Brain aerobic glycolysis and resilience in Alzheimer disease

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The distribution of brain aerobic glycolysis (AG) in normal young adults correlates spatially with amyloid-beta (Aβ) deposition in individuals with symptomatic and preclinical Alzheimer disease (AD). Brain AG decreases with age, but the functional significance of this decrease with regard to the development of AD symptomatology is poorly understood. Using PET measurements of regional blood flow, oxygen consumption, and glucose utilization—from which we derive AG—we find that cognitive impairment is strongly associated with loss of the typical youthful pattern of AG. In contrast, amyloid positivity without cognitive impairment was associated with preservation of youthful brain AG, which was even higher than that seen in cognitively unimpaired, amyloid negative adults. Similar findings were not seen for blood flow nor oxygen consumption. Finally, in cognitively unimpaired adults, white matter hyperintensity burden was found to be specifically associated with decreased youthful brain AG. Our results suggest that AG may have a role in the resilience and/or response to early stages of amyloid pathology and that age-related white matter disease may impair this process.

Alzheimer’s disease | aerobic glycolysis | resilience | aging | white matter hyperintensities

The healthy human brain largely relies upon glucose to fuel mitochondrial respiration. Yet, in young adults, a portion of resting glucose consumption exceeds that predicted by oxygen consumption rates (1). Though the role(s) of this excess glucose utilization, i.e., aerobic glycolysis (AG), remain uncertain, some studies suggest that AG in the brain may support neurite outgrowth (2, 3), myelination (4–7), learning (8, 9), reducing oxidative stress (10), rapid and anticipatory neuronal activity (11), and microglial activity (12, 13). AG in the young adult occurs more so in regions that are transcriptionally neotenous and evolutionarily expanded in humans (14). Prior studies in humans demonstrate that brain AG decreases on average in healthy older adults, based on whole brain quantitative measurements (15, 16) as well as in terms of its regional pattern in young adults (17). Moreover, sex influences the youthful pattern of brain glycolysis, being relatively more preserved in cognitively unimpaired aging females than in males (18).

AG in the human brain is also affected by Alzheimer disease (AD). Whole brain estimates show that early AD is associated with a significant decrease in glucose consumption rates compared to a relatively smaller change in oxygen consumption (19–21). Interestingly, amyloid deposition in both cognitively intact and impaired adults follows a regional pattern that matches that of brain AG in young adults (22, 23). Although several studies have studied total regional brain glucose consumption in relation to cognitive impairment with 18FDG-PET alone, none to our knowledge has studied how regional AG is specifically affected, as compared to the larger component of brain glucose use that occurs for oxidative phosphorylation.

Here we investigate regional brain AG in AD by combining 18FDG-PET with 15O-labeled water (H₂O), oxygen (O₂), and carbon monoxide (CO) positron emission tomography (PET) to estimate glucose and oxygen metabolism together—and thereby AG—in individuals further characterized with amyloid imaging and cognitive testing. Our primary hypotheses were that youthful brain AG will be reduced in cognitively impaired individuals and preserved in cognitively intact individuals with biomarker-defined (i.e., brain amyloid positive) AD, as a reflection of brain resilience to AD pathology.

Results

Study Overview. All research participants provided informed consent, and all study procedures were approved by the Washington University School of Medicine Institutional Review Board. A total of 353 multi-tracer metabolic PET sessions were performed in 285 adult individuals (25 to 92 y old, 55% female) between the years of 2013 and 2021. Portions of these data, now labeled as the Aging Metabolism & Brain Resilience (AMBR) study, have been published previously (17, 18, 23–25).

Significance

Brain aerobic glycolysis (AG) decreases with age and correlates regionally with amyloid-beta deposition in Alzheimer disease (AD). Using PET measurements of AG, this study now demonstrates that brain AG loses its youthful pattern in cognitively impaired individuals. In cognitively unimpaired individuals, however, the youthful pattern of brain AG is preserved/highened in the presence of amyloid deposition, yet conversely decreased in the presence of aging-related white matter hyperintensities. These findings suggest that brain AG changes dynamically according to aging-related pathology, with implications for the development and progression of AD.
Amyloid status was unavailable in 80 sessions, including in only 18 individuals ≥60 y old and in 62 individuals <60 y old; note that all 40 participants <60 y old who underwent amyloid PET imaging were found to be negative. Accordingly, absent amyloid status was considered to be amyloid negative for statistical analyses unless proven otherwise. Cognitive status was typically defined using the Clinical Dementia Rating® (CDR®) scale, specifically using the sum-of-boxes score; when CDR could not be fully completed (n = 39), cognitive status (normal versus impaired) was instead inferred from additional cognitive testing data. Further details on study procedures are provided below (Methods).

