Figure S1, Related to Figure 1

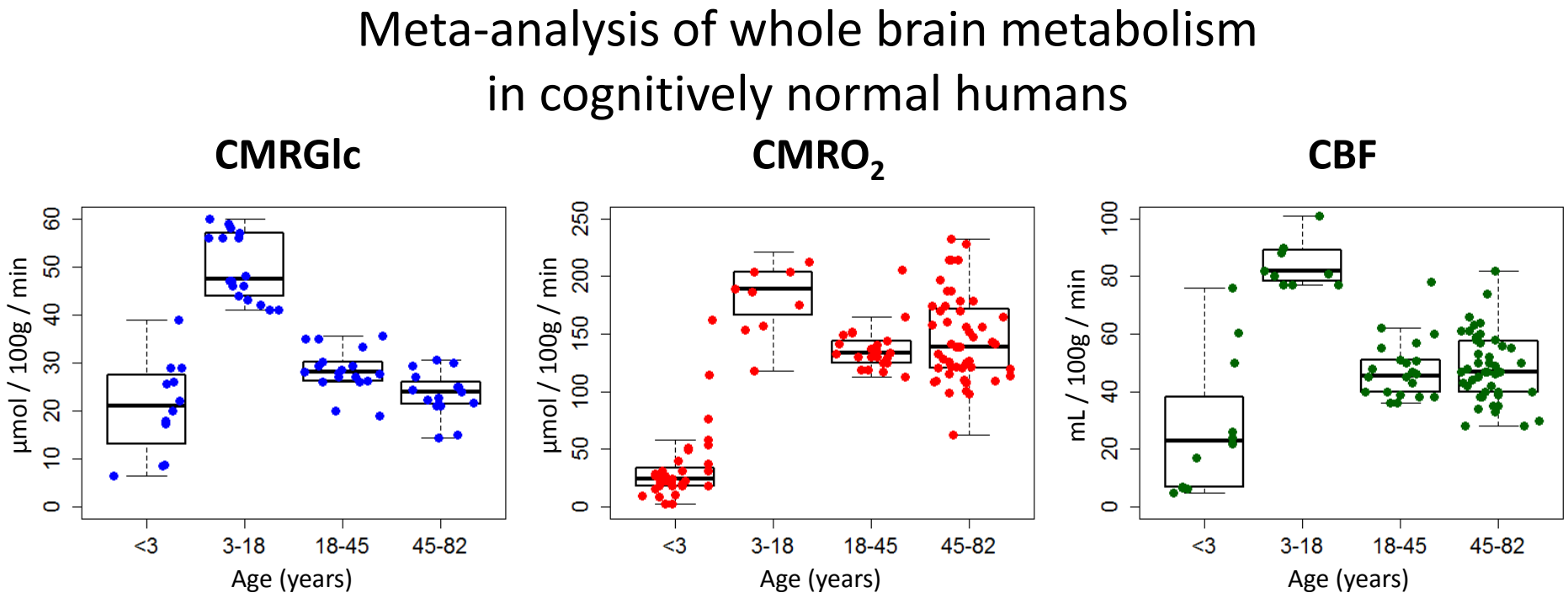

Figure S1. Meta-analysis of whole brain metabolism in cognitively normal humans. Related to Figure 1. Data points from 15 different studies of normal human whole brain metabolism, including those using (modified) Kety-Schmidt and imaging, predominantly PET based methods, were collected across the human lifespan (see Goyal et al. Cell Metabolism 2014 for details). The individual data points and box plots within 4 different age groups are shown above. Loess curves were fit to the adult portions of these curves (i.e., age > 18 years), as shown in Figure 1, to determine literature-based age-normed whole brain values for each parameter as described in the main text. Of note, while it is evident that CMRGlc falls with age during adulthood, neither $CMRO_2$ nor CBF significantly change with age. Recently published evidence (not included in this meta-analysis) supports the latter findings, though there may be slight decrease in CBF with normal human aging in females (Aanerud et al. Sex differences in human cortical blood flow and energy metabolism. JCBFM 2016).

