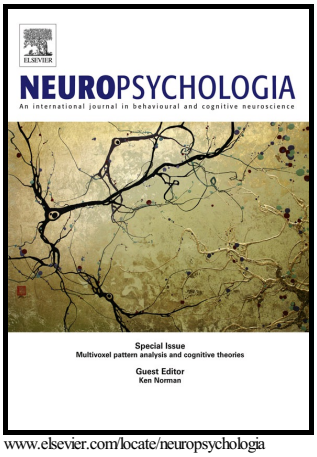

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Temporal Gradient During Famous Face Naming is Associated with Lower Cerebral Blood Flow and Gray Matter Volume in Aging

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ABSTRACT

Objective: Evidence suggests that famous face naming may be a cognitive ability especially sensitive to the early pathological processes of Alzheimer's disease (AD) and that those at risk for AD may demonstrate a Ribot temporal gradient (RTG), characterized by better performance for naming remote famous faces than for naming recent famous faces. Reductions in cerebral blood flow (CBF) and gray matter volume (GMV) have been implicated in the neuropathological cascade of AD and show utility as biomarkers of AD risk. We examined whether a RTG during

famous face naming was associated with lower CBF and/or GMV among a group of cognitively normal older adults.

Methods: Voxel-wise independent samples *t*-tests were employed to contrast resting CBF values between those who exhibited a RTG (RTG+) during a famous face naming task and those who did not (RTG-) among a sample of 52 cognitively normal older adults (25 RTG-, 27 RTG+; mean age=73). Groups were also compared on GMV using a voxel-wise general linear model.

Results: Significant group differences in CBF and GMV were found, whereby the RTG+ group demonstrated reduced CBF and GMV within medial temporal lobe regions (hippocampus, parahippocampal gyrus), relative to the RTG- group.

Conclusions: This represents the first study to show that cognitively intact older adults who demonstrate a RTG during famous face naming exhibit vascular dysregulation and structural changes similar to that seen in AD risk. Findings suggest that famous face naming ability may be particularly sensitive to the very early brain changes associated with AD.

Keywords (6): preclinical Alzheimer's disease, Ribot temporal gradient, famous face naming, cerebral blood flow, arterial spin labeling, magnetic resonance imaging, cognitive aging

1. Introduction

Alzheimer's disease (AD), characterized by progressive cognitive decline and anterograde memory deficits, is the leading cause of dementia in the elderly (Alzheimer's Association, 2016). Although no curative treatment currently exists, accumulating evidence suggests that neuropathological changes associated with AD begin years to decades before the clinical features are apparent (Jack et al., 2010), offering an opportunity for intervention with preventive or disease-modifying therapy. With a rapidly growing aging population, and age as the single greatest risk-factor for developing AD, identifying the earliest, most reliable, and non-invasive markers of preclinical AD is one of the greatest research challenges of the next decade.

Although many advances have been made regarding the pathology of AD, this disease manifests primarily as a cognitive disorder. As such, the field of neuropsychology has much to offer in terms of improving the characterization and detection of cognitive changes observed in normal

aging and AD-risk. Accordingly, increasing efforts have aimed to identify cognitive markers that can differentiate normal aging from AD-risk. Although the assessment of cognitive changes in AD and AD-risk have largely focused on episodic memory, mounting evidence suggests that semantic abilities may be some of the earliest impacted by AD-risk/pathology. For example, measures of semantic knowledge (i.e., naming, vocabulary, category fluency) demonstrate greater impairment than other cognitive domains, including episodic memory, both six (Wilson, Leurgans, Boyle, & Bennett, 2011) and two years (Mickes et al., 2007) prior to AD diagnosis. In fact, one type of semantic knowledge, person-identity knowledge (ability to identify famous faces), thought to involve a significant autobiographical episodic component in addition to a semantic component (Westmacott & Moscovitch, 2003), appears acutely sensitive to early and subtle deficits in AD-risk (Ahmed, Arnold, Thompson, Graham, & Hodges, 2008; Arango-Lasprilla, Cuetos, Valencia, Uribe, & Lopera, 2007; Cuetos, Rodríguez-Ferreiro, & Menéndez, 2009; Estévez-González et al., 2004; Seidenberg et al., 2009). Evidence also suggests that mild cognitive impairment (MCI) and AD patients exhibit a temporal gradient for remembered information, whereby memory performance is better for items from remote periods than for more recent periods (Greene & Hodges, 1996; Hodges, Salmon, & Butters, 1993; Seidenberg et al., 2009), demonstrating sensitivity to memory age (the time interval since initial encoding). Consistent with an anterograde memory deficit, this pattern of performance is referred to as a Ribot temporal gradient (RTG) and is thought to reflect a process of memory consolidation that renders remote memory retrieval dependent on neocortical structures rather than those of the medial temporal lobe (MTL), while recent memory retrieval remains highly MTL-dependent (Haist, Bowden Gore, & Mao, 2001; McGaugh, 2000; Squire & Alvarez, 1995). With the ability to directly manipulate remote versus recent memory retrieval processes, famous person-identity tasks have proven particularly useful in detecting temporal gradients. Taken together, this evidence supports the notion that a RTG during famous face naming might serve as a sensitive tool for identifying those at risk for AD and future cognitive decline, suggesting its usefulness as a cognitive marker of AD-risk.

