

A Network-Diffusion Model of Alzheimer's Disease Estimating both Disease's Progression and Foci

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Introduction

Alzheimer's Disease (AD) is a highly prevalent form of dementia whose precise pathophysiological mechanisms affecting both grey matter (GM) and white matter (WM) tissues are still largely unknown. So is the exact progression of the disease and a large body of research aims at finding not only the anatomical origin(s) of AD but also means of anticipating its course, since progress in both these axes would lead to potential breakthroughs in diagnostic, prognostic, and clinical trial assessment. In this work we model AD as a diffusion process on the brain connectivity network to allow estimating both the foci of the disease and its time course.

Material & Methods

Healthy subjects (HS) from whom was evaluated the reference connectivity network: 73 healthy subjects [F/M=33/40; 30.2 ± 6.7 years]

Imaging data acquisition (for HS): acquired on a 3 T GE Signa EXCITE scanner as detailed in [1]. Diffusion MRI (dMRI) data were obtained along 55 isotropically distributed directions, with b values of 0 and 1000 s.mm² resulting in 72 contiguous 1.8 mm-thick slices with 0.9 x 0.9 mm² in-plane resolution. T1 weighted sequence was a 3D fast spoiled gradient-recalled echo sequence (TE/TR = 1.5/6.3 ms) with 0.9 x 0.9 x 1 mm³ resolution.

Reference connectivity matrix calculations: T1 images were segmented in GM, WM and CSF tissue classes with GM being further parcellated according to the 116- region Automated Anatomical Labelling (AAL) atlas [1]. The N=90 cerebrum regions were kept and the 26 cerebellum regions discarded. For each HS the parcellated GM was then transformed to subject dMRI space where its interface with WM was used as seed for whole brain tractography as described in [2]. The strength connectivity c_{ij} of any pair of atlas regions $\{i, j\}$ was calculated with the anatomical connection probability (ACP) formula [3] applied to the tracts interconnecting them. All the $\{c_{ij}\}$ form a NxN connectivity matrix $C=[c_{ij}]_{N \times N}$ which can be thought as the matrix representation of a network having for nodes and edges the atlas regions and their connectivity strengths respectively (Figure 1). The "healthy" reference connectivity matrix was taken as the mean of all HS connectivity matrices.

GM atrophy patterns of AD patients: A two sample t-test between the 116-region GM volumes in 99 AD patients [F/M=39/60; 75.8 ± 7.1 years] and 95 normal controls (NC) [F/M=37/58; 74.5 ± 5.7 years] gave the atrophy metric vector **A** between AD and NC in the 90 cerebrum regions of the AAL atlas (Figure 2). AD and NC imaging data were all obtained from the AD Neuroimaging Initiative (ADNI) database with AD subjects simply chosen as those diagnosed as having AD.

AD disease model and predicted state: AD was modeled as a diffusion process within the connectivity network such that a pathological agent in region i with concentration x_i would diffuse to region j according to the agent concentration difference $(x_j - x_i)$ and inter-region connection strength c_{ij} : $dx/dt = \beta c_{ij} (x_j - x_i)$ where β is a diffusivity constant. In vector form this equation becomes $d\mathbf{x}/dt = \beta \mathbf{L} \mathbf{x}$ where **L** is the graph Laplacian [4]. The predicted diffusion state at a time t given an initial state \mathbf{x}_0 is then given by $\mathbf{x}(t) = \exp(-\beta \mathbf{L} t) \mathbf{x}_0$.

Correlation between atrophy pattern and diffusion model: The aim was to evaluate which atlas region i provides the best match $\mathbf{x}_{seed i}(t)$ to the atrophy pattern when it is chosen as the seed (i.e. such as $\mathbf{x}_{seed i}(0) = \mathbf{i}$). Each region i of the cerebrum was therefore tested in turn as the initial state $\mathbf{x}_{seed i}(0)$ and for each trial the correlation between the atrophy metric **A** and $\mathbf{x}_{seed i}(t)$ was evaluated on a range of time t values (more exactly βt values, β being constant) large enough for $\mathbf{x}_{seed i}(\beta t)$ to converge for all i . The maximum correlation $R_{seed i}$ in this range occurred at time t_{max} when the diffusion state $\mathbf{x}_{seed i}(t_{max})$ best correlates with the atrophy state **A** (Figure 4). The regions i which provided the highest correlations $R_{seed i}$ should be the foci of AD as according to the diffusion model. Note that the logit correlation was used:

$$R_{seed i} = \max_t (\text{logit}(\mathbf{x}_{seed i}(t)) \cdot \mathbf{A} / (\text{norm}[\text{logit}(\mathbf{x}_{seed i}(t))] \times \text{norm}[\mathbf{A}]))$$

Evolution of AD according to the diffusion model: the region i providing the maximum $R_{seed i}$ was used as the initial state $\mathbf{x}_{seed i}(0)$ to model the general diffusion of AD.