From the metabolic PET measures, the glycolytic index (GI, a relative measure of AG), cerebral metabolic rate of glucose (CMRGlc), cerebral metabolic rate of oxygen (CMRO$_2$), and cerebral blood flow (CBF) were calculated and partial volume corrected to regions defined by the Desikan–Killiany atlas and FreeSurfer subcortical parcellations. Symptomatic and “preclinical” (i.e., asymptomatic) AD were defined as individuals with brain amyloid positivity and with cognitive impairment versus without cognitive impairment, respectively.

**Analysis Overview.** For each PET session and independent metabolic measure (GI, CMRGlc, CMRO$_2$, and CBF), a "youthful pattern" was defined based on its correlation to average gray matter regional values calculated in a separate, previously published but re-processed dataset comprising a cohort of young healthy adults (“N33 cohort,” 20 to 34 y old) (Fig. 1) (26). The N33 cohort was used to define the youthful pattern for each metabolic parameter in order to avoid biasing results derived from the larger AMBR cohort. However, as the N33 data were acquired approximately a decade prior with different scanner technology, an outlier region (the pars orbitalis) was identified and was removed from further analysis a priori. The AMBR data were subjected to quantile normalization for each metabolic measure to remove “batch” effects that could have arisen during the 9 y of data collection. A Spearman rank correlation rho was then calculated for each PET session in the AMBR study as compared to the group results from the N33 cohort to calculate the "youthful metabolic index" of each metabolic measurement at the time of that PET session. These measures were subsequently related to age, sex, amyloid positivity, and cognitive status using generalized linear and mixed models, as computed in R with missing observations omitted.

**Youthful Brain Metabolism Decreases Variably with Age and Sex.** For all metabolic measures, the youthful pattern was maintained in young adults from the AMBR cohort (Fig. 2). With increasing age, this youthful pattern for all metabolic parameters was variably maintained, with increasing degrees of inter-individual variability in patterns of brain metabolism, particularly for GI.

Prior observations on a subset of these data (obtained prior to 2017) suggested that the youthful pattern of brain metabolism is more typically preserved in cognitively intact females than in males (18). Subsequent studies using brain age estimations have reported similar findings with $^{18}$FDG-PET and brain MRI (27–29). Here, female sex was again associated with a higher youthful GI index when controlling for age and amyloid status ($P < 0.05$). This was true also for the youthful CMRO$_2$ index ($P < 0.005$), but not significantly so for the youthful CMRGlc and CBF indices. With a smaller subset of the data obtained since 2017 in cognitively unimpaired individuals (n = 163), age but not sex remained significant, and further analysis found a sex-by-age interaction to be significant ($P < 0.05$) such that the youthful GI index declined faster for males than females with increasing age. Given these findings, age and sex were included as covariates in the subsequent analyses.

**Cognitive Impairment Is Associated with Decreased Youthful Brain Glycolysis.** Cognitive impairment, as measured by CDR sum of boxes, was associated with age ($P < 0.005$), male sex ($P < 0.05$), and amyloid positivity ($P < 0.001$). Cognitive impairment was further highly associated with decreased youthful GI index ($P < 0.001$) and youthful CMRGlc index ($P < 0.05$), controlling for age, sex, and amyloid status. Moreover, loss of youthful GI was associated with AD specifically ($P < 0.05$), controlling for age and sex, as well as with cognitive impairment across amyloid positive individuals ($P < 0.01$). However, neither the youthful CMRO$_2$ nor CBF indices were significantly associated with cognitive impairment. These results suggest that early cognitive impairment is associated with changes specifically in glycolysis.

