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Neuroimaging and clinical characteristics of cognitive migration in community-dwelling older adults

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ABSTRACT

Background: Multiple neuroimaging and clinical biomarkers have been identified to predict cognitive decline and clinical progression to mild cognitive impairment (MCI) or dementia. However, early biomarkers associated with *transition to and reversion from cognitive impairment* (cognitive migration) require further understanding. We investigated the impacts of baseline neuroimaging and clinical biomarkers on cognitive migration in a community-dwelling older cohort.

Methods: We studied 391 participants from the Wake Forest Alzheimer's Disease Research Center Clinical Core cohort who underwent neuropsychological assessment and magnetic resonance imaging (MRI). At baseline, each participant was categorized to a functional/cognitive state using global Clinical Dementia Rating (CDR) score: CDR = 0 indicates normal cognitive function; CDR = 0.5 is minimal cognitive impairment. The primary outcome was cognitive migration status determined by CDR change between baseline and follow-up (mean difference = 13.9 months): CDR-0 Stables (no migration; maintained CDR = 0), CDR-0.5 Stables (no migration; maintained CDR = 0.5), Migrants^{-} (negative migration; CDR 0 to CDR 0.5), and Reverters^{+} (positive migration; CDR 0.5 to CDR 0). Baseline T1-weighted MRI was analyzed for gray matter (GM) volume using voxel-based morphometry (VBM). For VBM, we used a two-sample *t*-test controlling for age, sex, education years and intracranial volume for group comparisons: CDR-0 Stables vs CDR-0.5 Stables, CDR-0 Stables vs Migrants^{-}, CDR-0.5 Stables vs Reverters^{+} and Migrants^{-} vs Reverters^{+} (thresholded at k = 30 voxels, p <.01 uncorrected). Oral Glucose Tolerance Testing (OGTT-2h) assessed blood glucose 120-minute post challenge. Multinomial logistic regression estimated average predicted probabilities of cognitive migration status using OGTT-2h and age range (55–65, 65–75 and 75+) as predictors.

Results: VBM analyses revealed lower GM volume in inferior and middle temporal gyri, hippocampus, parahippocampal gyrus, and superior and inferior frontal regions in Migrants^{-} and CDR-0.5 Stables. Predicted probabilities indicated that individuals aged 55–65 with normal OGTT-2h levels were more likely to have better cognitive migration status (e.g., CDR-0 Stables or Reverters^{+}) than those aged 75+ with high OGTT-2h.

Conclusions: Lower GM volumes and high OGTT-2h glucose levels may predict worse cognitive migration status in early stages of disease. The opposite is true for better cognitive migration. Validating these biomarkers may guide clinical diagnosis and treatments.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by worsened brain structural and functional integrity and cognition over time (Karantzoulis and Galvin, 2011; Masters, 2015). Abnormal buildups of modified (misfolded) amyloid beta (Aβ) and tau proteins in the brain are pathological hallmarks of AD dementia, implicated in neurodegeneration, functional impairment, and cognitive

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decline. Aging is the greatest risk factor for AD (Guerreiro and Bras, 2015; Hersi, 2017). By 2050, twice as many Americans age 65 and older are projected to have AD dementia Alzheimer's disease facts and figures (2021). Biomarkers are crucial to detection and diagnosis of early stages of AD and important targets in drug discovery (Karlawish, 2017).

Neuroimaging and fluid biomarkers are widely used for detecting and monitoring AD (Perrin et al., 2009; Sperling, 2011). Research in cognitively normal older adults has identified extensive clinical characteristics and neuroimaging biomarkers that predict cognitive decline and clinical shift to mild cognitive impairment (MCI) or AD dementia (Sperling, 2018; Jack, 2018; Sperling, 2019; Lim, 2013; Jack, 2017). These include the pathological accumulations of Aβ and tau, and brain glucose hypometabolism measured by Positron Emission Tomography (PET); reduced cortical thickness and brain volume, increased white matter hyperintensities (WMH), and altered structural and functional connectivity measured by Magnetic Resonance Imaging (MRI); genetic predisposition such as carrying one or two Apolipoprotein E *(ApoE)* ε4 alleles; and subtle changes in cognitive performance, especially in memory and executive function domains. As indicated in the AD continuum/biomarker cascade (Jack, 2013), high Aβ burden and elevated tau as well as some brain volume loss appear in the preclinical and prodromal stages of AD. Therefore, even in the earliest stages of preclinical AD, long before cognitive impairment and dementia are present, biomarkers may provide crucial evidence allowing for prediction of the incidence and the development of AD.

Measurements of glucose tolerance have been found to predict cognitive decline and the risk of AD (Toppala, 2021; Hanson, 2016). Impaired glucose tolerance (IGT) may be associated with MCI, and thus may present a risk factor for impaired cognitive function in early stages of AD dementia (Thambisetty, 2013). Glucose levels measured during an oral glucose tolerance test (OGTT), a sensitive screening tool, can inform metabolic function and glucose homeostasis and detect IGT (Nathan, 2007). We examined this measure as a potential independent predictor of cognitive migration status.

