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Impaired glucose tolerance in midlife and longitudinal changes in brain function during aging

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ABSTRACT

We investigated whether individuals with impaired glucose tolerance (IGT) in midlife subsequently show regionally specific longitudinal changes in regional cerebral blood flow (rCBF) relative to those with normal glucose tolerance (NGT). Sixty-four cognitively normal participants in the neuroimaging substudy of the Baltimore Longitudinal Study of Aging underwent serial ^{15}O-water positron emission tomography scans (age at first scan, 69.6 ± 7.5 years) and oral glucose tolerance tests 12 years earlier (age at first oral glucose tolerance test, 57.2 ± 11.1 years). Using voxel-based analysis, we compared changes in rCBF over an 8-year period between 15 participants with IGT in midlife and 49 with NGT. Significant differences were observed in longitudinal change in rCBF between the IGT and NGT groups. The predominant pattern was greater rCBF decline in the IGT group in the frontal, parietal, and temporal cortices. Some brain regions in the frontal and temporal cortices also showed greater longitudinal increments in rCBF in the IGT group. Our findings suggest that IGT in midlife is associated with subsequent longitudinal changes in brain function during aging even in cognitively normal older individuals.
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1. Introduction

Abnormalities in glucose homeostasis are intrinsic to the transition from normoglycemia through impaired glucose tolerance (IGT) to type 2 diabetes (de Vegt et al., 2001; Petersen and McGuire, 2005) and are also believed to mediate increased risk of cognitive impairment and all-cause dementia, including Alzheimer's disease (AD). Numerous epidemiological studies from diverse ethnic populations have also demonstrated that type 2 diabetes is an independent risk factor for AD and age-related cognitive decline (Ohara et al., 2011; Schrijvers et al., 2010; Yaffe et al., 2012).

Despite a large number of studies suggesting an association between IGT and diabetes with cognitive impairment, the temporal relationship between these presumed risk factors for AD and longitudinal changes in brain function remains unclear. This question assumes greater relevance in light of recent studies suggesting that targeting insulin resistance and/or promoting insulin sensitivity might be a promising approach to disease modification in patients with AD and a strategy for secondary prevention in at-risk individuals (Bourdel-Marchasson et al., 2010; Watson and Craft, 2003). Understanding the influence of IGT in midlife on subsequent changes in brain function in cognitively normal older individuals is likely to provide important insights into the development of strategies aimed at interventions during the early presymptomatic stages of AD.

A recent functional neuroimaging study by Craft and colleagues using ^{18}fluorodeoxyglucose-positron emission tomography (PET) demonstrated reductions in the cerebral metabolic rate for glucose (CMRglu) in elderly individuals with insulin resistance in a pattern similar to that observed in patients with AD and mild cognitive impairment (MCI) (Baker et al., 2011). However, the cross-sectional design of this study did not allow the authors to investigate the association between antecedent IGT and subsequent changes in brain function over time. Similarly, the small number of individuals in this study precluded demonstration of significant intergroup differences in CMRglu between the insulin-resistant and normal groups.

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In the current study, we applied ^{15}O-water PET imaging of regional cerebral blood flow (rCBF) within the neuroimaging substudy of the Baltimore Longitudinal Study of Aging (BLSA) to investigate the relationship between IGT in midlife and subsequent longitudinal changes in brain function in cognitively normal older individuals. Our hypothesis was that individuals with midlife IGT will show subsequent differential patterns of change over time in resting-state rCBF relative to normoglycemic participants.

2. Methods

2.1. Subjects

The BLSA began in 1958 and is one of the largest and longest-running longitudinal studies of aging in the United States (Ferrucci, 2008). The community-dwelling unpaid volunteer participants are predominantly white, of upper-middle socioeconomic status, and with an above average educational level. In general, at the time of entry into the study, participants had no physical and cognitive impairment (i.e., Mini Mental State Examination score $\leq$24) and no chronic medical condition with the exception of well-controlled hypertension.

The BLSA Neuroimaging substudy began in 1994 (Resnick et al., 2000). BLSA participants were initially prioritized for admission to the neuroimaging study based on health considerations and the amount of previous cognitive data available for each individual. At enrollment, participants were free of central nervous system disease (e.g., epilepsy, stroke, bipolar illness, dementia), severe cardiac disease (e.g., myocardial infarction, coronary artery disease requiring angioplasty or coronary artery bypass surgery), pulmonary disease, or metastatic cancer.

