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Glucose hypometabolism is highly localized, but lower cortical thickness and brain atrophy are widespread in cognitively normal older adults

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Nugent S, Castellano CA, Goffaux P, Whittingstall K, Lepage M, Paquet N, Bocti C, Fulop T, Cunnane SC. Glucose hypometabolism is highly localized, but lower cortical thickness and brain atrophy are widespread in cognitively normal older adults. *Am J Physiol Endocrinol Metab* 306: E1315–E1321, 2014. First published April 15, 2014; doi:10.1152/ajpendo.00067.2014.—Several studies have suggested that glucose hypometabolism may be present in specific brain regions in cognitively normal older adults and could contribute to the risk of subsequent cognitive decline. However, certain methodological shortcomings, including a lack of partial volume effect (PVE) correction or insufficient cognitive testing, confound the interpretation of most studies on this topic. We combined [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) and magnetic resonance (MR) imaging to quantify cerebral metabolic rate of glucose (CMRg) as well as cortical volume and thickness in 43 anatomically defined brain regions from a group of cognitively normal younger (25 $\pm$ 3 yr old; $n = 25$) and older adults (71 $\pm$ 9 yr old; $n = 31$). After correcting for PVE, we observed 11–17% lower CMRg in three specific brain regions of the older group: the superior frontal cortex, the caudal middle frontal cortex, and the caudate ($P \leq 0.01$ false discovery rate-corrected). In the older group, cortical volumes and cortical thickness were 13–33 and 7–18% lower, respectively, in multiple brain regions ($P \leq 0.01$ FDR correction). There were no differences in CMRg between individuals who were or were not prescribed antihypertensive medication. There were no significant correlations between CMRg and cognitive performance or metabolic parameters measured in fasting plasma. We conclude that highly localized glucose hypometabolism and widespread cortical thinning and atrophy can be present in older adults who are cognitively normal, as assessed using age-normed neuropsychological testing measures.

aging; positron emission tomography; cerebral glucose metabolism; cortical volume; cortical thickness

GLUCOSE UPTAKE IN THE BRAIN is determined by synaptic function and neuronal activity (35, 41). Thus, cortical gray matter areas have higher glucose uptake because they have higher neuronal density than white matter areas (2). In Alzheimer's disease, the parietal and temporal cortex exhibit lower glucose uptake that is proportional to the severity of the disease (7, 26). A common interpretation of this regionalized decline in brain glucose uptake is that it is a consequence of neuronal deterioration and death (6). Although neuronal death would certainly reduce glucose consumption, several studies suggest that regional brain glucose hypometabolism can be present in those at genetic or familial risk of Alzheimer's disease who do not yet show clinical evidence of cognitive decline (27, 32, 34) and as early as in young adulthood (33). The implication is that regional brain glucose hypometabolism may not be simply the result of neuropathology and neuronal death but could also be contributing to the risk of subsequent aging-related cognitive decline and Alzheimer's disease (9).

Aging is the main risk factor for Alzheimer's disease, so it is important to determine whether brain glucose hypometabolism could be present before or only after the onset of aging-associated cognitive decline. Most reports on brain glucose metabolism in older adults have one or more of the following limitations that make it difficult to be certain whether regional brain glucose hypometabolism was present in individuals who do not present with cognitive decline (9): *1*) brain glucose uptake was not corrected for partial volume effects (PVE) in positron emission tomography (PET) with [^{18}F]flurodeoxyglucose ([^{18}F]FDG); *2*) brain glucose uptake was not quantified, i.e., the cerebral metabolic rate of glucose (CMRg; μmol·100 g^{-1}·min^{-1}) of the global or regional differences in glucose uptake was not shown; *3*) cognitive evaluation was insufficient in order to be certain that all of the older participants were definitely cognitively normal for their age; or *4*) whether the older participants were medicated for conditions that may affect brain glucose metabolism and their risk of cognitive decline was unclear (25).

PVE is an important potential confounder because estimates of the true radioactivity of PET radiotracers in small brain regions are influenced by the radioactivity in adjacent regions (14, 31). PVE is particularly marked when cortical atrophy is present, which is a common feature of the aging brain (1). Thus, accurate quantification of CMRg in the aging brain requires PVE correction (9, 36, 48). Three PET studies in older adults reported that no age-related differences in brain glucose metabolism were present after correction for PVE (10, 22, 48). Two other studies found that after PVE correction, brain glucose hypometabolism was indeed present in the frontal cortex alone (24) or principally in the frontal cortex but also in specific temporal and subcortical regions (28).

Of the aforementioned studies, only two of them (22, 24) also administered an in-depth battery of cognitive tests sufficient to fully evaluate the cognitive status of their young and older participants undergoing [^{18}F]FDG-PET. Others did not report having performed any assessment of cognition (10) or administered only the mini-mental state examination [MMSE; (19)], which provides only a rudimentary evaluation of global cognitive status (28, 48). If regional brain glucose hypometabolism is truly a feature of normal aging in cognitively healthy

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adults, it seems most likely to be present in the frontal cortex (24), but the actual magnitude of this deficit remains unclear. The inclusion of a measure of the actual magnitude of glucose hypometabolism would be useful because it would provide a potential therapeutic target for treatment using alternative brain fuels that could potentially compensate for brain glucose hypometabolism (9).

