et al., 2012; Sleegers et al., 2010). Originally identified in several targeted studies (Corder et al., 1993, 1994; Talbot et al., 1994; Saunders et al., 1993), the e4 allele of *APOE* is the most well-known genetic variation associated with increased AD risk and has been confirmed repeatedly in multiple populations around the world. Later, large-scale genome-wide association studies (GWASs) identified and validated 20 novel risk genetic loci (Lambert et al., 2013; Hollingworth et al., 2011; Harold et al., 2009; Naj et al., 2011; Seshadri et al., 2010), which have been recently found to differentially regulate brain amyloidosis across different disease stages (Apostolova et al., 2018). 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) (Weiner et al., 2010; Saykin et al., 2015), 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. We focus our analysis on link level measures, including fibre anisotropy, fibre 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 highly reliable connectivity 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, rs10498633 in *SLC24A4* was found to be significantly associated with anisotropy, total number and length of fibres including some connecting hemispheres, which is consistent with existing findings. rs429358 in top AD risk gene *APOE* only shows nominal significance of association with the density of fibres between Subcortical and Cerebellum ($p = 2.71 \times 10^{-6}$).

2 Methods

2.1 ADNI Cohort

Data used in this study were obtained from the Alzheimer's disease neuroimaging initiative (ADNI) database (Saykin et al., 2015; Weiner et al., 2010). Involving researchers from more than 50 sites in the USA and Canada, the ADNI aims 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 enrolment and/or genetic sample collection and protocols were approved by each participating study and sites' Institutional Review Board.

2.2 Brain connectivity measures

The DTI data was first denoised and corrected for motion and distortion using the approach described in a previous study (Manjón et al., 2013). Tractography was performed in Camino (Cook et al., 2006) based on white matter fibre orientation distribution function (ODF). Streamlines were modelled with a multi-tensor modelling approach, where voxels will fit up to two fibre orientations. Second, the sMRI scans were registered to the b0 volume of DTI data using the FNIRT toolbox (Jenkinson et al., 2012) and 278 brain regions of interest (ROIs) were extracted following (Shen et al., 2013). The final networks between 278 brain ROIs were constructed using fibres going through white matter and connecting ROIs. In this project, we focus on the link level measures and calculated the fibre anisotropy (FA), length of fibres (LOF) and number of the fibres (NOF) connecting each pair of ROIs. Considering that the number of fibres are partially dependent on the surface area of their connected ROIs, we derived a new measure, the fibre density (FD), for the following association analysis, which is the fraction between number of fibres and the average surface of grey-matter regions i and j.

2.3 Reliability test

Considering that some steps in the DTI processing pipeline are subject to random factors, e.g., when identifying the streamlines, the initial seed selection may lead to different results, 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, without changing any parameters, and quantified the reliability of FA, FD and LOF measures by calculating their intraclass correlation coefficients (ICC) across three runs.

2.4 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 (Nho et al., 2013). The un-genotyped SNPs were imputed using MACH and minimac in a two-stage procedure following a previous study (Nho et al., 2015). 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 Apostolova et al. (2018) were included for the association analysis (Table 1).

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

2.5 Brain connectomics genetics association

We performed a targeted genetic association analysis between each pair of SNP and link level feature by employing a general linear model (GLM) approach in R. Shown in equation (1) is the final linear model we applied with age at scan and gender as independent variables. Here, $i \in \{1, 2, ..., 82321\}$ and $j \in \{1, 2, ..., 34\}$. $Link_i$ is the ith link level measure, e.g., fibre anisotropy of the link between two brain ROIs in Shen atlas. For fair comparison of genetic effect on different measures, FA, LOF and FD measures were normalised to have zero mean and standard deviation as one. In the subsequent analysis of brain connectivity to examine the association between candidate SNPs and brain-wide connectivity measures, multiple comparison correction was enforced using the Bonferroni method at a 0.05 level of significance with the total number of test estimated to be 82,321 $\times$ 34 = 2,798,914.

$$Link_i = Age + Gender + SNP_j \tag{1}$$

3 Results

3.1 Subject

All the subjects included in this study are participants from the ADNI-2 and ADNI-GO stages. Among all 273 Caucasian subjects with DTI scans, 178 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 178 subjects.

