

Computerized Cognitive Training in Mild Cognitive Impairment: Findings in African Americans and Caucasians

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Abstract

BACKGROUND: African Americans with MCI may be at increased risk for dementia compared to Caucasians. The effect of race on the efficacy of cognitive training in MCI is unclear.

METHODS: We used data from a two-site, 78-week randomized trial of MCI comparing intensive, home-based, computerized training with Web-based cognitive games or Web-based crossword puzzles to examine the effect of race on outcomes. The study outcomes were changes from baseline in cognitive and functional scales as well as MRI-measured changes in hippocampal volume and cortical thickness. Analyses used linear models adjusted for baseline scores. This was an exploratory study.

RESULTS: A total of 105 subjects were included comprising 81 whites (77.1%) and 24 African Americans (22.8%). The effect of race on the change from baseline in ADAS-Cog-11 was not significant. The effect of race on change from baseline to week 78 in the Functional Activities Questionnaire (FAQ) was significant with African American participants' FAQ scores showing greater improvements at weeks 52 and 78 ($P = 0.009$, $P = 0.0002$, respectively) than white subjects. Within the CCT cohort, FAQ scores for African American participants showed greater improvement between baseline and week 78, compared to white participants randomized to CCT ($P = 0.006$). There was no effect of race on the UPSA. There was no effect of race on hippocampal or cortical thickness outcomes.

CONCLUSIONS: Our preliminary findings suggest that web-based cognitive training programs may benefit African Americans with MCI at least as much as Caucasians, and highlight the need to further study underrepresented minorities in AD prevention trials. (Supported by the National Institutes of Health, National Institute on Aging; ClinicalTrials.gov number, NCT03205709.)

Key words: Race, ethnicity, health disparities, brain health, Alzheimer's.

Introduction

African American communities are disproportionately affected by Alzheimer's disease (AD) with the development of clinical AD being two times more likely than in Caucasians (1-5). Mild cognitive impairment (MCI) is a condition that precedes dementia, and those with amnesic MCI are at an increased likelihood of developing AD (6). African Americans may be at increased likelihood of developing MCI (7), and may experience a faster rate of cognitive decline, when diagnosed with MCI, in comparison to other races (1-5, 8). Although the reasons behind this disparity are not fully known, possible explanations range from racial differences in socio-economic factors such as access to education, lifestyle factors, genetics, cardio-metabolic disease risks as well as neurobiological processes such as cortical amyloid deposition (1-5, 8-14).

There has been increased interest in the use of computerized cognitive training through web or phone-based video games (CCT) as a therapeutic for mild cognitive impairment, as it has shown the potential to improve cognitive domains in older patients with both normal and impaired cognition (15-19). Additionally, further studies have demonstrated improvements in gait, cognitive processing, delayed memory, attention, and executive functioning in MCI patients engaging with CCT interventions (15-26). In a 78-week, controlled trial, we recently reported that computerized crossword puzzle training (CPT) was superior to computerized games in improving cognition and daily functioning and slowing atrophy in MCI patients (18).

Until a few years ago, clinical trials exploring cognitive benefits due to online brain training have largely been completed in Caucasians and Asians (20-26), with many studies failing to include data on the racial characteristics of the sample. In one systematic review of 31 studies on cognitive training, only 12 were found to report on the racial background of study samples (27) with the

inclusion of non-white participants relatively limited to 75% of these studies. One study of a cognitive training program specific to African Americans at risk of falling found a clinically meaningful improvement in balance and gait (28). Another study, a sub-group analysis of the benefit of cognitive training in minority elder adults enrolled in the SeniorWISE trial (29), found that African Americans and Hispanic-identifying individuals had greater gains on the visuospatial memory test than white participants. Furthermore, African American participants improved in instrumental activities of daily living over the course of the study (29). To our knowledge, there are no other studies that have examined Caucasian versus African American differences in cognitive brain training outcomes in older adults.

The aim of this paper was to use data from a 78-week randomized clinical trial of cognitive training in MCI (Cognitive Training and Neuroplasticity in Mild Cognitive Impairment trial [COG-IT]) to examine differences between Caucasians and African Americans in cognitive, functional and brain atrophy outcomes.