In the current study, we defined cognitive migration as a spectrum/flow rather than a binary outcome to better understand not only the age-related shift from normal cognition (NC) to a relatively worse cognitive state (i.e., MCI), but also reversion from impaired cognition to NC. Early in disease progression, individuals with NC may migrate to MCI; the opposite can occur, as some individuals with MCI may revert to a relatively better cognitive state (i.e., NC) (Hampel and Lista, 2016; Angevaare, 2021). Notably, imaging biomarkers of disease (e.g., amyloid and tau PET) and neurodegeneration may track and predict such migrations. Additional factors such as age, genetics and lifestyle may also contribute to cognitive migration in early stages of disease. However, our knowledge of biomarkers related to cognitive migration in AD is limited, as most previous studies have explored only monotonic disease progression, from NC to MCI and dementia. The study of cognitive migration flow may help us understand not only the risks for cognitive impairment and disease progression but also elucidate markers for cognitive improvement in older individuals. Therefore, further research is needed to better understand how clinical and imaging measures may predict cognitive migrations –the potential for both decline and improvement– in early stages of disease.

Our study aimed to identify clinical characteristics and neuroimaging biomarkers that may impact cognitive migration over one year. We investigated baseline neuroimaging and clinical measures in participants aged 55 and older from the Healthy Brain Study (HBS) of the Wake Forest Alzheimer's Disease Research Center (ADRC). We used global clinical dementia rating (CDR) (Morris, 1993), a widely used clinical staging tool, at baseline and one-year follow-up to determine cognitive migration status. We hypothesized that baseline clinical and neuroimaging measures would predict cognitive migration at one year.

2. Materials and methods

2.1. Participants

664 participants aged 55 and older enrolled into the ongoing, longitudinal HBS between 2016 and 2021. Exclusion criteria included: large vessel stroke; neurologic diseases that might affect cognition other than AD; evidence of organ failure, active cancer, uncontrolled clinical depression, psychiatric illness, current use of insulin, history of substance abuse or heavy alcohol consumption within previous 10 years. HBS was approved by the Wake Forest Institutional Review Board; written informed consent was obtained for all participants and/or their legally authorized representatives. The initial visit (IV1) included clinical evaluation, physical examination, brain MRI, OGTT (Metter, 2008) and extensive cognitive testing using the Uniform Dataset version 3 (UDS3) (Weintraub, 2018). In this current study, we considered participants with global CDR scores of 0 (normal or no impairment) and 0.5 (minimal impairment) at two time points for evaluation of cognitive migration status and to understand cognitive migration in the earliest stages of disease. Cognitive Migrator groups were defined based on global CDR change between IV1 and 1-year follow-up (FU1). Of 664, 391 participants completed both in-person IV1 and either in-person or telephone FU1 visits, and had available baseline MRI, clinical and cognitive data. Those who did not migrate and maintained a CDR score of either 0 or 0.5 at both IV1 and FU1 visits were classified as CDR-0 Stables (n = 195) and CDR-0.5 Stables (n = 111), respectively. Those who migrated negatively from 0 to 0.5 were classified as Migrants^{-} (n = 35), and those who positively migrated to 0 from 0.5 were classified as Reverters^{+} (n = 50).

2.2. Neuroimaging, clinical and cognitive assessments

All IV1 measures and biomarkers included in this study are

Table 1
Participant demographic and clinical measures by cognitive migration status.

Baseline Demographic and Clinical Characteristics					
VARIABLES:	CDR-0 Stables (n = 195)	Migrants^{-} (n = 35)	CDR-0.5 Stables (n = 111)	Reverters^{+} (n = 50)	*p*
Age, mean (SD)	68.6 (7.7)	72.8 (8.4)	73.9 (7.0)	69.6 (8.7)	**<0.001**
Sex, N females (%)*	141 (72.3)	28 (80)	64 (57.7)	33 (66)	**0.023**
Education, mean (SD)	16.3 (2.5)	14.8 (2.3)	15.2 (2.6)	16.1 (2.3)	**<0.001**
ApoE ε4, N of carriers (%)*	58 (30.4)	4 (12.1)	42 (39.6)	14 (28.6)	**0.025**
BMI (kg/m^2), mean (SD)	27.8 (5.8)	27.1 (5.5)	26.9 (4.5)	28.8 (5.4)	0.213
OGTT-2h (mg/dL), mean (SD)	133.5 (41.9)	152.9 (55.6)	148.4 (43.8)	133.5 (35.4)	**0.010**
MoCA (0–30), mean (SD)	26.3 (2.6)	24.1 (2.9)	21.8 (3.6)	24.2 (3.4)	**<0.001**
PACC5 (z score), mean (SD)	0.076 (0.7)	−0.424 (0.6)	−1.282 (0.9)	−0.514 (0.7)	**<0.001**