Therefore, the primary aim of the present study was to quantify the magnitude of regional CMRg (μmol·100 g^{-1}·min^{-1}), including PVE correction, in young and older adults who were cognitively normal for their age. Participants were screened for normal cognition by a comprehensive battery of neurocognitive tests. Scaled age-corrected scores were compared between the two groups to determine whether cognitive deficits were present in the older participants. We are not aware of any studies in which these three attributes have been reported in a single [^{18}F]FDG-PET study during aging. Magnetic resonance (MR) images were acquired to correct for PVE but also to permit the reporting of regional brain volumes and cortical thickness. Cortical thickness declines on the order of 0.2%/yr in individuals >55 yr of age, particularly in the temporal and occipital cortex (43). Hypertension and mild metabolic dysregulation are common in the elderly and are important risk factors for the development of Alzheimer's disease (20, 50). Therefore, the secondary aims of the present study were to compare CMRg between older participants who were and were not taking antihypertensive medication and to determine whether there was an association between blood parameters associated with glucose metabolism and global or regional CMRg.

EXPERIMENTAL PROCEDURES

Participants. Ethical approval for this study was obtained from Centre de Santé et de Services Sociaux-Institut Universitaire de Gériatrie de Sherbrooke and Centre Hospitalier Universitaire de Sherbrooke ethics committees. All participants provided written informed consent prior to study entry. Participants were between either 18 and 30 (young adult group; $n = 25$) or 65 and 85 yr of age (older adult group; $n = 31$). They all underwent a prescreening visit, which included analysis of a blood sample collected after an overnight fast and completion of a medical history questionnaire. Exclusion criteria included a MMSE score of <26, smoking, diabetes, or glucose intolerance [elevated fasting plasma glucose according to World Health Organization (47) recommendations (≥6.1 mM) or glycated hemoglobin (Hb A_{1c}) ≥6.5%], and evidence of overt heart, liver, or renal disease and untreated hypertension, dyslipidemia, or thyroid disease. None of the young participants were medicated. Thirteen of the 31 older adult participants were taking prescription medication for hypertension (Irbesartan, Ramipril, or Telmisartan). Five had prescriptions for statins (Atorvastatin and Rosuvastatin), and five were taking a synthetic form of the thyroid hormone thyroxine (levothyroxine).

Cognitive tests. Tasks for which response time was the primary measurement or those that were highly dependent on processing speed were classified as being in the processing speed domain (Table 2). These tasks included *conditions 1–3* of the Trail Making Test and *conditions 1–2* of the Color-Word interference test from the Delis-Kaplan Executive Function System (D-KEFS) (12) as well as Symbol Search and Coding tests from the Wechsler Adult Intelligence Scale (WAIS-IV) (44). Tasks related to executive function included Letter-Number Sequencing from the Wechsler Memory Scale (WMS-III) (45), *condition 4* of the Trail Making Test, *conditions 3* and *4* of the Color-Word interference test D-KEFS, and *conditions 1–3* of the Verbal Fluency Test from the D-KEFS. Memory tests were classified into two domains: immediate and delayed. Immediate recall memory was assessed using the Logical Memory I, Verbal Paired Associates I, and Spatial Span tests from the WMS-III (45), as well as the Digit Sequence test from the WAIS-IV, and immediate recall test from the Rey Complex Figure Test (RCFT) (40). Delayed memory was assessed using the Logical Memory II and Verbal Paired Associates II from the WMS-III (45) and delayed recall from the RCFT (40).

MR images. For each participant, T_1-weighted MR images were acquired on a 1.5 Tesla scanner (Magnetom Symphony; Siemens Medical Solutions, Erlangen, Germany). The parameters of the gradient echo sequence were repetition time/echo time − 16.00/4.68 ms,

Table 1. *Characteristics of the study participants*

	Young	Older Adults	*P* Value
No. of subjects	25	31	
Age, yr	25 ± 3	71 ± 9	≤0.0001
Sex (males/females)	11/14	14/17	
Height, cm	172 ± 11	164 ± 10	0.001
Weight, kg	69 ± 13	72 ± 16	NS
Body mass index, kg/m^2	23 ± 3	26 ± 4	0.022
Fasting plasma measurements			
Glucose, mM	5.0 ± 0.5	5.1 ± 0.5	NS
Acetoacetate, mM	0.15 ± 0.09	0.12 ± 0.05	NS
β-Hydroxybutyrate, mM	0.32 ± 0.25	0.23 ± 0.12	NS
Cholesterol, mM	4.4 ± 1.1	4.6 ± 1.2	NS
Triglycerides, mM	0.8 ± 0.3	0.9 ± 0.4	NS
Free fatty acids, mM	0.8 ± 0.2	0.9 ± 0.3	NS
Insulin, IU/l	4.1 ± 2.1	5.2 ± 2.2	NS
Hb A_{1c}, %	5.2 ± 0.2	5.8 ± 0.3	≤0.0001
Albumin, g/l	45 ± 3	43 ± 2	0.001
Aspartate aminotransferase, IU/l	23 ± 11	24 ± 5	NS
Alanine aminotransferase, IU/l	19 ± 9	22 ± 7	NS
Thyroid stimulating hormone, mIU/l	2.3 ± 0.7	2.7 ± 1.0	NS
HDL cholesterol, mmol/l	1.5 ± 0.3	1.4 ± 0.3	NS
LDL cholesterol, mmol/l	2.2 ± 0.7	2.8 ± 0.8	NS
Creatinine, μmol/l	72 ± 13	74 ± 17	NS

Values are means ± SD. NS, nonsignificant. *P* values were calculated using unpaired *t*-test, and a χ^2 test was used to evaluate sex differences between age groups, uncorrected for multiple comparisons.