![Fig. 1. Schematic overview of youthful brain metabolism calculation. Separate resting PET and MRI scans were obtained in individuals. PET scans were preprocessed and then combined with MRI to calculate partial volume corrected regional standardized uptake value ratio (SUVR) values in the gray matter. Each individual map of brain metabolism and CBF was then compared to the corresponding group map obtained in the separate N33 young adult cohort using a Spearman correlation. The final rho value was used as the “youthful metabolic index” for that individual and specific metabolic parameter (GI, FDG, oxygen metabolism, and CBF). (Figures are intended for schematic purposes only.)](https://doi.org/10.1073/pnas.2212256120)
Cognitive Resilience Is Associated with Preserved Youthful Brain Glycolysis. If loss of the youthful glycolysis pattern during early cognitive impairment is due to direct effects of amyloid deposition rather than downstream neurodegeneration, we would predict that the youthful GI index would be lower also in amyloid positive, cognitively intact individuals. However, when restricting our analysis to individuals with CDR = 0, we did not find this relationship. Instead, amyloid positivity in cognitively intact individuals correlated with higher youthful GI index (P < 0.01), suggesting that preservation of AG in the typical glycolytic areas of youth is associated with asymptomatic presence of brain amyloid (Fig. 3).

Given the presence of longitudinally repeated measures in a subset of individuals within the AMBR dataset, a mixed effects model was constructed to account for subjects as a random effect. The youthful GI index was further normalized using a Yeo–Johnson transformation (30). This model again confirmed that the preservation of AG was on average, higher in amyloid positive, cognitively intact individuals (P < 0.05). The same analysis for total CMRGlc, CMRO2, and CBF did not reveal a similar significant relationship for any of these other metabolic parameters. Thus, the association between youthful brain metabolism and cognitive resilience in amyloid positive individuals is specific to brain AG.

Specific Brain Regions Show Reduced AG in Aging and AD. The results above investigate the preservation or loss of a youthful regional pattern of metabolism. This analysis was prescribed a priori to maximize signal-to-noise by using an omnibus measure of regional brain metabolism. However, effects of AD on brain metabolism may extend beyond a decrease in the youthful pattern of brain metabolism. We therefore computed region-by-region generalized regression models to explore the effects of age and AD on group-normalized GI within each region independently. As our metabolic data are not quantitative, only regions with significant negative changes in metabolism are included here, accounting for prior studies that demonstrate that whole brain glycolysis quantitatively decreases with age and in Alzheimer’s disease (14–15, 16–21).

Increased age was associated with decreases in GI in the superior frontal, superior parietal, caudal middle frontal, medial orbitofrontal, and entorhinal cortices (Fig. 4). These age-related changes mirror those regions with the highest GI in young healthy adults (see Fig. 1, N33 group average). Controlling for...
age and sex, AD status was associated with significantly reduced GI in the rostral middle frontal, inferior temporal, inferior parietal, lateral orbitofrontal, middle temporal cortices, and precuneus (Fig. 4).

White Matter Hyperintensity Burden Is Specifically Associated with Reduced AG. White matter hyperintensities (WMH) are nearly ubiquitous in the aged human brain, though the volume of WMH varies considerably across individuals; higher volumes are associated with increased risk of cognitive decline. Given that WMH are located along tracts connecting gray matter regions, increased WMH burden might be a key factor that reduces gray matter AG in the aging brain. A recent study from our lab on a small selected subset of these data used a different analytical approach to focus on how WMH burden influences white matter metabolism; this study found relatively reduced total gray matter glycolysis in older adults with significant WMH (25). To reproduce this preliminary finding with an independent sample, now controlled for amyloid status, we applied the approach developed here in the present study to determine whether WMH volumes might also correlate with reduction in the youthful GI index.

We acquired 1 mm³ isotropic fluid attenuated inversion recovery (FLAIR) sequences during 104 PET sessions in cognitively unimpaired individuals of the AMBR cohort. WMH were then segmented using intensity thresholding, manual selection of lesions, re-thresholding, and quality control (see Methods below for details). Since WMH volumes fit a log-normal distribution in this cohort, they were then log transformed before comparing to brain AG and the other metabolic measures. Controlling for age, sex, and amyloid status, global WMH volumes were significantly associated with reduced youthful GI index \((P < 0.002)\) (Fig. 5A). This was not true for the other metabolic measures \((P > 0.05)\;\text{Fig. 5B})