Results

Correlation between atrophy pattern and diffusion model: Out of the 90 cerebrum seed regions tested, the ones which provided the best match with the observed atrophy pattern were the left and right hippocampus ($R_{left}=0.48$, $R_{right}=0.45$), left and right caudate ($R_{left}=0.49$, $R_{right}=0.47$), left and right putamen ($R_{left}=0.44$, $R_{right}=0.42$) as well as left amygdala ($R=0.43$) – all at around the same time t_{max} (Figure 4). The ones with worse correlation (having their maximum correlation during the final steady state for which $R \approx 0.39$) were superior and middle frontal gyri.

Evolution of AD according to the diffusion model: When seeding from the hippocampus (Fig 3 – left), the course of AD as given by the diffusion model first spreads to mesial temporal lobe (Fig 3 – middle) before continuing to the frontal-temporal-parietal association areas (Fig 3 – right).

Discussion and conclusion

From a relatively simple diffusion model of AD, findings remarkably close to what is currently known of the disease were demonstrated. A large amount of evidence points to disease foci including the hippocampus and amygdala while frontal areas – among the worst seed candidates – have been indeed shown not to be foci but instead being affected last in AD progression. Furthermore atrophy of the caudate has been found to be presymptomatic to AD [5] while atrophy of the putamen was demonstrated to be significantly reduced in patients diagnosed with probable AD [6]. Interestingly, the left hemispherical part of the regions best predicting AD progression provided better correlation than their right counterpart. This is in line with the asymmetry reported in GM loss dynamics in AD [7]. The added result of the modeled AD progression mimicking the known time course of the disease (affecting the limbic lobe at early stages and the frontal lobe at later stages) gives support to pathophysiological mechanisms acting as a diffusion process. A crucial advantage of the proposed model is that it is deterministic. Not only can it assess likely AD foci by going back in time but importantly it can also estimate a later state for any given time point. If proved reliable and accurate, this model would be particularly useful for both prognostic and clinical trial assessment as it could both predict cognitive decline and quantify treatment-induced deviation from this anticipated decline.

References

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- [7] Thompson et al., J. Neurosci., 23, 994–1005, 2003

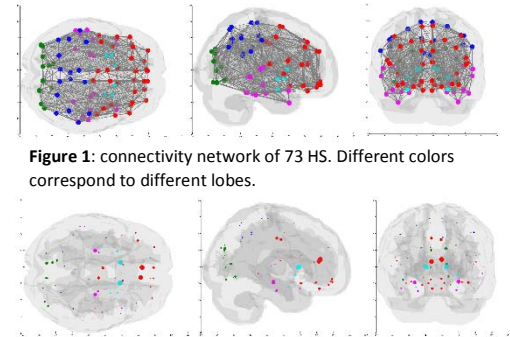


Figure 1: connectivity network of 73 HS. Different colors correspond to different lobes.

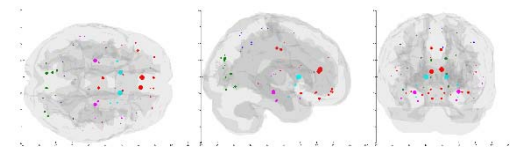


Figure 2: atrophy pattern in AD patients (two sample t-test)

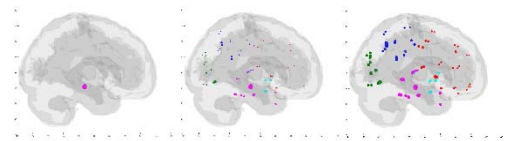


Figure 3: diffusion model seeded in the hippocampus

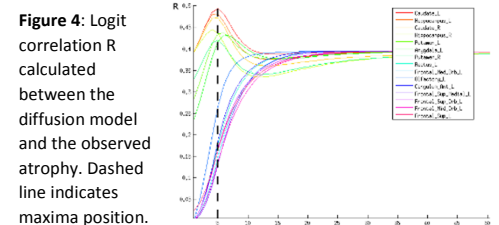


Figure 4: Logit correlation R calculated between the diffusion model and the observed atrophy. Dashed line indicates maxima position.