20° flip angle, 1 mm^3 isotropic voxel size, 256 × 240 × 192 mm field of view, and matrix size of 256 × 256 × 164. A set of 20 FLAIR images was also acquired in the axial direction. The parameters were repetition time/echo time − 8,500/91 ms, 2,400-ms inversion time, echo train length of 17, matrix size of 256 × 192 for a 230 × 172.5 mm^2 field of view, slice thickness of 6 mm, and spacing between slices of 1.2 mm. FLAIR and T_1 MR images of the brain were reviewed by a neurologist, and no evidence of structural abnormality was found in any young or older participants.

Volume and cortical thickness. Gray matter volumes and cortical thickness were determined using FreeSurfer pipeline Suite 5.0 (Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Cambridge, MA). The cortex was automatically parcellated into 43 regions of interest (ROI) that were averaged for the left and right hemispheres. Briefly, this processing included the removal of nonbrain tissue using a hybrid watershed/surface deformation procedure (37), automated Talairach transformation, segmentation of white and gray matter (16, 17), intensity normalization (42), and topology correction (15, 38). Then the surface deformation was used to form tissue boundaries (11). Next, the cerebral cortex was parcellated using a sulcal depth-based anatomic parcellation method (13). Regional brain volumes were then normalized using intracranial volumes (46).

PET and cerebral metabolic rate of glucose. Brain PET scans were performed on a Philips Gemini TF PET/CT scanner (Philips Medical System, Eindhoven, The Netherlands) using a dynamic list mode acquisition, with time of flight enabled, an isotropic voxel size of 2 mm^3, field of view of 25 cm, and an axial field of 18 cm. Time frames were allocated according to 12 × 10 s, 8 × 30 s, 6 × 4 min, and 3 × 10 min for a total scan length of 60 min. After breakfast, each participant fasted for 6–7 h before scanning, which was performed at around 3 PM. Each participant's head was positioned in the headrest and gently restrained with straps in a dark quiet environment. An indwelling venous catheter was introduced into a forearm vein that was placed in a hand warmer at 44°C (30). A second catheter was placed in the contralateral forearm vein for the injection of 5 mCi of [^{18}F]FDG, which was infused over 20 s using an infusion pump. Blood samples were obtained at 3, 8, 16, 24, 35, and 55 min after [^{18}F]FDG infusion. Radioactivity in plasma samples was counted in a γ-counter (Cobra; Packard) cross-calibrated with the PET scanner.

PET images underwent a series of preprocessing steps to produce quantitative images of brain glucose uptake. First, PET images were automatically coregistered to each participant's respective MR image using a cross-modality three-dimensional image fusion tool implemented in PMOD 3.3 (PMOD Technologies, Zurich, Switzerland). Coregistered PET images were then corrected for PVE using the modified Müller-Gartner method (31), which is fully implemented in the PVElab software (http://nru.dk/downloads/software).

Quantification of CMR requires an arterial input function, which is defined as the rate of arrival of the PET tracer to the tissue of interest. Arterial input functions were determined by tracing ROIs on the internal carotid arteries with the aid of coregistered MR images, as validated previously in humans (49). The calculated activity within the ROI was corrected to the radioactivity of the plasma samples obtained during PET image acquisition. The lumped constant used to calculate CMRg was set to 0.80 (21). CMRg was expressed as micromoles per 100 grams per minute using the graphical Patlak model (29). CMRg is calculated as the product of the rate constant (K) for the tracer uptake multiplied by the plasma concentration of glucose. CMRg data were averaged within each ROI defined by FreeSurfer Suite 5.0.

Plasma metabolites. All metabolites were measured using an automated clinical chemistry analyzer (Dimension Xpand Plus; Siemens Healthcare Diagnostics, Deerfield, IL). Plasma insulin was analyzed by commercial enzyme-linked immunosorbent assay (Alpco, Salem, NH) with a Victor X4 multilabel plate reader (Perkin-Elmer, Woodbridge, ON, Canada).

Data presentation and statistical analysis. Data are presented as means ± SD. Levene's test was used to assess the normality of data ($P \leq 0.05$), and t-tests with unequal variance were employed if Levene's test was significant. Brain regions refer to gray matter only, with white matter being identified separately. Independent Student t-tests were used to compare CMRg between the young and older groups. All statistical analyses were carried out using SPSS 17.0 software (SPSS, Chicago, IL). The GLM procedure from SPSS with education introduced as a covariate was used to compare cognitive test scores of the younger and older adults. Percent difference between the two groups was expressed as ([older − young]/young × 100). These comparisons underwent a $P \leq 0.01$ false discovery rate (FDR) correction (5). Pearson correlations were performed to assess associations between CMRg and regional gray matter volume or cortical thickness.

RESULTS

Metabolic parameters. The older adults were 5% shorter ($P = 0.001$) and had 4% lower plasma albumin ($P = 0.001$), 13% higher body mass index ($P = 0.022$), and 12% higher Hb A_{1c}