Linking performance on a famous face naming task with neural markers of AD-risk represents the next step toward identifying neuropsychological tests sensitive to early AD-risk-related changes. Cerebral blood flow (CBF), or the rate of delivery of arterial blood to the capillary bed

in a volume of tissue, is an indirect measure of neural function that can reliably distinguish between normal controls and those with AD, identify those at risk for MCI and AD, and predict conversion to MCI and AD (Hays, Zlatar, & Wierenga, 2016; Wierenga, Hays, & Zlatar, 2014). While some evidence suggests that AD-risk is associated with lower CBF, particularly in medial temporal lobe (MTL) regions, other studies support *higher* CBF among those at risk (Hays et al., 2016). These conflicting results are likely due to differences in sample characteristics (e.g., operational definitions of MCI or normal control, APOE genotype, age), or methodological differences (e.g., imaging modality limitations, statistical or experimental control of confounding variables). CBF alterations, (hyperperfusion and/or hypoperfusion) in AD-risk are consistent with the vascular theory of AD, which holds that vascular damage contributes to the pathogenesis of the disease (de la Torre, 2010). Another widely accepted pathological characteristic of AD, gray matter volume (GMV) reduction (Wang et al., 2015), has also shown utility in identifying those in the earliest stages, with longitudinal studies demonstrating that cognitively intact older adults who exhibit lower MTL GMV at baseline are more likely to develop MCI or AD in the future (den Heijer et al., 2006; C. D. Smith et al., 2007; Tondelli et al., 2012). Unlike CBF, which has demonstrated regionally specific decreases *and* increases in AD-risk, GMV appears to demonstrate reliable reductions across the AD continuum. As such, the combined use of CBF and GMV measurement, along with sensitive neuropsychological tests of person-identity knowledge may lead to a better characterization of the very early brain and cognitive changes that accompany AD-risk.

Taken together, this evidence suggests that those who demonstrate a RTG during famous face naming (RTG+) may show greater brain changes associated with AD risk than those who do not demonstrate this pattern of performance (RTG-). However, to our knowledge, no study has compared these groups (RTG+, RTG-) on neural markers of AD-risk. Such a group comparison may elucidate a clinically meaningful and useful cognitive marker of AD-risk, enabling simple and easy identification of individuals who may benefit from early intervention or targeted clinical trials. In order to bridge this gap in the literature, our study used non-invasive arterial spin labeling (ASL) magnetic resonance imaging (MRI) to measure CBF and included a high resolution structural scan to measure GMV in cognitively normal older adults. A famous face naming task was administered on the day of scan to determine if CBF and GMV differed based

on the presence of a RTG during famous face naming. Based on previous reports, we hypothesized that famous face naming RTG status would have direct associations with CBF and GMV, such that those who demonstrate a RTG (i.e., cognitive performance consistent with anterograde deficits) would exhibit relative reductions in CBF and GMV in MTL regions associated with AD (hippocampus), supporting its potential utility as a marker of AD-risk.

2. Methods

2.1 Participants

See **Table 1** for participant demographic and cognitive characteristics. Participants were community-dwelling older adult volunteers enrolled in a longitudinal study of aging at the VA San Diego Healthcare System (VASDHS). Fifty-two cognitively normal participants between the ages of 65 and 85 (mean age = 72.6, SD = 5.2) with available data were included in the current analyses. Twenty-seven participants demonstrated a famous face naming RTG (RTG+) and 25 did not (RTG-). All participants were administered a full neuropsychological battery prior to undergoing the MRI scan. Directly after completing the scan, participants were administered the famous face task outside of the scanner. Normal cognitive function was determined based on a comprehensive neuropsychological test battery. Participants were excluded if performance on more than one measure within a cognitive domain was more than 1 standard deviation below age-appropriate norms, consistent with the empirically-derived criteria for diagnosis of MCI developed by Jak and colleagues (Jak et al., 2009), or if overall performance on the Dementia Rating Scale (DRS) was more than 1 standard deviation below age-appropriate norms (see **Table S1** in the Supplement for specific cognitive tests, domains, and normative data). Potential participants were excluded if they had a dementia or MCI diagnosis, a history of severe head injury, uncontrolled hypertension, or had a Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Axis I diagnosis of learning disability, attention deficit disorder, mood disorder, or substance abuse. In addition, participants were excluded if they had contraindications to MRI scanning such as ferrous implants or a pacemaker. All participants provided written informed consent prior to enrollment and data were collected in accordance with all ethical standards as stipulated by the UCSD and VASDHS institutional review board-approved procedures.

Table 1. Participant demographic and cognitive characteristics.