The *p*-values are determined by One-Way ANOVA, except Sex and *ApoE* ε4. *Pearson's chi-square test. *ApoE* ε4 available data = 379.
OGTT-2h available data = 351. MoCA available data = 390. PACC5 available data = 389.
ApoE: Apolipoprotein E; BMI: Body Mass Index; MoCA: Montreal Cognitive Assessment; OGTT-2h: Oral Glucose Tolerance Test at 120 min; PACC5: Preclinical Alzheimer's Cognitive Composite.

summarized in Tables 1 and 2. Participants underwent brain MRI, including T1-weighted (T1w) and T2-Fluid Attenuated Inversion Recovery (FLAIR) images, and comprehensive clinical and cognitive assessments. Anatomical T1w and FLAIR images were acquired on a 3T Siemens Skyra scanner using a 3D volumetric magnetization prepared rapid gradient echo (MPRAGE) sequence with a resolution of 1 mm × 1 mm × 1 mm (TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; flip angle = 9°; FOV = 240×256). T1w images were processed with FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu) (Fischl, 2012; Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000; Fischl, 2004) for brain regional volume and thickness measurements and Statistical Parametric Mapping (SPM) version 12 (https://www.fil.ion.ucl.ac.uk/spm/) (Ashburner, 2012) for voxel-based analysis. Neuroimaging markers generated using FreeSurfer were areas affected earliest and most profoundly by the disease, as follows: a cortical thickness measure of temporal lobe meta region of interest (Temporal Meta ROI) which includes bilateral regions of entorhinal cortex, fusiform gyri, inferior temporal gyri, and middle temporal gyri; a measure of head size, total intracranial volume (ICV), and hippocampal volume (HCV) expressed as % of total ICV. Temporal Meta ROI thickness was not scaled to total ICV, as described (Schwarz, 2016). Additionally, we examined WMH volume expressed as % of total ICV and log transformed. WMHs were extracted from FLAIR images by the lesion growth algorithm (Schmidt, 2012) using a Lesion Segmentation Tool version 3.0.0 (https://www.applied-statistics.de/lst.html) for SPM.

The OGTT was administered to participants with no history of diabetes. Fasting (12 h) participants underwent OGTT by first completing a glucose measurement (OGTT-0 min) prior to glucose challenge (ingesting a 75-gram mixture of dextrose dissolved in water), followed by serial blood draws for additional blood glucose measurements at 15-, 30-, and 120-minutes post-challenge using the Hemocue whole blood glucose analyzer. The 120-minute OGTT (OGTT-2h) is a sensitive measure of glucose tolerance (Association, 2020). OGTT-2h > 140 mg/dL indicates impaired glucose tolerance (IGT). Fasting blood was also drawn to measure glycated hemoglobin A1c (HbA1c). HbA1c levels ≥ 5.7 % was considered impaired glucose metabolism and insulin resistance (Abid et al., 2016). However, we did not include data for fasting glucose (OGTT-0 min) and HbA1c measures in our statistical analyses.

The global CDR change between IV1 and FU1 (mean difference = 13.9 months) was used to define the primary clinical outcome, cognitive migration status: CDR-0 Stables (no migration; maintained CDR = 0), CDR-0.5 Stables (no migration; maintained CDR = 0.5), Migrants^{-} (negative migration; CDR 0 to CDR 0.5), and Reverters^{+} (positive migration; CDR 0.5 to CDR 0). The CDR was administered to participants by trained raters, and was evaluated independently from all other cognitive measures and biomarkers.

Table 2
Baseline differences in neuroimaging markers by cognitive migration status.

MARKERS:	CDR-0 Stables (n = 195)	Migrants^{-} (n = 35)	CDR-0.5 Stables (n = 111)	Reverters^{+} (n = 50)	*p*
Temporal Meta ROI (mm), mean (SD)	2.82 (0.13)	2.76 (0.13)	2.71 (0.17)	2.77 (0.13)	**<0.001**
ICV (L), mean (SD)	1.49 (0.15)	1.47 (0.16)	1.48 (0.18)	1.50 (0.18)	0.705
HCV (% of ICV), mean (SD)	0.51 (0.07)	0.50 (0.09)	0.45 (0.08)	0.49 (0.08)	**<0.001**
LogWMH, mean (SD)	0.85 (1.10)	1.48 (1.08)	1.66 (1.04)	1.18 (1.17)	**<0.001**

The *p*-values are determined by One-Way ANOVA. ROI: Region of Interest; ICV: Intracranial Volume; HCV: Hippocampal Volume; LogWMH: Log Transformed White Matter Hyperintensities.

