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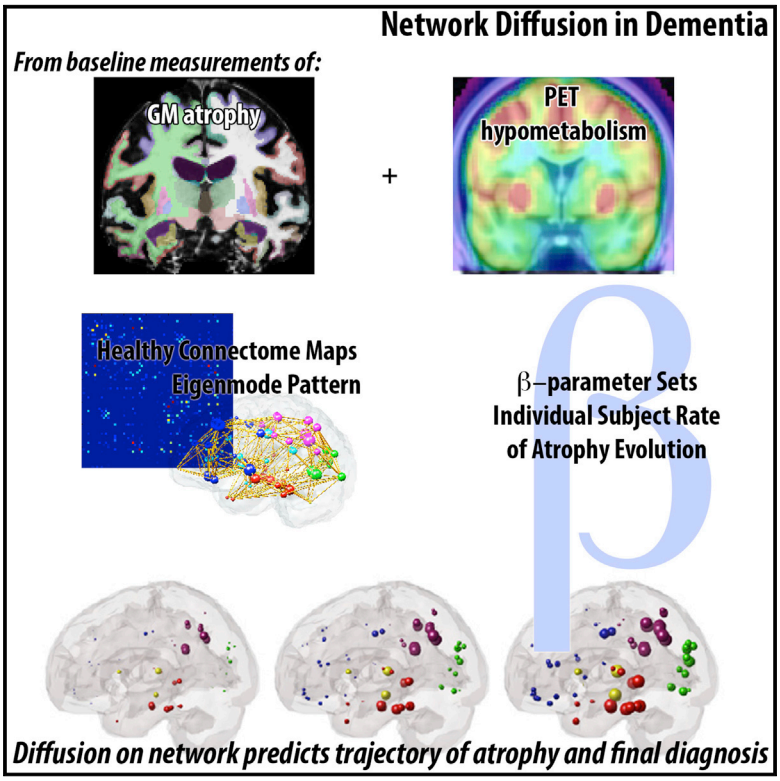
Network Diffusion Model of Progression Predicts Longitudinal Patterns of Atrophy and Metabolism in Alzheimer's Disease

Graphical Abstract



Highlights

- A network diffusion model captures transneuronal spread of AD pathology
- The model predicts future atrophy/metabolism states from baseline regional statistics
- The ADNI-cohort-validated model has high predictability of end-study atrophy/metabolism
- The practical implication is a potential prognostic biomarker

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In Brief

Alzheimer's disease spreads stereotypically in the brain from hippocampus to temporal, parietal, and prefrontal cortices. Using a computational network diffusion model to capture this spread, Raj et al. obtain a prognostic Alzheimer assessment tool that accurately predicts future patterns of brain atrophy starting from baseline MRI data of 418 patients.

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Network Diffusion Model of Progression Predicts Longitudinal Patterns of Atrophy and Metabolism in Alzheimer's Disease

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SUMMARY

Alzheimer's disease pathology (AD) originates in the hippocampus and subsequently spreads to temporal, parietal, and prefrontal association cortices in a relatively stereotyped progression. Current evidence attributes this orderly progression to transneuronal transmission of misfolded proteins along the projection pathways of affected neurons. A network diffusion model was recently proposed to mathematically predict disease topography resulting from transneuronal transmission on the brain's connectivity network. Here, we use this model to predict future patterns of regional atrophy and metabolism from baseline regional patterns of 418 subjects. The model accurately predicts end-of-study regional atrophy and metabolism starting from baseline data, with significantly higher correlation strength than given by the baseline statistics directly. The model's rate parameter encapsulates overall atrophy progression rate; group analysis revealed this rate to depend on diagnosis as well as baseline cerebrospinal fluid (CSF) biomarker levels. This work helps validate the model as a prognostic tool for Alzheimer's disease assessment.

INTRODUCTION

Alzheimer's disease (AD) is an amyloid-facilitated tauopathy (Braak et al., 2000) whose origin and subsequent advance within the brain is well characterized: the disease begins in the mesial temporal lobe, an event accompanied by the accumulation of misfolded β-amyloid and *tau* proteins, and thence progresses along fiber pathways. Histopathological evidence of this highly stereotyped progression has come to be known as the Braak model (Braak and Braak, 1996): neurofibrillary tau tangles are first found in entorhinal cortex and hippocampus (stages I–II), then spread into the amygdala and basolateral temporal lobe (stages III–IV), followed by isocortical association areas (stages V–VI). Morphological changes accompanying this pathological progression are clearly visible on MRI, especially from cross-sectional and longitudinal morphometric mapping (Fischl et al., 2002; Klauschen et al., 2009; Smith et al., 2004; Wu et al., 2007). Longitudinal studies (Apostolova and Thompson, 2008; Apostolova et al., 2007; Thompson et al., 2003; Whitwell et al., 2007) confirm that progression follows vulnerable fiber pathways rather than spatial proximity (Englund et al., 1988; Kuczynski et al., 2010; Villain et al., 2008), closely mirroring Braak pathological stages (Whitwell et al., 2007).

Until recently, the causative mechanisms for this networked spread were thought to be passive, including secondary Wallerian degeneration, disconnection, loss of signaling, axonal reaction, and postsynaptic dendrite retraction (Seeley et al., 2009). The latest evidence, however, favors a transneuronal "prion-like" mechanism (Frost and Diamond, 2010; Jucker and Walker, 2013), whereby implicated proteins misfold, trigger misfolding of adjacent same-species proteins, and thereupon cascade along neuronal pathways via transsynaptic or transneuronal spread (Clavaguera et al., 2009; Frost et al., 2009; Jucker and Walker, 2011, 2013; Palop and Mucke, 2010). Exogenous seeding of pathogenic proteins in the hippocampus caused remote pathology in connected regions (Clavaguera et al., 2009; Jucker and Walker, 2013). Seeded templating of misfolded protein species can therefore be thought of as the causative "propagating" event, and other observed phenotypes—hypometabolism, atrophy, and cognitive dysfunction—result from the pathology.

Recently, transneuronal transmission was mathematically modeled in our laboratory (Raj et al., 2012) by a diffusive mechanism mediated by and restricted to the brain's connectivity network, and the resulting topography of the disease was mathematically deduced. The network was obtained using diffusion MRI-derived healthy "connectomes" (Lo et al., 2010). Intriguingly, the macroscopic consequences of diffusive prion-like propagation (the network diffusion or ND model) on healthy