Discussion

Aging is associated with increased inter-individual variability in a variety of domains, including those related to brain function, structure, and neurodegeneration (31–33). Here, we show that aging is similarly associated with increasingly variable changes in brain
metabolism. As previously reported in a subset of these data, sex accounts for some of this inter-individual variability. Now, we find that early cognitive impairment is associated with loss of the youthful pattern of brain AG and total glucose use, but not in the pattern of CMRO₂ nor CBF. This parallels our prior PET study showing that loss of brain AG is specifically associated with tau deposition in AD (24), as well as other whole brain studies of brain metabolism using the invasive Kety-Schmidt technique, where brain glucose consumption rates were shown to fall first during early stages of dementia, followed by decreases in oxygen consumption in later stages of dementia (19–21). The reasons for a selective association between early symptomatic AD and loss of brain glycolysis are not yet clear, but this finding argues against ischemic processes and primary mitochondrial failure as causing a transition to early AD, since both of these would be expected to initially reduce CMRO₂ and CBF similar to or more so than glycolysis.

**Fig. 4.** Associations of regional glycolysis (GI) with aging and AD. The associations of aging and symptomatic AD with GI were explored at a regional level. Regression models were constructed for each independent gray matter region relating GI to age, sex, and AD and subject as a random effect. As this was an exploratory non-quantitative analysis, only regions showing a significant decrease (defined as t-score < −1.96, uncorrected) in GI are shown here, noting that both age and AD are known to be associated with lower whole brain AG (17, 19, 20). AD was associated with decreases in the precuneus, prefrontal, lateral parietal, and temporal regions. Aging was associated with relative decreases primarily in medial frontal and dorsal frontal and parietal areas, consistent with that reported previously. (In the upper right graph, blue and red dots reflect individuals without and with symptomatic Alzheimer disease, respectively. In the lower right graph, blue and red dots reflect individuals without and with brain amyloid positivity, respectively.)

**Fig. 5.** Association of WMH with youthful brain metabolism in cognitively normal individuals. (A) WMH volume (log transformed) was negatively associated with the youthful pattern of AG (GI) (P < 0.002). Amyloid positive participants are shown in yellow and negative individuals in blue. (B) Model predictions for the association between youthful metabolic indices and WMH volume are shown for males (similar findings are seen in females). Unlike brain AG (GI, blue), neither total glucose consumption (FDG, pink), blood flow (CBF, yellow), nor oxygen consumption (CMRO₂, red) was significantly associated with WMH volume (P > 0.05). 95% CIs are shown in gray. All models in (A) and (B) are adjusted for age, sex, and amyloid status.
Instead, preferential loss of cells or cellular components that rely more upon glycolysis, including synapses, axons, or glia, might explain why glycolysis decreases first in early AD. Loss of allostatic mechanisms and synaptic plasticity is another possible hypothesis.

In contrast to the loss of glycolysis in early dementia, asymptomatic individuals with amyloid positivity demonstrate preservation of the youthful pattern of brain AG when compared to cognitively normal individuals without amyloid pathology; a similar finding was not seen for the other metabolic parameters nor CBF. We suggest a few possible, and not mutually-exclusive, explanations for this intriguing finding. It is possible that increased AG in these individuals reflects resilience mechanisms that allow them to preserve their cognitive function despite amyloid pathology. Our results parallel a prior study showing that 18FDG uptake was increased in select regions of highly cognitively resilient, aged individuals, including medial frontal and anterior cingulate areas, which typically show high AG during youth (34). Accordingly, much like Wald's famous analysis of survivorship bias when investigating bullet holes in returning wartime airplanes (35), the apparent "effects" of amyloid on brain metabolism in cognitively intact individuals might actually reflect resilience mechanisms to pathology, rather than amyloid-related damage. Cohort studies like these that require participant dedication, resources, and/or altruism might further potentiate selection bias toward individuals with such resilience to neurodegeneration. These collective effects, what we have previously described as "resilience bias" (36), might explain the relative preservation of brain AG in asymptomatic amyloid positive individuals seen here.