Neuropsychological battery scores were obtained using the UDS3, including Montreal Cognitive Assessment (MoCA), Craft Story, Benson Figure, Number Span, Verbal Fluency (letters CFL), Category Fluency (CATFLU: Animals and Vegetables), Trail Making Test, and the Multilingual Naming Test. In addition, supplemental tests to assess participants' current and past cognitive performance were administered, including: Mini-Mental State Exam (MMSE), American National Adult Reading Test, Digit Symbol Substitution Test (DSST), Free and Cued Selective Reminding Test (FCSRT), and the Rey Auditory Verbal Learning Test (RAVLT). Cognitive measures evaluated in the current study included total MoCA scores and the preclinical Alzheimer's cognitive composite (PACC5) (Donohue, 2014; Papp, et al., 2017) z-score. PACC5, sensitive to preclinical changes in cognitive performance, was calculated using FCSRT total, DSST total, CATFLU, Craft Story Delayed Recall, and MMSE total scores using 230 participants with CDR = 0 at IV1 as a reference group. Lower PACC5 values indicate worse cognition (Mayblyum, 2021). *APOE* carrier status was defined as the presence of one or more *APOE* ε4 alleles (most common gene variant for AD risk).

2.3. Statistical analyses

All statistical analyses for demographic comparisons, cognitive measures and neuroimaging biomarkers were performed in SPSS 26 (www.ibm.com/analytics/spss-statistics-software). Image processing, and statistical models and mapping were performed using cat12 toolbox in SPM12 run in MATLAB (R2020a; www.mathworks.com) (Ashburner, 2012; Ashburner, 2009; Gaser and Dahnke, 2016). A primary focus of this work was voxel-based morphometry (VBM) (Ashburner, 2009; Ashburner and Friston, 2000; Chételat, 2005), the most widely used method for computational anatomy, using SPM12 for exploratory gray matter (GM) volume analysis. We used Automated Anatomical Labelling Atlas 3 (AAL3) for SPM12 overlaid on significant voxel-wise findings in template space to provide information on spatial location of results and to define brain areas that are associated with cognitive migration (Rolls, 2020). 1 Migrant^{-} was excluded from VBM analyses due to bad GM segmentation during image processing. In our primary VBM analyses, we performed whole-brain exploratory analysis using a two-sample *t*-test controlled for age, sex, education years and total ICV, thresholded at a less-stringent $p < .01$ (uncorrected) with a cluster size (k) of 30 voxels for group comparisons: CDR-0 Stables vs CDR-0.5 Stables, CDR-0 Stables vs Migrants^{-}, CDR-0.5 Stables vs Reverters^{+} and Migrants^{-} vs Reverters^{+}. Additionally, we applied family-wise error (FWE) at $p < .05$ and false discovery rate (FDR) correction to our analyses. Finally, we repeated our primary analyses correcting for time difference between baseline and follow-up visits. As results did not differ (data not shown), we present results without controlling for time differences.

Violin plot with box-plot distributions for OGTT-2h and multinomial logistic regression (MLR) were performed in R (R Core Team, 2020; www.R-project.org/) using the *ggplot2* package and the *multinom* function from the *nnet* package to estimate an MLR model (Wickham, 2016; Venables, 2002). In this model, cognitive migration status was the categorical primary outcome variable, and OGTT-2h and age range (a three-level categorical variable: 55–65, 65–75 and 75+) were predictor variables. We first calculated the relative risk ratios for a unit change in the predictor variables. Next, we generated predicted probabilities for each of our outcome levels (CDR-0 Stables, Migrants^{-}, CDR-0.5 Stables and Reverters^{+}) to better understand the model.

3. Results

Table 1 lists the baseline demographic and clinical characteristics among groups. A majority were female. CDR-0.5 Stables and Migrants^{-} were older, on average 73 years old, and had lower education years and higher OGTT-2h values. Interestingly, Migrants^{-} had very few copies of *ApoE* ε4 compared to other groups. A post hoc Tukey test revealed that

CDR-0.5 Stables, Reverters^{+}, and Migrants^{-} had significantly worse MoCA and PACC5 scores than CDR-0 Stables (p <.05).

Table 2 presents baseline MRI measures previously identified as early markers of disease (Schwarz, 2016; Jack, 2017). CDR-0.5 Stables had significantly lower Temporal Meta ROI thickness than CDR-0 Stables and Reverters^{+} and lower HCV than CDR-0 Stables, Reverters^{+}, and Migrants^{-} (Tukey p <.05). LogWMH volumes were significantly higher in CDR-0.5 Stables vs CDR-0 Stables and Migrants^{-} vs CDR-0 Stables (Tukey p <.05) and marginally in CDR-0.5 Stables vs Reverters^{+} (Tukey p =.055). VBM analysis for whole-brain explorations (p <.01 uncorrected, k = 30 voxels) revealed significant GM volume differences in group comparisons. Migrants^{-} had lower volumes in left middle temporal (Fig. 1a, T = 3.02) and superior frontal gyri (Fig. 1b, T = 4.17) than CDR-0 Stables and Reverters^{+}, respectively. CDR-0.5 Stables had lower left inferior temporal gyrus (Fig. 1c, T = 5.16) and hippocampus (Fig. 1c, T = 4.22; Fig. 1d, T = 3.46), and right parahippocampal (Fig. 1c, T = 5.10), middle temporal (Fig. 1c, T = 4.05) and inferior (Fig. 1c, T = 4.16) and superior frontal (Fig. 1c, T = 3.73) gyri and hippocampus (Fig. 1c, T = 4.76; Fig. 1d, T = 3.61) than CDR-0 Stables and Reverters^{+}, respectively. Detailed results on significant findings from Fig. 1 are presented in Supplementary Table S1. Maps using FWE-corrected p <.05 showed significant associations with temporal regions only in CDR-0.5 Stables < CDR-0 Stables (Supplementary Fig. S1). Other contrasts did not survive with a more stringent threshold (data not shown).