Table 2. *Cognitive test scores in the younger and older participants*

	Young Adults	Older Adults
Processing speed		
D-KEFS trail-making visual scanning	15.6 ± 4.3	26.2 ± 9.2*
D-KEFS trail number sequence	21.0 ± 6.4	49.1 ± 23.9*
D-KEFS trail letter sequence	23.1 ± 5.8	48.8 ± 20.0*
D-KEFS stroop color naming	27.2 ± 4.0	33.5 ± 6.8
D-KEFS stroop word reading	20.8 ± 2.8	24.6 ± 4.9
WAIS-IV symbol search	37.6 ± 7.2	22.7 ± 6.3*
WAIS-IV code	82.7 ± 13.0	54.4 ± 11.7*
Executive function		
D-KEFS trail number-letter sequence	52.3 ± 13.3	118.5 ± 50.9*
D-KEFS stroop inhibition	43.2 ± 10.0	70.3 ± 17.9*
D-KEFS stroop inhibition/switching	56.3 ± 12.5	76.6 ± 17.0*
D-KEFS verbal fluency letter fluency	37.5 ± 10.1	34.1 ± 10.5
D-KEFS verbal fluency category fluency	45.1 ± 7.7	35.3 ± 7.2*
WMS-III letter-number sequencing score	12.1 ± 2.2	8.9 ± 1.8*
Immediate memory		
WMS-III logical memory total recall	57.3 ± 6.0	43.9 ± 9.4*
WMS-III verbal paired associates total recall	24.4 ± 5.8	18.2 ± 9.0
WMS-III spatial span total	18.7 ± 4.2	15.0 ± 4.1
WAIS-IV digit sequence total	29.3 ± 4.6	22.6 ± 5.4*
RCFT immediate recall	29.3 ± 5.5	21.7 ± 6.7
Delayed memory		
WMS-III logical memory total delay recall	39.9 ± 4.1	28.0 ± 7.1*
WMS-III verbal paired associates total delay recall	7.6 ± 0.7	5.6 ± 2.5
RCFT delay recall	29.8 ± 4.9	21.5 ± 6.2*

All results are expressed as the mean raw score ± SD, with education included as a statistical covariate; $n = 18$ young adults and 26 older adults. D-KEFS, Delis-Kaplan Executive Function System (12); WAIS-IV, Wechsler Adult Intelligence Scale-IV (44); WMS-III, Wechsler Memory Scale-III (45); RCFT, Rey Complex Figure Test (40). *$P \leq 0.01$, false discovery rate correction for multiple comparisons.

Table 3. *CMRg in young and older adults*

	Young Adults	Older Adults	%Difference
Frontal			
Superior	40 ± 7	35 ± 5	−12*
Rostral middle	43 ± 8	39 ± 5	−8
Caudal middle	42 ± 7	37 ± 5	−11*
Parsopercularis	40 ± 7	37 ± 4	−7
Parstriangularis	41 ± 8	38 ± 5	−8
Parsorbitalis	42 ± 10	40 ± 7	−4
Lateral orbital	38 ± 7	35 ± 5	−7
Medial orbital	36 ± 6	34 ± 4	−6
Precentral	37 ± 6	35 ± 4	−5
Paracentral	33 ± 6	35 ± 4	4
Pole	45 ± 9	42 ± 9	−7
Temporal			
Superior	32 ± 5	31 ± 4	−2
Middle	35 ± 6	33 ± 4	−7
Inferior	34 ± 7	32 ± 5	−7
Fusiform	29 ± 4	29 ± 4	0
Entorhinal	24 ± 5	24 ± 3	1
transverse	38 ± 6	40 ± 5	4
Pole	27 ± 5	25 ± 4	−7
Hippocampus	21 ± 3	21 ± 2	−2
Parahippocampus	26 ± 4	26 ± 3	−2
Parietal			
Superior	36 ± 6	35 ± 5	−3
Inferior	38 ± 6	35 ± 5	−8
Supramarginal	37 ± 6	35 ± 5	−4
Precuneus	38 ± 6	40 ± 5	3
Occipital			
Lateral	34 ± 6	31 ± 6	−8
Lingual	32 ± 5	33 ± 4	2
Cuneus	38 ± 6	38 ± 5	1
Cingulate			
Rostral anterior	31 ± 5	30 ± 4	−4
Caudal anterior	30 ± 5	30 ± 4	0
Posterior	35 ± 6	34 ± 5	0
Isthmus	36 ± 6	35 ± 5	−2
Subcortical	29 ± 4	27 ± 3	−4
Thalamus	27 ± 5	26 ± 3	−3
Caudate	34 ± 5	28 ± 4	−17*
Putamen	31 ± 5	29 ± 3	−7
Pallidum	21 ± 4	21 ± 2	−2
Amygdala	19 ± 3	19 ± 3	−2
Insula	29 ± 4	27 ± 3	−4
Pericalcarine	36 ± 5	36 ± 5	−1
White matter	23 ± 3	22 ± 3	−2

Values are means ± SD and in μmol·100 g^{-1}·min^{-1}; $n = 25$ young adults and 31 older adults. CMRg, cerebral metabolic rate of glucose. Difference column is (older − young)/young × 100%. *Statistically significant difference between young and older adults after $P \leq 0.01$, false discovery rate correction for multiple comparisons.

($P \leq 0.0001$) when compared with the younger participants (Table 1).

Cognitive battery. There were several differences between the young and older participants regarding raw cognitive test scores corrected for education (Table 2). To evaluate performance compared with age-matched peers and to determine whether participants in our older group presented with cognitive deficits, raw cognitive scores were corrected for age in addition to education and were presented as scaled scores. Statistical analysis of scaled scores showed no difference between the two groups in either the speed processing or executive function domains ($P \geq 0.20$). However, older participants scored 9–10% higher than the young group in immediate and delay recall tasks from the RCFT ($P = 0.001$).

CMRg. After PVE correction, whole brain gray or white matter CMRg was not significantly different between the two groups ($P = 0.312$). FDR-corrected CMRg ($P \leq 0.01$) was significantly lower in the older adults in the superior frontal cortex (−12%, $P = 0.005$), caudal middle frontal cortex (−11%, $P = 0.005$), and caudate nucleus (−17%, $P \leq 0.0001$) (Table 3 and Fig. 1).