Figure S2, Related to STAR Methods

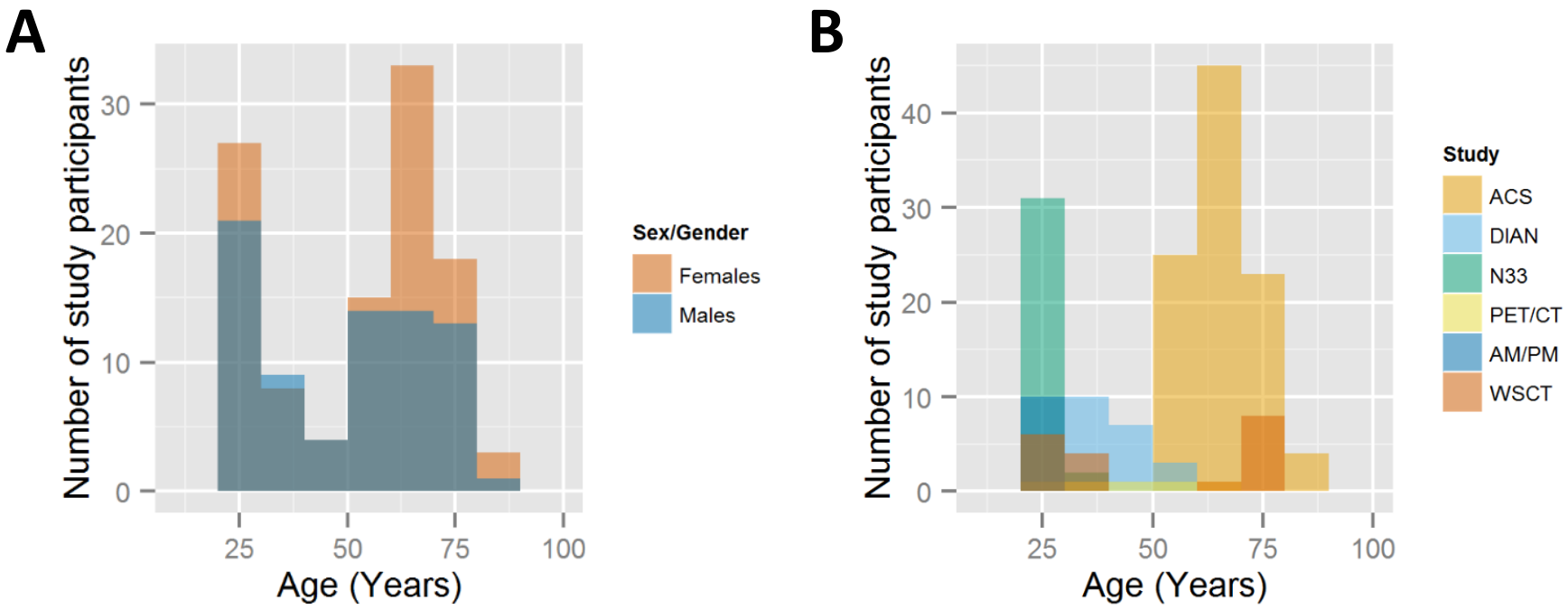

Figure S2. Participant histograms for the cohort investigated in this study. Related to STAR Methods: Experimental Models and Subject Details. **(A)** Age and sex / gender distribution of the study participants. The histograms for females (orange) and males are overlapping (green represents the overlap). **(B)** The participants participated in six different studies which largely focused on either young adults or older adults; therefore there is a relative dearth of participants in the 35-55 year old age group. The six studies included: Adult Children Study (ACS), Dominantly Inherited Alzheimer Network (DIAN) Study, Vaishnavi et al. 2010 (N33), Shannon et al. 2014 (AM/PM), and unpublished data (PET/CT, WSCT).