Glucose levels during OGTT-2h by each cognitive migrator group are in Fig. 2. CDR-0 Stables and Reverters^{+} had the lowest and Migrants^{-} the highest mean OGTT-2h. Pair-wise comparisons revealed statistically significant differences between CDR-0 Stables and CDR-0.5 Stables (Tukey p = 0.032) and marginal differences between CDR-0 Stables and Migrants^{-} (Tukey p = 0.087). Fig. 3 illustrates our MLR results as the averaged predicted probabilities of each cognitive migration level for different values of OGTT-2h glucose levels, our continuous predictor

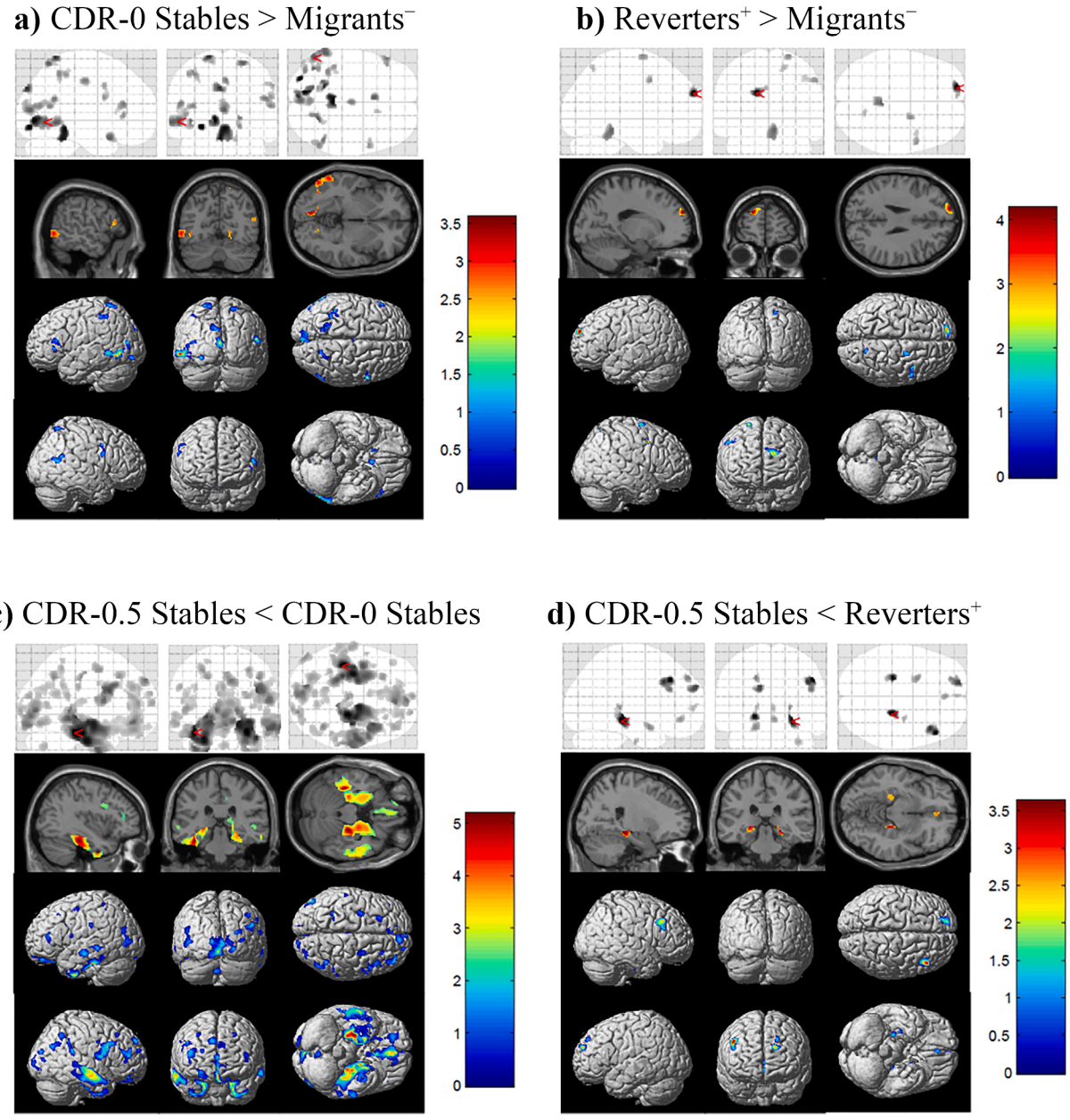

Fig. 1. VBM results are shown as statistical t maps thresholded at k = 30 voxels, p <.01 (uncorrected) for GM volume differences in t-contrasts of interest: a) CDR-0 Stables vs Migrants^{-}, b) Reverters^{+} vs Migrants^{-} c) CDR-0.5 Stables vs CDR-0 Stables, and d) CDR-0.5 Stables vs Reverters^{+}. Colorbars indicate t values for each contrast.