	RTG- (N=25)		RTG+ (N=27)					
	Mean	SD	Mean	SD	t / $\chi 2$	*df*	*p*	*Cohen's d / Cramer's V*
Age (years)*	71.6	4.59	73.59	5.56	-1.41	49.4	0.167	0.389
Gender (male/female)	10/15	--	10/17	--	0.05	1	0.826	0.077
Education (years)	16.28	2.25	16.26	2.26	0.03	50	0.974	0.009
ApoE genotype (ε4+/ ε4-)	8/17	--	10/17	--	0.35	1	0.556	0.077
Stroke Risk (%)	9.04	6.60	8.59	4.17	0.30	50	0.770	0.082
Average Systolic BP	127.92	15.29	128.44	18.21	-0.11	48	0.913	0.031
Average Diastolic BP	77.26	8.20	73.92	9.09	1.33	46	0.189	0.385
Whole Brain rCBF (ml/100g/min)*	73.82	12.24	71.26	12.72	0.74	49.9	0.464	0.205
Whole Brain GMV (ml)*	641.36	27.33	630.21	37.44	1.23	47.5	0.224	0.338
FF Naming total score	50.26	10.61	47.78	8.46	0.94	50	0.354	0.260
Recent FF Naming score	25.86	5.09	22.59	4.69	2.41	50	0.020**	0.669
Remote FF Naming score	24.40	5.62	25.11	3.87	0.54	50	0.595	0.148
RTG (Recent – Remote)	1.46	1.56	-2.51	1.68	8.82	50	<0.001**	2.455
DRS Total Score	141.36	2.02	140.22	2.98	1.60	50	0.116	0.445
WMS-R LM Immediate Recall SS	13.72	1.86	13.52	2.70	0.31	50	0.756	0.086

WMS-R LM Delayed Recall SS	13.76	1.88	14.19	2.39	-0.71	50	0.481	0.199
CVLT-2 List 1–5 total t-score	58.24	10.67	53.26	12.05	1.57	50	0.122	0.437
CVLT-2 SD Free Recall z-score	0.58	1.11	0.48	1.23	0.30	50	0.763	0.085
CVLT-2 LD Free Recall z-score	0.50	0.88	0.39	0.97	0.44	50	0.659	0.119
DKEFS CW Inhibition SS	11.79	1.82	11.23	2.18	0.98	48	0.330	0.278
DKEFS CW Inhibition Switch SS	11.96	2.22	11.38	2.55	0.85	48	0.401	0.242
Trail Making Test-B t-score	56.48	10.25	54.31	10.26	0.76	49	0.453	0.212
DKEFS CF Animals t-score	53.92	9.45	52.96	13.41	0.29	50	0.769	0.082
Boston Naming Test total t-score+	50.15	5.53	51.91	6.04	-0.74	22	0.466	0.303
MINT z-score+	0.29	0.82	0.32	0.51	-0.13	24	0.900	0.044

*FF= Famous face; RTG= Ribot temporal gradient; ApoE= Apolipoprotein E; BP= Blood pressure; rCBF= Resting cerebral blood flow; GMV= Gray matter volume; FF= Famous Face; DRS= Mattis Dementia Rating Scale; WMS= Wechsler Memory Scale; LM= Logical Memory; SS= Scaled score; CVLT= California Verbal Learning Test; SD= Short delay; LD= Long delay; DKEFS= Delis-Kaplan Executive Function System; CF= Category fluency; MINT= Multilingual Naming Test; df= Degrees of freedom. *Denotes equal variances not assumed (df reported are adjusted for unequal variances); **Denotes significance at p< 0.05; +in the assessment of confrontational word retrieval, half the sample was administered the Boston Naming Test and the other half was administered the MINT.*

2.2 Famous face naming RTG assessment

To determine a famous face naming RTG, representing a temporal gradient for when autobiographical episodic memory was likely first encoded, we used a famous face naming test developed by our research group. The famous face test stimuli consisted of 60 black and white photographs of famous faces. Stimuli included 30 remote famous faces (individuals who were

famous or achieved public prominence between 1960 and 1975) and 30 recent famous faces (individuals who were famous or achieved public prominence between 1995 and 2011; See **Figure 1**). Stimuli were selected based on fame era (recent versus remote) and orientation (forward facing), and included a range of fame categories (e.g., entertainment, sports, politics, science). Stimuli were then piloted on a normative sample and the 60 most recognizable faces were selected for inclusion in the famous faces naming test, with an overall average naming rate of 75%. The final set of recent faces included 20 living and 10 deceased individuals, of which 20 belonged to the entertainment/sports category and 10 belonged to the politics/science category. The final set of remote faces included 3 living and 27 deceased individuals, of which 22 belonged to the entertainment/sports category and 8 belonged to the politics/science category. The number of smiling and neutral faces were similar in each era. During test administration, participants were presented each photo and asked to name the famous face. There were no time limits imposed during this test, although most participants provided a naming response or reported not knowing the name within a few seconds (actual response times were not recorded). Possible scores on the famous face naming test ranged from 0 to 60, with each full correct response (correct first *and* last name) being assigned one point, each partial correct response (correct first *or* last name only, or a correct 'nickname') being assigned a half point, and each incorrect naming response (incorrect first *and* last name, or no name provided) being assigned zero points. Those who demonstrated better performance for naming of remote famous faces than recent famous faces (recent famous face naming score < remote famous face naming score) were classified as having shown a RTG (RTG+), while those that did not demonstrate this pattern of performance (recent famous face naming score ≥ remote famous face naming score) were classified as having not shown a RTG (RTG-).