Participants in the current report were 64 (mean age; 69.6 $\pm$ 7.5 years) nondemented individuals in the neuroimaging substudy of the BLSA, who underwent ^{15}O-water PET resting-state rCBF imaging scans and oral glucose tolerance tests (OGTT). Measurement of rCBF using ^{15}O-water PET is known to be a reliable marker of neuronal activity and we therefore used this measure as an indicator of brain function (Jueptner and Weiller, 1995). Serial OGTT data were acquired during each research visit since the entry of these participants into the BLSA. We included data from the earliest available OGTT since participant entry into the study. In participants who had OGTT data from multiple visits, we averaged the 2-hour post-glucose load plasma glucose values from all available OGTT measurements.

We excluded individuals with clinical strokes and brain trauma. Data from participants meeting consensus criteria for AD (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) and MCI were excluded from the time of onset of symptoms (McKhann et al., 1984; Petersen, 2004). Because the main focus of our current investigation was to explore the role of early abnormalities in insulin signaling on brain function rather than overt diabetes, 16 participants in the neuroimaging substudy with a clinical diagnosis of diabetes during follow-up were excluded. This study was approved by the local institutional review board. All participants provided written informed consent before each assessment.

2.2. Neuropsychological testing

During each annual neuroimaging visit, participants completed a battery of neuropsychological tests evaluating 6 cognitive domains. Mental status was assessed with the Mini Mental State Examination, memory was assessed using the California Verbal Learning Test, and Benton Visual Retention Test. Word knowledge and verbal ability were measured using Primary Mental Abilities Vocabulary. Verbal fluency was assessed by Letter (i.e., FAS) and Category fluency tests. Attention and working memory were measured by the Digit Span Test of the Wechsler Adult Intelligence Scale-Revised, and the Trail Making Test. Digits Backward, Trails B, and Verbal Fluency (categories and letters) assessed executive function. The Card Rotations Test assessed visuospatial function. Data from evaluations at each time point were used to examine differences in change in cognitive performance over time between IGT and normal glucose tolerance (NGT) groups.

2.3. OGTTs

Details of OGTT measurements in BLSA have been published previously (Metter et al., 2008). Briefly, participants were observed overnight in the research ward and fasted from 8 PM. They received the OGTT between 7 AM and 8 AM the next morning. Blood samples were drawn at 0, 20, 40, 60, 80, 100, and 120 minutes after an oral glucose load of 40 g/m^2 body surface area. Plasma glucose concentration was measured using the glucose-oxidase method as described previously (Metter et al., 2008). The American Diabetes Association guidelines were adopted to define IGT and NGT from the 2-hour post-glucose load concentrations of plasma glucose (IGT, 140–199 mg/dL, NGT, <140 mg/dL) (American Diabetes Association, 2004).

2.4. PET scanning parameters

Participants underwent PET scans at baseline (year 1) and at up to 8 annual follow-up exams. Each imaging session included a resting scan in which participants were instructed to keep their eyes open and focused on a computer screen covered by a black cloth.

PET measures of rCBF were obtained using [^{15}O] water. For each scan, 75 mCi of [^{15}O] water was injected as a bolus. Scans were performed on a GE 4096+ scanner, which provides 15 slices of 6.5 mm thickness. Images were acquired for 60 seconds from the time total radioactivity counts in the brain reached threshold level. Attenuation correction was performed using a transmission scan acquired before the emission scans.

2.5. PET data analysis

Data from PET scans obtained annually from baseline to the last available follow-up time points were used in the analyses. The PET scans were realigned and spatially normalized into standard stereotactic space and smoothed to full width at half maximum of 12 $\times$ 12 $\times$ 12 mm in the x, y, and z planes using a Gaussian filter. Next, the images were thresholded at 0.80 of the mean image intensity value of each scan to exclude peripheral signal scatter. The rCBF values at each voxel were ratio adjusted to the mean global flow estimated from gray matter intensity values and scaled to 50 mL/100 g/min for each scan to control for variability in global flow.

Using all annual scans for each subject, voxel by voxel differences in longitudinal change between the groups were assessed using group by time interactions. The mean interval between baseline and last follow-up PET scans was 7.5 ($\pm$0.9 SD) years. The results were adjusted for baseline age, sex, and the interval between the last OGTT assessment and the first PET scan. In secondary analyses, we also included each of the following additional covariates separately; apolipoprotein E (APOE) ε4 carrier status, body mass index (BMI), averaged over the follow-up interval of the OGTT, and the average 2-hour glucose value over the follow-up interval of the ^{15}O-water PET studies. Analyses were performed using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, London, UK).