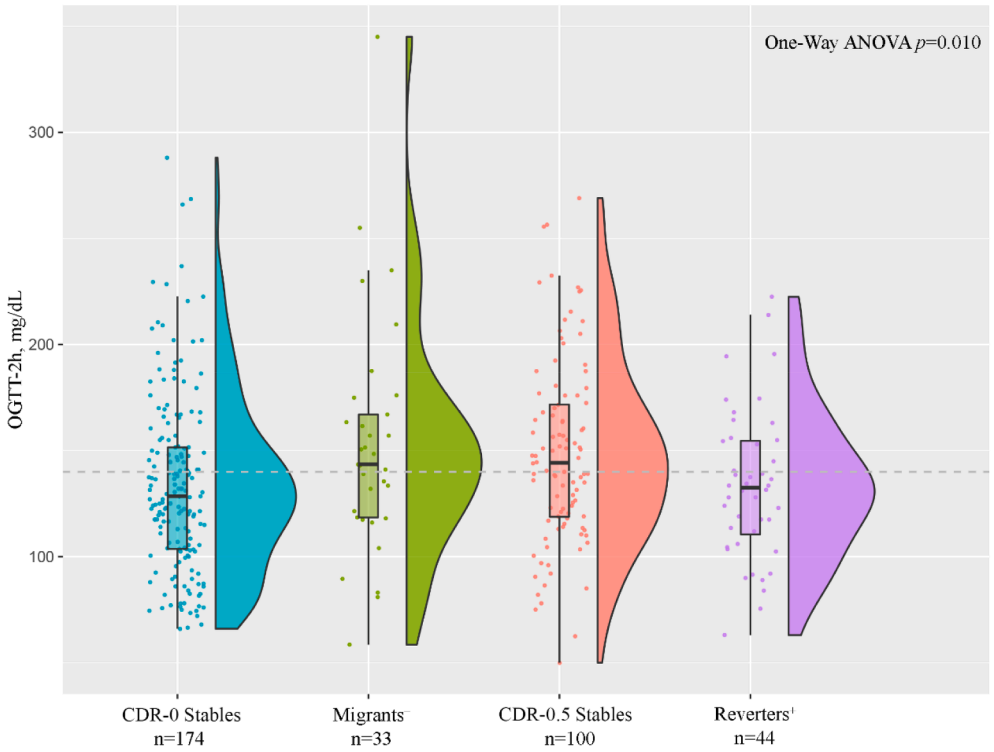

Fig. 2. Available OGTT-2h glucose levels for each group, shown as a violin plot with box-plot distributions. Dotted line at 140 mg/dL indicates the threshold for IGT status (≥140).