Figure 1. Famous face stimuli. *Examples of remote (Dick Clark and Dwight Eisenhower) and recent famous faces (Will Smith and Hillary Clinton).*

2.3 Apolipoprotein E genotyping

Genotyping was performed by the ADCS Biomarker Core at UCSD using real time PCR Restriction Fragment Length Polymorphism analysis. Genomic DNA was collected from participants using buccal swab and extracted using Qiamp DNA blood mini kit (Qiagen) followed by PCR amplification (Wierenga, et al., 2012).

2.4 MRI acquisition

Imaging data were acquired on a GE Discovery MR750 3T whole body system with a body transmit coil and an 8-channel receive-only head coil at the University of California San Diego Center for Functional MRI. The structural brain sequence consisted of a high-resolution T1-weighted Fast Spoiled Gradient Recall (3D FSPGR) scan: 172 1 mm contiguous sagittal slices, FOV = 25 cm, TR = 8 ms, TE = 3.1 ms, flip angle = 12, T1 = 600 ms, 256 x 192 matrix, Bandwidth = 31.25 kHz, frequency direction = S-I, NEX = 1, scan time = 8 min and 13 seconds. Resting CBF was acquired with the Multiphase Pseudocontinuous Arterial Spin Labeling (MPPCASL) sequence, which is optimized for robust CBF quantification (Jung, et al., 2010): tagging duration = 2 sec, TI = 3.6 sec, TR = 4.2 sec, TE = minimum, reps = 64, FOV = 22 x 22 cm, 20 5 mm axial slices with a single shot spiral acquisition, collecting 8 cycles where each cycle consists of 8 images acquired with unique phase offsets, acquisition time = 4:46 minutes. A spiral scan with a long TR (4000 ms) and short TE (3.4 ms) was also acquired to obtain an estimate of the equilibrium magnetization of cerebral spinal fluid, which is used to convert the perfusion signal into calibrated CBF units (mL blood/100g tissue/min). Finally, a minimum contrast image was acquired to adjust for transmit and receive coil inhomogeneities. Two field map scans were also acquired and used for off-line field map correction to help correct for signal bunching and dropouts in the frontal/medial temporal lobes.

2.5 MRI pre-processing

ASL image processing was performed with Analysis of Functional NeuroImages (AFNI, afni.nimh.nih.gov) (Cox, 1996), FMRIB Software Library (FSL, Oxford, United Kingdom), and locally created Matlab scripts. Field map correction was applied to the ASL time series prior to co-registration to the middle time point to minimize the effects of participant motion. For each participant, a mean ASL image was formed from the average difference of the control and tag images using surround subtraction to create an uncorrected perfusion time series, and slice timing delays were accounted for, making the inversion time (TI2) slice specific (Liu and Wong, 2005). This mean ASL image was then converted to absolute units of CBF (mL/100g tissue/min) using an estimate of the equilibrium magnetization of CSF as a reference signal (Chalela, et al., 2000). This procedure resulted in a calibrated perfusion value for each voxel. Skull stripping of the high-resolution T1-weighted image was performed using AFNI's 3dSkullStrip. Tissue segmentation was performed using FSL's Automated Segmentation Tool (FAST) algorithm (http://fsl.fmrib.ox.ac.uk/fsl/) to define cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM) regions. The high-resolution T1-weighted image and partial volume segmentations were registered to ASL space, and partial volume segmentations were down-sampled to the resolution of the ASL data. To correct the CBF measures for partial volume effects and ensure that CBF values were not influenced by known decreased perfusion in white matter or increased volume of CSF (Parkes, et al., 2004), we used the method previously reported by Johnson and colleagues (Johnson, et al., 2005). These calculations assume that CSF has 0 CBF, and that CBF in GM is 2.5 times greater than that in WM. The following formula was used to compute partial volume corrected CBF signal intensities: CBFcorr = CBFuncorr/(GM + 0.4 * WM). CBFcorr and CBFuncorr are corrected and uncorrected CBF values, respectively. GM and WM are gray matter and white matter partial volume fractions, respectively. Information from the high resolution structural image and the FSL FAST was used to determine the tissue content of each perfusion voxel. A 4.0 mm full-width, half-maximum Gaussian filter was applied to the CBFcorr data. Voxels with negative intensities were replaced with zero (Brown, et al., 2003) and GM voxels were thresholded at 0.9 probability. CBFcorr data were registered to the MNI-152 atlas using FMRIB's Non-linear Image Registration Tool (FNIRT), part of FSL and resampled to a 3x3x3 mm resolution grid.