Cortical volume and thickness. Gray matter volume was 13–33% lower in many brain regions in the older group (all $P \leq 0.01$, FDR corrected; Table 4). In the older participants, the lateral ventricles were more than twice the volume of those in the younger adults. Cortical thickness was 7–18% lower in many brain areas in the older group (all $P \leq 0.01$, FDR corrected; Table 5).

Antihypertensive medication. There were no significant differences in regional CMRg when older adults on antihypertensive medication ($n = 13$) were compared with older adults not on antihypertensive medication ($n = 18$).

Metabolic parameters in blood and regional CMRg. There were no statistically significant correlations between any of the measured metabolic parameters and CMRg in any region of the brain, including Hb A_{1c}, which was significantly higher in the older group (Table 1).

Cognitive function and regional CMRg. Correlations between raw cognitive test scores and CMRg were tested in the two frontal regions and caudate, which exhibited glucose hypometabolism in the older group. No significant correlations were observed between any of the regions exhibiting glucose hypometabolism and raw cognitive test scores (all $P > 0.05$).

DISCUSSION

The main outcome of this study was that our older group had significant regional brain glucose hypometabolism on the order

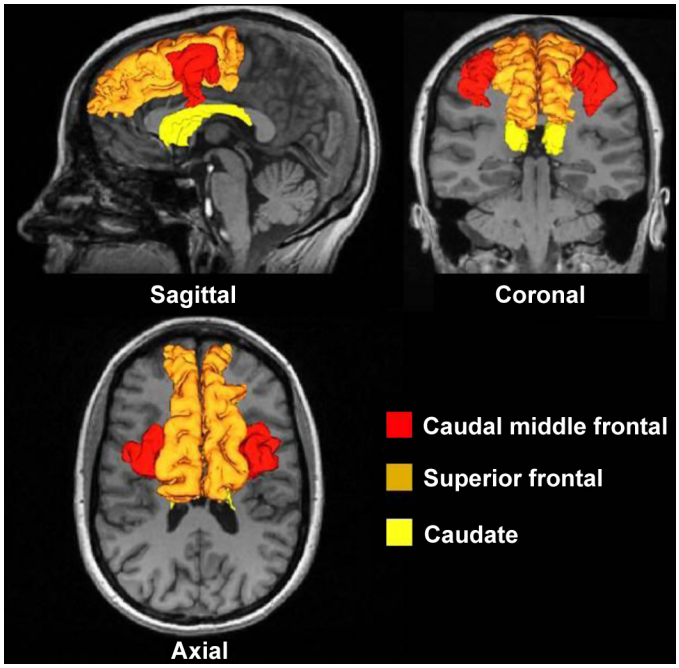

Fig. 1. Brain regions with significantly lower glucose uptake in the older group compared with the younger group, including the superior frontal cortex (orange), caudal middle frontal cortex (red), and caudate (yellow). All results were false discovery rate corrected for multiple comparisons; $P \leq 0.01$.

Table 4. *Regional gray matter volumes in young and older adults*

	Young Adults	Older Adults	%Difference
Frontal			
Superior	45 ± 6	35 ± 7	−23*
Rostral middle	33 ± 3	27 ± 6	−18*
Caudal middle	13 ± 2	10 ± 2	−20*
Parsopercularis	10 ± 2	7 ± 2	−29*
Parstriangularis	9 ± 1	6 ± 1	−33*
Parsorbitalis	5 ± 1	4 ± 1	−23*
Lateral orbital	17 ± 1	13 ± 3	−18*
Medial orbital	11 ± 1	9 ± 2	−15*
Precentral	24 ± 3	20 ± 4	−16*
Paracentral	7 ± 1	6 ± 2	−10
Pole	2 ± 0	2 ± 1	−26*
Temporal			
Superior	25 ± 2	20 ± 4	−22*
Middle	25 ± 2	19 ± 5	−22*
Inferior	24 ± 2	19 ± 4	−21*
Fusiform	21 ± 3	17 ± 4	−19*
Entorhinal	3 ± 1	4 ± 1	1
Transverse	2 ± 0	2 ± 0	−22*
Pole	5 ± 1	4 ± 1	−16*
Parahippocampal	5 ± 1	4 ± 1	−12
Parietal			
Superior	27 ± 5	22 ± 5	−16*
Inferior	29 ± 4	24 ± 6	−19*
Supramarginal	22 ± 3	17 ± 4	−22*
Precuneus	20 ± 3	16 ± 4	−17*
Occipital			
Lateral	23 ± 3	21 ± 4	−10
Lingual	15 ± 5	12 ± 2	−21*
Cuneus	6 ± 1	5 ± 1	−11
Cingulate			
Rostral anterior	5 ± 1	4 ± 1	−9
Caudal anterior	4 ± 1	4 ± 1	−11
Posterior	7 ± 1	6 ± 1	−14
Isthmus	5 ± 1	4 ± 1	−17*
Insula	15 ± 1	13 ± 3	−14*
Pericalcarine	5 ± 4	4 ± 1	−23*
Lateral ventricle	6 ± 3	12 ± 5	+123

Values are means ± SD and in ml; $n = 25$ young adults and 31 older adults. All data are corrected for intracranial volumes. Difference column is (older − young)/young × 100%. *Statistically significant difference between young and older adults after $P \leq 0.01$, false discovery rate correction for multiple comparisons.