Figure S3, Related to Figure 3

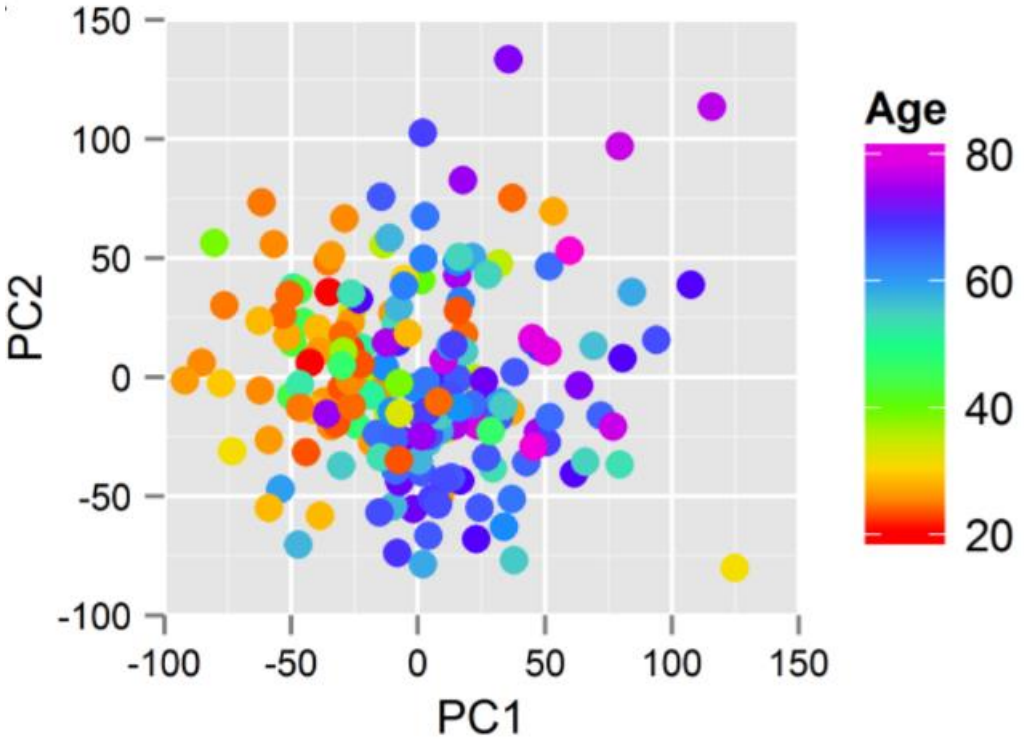

Figure S3. Age represents a large proportion of the variance in the quantile normalized brain metabolism data. Related to Figure 3. Multidimensional scaling (MDS) was applied to a distance matrix of the quantile normalized regional brain metabolism data across all PET sessions in the normative cohort. Each dot represents an individual PET session and the greater the separation between two dots, the larger the distance between their brain metabolism topography. The colors represent the age of the participant at the time of the PET session. This demonstrates that the normalized brain metabolism data from similar aged participants tend to be similar to one another. Note an outlier in the left lower corner; in order to minimize bias post-hoc, such outliers were not removed from further analysis unless first determined to be an outlier during data preprocessing.

Figure S4, Related to Figure 2

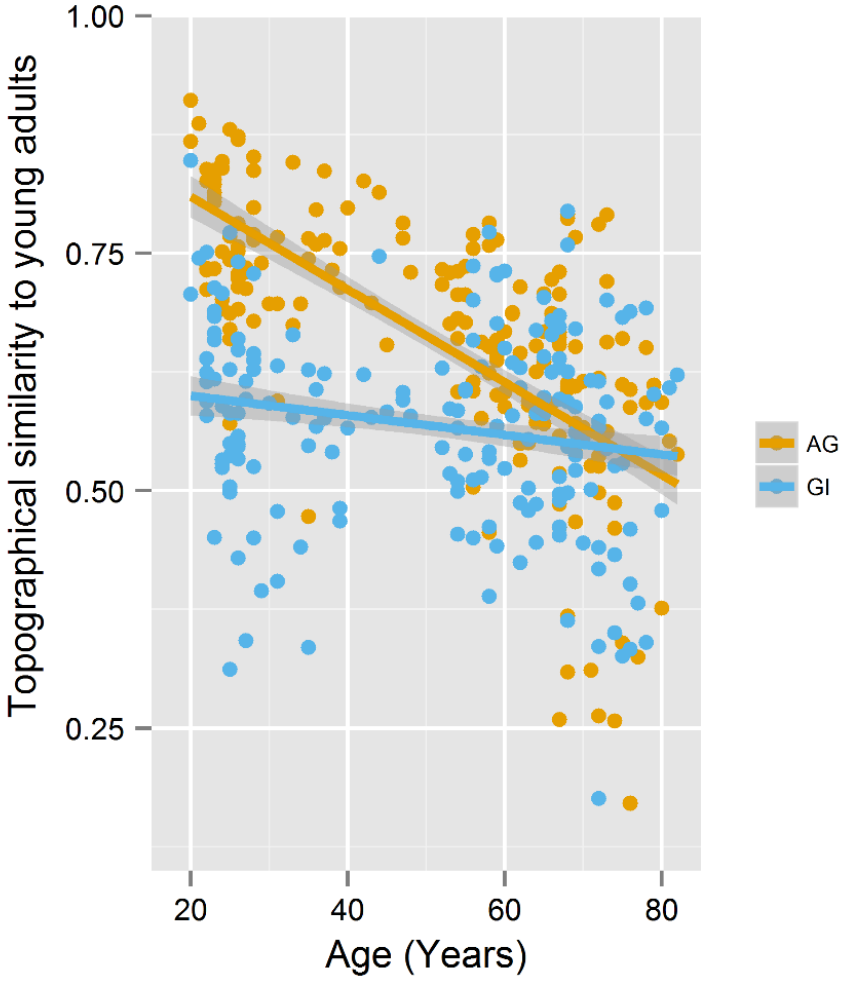

Figure S4. Comparison between the topography of brain AG and the Glycolytic Index (GI) during aging. Related to Figure 2. Whereas AG is measured using quantitative regional values for CMRGlc and $CMRO_2$, GI is measured by regressing out $CMRO_2$ from CMRGlc spatially in each individual PET session (Vaishnavi et al. 2010). The former (AG) relies on *a priori* whole brain measurements for CMRGlc and $CMRO_2$ (in this case derived from literature-based age-normalized estimates), whereas GI does not rely on such *a priori* factors. Thus, GI allows one to isolate the topographical changes in AG that are unrelated to whole brain quantitative changes in CMRGlc or $CMRO_2$. Here we find that the topography of GI also changes with age ($r = -0.20$, $p < 0.006$), suggesting that a large portion of the change identified in AG is related to whole brain changes in metabolism while another portion is related to changes in the intrinsic topographic relationship between CMRGlc and $CMRO_2$.