GMV image processing was performed using FSL- voxel based morphometry (VBM) (Douaud et al., 2007) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (S. M. Smith et al., 2004). First, structural images were brain-extracted and gray matter-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson, Jenkinson, & Smith, 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific gray matter template. Second, all native gray matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. Generally, Jacobian modulated gray matter values are referred to as gray matter volume, while unmodulated images are referred to as gray matter density maps (Eckert et al., 2006). The latter density maps are susceptible to poor registration as they reflect the proportion of gray matter relative to other tissue types within a region. Thus, here, we focus on gray matter volume estimates to investigate gray matter alteration.

2.6 Definition of search regions of interest

Given the known involvement of the MTL in AD-risk (den Heijer et al., 2006; C. D. Smith et al., 2007; Tondelli et al., 2012; Wierenga et al., 2014), a mask encompassing MTL structures, as defined on the MNI152 brain template, was created for use within the GMV and CBF analyses. Restricting the search space to a small number of a priori regions of interest (ROI) is recommended for smaller clinical samples to improve power and reduce an inflated false discovery rate (Poldrack et al., 2017). Further supporting our decision to restrict the search space to an a priori ROI, a recent study comparing voxel-based morphometry (VBM) to regional manual tracing methods found that restricting VMB analysis to anatomically defined ROIs not only did not detract from the usefulness of VBM, but in fact, complemented the semi-automated approach by revealing regional non-linear effects of age that would otherwise have gone undetected (Kennedy et al., 2009). As such, all analyses were restricted to our MTL mask, which combined the hippocampus and parahippocampal gyrus probabilistic labels from the

Harvard-Oxford atlas with the entorhinal cortex label (incorporating the perirhinal cortex) from the Juelich histological atlas.

2.6 Statistical analyses

T-tests were used to compare groups on age, years of education, whole brain resting CBF, whole brain GMV, vascular health measures, and cognitive variables. Chi-square tests were used to compare groups on sex and APOE status. Logistic regression was used to determine if age, education or scores on cognitive tests predicted RTG status.

A voxel-level independent samples *t*-test (3dttest++) was conducted in AFNI to contrast CBF values between groups within the MTL ROI. Analyses were adjusted for the effects of age and sex. Significance was determined by applying cluster-size correction derived from randomization of voxel-wise t-tests (via AFNI's Clustsim option in 3dttest++) and then feeding those randomized t-statistic maps into Monte-Carlo simulations directly for cluster-size threshold determination (via AFNI's 3dClustSim) to guard against false positives on data initially thresholded at a value of $p < 0.01$ (uncorrected). The Clustsim option added to the 3dttest++ command approach was developed in response to reports of inflated false positive rate (FPR) in fMRI group analysis tools (Eklund, Nichols, & Knutsson, 2016) and is recommended for use when t-tests from a univariate general linear model (GLM) are adequate for the group analysis in question (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Cox, Reynolds, & Taylor, 2016). Based on these simulations, it was determined that a minimum cluster volume of 270 μL (10 contiguous voxels) was required to correct for multiple comparisons at $p<0.01$ corresponding to a voxel-level threshold of $p<0.01$. A secondary exploratory whole-brain voxel-wise group comparison was also conducted. At the whole-brain level, a minimum cluster volume of 1098 μL (374 contiguous voxels) was required to correct for multiple comparisons at $p<0.01$ corresponding to a voxel-level threshold of $p<0.01$.

To compare groups on gray matter volume, a voxel-level GLM was applied using permutation based nonparametric testing (10,000 permutations) in FSL, correcting for multiple comparisons across space. The MTL ROI was then applied to the gray matter image from the study-specific template and groups were compared, adjusting for age and sex. Threshold-Free Cluster

Enhancement was used as a method for finding clusters in the data (Rajagopalan & Pioro, 2015) with thresholds set at $p < 0.05$, corrected.

To determine associations between CBF and GMV by group, CBF and GMV values were extracted from the whole brain and from clusters of significance, and regression models were employed in SPSS.