of 11–17% in gray matter of the superior frontal cortex, caudal middle frontal cortex, and caudate (Table 3 and Fig. 1). When cognitive status was assessed using scaled scores, the older group had similar scores to age-matched individuals and no evidence of cognitive deficit. Hence, regional brain glucose hypometabolism can be present in older individuals with no cognitive deficit. Whether this degree of glucose hypometabolism in these regions is predictive of the increased risk of Alzheimer's disease remains to be seen. In addition to demonstrating localized brain glucose hypometabolism relative to younger participants, we show that the volume of multiple brain regions was 13–33% lower and that widespread cortical thinning on the order of 7–18% was present in our older group (Tables 4 and 5). This suggests that individuals averaging 71 yr of age can be cognitively normal despite widespread declining gray matter volume, extensive cortical thinning, and localized glucose hypometabolism. Thus, we add to the emerging evidence that several changes are occurring in the brains of older individuals who do not present with cognitive deficit and who are considered to not be impaired when compared relative with age-matched peers (27, 32–34). Regional cortical atrophy and cortical thinning were more widespread and were generally of a greater magnitude in the older group than was regional brain glucose hypometabolism, indirectly suggesting that cortical thinning and atrophy may be occurring before glucose hypometabolism, as has been reported in previous longitudinal studies (4, 23). Furthermore, in regions commonly vulnerable to Alzheimer's disease pathogenesis, including the entorhinal, parahippocampal, and cingulate regions, glucose metabolism was relatively normal, and little atrophy was present. This suggests that regional brain atrophy during normal aging is distinct from that of Alzheimer's disease. Fjell et al. (18) performed a longitudinal study and found that entorhinal atrophy was significantly greater in mild cognitive impairment when compared with a cognitively normal age-matched group. Kalpouzos et al. (24) also reported that the hippocampus and posterior cingulate demonstrated the least deterioration in glucose metabolism during aging and suggested that alterations in these regions appear to reflect the separation between normal aging and Alzheimer's disease.

Table 5. *Cortical thickness in young and older adults*

	Young Adults	Older Adults	Difference
Frontal			
Superior	2.8 ± 0.3	2.3 ± 0.3	−18*
Rostral middle	2.6 ± 0.2	2.2 ± 0.2	−15*
Caudal middle	2.6 ± 0.3	2.2 ± 0.3	−15*
Parsopercularis	2.8 ± 0.2	2.4 ± 0.3	−16*
Parstriangularis	2.7 ± 0.2	2.3 ± 0.3	−17*
Parsorbitalis	3.0 ± 0.2	2.5 ± 0.3	−17*
Lateral orbital	2.9 ± 0.2	2.5 ± 0.2	−12*
Medial orbital	2.7 ± 0.2	2.4 ± 0.3	−10*
Precentral	2.3 ± 0.3	2.0 ± 0.3	−15*
Paracentral	2.1 ± 0.4	1.9 ± 0.3	−11
Pole	3.1 ± 0.3	2.7 ± 0.4	−13*
Temporal			
Superior	2.9 ± 0.2	2.5 ± 0.3	−12*
Middle	3.1 ± 0.2	2.7 ± 0.3	−13*
Inferior	3.0 ± 0.2	2.7 ± 0.3	−11*
Fusiform	2.7 ± 0.2	2.5 ± 0.3	−9*
Entorhinal	3.4 ± 0.3	3.1 ± 0.4	−9*
Transverse	2.4 ± 0.4	2.1 ± 0.4	−13
Pole	3.6 ± 0.4	3.3 ± 0.5	−8
Parahippocampal	2.9 ± 0.3	2.7 ± 0.3	−6
Parietal			
Superior	2.2 ± 0.3	2.0 ± 0.3	−10
Inferior	2.6 ± 0.2	2.3 ± 0.3	−13*
Supramarginal	2.7 ± 0.2	2.3 ± 0.3	−14*
Precuneus	2.4 ± 0.2	2.1 ± 0.3	−11*
Occipital			
Lateral	2.3 ± 0.2	2.1 ± 0.2	−7*
Lingual	2.1 ± 0.2	1.9 ± 0.2	−11*
Cuneus	1.8 ± 0.2	1.7 ± 0.2	−8
Cingulate			
Rostral anterior	2.9 ± 0.2	2.8 ± 0.4	−3
Caudal anterior	2.7 ± 0.2	2.6 ± 0.3	−4
Posterior	2.6 ± 0.2	2.4 ± 0.3	−8*
Isthmus	2.6 ± 0.2	2.3 ± 0.2	−12*
Insula	3.1 ± 0.1	2.8 ± 0.4	−10*
Pericalcarine	1.6 ± 0.3	1.4 ± 0.1	−11*

Values are means ± SD and in mm; $n = 25$ young adults and 31 older adults. Difference column is (older − young)/young × 100%. *Statistically significant difference between young and older adults after $P \leq 0.01$, false discovery rate correction for multiple comparisons.

The older group had normal age-corrected results on an extensive cognitive battery of tests, including the evaluation of various cognitive domains, processing speed, executive function, and memory. Indeed, the older group actually performed better than the younger group in delayed recall tasks from the RCFT after adjustment for age and education (data not shown), underlining their relatively healthy overall cognitive status. Since lower CMRg was observed in cortical areas responsible for higher cognitive functions (as opposed to primary sensory areas such as auditory, motor, and visual cortex), it is possible that glucose hypometabolism in these regions may be linked to a risk of future cognitive decline. Nevertheless, we did not observe a significant association between glucose hypometabolism in any of the three regions affected in the older group and raw cognitive test scores. Hence, the mild stage of brain glucose hypometabolism in our older participants did not appear to be linked directly to cognitive outcomes.