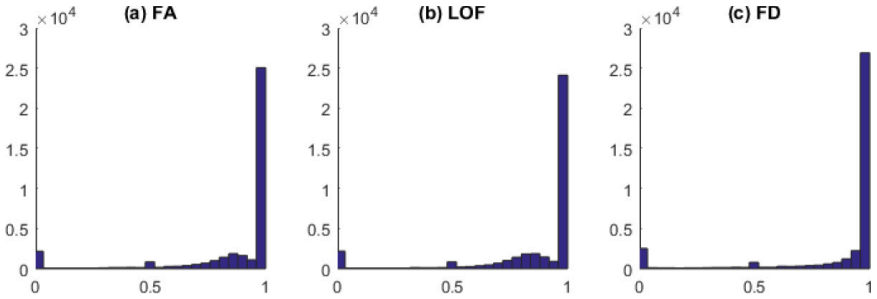
Table 2 Demographic information of all participants

	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

3.2 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, 26,886 out of 38,503 FA measures (69.83%) passed the reliability test with ICC greater than 0.9 (Koo and Li, 2016). For LOF and FD measures, there are 25,644 (66.6%) and 29,791 (77.37%) passing the same threshold. Shown in Figure 1 is the ICC distribution for FA, LOF and FD respectively. This similar reliability distribution is within our expectation since the major random effect that leads to the reliability issue is the seed selection when identifying streamlines, which however does not exert too much effect on the subsequent link level measure extraction. In this paper, we only included those measures ($N = 26,886 + 25,644 + 29,791 = 82,321$) with excellent reliability (ICC ≥ 0.9) for further analysis.

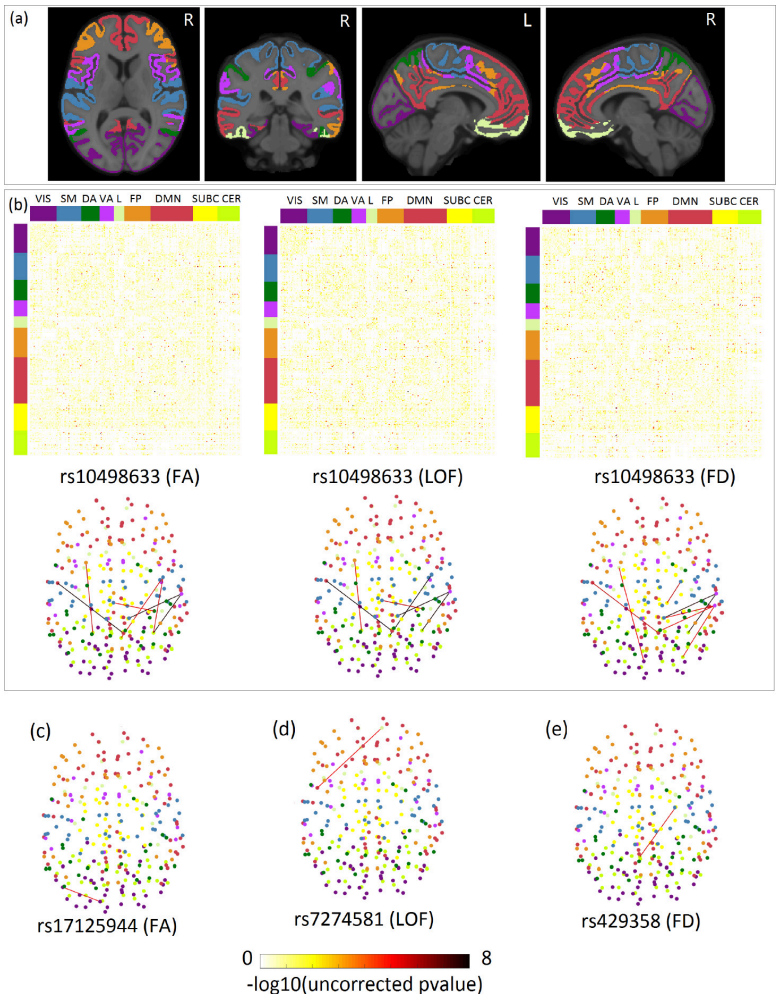
Figure 1 ICC distribution for all measures: (a) fibre anisotropy; (b) length of fibres and (c) fibre density (see online version for colours)



3.3 Genetic effect of AD risk genes on connectivity measures

We identified several significant associations 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). These seven brain groups/networks are identified as functionally distinct cortical regions in on a clustering analysis of resting-state functional connectivity MRI (Yeo et al., 2011). 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 Amico et al. (2017). Each Yeo ROI consists of multiple Shen ROIs.

