NeuroImage: Clinical 8 (2015) 660–666

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Altered whole-brain white matter networks in preclinical Alzheimer's disease

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ARTICLE INFO

Article history:
Received 26 February 2015
Received in revised form 17 June 2015
Accepted 20 June 2015
Available online 30 June 2015

Keywords:
Preclinical Alzheimer's disease
DTI
Brain network

ABSTRACT

Surrogates of whole-brain white matter (WM) networks reconstructed using diffusion tensor imaging (DTI) are novel markers of structural brain connectivity. Global connectivity of networks has been found impaired in clinical Alzheimer's disease (AD) compared to cognitively healthy aging. We hypothesized that network alterations are detectable already in preclinical AD and investigated major global WM network properties. Other structural markers of neurodegeneration typically affected in prodromal AD but seeming largely unimpaired in preclinical AD were also examined.

12 cognitively healthy elderly with preclinical AD as classified by florbetapir-PET (mean age 73.4 ± 4.9) and 31 age-matched controls without cerebral amyloidosis (mean age 73.1 ± 6.7) from the ADNI were included. WM networks were reconstructed from DTI using tractography and graph theory. Indices of network capacity and the established imaging markers of neurodegeneration hippocampal volume, and cerebral glucose utilization as measured by fludeoxyglucose-PET were compared between the two groups. Additionally, we measured surrogates of global WM integrity (fractional anisotropy, mean diffusivity, volume).

We found an increase of shortest path length and a decrease of global efficiency in preclinical AD. These results remained largely unchanged when controlling for WM integrity. In contrast, neither markers of neurodegeneration nor WM integrity were altered in preclinical AD subjects.

Our results suggest an impairment of WM networks in preclinical AD that is detectable while other structural imaging markers do not yet indicate incipient neurodegeneration. Moreover, these findings are specific to WM networks and cannot be explained by other surrogates of global WM integrity.

1. Introduction

The novel diagnostic concept of Alzheimer's disease (AD) includes subjects with AD dementia, prodromal AD and preclinical AD, i.e. cognitively healthy elderly with positive imaging or neurochemical biomarkers of AD (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). Biomarkers have been arranged along a hypothetical timeline, on which cerebral amyloid (Amyloid-β) deposition is assumed to be a very early event of AD, followed by synaptic dysfunction, hypometabolism and cortical and subcortical atrophy as markers of neurodegeneration (Jack et al., 2013; Jack et al., 2010). Histopathological studies of AD showed demyelination and axonal damage, which are likely to result in functionally relevant disconnections between brain areas in addition to a specific pattern of structural gray matter defects (Delbeuck et al., 2003). Diffusion tensor imaging (DTI) has been used successfully to detect deterioration of white matter (WM) integrity in vivo in AD and prodromal AD (Chua et al., 2008; Damoiseaux et al., 2009). Studies investigating WM in preclinical AD as of yet are rare and show heterogeneous results, reporting regional increases (Racine et al., 2014) and decreases of indices of WM integrity (Chao et al., 2013), or even both (Ryan et al., 2013). However they suggest early alterations of WM in AD.

Surrogates of whole-brain WM networks reconstructed from DTI and assessed by graph theory are a novel imaging marker that integrates microstructural and topological information of WM (Bullmore and Sporns, 2009; Iturria-Medina et al., 2007; Iturria-Medina et al., 2008). Several studies have so far demonstrated impairment of network

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

http://dx.doi.org/10.1016/j.nicl.2015.06.007

connectivity both in the prodromal and dementia stages of AD (Daianu et al., 2013; Lo et al., 2010; Wee et al., 2011), thereby supporting the notion of AD as a disconnection disease. Interestingly, Raj et al. demonstrated that AD cortical atrophy and hypometabolism patterns can be predicted from healthy WM network topology (Raj et al., 2012; Raj et al., 2015). Some of the mechanisms suggested, e.g. a prion-like propagation of disease agents along WM tracts, imply very early involvement of the WM network in AD pathology. Furthermore, a recent longitudinal study by Nir et al. showed that WM network architecture not only predicts cortical atrophy but also AD conversion in patients with mild cognitive impairment at risk for developing AD (Nir et al., 2015).

Taken together, these findings led us to hypothesize that WM network alterations might be detectable even at the preclinical stage of AD. In order to test this hypothesis, we examined group differences of network properties between subjects of preclinical AD, i.e. cognitively normal subjects with Amyloid-β deposition (Sperling et al., 2011), and normal controls. For comparison, we also examined other structural imaging markers of neurodegeneration that are known to be affected in prodromal AD, i.e. hippocampal volume and cerebral glucose metabolism. In order to show that WM network alterations are specific to network properties and do not simply reflect global WM integrity, we repeated analyses for WM volume, WM mean fractional anisotropy (FA) and WM mean diffusivity (MD).