Global or regional CMRg was not affected by whether or not the older group was taking antihypertensive medication. Whether untreated hypertension is associated with lower CMRg remains to be established. There was also no significant association between metabolic parameters measured in the blood and CMRg in any brain region. A study by Baker et al. (3) found that greater insulin resistance was related to lower CMRg in the frontal, parietotemporal, and cingulate regions in older adults newly diagnosed as prediabetic or type 2 diabetic. However, Baker et al. (3) did not apply a PVE correction to their [^{18}F]FDG-PET data. The relatively large variability in their plasma insulin values may also have permitted them to detect an inverse correlation with CMRg, a relationship that was precluded in our study by the narrow and normal range of fasting insulin found in our two groups. Hb A_{1c} was 12% higher in the older group but was still $<$6.0%, which is the suggested upper limit of normal for older nondiabetic adults (39). Although we did not find any significant correlations between CMRg and Hb A_{1c}, previous studies have found that higher fasting serum glucose levels are associated with glucose hypometabolism in regions commonly affected in Alzheimer's disease (8).

Limitations of this study include the inability to determine whether glucose hypometabolism does in fact appear before any measurable changes in regional brain volume or cortical thickness since we did not have a longitudinal design. We are presently reevaluating the group of older participants with a 2-yr followup scan that will help determine whether decreasing brain volume or cortical thickness precedes or follows decreasing CMRg. It is also possible that metabolic and structural differences in our older group were influenced by cohort effects rather than age effects per se; however, we made an effort to thoroughly define the cognitive and physical status of the groups, including an extensive cognitive battery and plasma metabolite evaluation.

In conclusion, when expressed quantitatively and with PVE and statistical correction for multiple comparisons, CMRg was 11–17% lower in the superior and caudal middle frontal cortex and in the caudate of our cohort of cognitively normal older adults. This aging-associated brain glucose hypometabolism was highly localized in contrast to cortical thinning and gray matter atrophy, both of which were widespread.

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DISCLOSURES

The authors declare no actual or potential conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

S.N., C.-A.C., T.F., and S.C.C. conception and design of research; S.N. and C.-A.C. performed experiments; S.N. and C.-A.C. analyzed data; S.N., C.-A.C., P.G., K.W., M.L., N.P., C.B., T.F., and S.C.C. interpreted results of experiments; S.N. prepared figures; S.N., C.-A.C., and S.C.C. drafted manuscript; S.N., C.-A.C., P.G., K.W., M.L., N.P., C.B., T.F., and S.C.C. edited and revised manuscript; S.N., C.-A.C., P.G., K.W., M.L., N.P., C.B., T.F., and S.C.C. approved final version of manuscript.

REFERENCES

1. **Anderton BH.** Ageing of the brain. *Mech Ageing Dev* 123: 811–817, 2002.
2. **Attwell D, Laughlin SB.** An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab* 21: 1133–1145, 2001.
3. **Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S.** Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol* 68: 51–57, 2011.
4. **Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC.** Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 367: 795–804, 2012.
5. **Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I.** Controlling the false discovery rate in behavior genetics research. *Behav Brain Res* 125: 279–284, 2001.
6. **Blennow K, de Leon MJ, Zetterberg H.** Alzheimer's disease. *Lancet* 368: 387–403, 2006.
7. **Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Sheline YI, Klunk WE, Mathis CA, Morris JC, Mintun MA.** Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci* 25: 7709–7717, 2005.
8. **Burns CM, Chen K, Kaszniak AW, Lee W, Alexander GE, Bandy D, Fleisher AS, Caselli RJ, Reiman EM.** Higher serum glucose levels are associated with cerebral hypometabolism in Alzheimer regions. *Neurology* 80: 1557–1564, 2013.
9. **Cunnane S, Nugent S, Roy M, Courchesne-Loyer A, Croteau E, Tremblay S, Castellano A, Pifferi F, Bocti C, Paquet N, Begdouri H, Bentourkia M, Turcotte E, Allard M, Barberger-Gateau P, Fulop T, Rapoport SI.** Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition* 27: 3–20, 2011.
10. **Curiati PK, Tamashiro-Duran JH, Duran FL, Buchpiguel CA, Squarzoni P, Romano DC, Vallada H, Menezes PR, Scazufca M, Busatto GF, Alves TC.** Age-related metabolic profiles in cognitively healthy elders: results from a voxel-based [18F]fluorodeoxyglucose-positron-emission tomography study with partial volume effects correction. *AJNR Am J Neuroradiol* 32: 560–565, 2011.
11. **Dale AM, Fischl B, Sereno MI.** Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9: 179–194, 1999.

