Inventory of Supplemental Information

Supplementary Experimental Procedures

1. Extraction of discordant regions, i.e. those that have much higher end-of-study atrophy than would be predicted from baseline atrophy

Summary of discordant regions (showing much higher end-of-study atrophy than would be predicted from baseline atrophy)

We investigated which brain regions displayed the most discordant atrophy in our MRI-derived volumetric series from ADNI cohort. These are the regions that fall within the "off-diagonal" areas in Figure 4, as described in the main body of the paper. In order to determine these regions, we back-projected the points shown in the scatter plots of Figure 4, and calculated how often each brain region fell within this off-diagonal zone. For the purpose of this exercise, the off-diagonal zone was defined as any point whose end atrophy was more than 3 times its baseline atrophy. The resulting data was converted to a histogram, as a ratio, such that a region mapped to 0 on this histogram would never end up in the discordant zone, whereas a region mapped to 1 would always end up in the discordant zone. These histogram ratios were then plotted on the whole brain using our standard glass-brain rendering, such that each region is depicted by a sphere. The size of the sphere is proportional to this discordant histogram ratio, and its color represents the lobe to which the region belongs. This data is shown in Figure SI-1. Only the MCI-converter group is being shown here.

2. Characterization of robustness via Monte Carlo simulation of additive noise in reference connectome

3. Characterization of robustness via Bootstrap analysis of variability among subjects

4. Detailed Methods and Acknowledgments pertaining to ADNI

Supplementary Figures

Supplemental Figure 1: **The relationship between regional atrophy/hypometabolism and their local rate of change of the entire ADNI patient cohort**. The top panel pertains to MRI-derived atrophy, and bottom panel to FDG-PET-derived hypometabolism. Left: measured data, middle: ND model predictions, right: predictions from both exponential and sigmoid models. The ND model is able to capture the essential atrophy-slope relationship in all its complexity. **Related to Figure 1.**

Supplemental Figure 2: "Glass brain" illustration of discordant regions. **Top**: The relationship between regional disease pattern and its rate of change. The spheres are proportional to group t-statistics over all ADNI patients: baseline FDG-derived regional hypometabolism (left), its rate of change evaluated at each region (middle), and the model predicted rate of change (right). Spheres are color-coded by lobe - frontal=blue,

parietal=purple, occipital=green, temporal=red, subcortical=yellow. The baseline pattern is not a good predictor of change in frontal and occipital regions. Black arrows point to specific structures that are discordant, including mesial temporal, frontal and occipital structures, where the network diffusion model appears to be a better predictor of change of atrophy.
Bottom: The most discordant regions with respect to longitudinal atrophy in the ADNI MCI-converter cohort. Sphere size is proportional to the frequency at which each region appears within the discordant zone. The most common discordant regions are found in the frontal, parietal and occipital lobes. **Related to Figures 1,2.**

Supplemental Figure 3: Histograms of subject-wise fitting of β (left) and post-onset time at baseline visit (right) on MRI atrophy data of the ADNI cohort. The 3 diagnostic groups are shown, from top to bottom: MCI non-converter, MCI converter, AD. The distribution of β appears to fit an exponential distribution in each case, but with a different mean parameter λ, as summarized in Table 3. Both Gaussian and exponential fitting indicate that β is significantly different between groups. The distribution of the post-onset time does not fit any recognizable distribution (except perhaps the uniform distribution), nor is its mean value different between groups. Similar results were found for FDG-PET-derived hypometabolism data, and they are summarized in Table 3 but not shown here. **Related to Experimental Procedures and Table 3.**

Supplemental Figure 4: Correlation between baseline CSF biomarkers and subject-wise fitted estimates of β (left) and post-onset time at baseline visit (right) of the ADNI cohort. From top to bottom: $A\beta - 42$, tau, p-tau, and $A\beta - 42/$ tau ratio. No significant result can be discerned in any of these plots, nor from the Pearson correlation R or p values indicated alongside. There is a mild negative association between baseline CSF $A\beta - 42$ and β, and a similar mild association between $A\beta - 42$ and post-onset time; both associations are in the expected direction but are not significant. Similar results were found for FDG-PET-derived hypometabolism data, and they are not shown here. **Related to Experimental Procedures and Results.**

Supplemental Figure 5: subject-wise fitted estimates of β after dichotomizing patients using CSF biomarkers and APOE status. **Top**: Histogram of fitted β after dichotomizing baseline CSF $A\beta - 42$ into pathologic (< 192 pg/ml) and non-pathologic (> 192 pg/ml). MRI-derived fitting is shown on the left and FDG-PET-derived fitting on the right. The distribution of β appears to fit an exponential distribution in each case, but with a different mean parameter λ, as summarized in Table 3. Since the 95% confidence interval of λ from the low and high $A\beta - 42$ groups do not overlap, we conclude that β, a marker of the rate of progression, is significantly different between them.
Bottom: Histogram of fitted β after dichotomizing subjects by APOE-ϵ4 allele status: non-carriers and homozygous and heterozygous carriers. The distribution of β appears to fit an exponential distribution in each case, but a significant difference in the fitted exponential mean parameter λ is noted only in the FDG case. **Related to Experimental Procedures, Results and Table 3.**

Supplemental Figure 6: Robustness analysis. **A**: The effect of additive noise in reference connectome on the performance of the predictive model. **Left**: Pearson's R statistic of correlation between measured atrophy pattern at end of study and the ND model evaluated on baseline atrophy pattern from all MCI-converter subjects in the ADNI-I database. Additive noise of increasing variance was added to the reference connectome and the model

was repeatedly computed on this noise-corrupted connectome. **Right**: R statistic between measured atrophy pattern of all AD subjects in ADNI-I database, against ND model prediction using baseline atrophy and noise-corrupted connectome. The mean R over N=100 independent trials is shown at each noise level by the blue curve, and the +/- 1 standard deviation is denoted by dotted red curves. At these levels of additive noise, which are mild to moderate, the performance of the model degrades gracefully and by only a small amount.
B: Bootstrap analysis of variability within patient groups: MCI-nonconverters (top), MCI-converters (middle) and AD (bottom). Non-parametric probability density estimates of the main outcome variable, the R of correlation between predicted and measured end atrophy are shown for each group, along with mean and 95% confidence intervals (vertical lines). Distribution of R with respect to MRI-derived atrophy is shown on the left and from FDG-PET-derived metabolism on the right. In each case the distribution is tight around the mean, with very little bias compared to the mean R statistic reported in Table 2 and Figure 2. The 95% confidence intervals from the above analysis are also reported on Table 3. **Related to Figure 2, Table 2, Results, Experimental Procedures and Supplementary Experimental Procedures.**