Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods.

Subject Amyloid Characteristics

Most of the ADAD participants and a subset of the LOAD participants underwent lumbar puncture that was assayed for CSF levels of $A\beta_{42}$. These levels were determined as previously described[1]. We present mean (standard deviation) values for each group (Table e1). The values are consistent with a diagnosis of AD (i.e., lower CSF $A\beta_{42}$ levels with advancing disease).

eTable. Mean concentration of Aβ42 in the CSF of each group

	M– CDR0 (N=20)	M+ CDR0 (N=25)	M+ CDR0.5 (N=12)	M+ CDR1 (N=7)	LOAD CDR0 (N=300)	LOAD CDR0.5 (N=62)	LOAD CDR1 (N=10)
CSF $A\beta_{42}$	791 (320)	630 (321)	438 (354)	387 (280)	636 (243)	439 (191)	305 (110)

MRI data acquisition

For both cohorts, neuroimaging was performed using 3T Siemens Tim Trio scanners (Erlangen, Germany) equipped with the standard 12-channel head coil. The scanner used for LOAD scan acquisition at the Knight Alzheimer Disease Research Center (ADRC) at Washington University in St. Louis (WUSTL) was one of 10 used for DIAN data acquisition, and all scanners used by DIAN (including the scanner at WUSTL) were calibrated and maintained using similar procedures. Resting state fMRI was acquired using 36 contiguous, 4.0-mm-thick slices oriented parallel to the anterior commissure/posterior commissure plane (4.0 mm approximately isotropic voxels) providing complete brain coverage. Participants were instructed to remain still with their eyes open and not fall asleep.

Pre-processing of all rs-fcMRI

Initial preprocessing of all rs-fcMRI data (both ADAD and LOAD) followed conventional methods as previously described[2,3], but importantly modified to correct for a non-optimal order of operations[4]. The preprocessing for the data proceeded as follows:

1. Images were corrected for slice-dependent time shifts relating to the interleaved acquisition
2. Images were further debanded to correct for systematic intensity differences in odd and even slices[5]. The debanding process is described below.
3. The data are then rigid body corrected for head movement within and between scan sessions (1 session in ADAD group, 2 sessions in LOAD group) and mode 1000 intensity scaling was performed[6].
4. Atlas transformation was achieved by computing a series of affine transforms aligning rs-fcMRI images along with structural images to a single group atlas. Head movement correction and atlas transformation were combined in a single resampling to isotropic 3mm voxels. Atlas transformation of the rs-fcMRI data was accomplished via structural images [3D sagittal T1-weighted magnetization-prepared rapid gradient echo imaging sequence (MPRAGE) in ADAD and LOAD plus high-resolution 2-D multi-slice oblique axial spin density/T2-weighted fast spin echo (FSE) scan in the LOAD group].
5. Volumes highly contaminated by movement[7] were removed and replaced with linear interpolations[8]. Only subjects with fewer than 40% of frames excluded were passed to the next stage of processing.
6. Signals of non-interest are identified in the white matter, ventricles, and global signal were extracted[9]. These time-series along with movement time-series and their first

temporal derivatives were then regressed from the BOLD time-series.

7. The residual BOLD time-series was then low-pass filtered to retain frequencies below 0.1Hz and spatially smoothed with a 6mm FWHM Gaussian blur.
8. The linearly interpolated volumes were then removed from subsequent analysis.

Debanding Procedure

The debanding procedure assumed that odd and even slices are affected by alternating multiplicative intensity errors. Thus, for every voxel in an even slice, the measured intensity is $\tilde{v}_{ik} = v_{ik}(1+\alpha)$, where v_{ik}(always positive) is the unbiased (true) intensity and the subscript indexes voxel i in slice k. Similarly, in odd slices, the measured intensity is $\tilde{v}_{ik} = v_{ik}(1-\alpha)$. Thus, measured intensities on successive slices are biased in the opposite direction (banding). The key operational assumption is that the true intensity profile across slices is, on average, locally linear. Accordingly, the average measured intensity on the slices above and below will differ from the current slice by $2s\alpha v_{ik}$, where $s = (-1)^k$ depends on the parity of the slice index. Therefore, ignoring the difference between v_{ik} and $\tilde{v}_{ik}$, we have

$$(1/2)(\tilde{v}_{i(k+1)} + \tilde{v}_{i(k-1)}) - \tilde{v}_{ik} \approx 2s\alpha\tilde{v}_{ik} \qquad \text{(S1)}$$

To solve for α, both sides of Eq. (S1.1) are weighted by $\tilde{v}_{ik}$, to emphasize bright voxels, and the resulting quantities are summed over the available data.

$$\alpha = \frac{\sum_{i,k}\left[(1/2)(\tilde{v}_{i(k+1)} + \tilde{v}_{i(k-1)}) - \tilde{v}_{ik}\right](-1)^k \tilde{v}_{ik}}{2\sum_{i,k}\tilde{v}_{ik}^2} \quad \text{(S2)}$$

It may be noted that banding is greatest during the first few volumes of each fMRI run, i.e., before achieving magnetization steady state. Having estimated α, the measured data are corrected by inverting $\tilde{v}_{ik} = v_{ik}(1+\alpha)$.

The debanding algorithm was originally developed to enable acquisition of interleaved fMRI data without slice gaps [6]. On an older 1.5T Siemens Vision scanner, which generated slice selection RF profiles using analog circuitry, the value of α in interleaved, 8mm slice fMRI data (after achieving magnetization steady state) typically was ~0.035. The corresponding figure for fMRI acquired on the Siemens 3T Trio scanner (4mm slices), which has digital RF circuitry, is 0.004. This small magnitude of banding artifact might be reasonably ignored, although we always apply the correction.

Resting-state network (RSN) composite correlation

For all participants, we extracted time-series data from thirty-five 6-mm radius spherical brain regions of interest (ROIs) distributed throughout 5 functionally-defined RSNs including the DMN, DAN, CON, SAL, and SMN[2]. We produced correlations by extracting the time course from each of the seed regions for each subject. Pearson correlation coefficients (*r*) were computed between the time course from a given region of interest (ROI) and the time course of each other ROI. Statistical tests of rs-fcMRI correlations were computed after application of Fisher's z transform.

A composite intra-network score was obtained for each of the 5 RSNs for each participant as previously described[2]. Briefly, intra-network composite scores were obtained by

averaging BOLD correlation values computed between ROIs belonging to a particular RSN and inter-network composite scores were obtained by averaging correlations from ROIs belonging to separate RSNs. Using a composite score for intra and inter-network comparisons serves to reduce the amount of data while reducing the potential impact of sampling error. We analyzed composite scores for 5 intra-network (DMN, DAN, CON, SAL, SMN) and 3 inter-network (DMN:DAN, DMN:SMN, CON:SMN) composites which we have previously shown to be affected by LOAD.[5]

eReferences.

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