2. Materials and methods

The data for the present study were obtained from the database of the Alzheimer's Disease Neuroimaging Initiative (ADNI), available at http://adni.loni.usc.edu. The ADNI was launched in the United States in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public–private partnership. 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 mild cognitive impairment (MCI) and early AD. For a more detailed and up to date description of the ADNI please refer to http://www.adni-info.org.

2.1. Subjects

Following the study design, the selection criteria for the database were classification as cognitively healthy and the availability of T1-weighted, florbetapir (AV45) and DTI imaging at baseline, yielding 47 subjects from the ADNI 2 phases of the ADNI project. One of these had to be excluded because of data corruption of the DTI scan and another subject was excluded because of extensive white matter pathology, defined as a visual Fazekas scale rating of 3 (Fazekas et al., 1987), all in all yielding 45 subjects that were included in the present study. The sample was dichotomized using a cutoff point for AV45-imaging standardized uptake value ratio (SUVR) of 1.1 (Joshi et al., 2012). 13 subjects with an SUVR ≥1.1 were classified as preclinical AD. 32 with an SUVR <1.1 were classified as normal controls (NC). One subject from each group later had to be excluded due to classification as outliers (see Section 3). For descriptive statistics of the subjects' demographical data, please refer to Table 1.

Table 1
Descriptive statistics of demographical data.

	Total sample	NC	Preclinical AD	p-Value
N	43	31	12	
Gender (f/m)	23/20	13/18	10/2	.015[a]
Age	73.1 ± 6.2	73.1 ± 6.7	73.4 ± 4.9	.886
Years of education	16.2 ± 2.7	16.7 ± 2.7	14.9 ± 2.4	.052

NC, normal controls. p-Values of between group differences were calculated using the chi-square test for gender, and t-test for all other variables.
[a] Considered statistically significant.

In ADNI, subjects undergo several neuropsychological examinations. For this study, we chose to report the well-known mini mental state examination (MMSE) and Alzheimer's disease assessment score — cognitive section (ADAS-Cog) in order to allow the reader to judge the cognitive state of the sample. Detailed information about neuropsychological testing and diagnostic criteria are available at the ADNI website (http://adni.loni.usc.edu/methods).

2.2. Imaging data acquisition

DTI and inversion-recovery spoiled gradient recalled (IR-SPGR) T1-weighted imaging data were acquired on several General Electric 3 T scanners using scanner specific protocols. Briefly, DTI data were acquired with a voxel size of $1.37^2 \times 2.70$ mm^3, 41 diffusion gradients and a b-value of 1000 s/mm^2. IR-SPGR data were acquired with a voxel size of $1.02^2 \times 1.20$ mm^3.

AV45 and fludeoxyglucose (FDG-PET) imaging data were acquired on several types of scanners using different acquisition protocols. In order to increase data uniformity, the data underwent a standardized preprocessing procedure at the ADNI project.

All imaging protocols and preprocessing procedures are available at the ADNI website (http://adni.loni.usc.edu/methods/).

2.3. AV45 and FDG-PET data processing

Subject AV45 and FDG standardized uptake value ratios (SUVRs) were calculated at ADNI core laboratories following a standardized pipeline that is available at the ADNI website (http://adni.loni.usc.edu/methods/pet-analysis/). Briefly, AV45 SUVR was calculated as the average of the uptake values of the frontal, angular/posterior cingulate, lateral parietal and temporal cortices divided by the mean uptake values of the cerebellum. FDG SUVR was calculated as the mean uptake of the left and right angular, bilateral posterior cingular and inferior temporal gyri normalized by the uptake of the pons/cerebellar vermis region.

2.4. DTI and T1-weighted imaging data processing

For detailed information on T1-weighted data processing, please refer to Appendix A — section Data processing. T1-weighted IR-SPGR data were automatically segmented using Freesurfer (https://surfer.nmr.mgh.harvard.edu/) in order to calculate white matter hypointensity volume (WMHV) and hippocampal volume. Additionally, IR-SPGR data were tissue segmented using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) in order to extract total gray matter (GM) and WM volume.

For detailed information on DTI data processing, please refer to Appendix A — section Data processing. DTI data were processed as previously described (Fischer et al., 2014). Briefly, diffusion tensors were fitted to the data using CAMINO (http://cmic.cs.ucl.ac.uk/camino/) and FA and MD maps were calculated and coregistered to IR-SPGR data in order to extract total WM mean FA and MD.

2.5. Network reconstruction

For detailed information on brain network reconstruction please refer to Appendix A — section Network reconstruction. Briefly, we defined the network nodes as the 111 cortical and subcortical brain areas defined by the Harvard–Oxford probabilistic brain atlas. Deterministic streamline tractography was conducted between each possible pair of the 111 brain regions and the number of resulting streamlines was considered the respective edge weight (Fischer et al., 2014; Hagmann et al., 2008; Li et al., 2009) (for exemplary tractography results please see Supplementary Fig. 1 of Appendix B). The resulting