In vitro and animal studies have similarly shown that glycolysis is enhanced in amyloid-beta resistant neurons (37–40). There are several potential mechanisms by which increased neuronal glycolysis might support resilience to amyloid pathology. In addition to producing reduced nicotinamide adenine dinucleotide (NADH) for oxidative capacity, glycolysis supplies several other critical metabolic pathways, including lactate production, biosynthesis of lipids, nucleic and amino acids, and reducing oxidative stress, namely via the pentose phosphate pathway. Through these metabolic pathways, glycolysis might support homeostatic maintenance of neuronal networks and synaptic plasticity, which could compensate for early subclinical sites of damage and oxidative stress. The concept that youthful patterns of brain AG might reflect greater metabolic resilience to amyloid pathology might also be directly related to amyloid deposition and could impair the role of microglia in response to amyloid pathology (34). Further investigations are needed to more fully understand the association between WMH, AD, and brain metabolism (25, 55).

Our study has important strengths including being the largest multi-tracer metabolic PET imaging study of its kind. However, a few important limitations warrant discussion. To limit participant burden, the PET methods employed in this cohort did not include arterial lines to fully quantify measures of brain metabolism, and normalization methods were used to minimize batch effects and improve signal-to-noise, thereby limiting the inferences that can be made from these results. Future studies using quantitative PET methods are underway, including with higher intrinsic spatial resolution and signal-to-noise to obviate the need for normalization. In a portion of this cohort, contemporaneous amyloid assessment was not available; assuming amyloid negativity in these cases might have decreased the observed associations between amyloid positivity and brain metabolism by slightly diluting the amyloid negative sample. Another caveat in this study is that only a small number of individuals underwent longitudinal assessments; thus, our results could conceivably be confounded by generational cohort effects. Ongoing longitudinal studies of brain metabolism—ideally spanning decades—would be necessary to overcome this limitation.

In conclusion, our study suggests that a preserved/heightened youthful pattern of brain AG is associated with initial asymptomatic brain amyloid pathology, whereas loss of this pattern occurs alongside cognitive impairment in AD. WMH are shown to be one factor that reduces gray matter AG. Further research investigating mechanisms by which AG is preserved or lost in the aging brain might reveal new opportunities to improve brain resilience to pathology.

**Methods**

**Participants and Regulatory Approvals.** This study was performed according to the principles outlined within the Declaration of Helsinki. All participants and/or their designated healthcare power of attorney consented to participation in one...
or more of these studies and for ongoing data analysis, as approved and overseen by the Washington University School of Medicine Institutional Review Board and the Radioactive Drug Research Committee. Data were gathered from participants enrolled in several different studies performed by the Vlassenko/Goyal (VG) Lab in the Neuroimaging Labs Research Center and the Knight Alzheimer Disease Research Center (ADRC), both at the Washington University School of Medicine in St. Louis.

A total of 285 individuals (55% women, self-reported sex/gender) aged 25 to 92 y were recruited from the Washington University community and the Knight ADRC. All participants had no neurological, psychiatric, or systemic medical illness that might compromise study participation. Individuals were excluded if they had contraindications to MRI, history of mental illness undergoing treatment, possible pregnancy, or medication use that could reliably interfere with brain function. Clinical cognitive status was assessed on the basis of the CDR (56) sum-of-boxes score (>0 versus 0), or when CDR was unavailable, based on a combination of medical history, self-report, and other available global cognitive tests, preferentially the ABB or Short Blessed Test, or as a last resort, the Montreal Cognitive Assessment corrected for education.

Brain Metabolism PET Imaging. All participants underwent metabolic brain PET and MRI structural imaging for registration and brain structure segmentation as previously described (17). All PET images were acquired in the eyes-closed waking state. No specific instructions were given regarding cognitive activity during scanning other than to remain awake. Briefly, 18F-FDG, 15O-02, 15O-H2O, and 15O-CO PET scans were performed on participants in the awake, eyes-closed state, and processed to yield regional maps of CBF, CMRO2, total CMRGlc, and AG (GI). Venous samples for analysis were collected from participants undergoing 3T (Trio or Prisma, Siemens) scanners including a 3D sagittal T1-weighted magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence, with resolutions ranging from 0.8 × 0.8 × 0.8 mm to 1 × 1 × 1 mm. A subset of individuals undergoing 3T MRI, 1 × 1 × 1 mm isotropic FLAIR sequences were obtained for WMH assessment.