12. **Delis D, Kaplan E, Kramer J.** *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: The Psychological Corporation, 2001.
13. **Destrieux C, Fischl B, Dale A, Halgren E.** Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage* 53: 1–15, 2010.
14. **Erlandsson K, Buvat I, Pretorius PH, Thomas BA, Hutton BF.** A review of partial volume correction techniques for emission tomography and their applications in neurology, cardiology and oncology. *Phys Med Biol* 57: R119–R159, 2012.
15. **Fischl B, Liu A, Dale AM.** Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging* 20: 70–80, 2001.
16. **Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM.** Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 33: 341–355, 2002.
17. **Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM.** Automatically parcellating the human cerebral cortex. *Cereb Cortex* 14: 11–22, 2004.
18. **Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM.** One-year brain atrophy evident in healthy aging. *J Neurosci* 29: 15223–15231, 2009.
19. **Folstein MF, Folstein SE, McHugh PR.** "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198, 1975.
20. **Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, Vendemiale G, Pilotto A, Panza F.** Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Res Rev* 9: 399–417, 2010.
21. **Graham MM, Muzi M, Spence AM, O'Sullivan F, Lewellen TK, Link JM, Krohn KA.** The FDG lumped constant in normal human brain. *J Nucl Med* 43: 1157–1166, 2002.
22. **Ibanez V, Pietrini P, Furey ML, Alexander GE, Millet P, Bokde AL, Teichberg D, Schapiro MB, Horwitz B, Rapoport SI.** Resting state brain glucose metabolism is not reduced in normotensive healthy men during aging, after correction for brain atrophy. *Brain Res Bull* 63: 147–154, 2004.
23. **Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, Shiung MM, Gunter JL, Boeve BF, Kemp BJ, Weiner M, Petersen RC; Alzheimer's Disease Neuroimaging Initiative.** Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* 132: 1355–1365, 2009.
24. **Kalpouzos G, Chetelat G, Baron JC, Landeau B, Mevel K, Godeau C, Barre L, Constans JM, Viader F, Eustache F, Desgranges B.** Voxel-based mapping of brain gray matter volume and glucose metabolism profiles in normal aging. *Neurobiol Aging* 30: 112–124, 2009.
25. **Kohler S, Baars MA, Spauwen P, Schievink S, Verhey FR, van Boxtel MJ.** Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span. *Hypertension* 63: 245–251, 2014.
26. **Mosconi L.** Glucose metabolism in normal aging and Alzheimer's disease: Methodological and physiological considerations for PET studies. *Clin Transl Imaging* 1: doi: 10.1007/s40336–013-0026-y, 2013.
27. **Mosconi L, Sorbi S, de Leon MJ, Li Y, Nacmias B, Myoung PS, Tsui W, Ginestroni A, Bessi V, Fayyazz M, Caffarra P, Pupi A.** Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *J Nucl Med* 47: 1778–1786, 2006.
28. **Nugent S, Tremblay S, Chen KW, Ayutyanont N, Roontiva A, Castellano CA, Fortier M, Roy M, Courchesne-Loyer A, Bocti C, Lepage M, Turcotte E, Fulop T, Reiman EM, Cunnane SC.** Brain glucose and acetoacetate metabolism: a comparison of younger and older adults. *Neurobiol Aging* 35: 1386–1395, 2014.
29. **Patlak CS, Blasberg RG, Fenstermacher JD.** Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 3: 1–7, 1983.
30. **Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE.** Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 6: 371–388, 1979.
31. **Quarantelli M, Berkouk K, Prinster A, Landeau B, Svarer C, Balkay L, Alfano B, Brunetti A, Baron JC, Salvatore M.** Integrated software for the analysis of brain PET/SPECT studies with partial-volume-effect correction. *J Nucl Med* 45: 192–201, 2004.
32. **Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D.** Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med* 334: 752–758, 1996.
33. **Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J.** Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci USA* 101: 284–289, 2004.
34. **Reiman EM, Uecker A, Caselli RJ, Lewis S, Bandy D, de Leon MJ, De Santi S, Convit A, Osborne D, Weaver A, Thibodeau SN.** Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. *Ann Neurol* 44: 288–291, 1998.
35. **Rocher AB, Chapon F, Blaizot X, Baron JC, Chavoix C.** Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. *Neuroimage* 20: 1894–1898, 2003.
36. **Rousset OG, Rahmim A, Alavi A, Zaidi H.** Partial volume correction strategies in PET. *PET Clin* 2: 235–249, 2007.
37. **Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B.** A hybrid approach to the skull stripping problem in MRI. *Neuroimage* 22: 1060–1075, 2004.
38. **Segonne F, Pacheco J, Fischl B.** Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging* 26: 518–529, 2007.
39. **Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL.** Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 362: 800–811, 2010.
40. **Shin MS, Park SY, Park SR, Seol SH, Kwon JS.** Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nat Protoc* 1: 892–899, 2006.
41. **Sibson NR, Dhankhar A, Mason GF, Rothman DL, Behar KL, Shulman RG.** Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proc Natl Acad Sci USA* 95: 316–321, 1998.
42. **Sled JG, Zijdenbos AP, Evans AC.** A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 17: 87–97, 1998.
43. **van Velsen EF, Vernooij MW, Vrooman HA, van der Lugt A, Breteler MM, Hofman A, Niessen WJ, Ikram MA.** Brain cortical thickness in the general elderly population: the Rotterdam Scan Study. *Neurosci Lett* 550: 189–194, 2013.
44. **Wechsler D.** *WAIS-IV Administration and Scoring Manual*. San Antonio, TX: The Psychological Corporation, 2008.
45. **Wechsler D.** *Wechsler Memory Scale* **(3rd ed.).** San Antonio, TX: The Psychological Corporation, 1997.
46. **Westman E, Aguilar C, Muehlboeck JS, Simmons A.** Regional magnetic resonance imaging measures for multivariate analysis in Alzheimer's disease and mild cognitive impairment. *Brain Topogr* 26: 9–23, 2013.
47. **WHO.** *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus*. Geneva: World Health Organization, 2011.
48. **Yanase D, Matsunari I, Yajima K, Chen W, Fujikawa A, Nishimura S, Matsuda H, Yamada M.** Brain FDG PET study of normal aging in Japanese: effect of atrophy correction. *Eur J Nucl Med Mol Imaging* 32: 794–805, 2005.
49. **Zhou S, Chen K, Reiman EM, Li DM, Shan B.** A method of generating image-derived input function in a quantitative ^{18}F-FDG PET study based on the shape of the input function curve. *Nucl Med Commun* 32: 1121–1127, 2011.
50. **Zou Y, Zhu Q, Deng Y, Duan J, Pan L, Tu Q, Dai R, Zhang X, Chu LW, Lu Y.** Vascular Risk Factors and Mild Cognitive Impairment in the Elderly Population in Southwest China. *Am J Alzheimers Dis Other Demen*. In press.