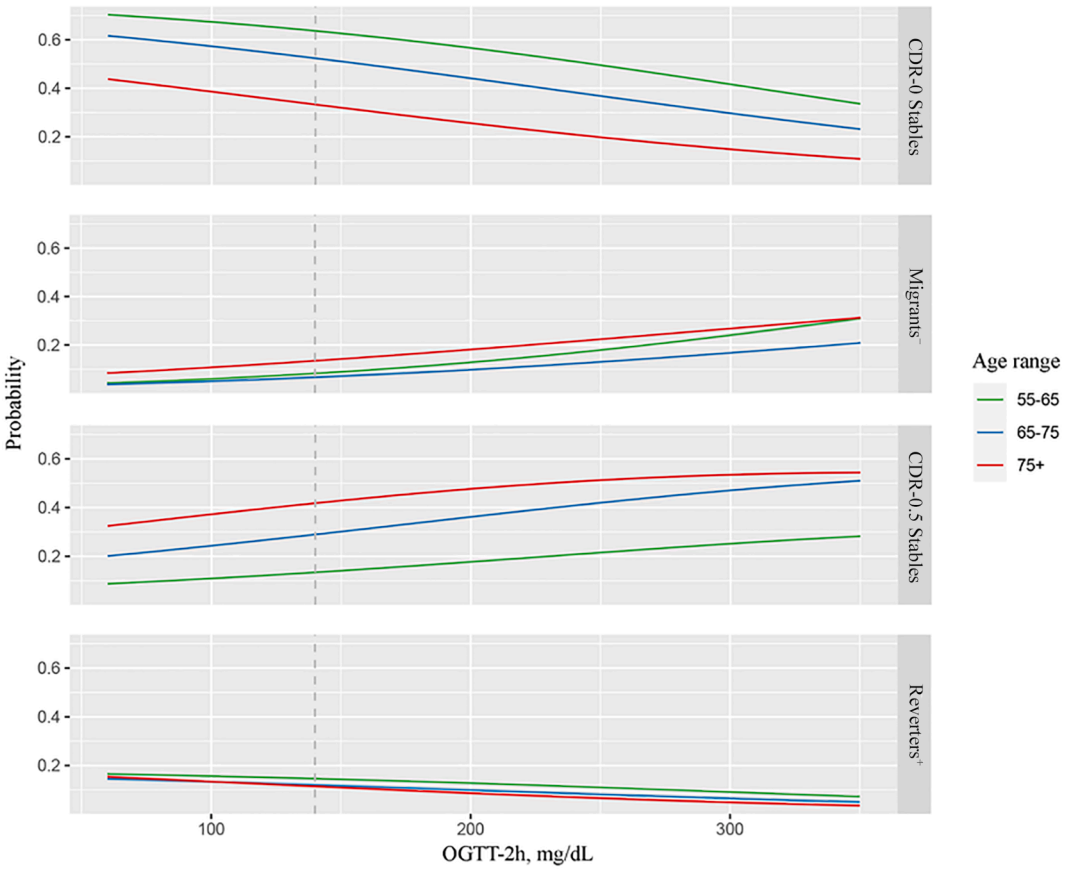

Fig. 3. Predicted probabilities for different cognitive migration levels across OGTT-2h by each age range. Dotted line at 140 mg/dL indicates the threshold for IGT status (≥140). Note that at any given OGTT-2h level and age group, each cognitive migration level complements each other (e.g., adds up to 1).

variable, within each level of age range. As the OGTT-2h levels increase, the probabilities for being CDR-0 Stables or Reverters^{+} decrease; the opposite pattern is seen for Migrants^{-} and CDR-0.5 Stables. For example, while the averaged probability of being a CDR-0 Stable is 0.67 for individuals aged 55–65 with normal OGTT-2h levels (<140), it is lower (<0.1) for being a Migrant^{-} with normal OGTT-2h levels in the lower age range (55–65). Higher OGTT-2h levels, indicative of IGT, are associated with higher probabilities for being a Migrant^{-} (0.22) and a CDR-0.5 Stable (0.50) over age 75 +. For Reverters^{+}, the averaged probability over normal OGTT-2h levels for all age range groups is consistently low (0.14) and decreases even more as OGTT-2h levels increase (<0.1).

4. Discussion

The goal of this study was to identify imaging biomarkers and clinical characteristics that are associated with cognitive migration in the earliest stages of AD. We assessed baseline MRI, metabolic and cognitive markers of older adults who maintained their cognitive status or migrated to a different status over one year of follow-up. Our results showed that Migrants^{-} and CDR-0.5 Stables had lower baseline GM volume than CDR-0 Stables and Reverters^{+}. As expected, lower volumes were seen in signature brain regions susceptible to AD. In addition, IGT as measured by OGTT-2h was associated with greater probability of migrating to a worse cognitive migration level. These data indicate that lower GM volume and IGT may predict worse cognitive migration in the development of cognitive impairment.

Our MRI findings are in agreement with a recent study (Rabin, 2020) that found reduced entorhinal thickness and smaller hippocampal volume predicted conversion to MCI within 5 years. However, we distinguished baseline differences in these markers in a shorter time interval (within a year). It is crucial to validate how such biomarkers may predict cognitive migration over shorter time intervals, as this may allow earlier and better prediction of cognitive impairment and dementia. For example, reversion to NC (Reverters^{+}) has been shown in MCI (Hampel and Lista, 2016). However, our knowledge of neuroimage-derived and clinical features related to this cognitive reversion is limited. Therefore, the contributions of the present study are significant because it is the first study to investigate the cognitive migration spectrum over a one-year period with multiple biomarkers contributing to multidirectional disease progression including reversion. Reversion may inform brain and cognitive reserve (Iraniparast, 2022). We focused on markers that may predict one-year CDR change as it exists in real life and poses a great importance in the field of MCI.

In our VBM analyses, we found the strongest cluster- and peak-level effects on temporal and frontal regions in CDR-0.5 Stables < CDR-0 Stables (Fig. 1c; Supplementary Table S1; Supplementary Fig. S1) with uncorrected p <.01 and FWE-corrected p <.05, as expected. The remaining contrasts showed significant peak-level effects on GM volumes only with uncorrected thresholds. This suggests that negative (Migrants^{-}) and positive (Reverters^{+}) migrations over a year are associated with small isolated regions rather than broadly clustered regions. We also note the sample size for Migrants^{-} (n = 35) and Reverters^{+} (n = 50) to be too small to observe larger effects.

Another recent study showed that higher OGTT-2h as a predictor of cognitive decline was associated with episodic memory worsening over 10 years (Toppala, 2021). In the present study, glucose levels during the OGTT-2h showed a promising effect on cognitive migration status, with better levels for better migration and worse levels with worse migration. Furthermore, we modeled OGTT-2h levels and three age groups (55–65, 65–75 and 75+) to predict the probabilities of different cognitive migration levels. As expected, CDR-0 Stables and CDR-0.5 Stables had the opposite predicted probabilities for worse migration status as the OGTT-2h levels increase at any given age group. Note that at any given OGTT-2h level and age group, each cognitive migration level complements each other (e.g., adds up to 1). For example, one's predicted probability for being a CDR-0.5 Stable at 140 mg/dL for an older age (75+) is higher (0.418) than being a CDR-0 Stable (0.333) or being a Migrant^{-} (0.135) or a Reverter^{+} (0.114).