Amyloid Brain PET Imaging. Research amyloid brain PET imaging was performed either with [11C]-labeled Pittsburgh Compound B ([11C]-PIB) (~12 mCi) or Florbetapir-F18 (~10 mCi), injected intravenously as a single bolus followed by 601°C-PIB or 70 Florbetapir-F18 minutes of brain PET imaging. PET imaging was performed on a Siemens Biograph PET/CT or HR + scanner (Siemens/CTI). All available amyloid imaging underwent an in-house routine amyloid brain PET processing pipeline that included the following processing steps: framework motion correction, registration to individual MRIT1 sequences, activity extraction within FreeSurfer v5.3 segmentations based on the Desikan-Killiany Atlas (57), and partial volume correction using the regional spread function implemented within a geometric transfer matrix framework, as has been described in detail previously (59–61). SUVR values were subsequently calculated for each segmented cortical and deep gray matter regions, referenced to the cerebellar gray matter (i.e., cerebellum SUVR = 1). A mean cortical SUVR (MC-SUVR) was calculated by averaging the SUVR values from prefrontal, parietal, and temporal cortical regions. Unless otherwise noted, a threshold MC-SUVR ≥ 1.42 is used to define a quantitatively “positive” amyloid 11C-PIB scan, based on previously published studies (24, 62–64).

Amyloid status was considered to remain positive after any positive PET scan. Conversely, amyloid status was considered to have been negative for the duration prior to any negative amyloid test. Otherwise, amyloid status was determined based on amyloid testing performed within 2 y (or in one case, within 2.5 y) of the metabolic PET imaging. When a research amyloid scan was unavailable, the results from a clinical amyloid scan and/or CSF testing, if available, were used instead to determine amyloid status at the time of the metabolic PET session. When amyloid status was unavailable, it was assumed to be negative for statistical analyses unless proven otherwise.

MRI Imaging. MRI scans were obtained in all individuals to guide anatomic localization and identify specific gray matter regions. High-resolution structural images were acquired using 1.5T (Vision, Siemens) and 3T (Trio or Prisma, Siemens) scanners including a 3D sagittal T1-weighted magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence, with resolutions ranging from 0.8 × 0.8 × 0.8 mm to 1 × 1 × 1 mm. A subset of individuals undergoing 3T MRI, 1 × 1 × 1 mm isotropic FLAIR sequences were obtained for WMH assessment.

FreeSurfer Analysis: FreeSurfer v5.3 software (57, 65, 66) was used to segment the brain into well-defined cortical and subcortical, gray and white matter regions of interest (ROIs) based on individual magnetization prepared rapid gradient echo (MPRAGE) MRI scans using the Desikan-Killiany and base FreeSurfer subcortical atlases. These ROIs were then used for the regional estimation of all PET metabolism parameters.

WMH Measurement. WMH severity was quantified by segmenting high signal intensity regions on individual FLAIR scans using the manually segmented intensity thresholds method. Each FLAIR scan was first preprocessed with tools in FMRIB Software Library (FSL) for brain extraction (67), bias field correction (68), and rigid body registration (69) to an individual’s corresponding T1 image. For segmentation, an intensity threshold of ≥1.2 SD was applied with an in-house MATLAB script at each axial slice. This threshold has shown to maximize the sensitivity for manually identifying WMH, as applied in other neurodegenerative cohorts (70, 71). Manual tracings were then performed where needed by identifying true lesions from false positives due to motion, fat signal, ventricles, or other sources that would not be considered WMH. To ensure that all WMH clusters were fully represented, the manually selected clusters were treated as seed regions and allowed to expand one voxel outward in all directions with a signal intensity restriction of ≥0.5 SD. All WMH binary masks were drawn by the same two raters. A neuroradiologist subsequently reviewed the WMH segmentations for accuracy.

Data, Materials, and Software Availability. The R script used to produce the figures and results is available upon request, edited to remove identifiers. Data availability is based on prior subject consents and the 2018 Common Rule (72). Coded, processed regional data prior to further data and statistical analyses are available from the study authors upon reasonable request by a qualified researcher following a data use agreement. Further requests for raw imaging data should be directed to the VG Lab and the Knight ADRC studies from which these data were gathered.

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