Figure 2 Heatmap of all SNP-connectivity associations and brain map of selected connectivities with uncorrected p $\leq$ 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 colourbar 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 and (e) Brain map of the association between rs429358 and FD measures. All the links in the brain connectivity map share the same colourmap with the dots in the heatmap. Yeo parcellation in (a), top and side colourbars in (b), and all the nodes in the brain connectivity map share the same colour scheme



For FA measure, the genetic effect of rs10498633 in *SLC24A4* achieved brain-wide significance after enforcing the stringent Bonferroni correction based on the total number of connectomic measures and risk SNPs ($p = 0.05/(26886 + 25644 + 29791) \times 34 = 2 \times 10^{-8}$). It showed association with the anisotropy of fibres 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 fibres connecting Cerebellum and Somato-Motor, Ventral Attention and Cerebellum, Ventral Attention and Subcortical, and within Default Mode Network etc. In addition, other SNPs such as rs11771145 and rs10498633 are found to be nominally associated with the fibres connecting Cerebellum and Somato-Motor, Dorsal Attention and Somato-Motor respectively. rs429358 in top AD risk gene *APOE* only shows nominal significance of association with the density of fibres between Subcortical and Cerebellum ($p = 2.71 \times 10^{-6}$).

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 $\geq$ 0.9 and uncorrected p $\leq$ 5e-6. Links in the bottom panel are corresponding to the dots in the top panel. Different node colours in the brain connectivity map indicate the Yeo group information of each ROI. Among all the fibres 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.

4 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 fibre 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 grey matter density, brain metabolism (Stage et al., 2016) and DNA methylation in prefrontal cortex (Yu et al., 2015). However, due to the limited access to brain tissues, there is few studies looking into the role of *SLC24A4* in brain and our knowledge in that part is still very limited. Recently emerging databases in tissue-specific gene expression and expression quantitative trait (eQTL), however, allow us to peek into this from a different perspective. 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, Putamen, etc. This was later confirmed in several other emerging databases, such as the genotype-tissue expression project (GTEx) (www.gtexportal.org), the Human Protein Atlas (HPA) (www.proteinatlas.org), and the Functional Annotation of The Mammalian Genome (FANTOM) (fantom.gsc.riken.jp). In particular, it was consistently found that the RNA expression of *SLC24A4* is very selectively high in hippocampus, a subcortical region that plays a key role in memory performance and is well known to be AD-relevant. All of these enriched brain regions were consistent with our findings that the links connecting these regions are affected by the SNP rs10498633 in *SLC24A4*. In addition, another large-scale eQTL analysis (www.braineac.org) show that rs10498633 is an eQTL in several subcortical

regions and white matter where the fibres are located. Taken together, these evidence gives strong support to our connectomics-genetics association findings. It also suggests potential role of rs10498633 in regulating the brain connectivity by mediating the expression of certain genes including *SLC24A4*.

Table 3 Top five associations between AD risk SNPs and brain connectivity measures.

Data type	*SNP*	*Yeo ROI1*	*Yeo ROI2*	*Beta*	*p(uncorrected)*	*ICC*
Fibre	rs10498633	DMN	DMN	0.89	1.44E-08	1.00
anisotropy	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
	rs10498633	CER	SM	0.75	2.08E-06	1.00
Length	rs10498633	CER	SM	0.90	8.73E-09	1.00
of fibres	rs10498633	DMN	DMN	0.90	9.06E-09	1.00
	rs10498633	VA	CER	0.88	1.68E-08	1.00
	rs10498633	VA	SUBC	0.88	1.68E-08	1.00
	rs10498633	DA	SM	0.76	1.54E-06	1.00
Fibre	rs10498633	VA	CER	0.88	1.76E-08	1.00
density	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

As an exploratory and targeted imaging genetics analysis, this study has several limitations. First, since we only focused on three link-level measures and one third of the links are excluded due to poor reliability, there may be many other significant associations beyond what we have reported. Also, the connectomic features are treated individually without considering their correlation structure. Therefore the Bonferroni significance level may be overly conservative. Second, due to the small sample size, this study explored the imaging genetics association by coupling all diagnosis groups together and cannot reveal the group specific associations between connectomic and genetic variations, which is another important research topic for future investigation. Finally, due to the lack of data, we were not able to perform the validation analysis. However, recent release of genotype data from the Human Connectome Project makes this possible and we will validate our findings using this cohort in the near future.

5 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 fibres, which connect subcortical regions, cerebellum and part of the cerebral cortex regions involved in the default mode network. Given that *SLC24A4* is highly expressed in those regions and rs10498633 is an eQTL locus of *SLC24A4* in subcortical brain regions, we hypothesise that the regulation role of rs10498633 in brain network may be achieved by mediating the expression of certain genes including *SLC24A4*.

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