Research on AD progression has primarily focused on biomarkers related to cognitive decline and conversion to MCI and dementia. This limits the understanding of important predictors of reversion in the context of cognitive migration. The present study shows that Reverters^{+} have greater baseline GM volume than Migrants^{-} and CDR-0.5 Stables. In addition, normal glucose tolerance was only seen in Reverters^{+} and CDR-0 Stables. This suggests that better metabolic and brain health may predict cognitive reversion despite worse baseline cognitive status.

Our findings on OGTT-2h in non-diabetic participants and GM volume for cognitive reversion may be important especially as the field of AD begins to develop therapies such as multidomain lifestyle interventions that may target metabolic risks for neurodegeneration and cognitive decline (Shimada, 2019; Dhana, 2020; Kanaya, 2004; Kalmijn, 1995; Watts, 2013; Liu, 2015; Neergaard, 2017). MRI is more commonly used and available at clinical settings than other imaging assessments such as PET. Therefore, using MRI markers with other clinical assessments such as OGTT-2h can inform one's chances of cognitive migration (decline or reversion). However, more research is needed to understand the interaction between modifiable lifestyle factors and known AD biomarkers on cognitive migration in preclinical AD.

Several strengths and limitations of our work are worth noting. The major strength of our study is our multidirectional *cognitive migration* approach to investigate predictive markers for cognitive transitions within one year. Reversion to NC (CDR-0.5 to CDR-0) and negative migration (CDR-0 to CDR-0.5) are existing crucial cognitive fluctuations to understand biomarker characteristics and modifiable risk factors within shorter time intervals. Increasing knowledge of markers indicated in cognitive migration within one year will help screen older adults with higher chance of worse migration or reversion. Reversion is especially important at clinical settings to target markers for delays in cognitive impairment trajectories. An inherent limitation of such an approach is that all observations made here need to be further replicated in the general population.

Interestingly, we found that our Migrants^{-} group had very few *ApoE* ε4 carriers compared to other groups. Noting the sample size for this group (n = 35), it is difficult to draw conclusions for the effect of *ApoE* ε4 noncarriers on their worse cognitive migration within one-year. We also note sample size limitations in our Reverters^{+} groups and lack of AD biomarker data availability such as PET and CSF of amyloid and tau in our cohort. Another limitation to our VBM analysis is that it is an exploratory examination of whole brain, not a specific ROI. Using a less-stringent visualization voxel-wise threshold limits our interpretation for our VBM findings. From our data alone it is unlikely to reliably draw conclusions about changes in GM volume and cognitive migration over time. Longitudinal studies investigating more follow-up data on neuroimaging markers and clinical characteristics in a wider spectrum of cognitive migration are warranted. Additionally, a comprehensive exploration of OGTT data and other metabolic measures such as insulin resistance with respect to brain imaging data including GM analyses is warranted. Finally, a future direction of this work examining PET or CSF AD biomarkers of Aβ and tau and additional MRI analysis including functional connectivity will confirm our findings in a larger sample data when available.

5. Conclusion

In this study, we focused on specific MRI markers and a metabolic measure, glucose levels during OGTT-2h, for tracking cognitive migration. Our goal was to better understand the baseline markers which may predict one-year cognitive status change. We found an association between lower GM volume and worse cognitive migration (CDR-0.5 Stables and Migrants^{-}). High glucose levels during OGTT-2h were also associated with worse cognitive migration status. Our work provides an

understanding of the relationship between GM integrity and glycemic health and cognitive migration in the cognitive aging-MCI spectrum.

CRediT authorship contribution statement

Tugce Duran: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. **James R. Bateman:** Conceptualization, Formal analysis, Writing – review & editing, Conceptualization, Formal analysis, Writing – review & editing. **Benjamin J. Williams:** Supervision, Writing – review & editing. **Mark A. Espeland:** Supervision, Writing – review & editing. **Timothy M. Hughes:** Supervision, Writing – review & editing. **Stephanie Okonmah-Obazee:** Writing – review & editing. **Melissa M. Rundle:** Writing – review & editing. **Suzanne Craft:** Funding acquisition, Resources, Supervision, Writing – review & editing. **Samuel N. Lockhart:** Funding acquisition, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ms. Tugce Duran, Drs. James Bateman, Benjamin Williams and Melissa Rundle, and Ms. Stephanie Okonmah-Obazee have no declarations of interest. Drs. Mark Espeland, Timothy Hughes, Suzanne Craft and Samuel Lockhart receive NIH grant support. Dr. Espeland also receives funding from the Alzheimer's Association. Dr. Craft also reports financial interest from vTv Therapeutics, T3D Therapeutics, Cyclerion Inc., and Cognito Inc.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103232.

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