3. Results

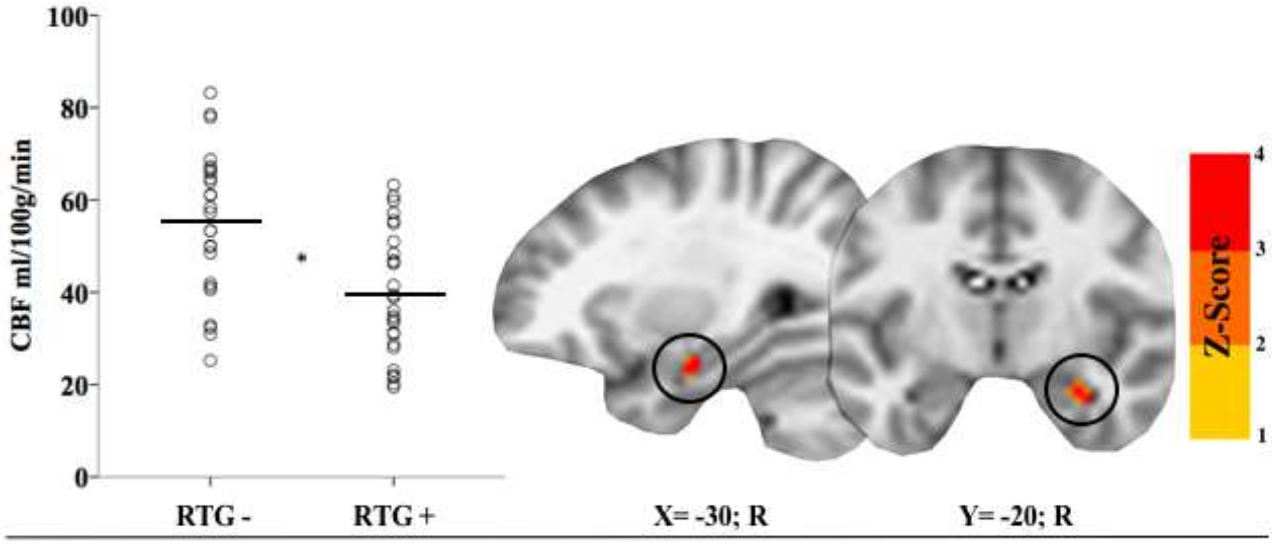
3.1 Group differences in assessment variables

Groups did not differ significantly on age, sex, years of education, APOE status, percent stroke risk, blood pressure, whole brain resting CBF, whole brain GMV, DRS total score, nor any of the other cognitive tests used to determine cognitive status (all *p*s > .05). Groups did not differ significantly on scores of remote famous face naming, nor did they differ on total scores of famous face naming. Groups only differed significantly on scores of recent famous face naming (see **Table 1**). Similarly, post-hoc logistic regression analyses demonstrated that RTG status was not predicted by age, education, APOE genotype, nor performance on any of the cognitive tests used to determine cognitive status (all *p*s >.05).

3.2 ROI group difference in CBF

A significant group difference in resting CBF was found in one cluster within the right hippocampus ($p<.01$, corrected). Compared to the RTG- group, those in the RTG+ group exhibited lower CBF (see **Figure 2**). Cluster location with coordinates, corresponding Z-value, and effect size is listed in **Table 2**.

Figure 2. ROI group difference in CBF



*Note: RTG= Ribot temporal gradient; CBF= Cerebral blood flow; R= Right; L= Left. Bars represent group mean. *Denotes significance at p<0.01, corrected.*

Table 2. ***ROI group difference in CBF***

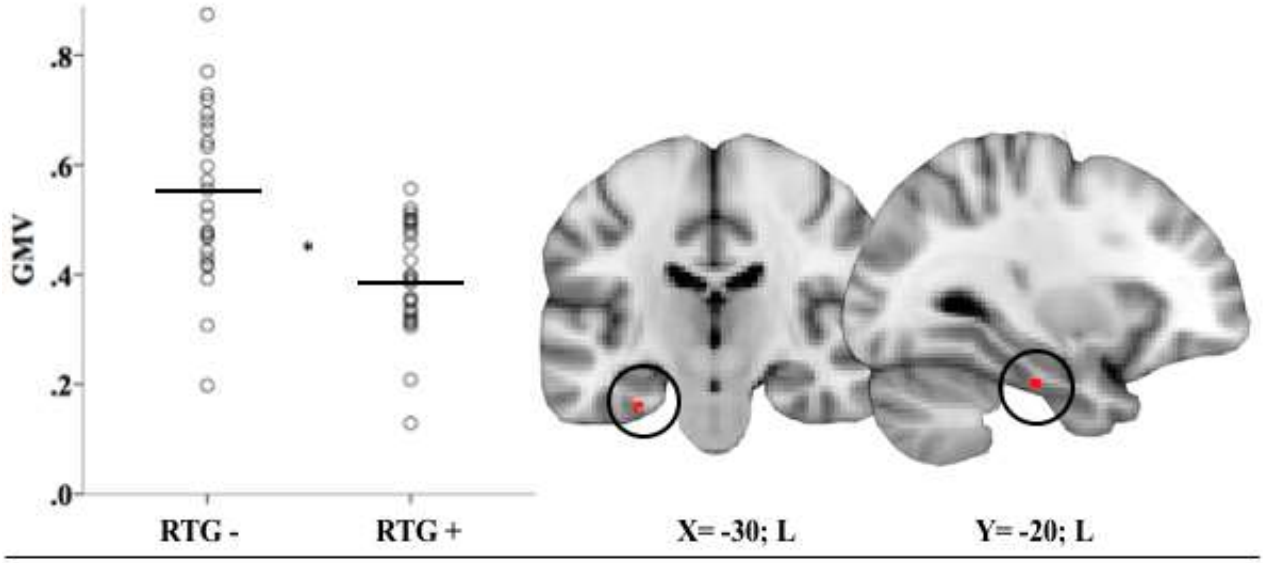
Cluster Location	Cluster Volume	X	Y	Z	Max z-value	Cohen's *d*
R Hippocampus	297 µL (11 voxels)	33	-12	-24	2.88	0.89

Note: ROI= Region of interest; CBF= Cerebral Blood Flow; R= Right; L= Left. X, Y, and Z coordinates represent the peak Z-value in MNI space.

