Supplementary Methods

Removal of Non-brain Tissues: The skull is removed using an atlas-based method (Aljabar et al., 2009), followed by human quality control so only minor cleanup is required, if so. Structural MRI brain images are then nonlinearly registered by cubic B-spline deformation (Rueckert et al., 2006) to a minimal deformation template (Kochunov et al., 2001) adapted for age 60 and above.

Image Intensity Inhomogeneity Correction: ADNI utilizes a template-based iterative method for correcting field inhomogeneity bias (Fletcher et al., 2012a). At each algorithm iteration, the update of a B-spline deformation between an unbiased template and the subject image is interleaved with estimation of a bias field based on the current template-to-image alignment. The bias field is modeled using a spatially smooth thin-plate spline interpolation based on ratios of local image patch intensity means between the deformed template and subject images. This is used to iteratively correct subject image intensities which are then used to improve the template-to-image deformation.

Gray and White Matter Measurement: The segmentation algorithm is based on an Expectation-Maximization (EM) algorithm that iteratively refines its segmentation estimates to produce outputs that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness (Fletcher et al., 2012b; Rajapakse et al., 1996). Like all EM algorithms, the system must be initialized with a reasonable estimate. This initial estimate is produced from the template-space warps of previously segmented images; because locations of WM/GM tissues are known in the template space, transforming these masks back to each image's native space produces rough estimate 3-tissue segmentations. The mean and standard deviation of the image intensities is then calculated in locations labeled as each tissue type. These values then form the initial parameters for a Gaussian model of image intensity for each class. At each iteration, the algorithm uses a Gaussian model of T1-weighted image intensity for each tissue class, in order to produce a segmentation. In the first iteration, these models are estimated as described above. The segmentation yielded by these appearance models alone is then refined using a Markov Random Field (MRF) model, which produces a label map consistent with both the input intensities and image smoothness statistics. Inference in the MRF is computed using an adaptive priors model (Fletcher et al., 2012b). This refined segmentation from the MRF is then used to compute new Gaussian intensity models for each tissue class, and the algorithm repeats, iteratively switching between calculating Gaussian appearance models and MRF-based segmentation, until convergence.

Automatic Hippocampal Segmentation: The IDeA lab employs a standard atlas based diffeomorphic approach (Vercauteren et al., 2007) with the minor modification of label refinement. This approach was further modified to include the EADC-ADNI harmonized hippocampal masks to assure standardization across cohorts. Therefore, the following approach was adapted: 1) Subject image pre-processing with extraction of intracranial cavity, non-uniformity correction, tissue classification as discussed above; 2) Atlas Registration of all EADC-ADNI hippocampal masks (Boccardi et al., 2015a; Boccardi et al., 2015b; Bocchetta et al., 2015; Frisoni et al., 2013; Frisoni and Jack, 2015) to each subject; 3) Atlas Fusion utilizing MALF (Wang and Yushkevich, 2012; Wang et al., 2015); and 4) Intensity-based label refinement.

ROI-based Analysis: Software developed by the IDeA laboratory allows the creation of any set of user-defined ROIs or utilization of published ROIs. The lab provides multiple sets of predefined regions of interest including lobar volumes, the Desikan-Killiany Atlas from Freesurfer (Desikan et al., 2006) and Brodmann areas defined by an expert anatomist (Lee et al., 2010). Regional measures are calculated by back transformation of the atlas into segmented image native space. A voting scheme is used to assure precise labelling of each region after interpolation of the atlas into native space.

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Supplementary Table S1: Principal components of the 64 regional GMVs

Component	Component name	Component	Cumulative %	Loading
1	Somatomotor complex	Precentral (L)	44.3%	0.830
		Paracentral (L)		0.793
		Precentral (R)		0.784
		Paracentral (R)		0.731
		Postcentral (L)		0.706
		Postcentral (R)		0.583
		Superior frontal (L)		0.554
		Caudal middle frontal (L)		0.542
		Caudal middle frontal (R)		0.523
		Superior frontal (R)		0.498
		Posterior cingulate (L)		0.443
2	Inferior / superior parietal cortex	Inferior parietal (R)	48.7%	0.831
		Superior parietal (L)		0.799
		Inferior parietal (L)		0.778
		Supramarginal (L)		0.714
		Precuneus (L)		0.700
		Middle temporal (R)		0.694
		Supramarginal (R)		0.669
		Superior parietal (R)		0.658
		Precuneus (R)		0.647
		Middle temporal (L)		0.593
		Inferior temporal (R)		0.430
		Inferior temporal (L)		0.419
3	Hippocampal complex	Hippocampus (L)	52.6%	1.071
		Hippocampus (R)		1.062
		Entorhinal (L)		0.827
		Entorhinal (R)		0.807
		Parahippocampus (R)		0.782
		Parahippocampus (L)		0.686
4	Occipital cortex	Pericalcarine (L)	55.9%	0.875
		Pericalcarine (R)		0.795

		Lingual (L)		0.789
		Lingual (R)		0.704
		Lateral occipital (L)		0.670
		Cuneus (L)		0.655
		Cuneus (R)		0.644
		Lateral occipital (R)		0.589
5	Inferior frontal gyrus	Pars triangularis (R)	58.5%	0.841
		Pars triangularis (L)		0.838
		Pars orbitalis (L)		0.816
		Pars orbitalis (R)		0.620
		Medial orbitofrontal (L)		0.543
		Rostral middle frontal (R)		0.539
		Rostral middle frontal (L)		0.530
		Medial orbitofrontal (R)		0.502
		Pars opercularis (R)		0.445
		Lateral orbitofrontal (R)		0.439
6	Anterior cingulate	Caudal anterior cingulate (R)	60.8%	0.799
		Caudal anterior cingulate (L)		0.762
		Rostral anterior cingulate (R)		0.599
		Rostral anterior cingulate (L)		0.595
7	Posterior cingulate	Posterior cingulate (R)	62.6%	0.862
		Posterior cingulate (L)		0.853
		Insula (R)		0.416
		Inferior temporal (L)		0.403
8	Isthmus cingulate	Isthmus cingulate (L)	64.3%	0.743
		Isthmus cingulate (R)		0.721
		Transverse temporal (R)		0.573
		Transverse temporal (L)		0.502

R = Right; L = Left