3.3 ROI group difference in GMV

A significant group difference in GMV was found in one cluster within the left parahippocampal gyrus (p<.05, corrected). Compared to the RTG- group, those in the RTG+ group demonstrated lower GMV (see **Figure 3**). Cluster location with coordinates, corresponding z-value, and effect size is listed in **Table 3**.

Figure 3. ***ROI group difference in GMV***



*ROI=Region of interest; RTG= Ribot temporal gradient; GMV= Gray matter volume; R= Right; L= left. Bars represent group mean. *Denotes significance at p<0.05, corrected.*

Table 3. ***ROI group differences in GMV***

Cluster Location	Cluster Volume	X	Y	Z	Max z-value	Cohen's *d*
L parahippocampal gyrus	56 µL (7 voxels)	-30	-20	-26	0.956	0.27

Note: ROI= Region of interest; GMV= Gray matter volume; R= Right; L= Left; X, Y, and Z coordinates represent the peak Z-value in MNI space.

3.4 Exploratory analysis of whole brain group differences in CBF

Whole brain voxel-wise t-test results did not survive a per voxel $p < 0.01$ after correcting for multiple comparisons, requiring a cluster size of 374 contiguous voxels.

3.5 Associations between CBF and GMV

Associations between whole brain CBF and GMV by group, controlling for age and sex, were not significant (all *p*s > .05). When restricting analyses to clusters showing significant group differences in CBF and GMV, a significant association was found in the RTG+ group, whereby lower CBF within the right hippocampal cluster was associated with lower GMV within the left parahippocampal gyrus cluster ($\beta = 0.65$, $t = 2.56$, $p = .002$). The RTG- group did not show an

association between CBF and GMV within clusters that showed significant group differences ($p > .05$).

4. Discussion

Results showed that cognitively intact older adults who demonstrated better performance for naming of remote famous faces than recent famous faces exhibited lower MTL CBF and GMV compared to those who did not demonstrate this pattern of famous face naming performance. In other words, current findings demonstrate that those who exhibit a famous face naming RTG display brain patterns typically associated with age-related cognitive decline and AD-risk (i.e., lower MTL CBF and GMV). This suggests that those in the RTG+ group may be at higher risk for future cognitive decline than those in the RTG- group. This is the first study, to our knowledge, to demonstrate effects of a RTG for famous face naming on both CBF and GMV among a group of cognitively intact older adults. Given that the RTG- and RTG+ groups did not differ on other AD-risk variables (e.g., cognitive performance on other memory tasks, APOE genotype, age, education), results support the notion that the presence of a RTG may reflect an independent early cognitive risk factor sensitive to relative hypoperfusion and GMV reduction within regions associated with AD-risk.

Hypoperfusion within the RTG+ group, compared to the RTG- group, was observed in the right hemisphere of the brain (right hippocampus), while relative reductions in GMV were observed in the left hemisphere of the brain (left parahippocampal gyrus). While the current study did not test laterality directly, our GMV findings are consistent with existing evidence suggesting that AD-related changes tend to be more prominent in the left-hemisphere, and the CBF findings suggest that neurovascular changes in AD-risk may be less left-localized than previously believed. It is also possible that the left-sided asymmetry typically associated with AD-risk is specific to structural brain changes (GMV), rather than the functional changes reflected by CBF measurement. Given that our groups were wholly defined by famous face naming performance, findings are also concordant with evidence showing that the right temporal lobe plays a prominent role in processing person-based semantic knowledge (Joubert et al., 2006) and that recognition of familiar faces show a prevalent right lateralization (Gainotti, 2013).

Although the underlying mechanisms associated with the observed CBF differences between our groups are still unknown, other studies showing CBF alteration among those at risk for AD have interpreted these changes as responses to neurovascular damage. More specifically, CBF alteration is thought to reflect neurovascular adjustments to maintain oxygen availability within the tissue (Ostergaard et al., 2013). While groups did not appear to differ in terms of vascular health (e.g., percent stroke risk, blood pressure) or APOE genotype, it should be noted that the vascular health variables collected in the current study are somewhat crude and peripheral in nature. Furthermore, their association with neural function and demand is still largely unknown. As such, it is possible that within our cognitively normal sample, those in the RTG+ group are exhibiting early signs of neurovascular damage. Given that changes in brain structure are thought to represent expression of decreased synaptic density, neuronal loss, and cell shrinkage, our finding of 30% less gray matter within the left parahippocampal gyrus in those within the RTG+ group, further corroborates the notion of early brain changes within this group that have been associated with AD-risk.

The current findings are in line with those of a 2013 longitudinal study showing that a RTG for famous *name recognition* (rather than famous *face naming*) was associated with future cognitive decline. More specifically, results from this earlier study showed that cognitively normal older adults who demonstrated memory decline over an 18-month follow-up period exhibited poorer baseline performance for recognition of recent, but not remote famous names, compared to non-decliners and that the strength of the RTG during this task was associated with baseline hippocampal volume (Seidenberg et al., 2013). Our cross-sectional results complement this earlier longitudinal study through employment of a similar, but more difficult, famous face task that placed greater demands on lexical-semantic retrieval processes (e.g., generating names for famous faces rather than identifying written names as famous or not), and the combined collection of both functional and structural neuroimaging biomarkers. As such, our findings add to the literature demonstrating that a famous face naming RTG is sensitive to cross-sectional differences in brain function and structure that have been associated with AD and AD-risk, within a group of cognitively intact older adults.

In conclusion, the current findings support the notion that cognitively intact older adults who demonstrate a RTG during a famous face naming task exhibit relative decreases in resting CBF and GMV in the MTL, compared to those who do not demonstrate this pattern of performance. Given the role of the MTL in recent memory retrieval and the prominence of its early changes in AD pathophysiology, results suggest that individuals who demonstrate an RTG may be at greater risk for developing AD. Moreover, these results suggest that semantic knowledge deterioration may be one of the earliest detectable cognitive changes associated with aging and/or AD-risk. More broadly, findings also support the role of the hippocampus in memory consolidation and add to an accumulation of evidence supporting links between vascular dysregulation (hypoperfusion), structural change, and cognitive aging. Elucidating the early vascular and cognitive changes that accompany AD risk could lead to the identification of vasoprotective treatments with the potential to delay or prevent the onset of AD. Although future longitudinal research is needed to determine whether those who demonstrate a famous face naming RTG will go on to develop AD, the current results support the famous face naming RTG as a valid construct to possibly detect those who show brain perfusion and atrophy patterns similar to those seen in AD-risk. Given the ease of use, low-cost, and non-invasive nature of the famous face naming task, it provides a promising area of future research. Integrating the famous face naming task with other known markers of preclinical AD, such as cerebral spinal fluid or PET imaging biomarkers of amyloid-beta and tau, could lead to earlier and more accurate identification of those who would likely benefit from treatments aimed at preventing cognitive decline and AD.

4.1 Strengths and limitations

Limitations of the current study include a relatively small sample size of 52, which may have affected the power to detect group differences, and a correlational design, which restricted our ability to draw causal conclusions from our results. Furthermore, exploring the RTG variable dichotomously may have imposed some limitations, as information is typically lost when cases below the threshold are treated as equivalent. However, dichotomization of explanatory variables does not necessarily cause a decrease in measured strength of associations (Farrington & Loeber, 2000). More importantly, dichotomization supports a “risk factor” approach to the explanation and prediction of psychiatric or cognitive disorders and facilitates the identification of at-risk individuals who may possess several risk factors, which may be especially useful in targeted

prevention efforts (Farrington & Loeber, 2000; Kraemer, 1997). It is also important to note that the famous face naming task was performed outside the scanner (following the MRI scan). Assessing functional changes in CBF during famous face naming within the scanner might provide a more direct assessment of this relationship. The cross-sectional nature of this study and the cognitively normal status of the sample also limited our ability to determine whether the association between the famous face naming RTG and CBF represent normal or pathologic processes. Finally, the generalizability of these results may be impacted by the relatively high average level of education within our sample. Future longitudinal studies with large and diverse samples of cognitively normal adults and those with MCI are needed to replicate the current findings and determine if the famous face naming task can predict progression from normal aging to MCI and AD. Moreover, further investigation of this construct and its neurobiological correlates among larger samples is needed in order to determine optimal clinical cutoff points for the RTG during famous face naming as a marker of AD-risk.

Despite these limitations, the current study benefited from the use of non-invasive MRI to measure CBF and GMV, the availability of several cognitive test performances to characterize cognitive status, and the combined measurement of both structural (GMV) and functional (CBF) neuroimaging biomarkers, which allowed us to better interpret CBF alteration in the context of risk for cognitive decline and AD. While some AD-related CBF studies have failed to exclude or control for psychiatric, medical, or demographic factors that might contribute to cognitive, CBF, or GMV changes, the current study excluded any subjects with a history of severe head injury, uncontrolled hypertension, or a diagnosis of learning disability, attention deficit disorder, mood disorder, or substance abuse. Moreover, we statistically adjusted for age and sex, and groups were equivalent on APOE ε4 genotype and general vascular health, making this a well-characterized and somewhat homogeneous sample of older adults, reducing confounds generally found in the literature.

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Highlights

- A temporal gradient during famous face naming was evident in some older adults
- The temporal gradient was linked to lower cerebral blood flow and gray matter volume
- Famous face naming ability may be sensitive to brain changes in Alzheimer's disease