Methods

Study Design and Subjects

The COG-IT study design (18) and primary findings have been described elsewhere (18, 30). All enrolled participants provided written consent, and the study was approved by each site's respective institutional IRBs. MCI participants were recruited using criteria described previously (18) and stratified by age and severity. Participants were then randomly assigned to either CCT or CPT training arms for this 78-week, single-blind, two-site study. The training was delivered through Lumosity, a web-based platform. In both study arms, participants completed four 30-minute training sessions per week during the first 12 weeks. After this period, participants completed booster sessions at predetermined time points. Participants were scheduled for five in-clinic visits (Weeks 0, 12, 32, 52, and 78) to complete one 30-minute training session and neuropsychological testing. At baseline and at week 78, participants completed a brain MRI scan for assessment of cortical thickness and hippocampal volume (18). Race was self-identified by participants. Of the 107 participants from the original study that met the trial's inclusion criteria, 105 who were racially categorized as African American or Caucasian (white) were included in the analysis, irrespective of ethnicity. Data were available from four groups: African American participants assigned to CPT, African American participants assigned to CCT, white participants assigned to CPT, and white participants assigned to CCT.

Cognitive, Functional and MRI Outcomes

Our analysis evaluated the effect of race on cognitive, functional, and MRI outcomes. The cognitive outcome

was the change in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog-11) total score from baseline to week 78 (18). Functional outcomes included the change from baseline to week 78 on the University of California, San Diego Performance-Based Skills Assessment (UPSA) and the informant-reported Functional Activities Questionnaire (FAQ) (18). The UPSA measures performance in everyday activities such as financial and planning skills, while the FAQ assesses activities of daily living, including the participant's ability to shop, manage bills, and meal preparation. MRI outcomes, collected via imaging at baseline and at week 78, were changes in cortical thickness and hippocampal volume. FAQ and UPSA were selected to include one informant based and one performance based measure, respectively. The MRI sample was slightly smaller due to the exclusion of subjects who failed imaging QC criteria (18); (Table 4).

Statistical Analysis

Using Wilcoxon's rank sum test for continuous variables and Fisher's exact test for categorical variables, baseline demographic, cognitive, and imaging data were compared between African American and white participants. As such this was an exploratory, secondary, data analysis from the COG-IT study. Linear mixed-effects models were employed to evaluate the effect of race, treatment, and their interaction on change in the cognitive and functional outcome measures (baseline minus week 78). Linear regression models evaluated the effect of race on MRI outcomes, including the change from baseline to week 78 (i.e., baseline minus week 78), on the hippocampal volume and cortical thickness. Both the linear mixed effects models and linear regression models were adjusted for baseline values of the outcome measures, site, sex, age, and years of education.

Results

Baseline Characteristics of Participants

A total of 105 subjects were included, comprising 81 whites (77.1%) and 24 African Americans (22.8%) (Figure 1). African American participants were on average, eight years younger than white participants (Table 1) and had fewer years of education. There was also a greater percentage of males in the white cohort. Although there was a numerically greater percentage of EMCI participants among African Americans than whites, this was not statistically significant. Figure 1 depicts the flow of subjects throughout the study. Additional baseline comparisons of neuropsychological tests and brain morphometric features are shown in Table 1.

Table 1. Baseline Characteristics of Study Sample

Variable	White	African American	p_value
Sample size	N=81	N=24	.
Male / Female (%)	51/49	17/83	0.004*
Education	17.07 ± 3.30	15.42 ± 2.26	0.014*
Age	73.09 ± 8.80	65.71 ± 5.59	<0.001*
EMCI ¹ / LMCI ² (%)	37/63	54/46	0.160
ApoE ³ e4 (positive) (Y/N) (%)	47/53	38/62	0.488
Baseline MMSE ⁴	26.91 ± 1.67	27.13 ± 1.62	0.449
Baseline ADAS-Cog ⁵	9.75 ± 3.74	9.17 ± 2.24	0.742
Baseline FAQ ⁶	3.58 ± 4.07	2.42 ± 3.60	0.217
Baseline UPSA ⁷	80.41 ± 11.31	83.08 ± 10.75	0.326
baseline hippocampal volume (mm ³)	3032 ± 422.3	3040 ± 344.3	0.952
baseline cortical thickness (mm)	2.34 ± 0.10	2.37 ± 0.09	0.162
Oral Cholinesterase Inhibitor use (Y/N) (%)	10/90	25/75	0.083
Memantine use (Y/N) (%)	4/96	0/100	1.000

1. EMCI, early mild cognitive impairment; 2. LMCI, late mild cognitive impairment; 3. ApoE4, apolipoprotein E gene; 4. MMSE, Mini-Mental State Examination; 5. ADAS-Cog, Alzheimer’s Disease Assessment Scale-Cognitive subscale; 6. FAQ, Functional Activity Questionnaire; 7. the University of California, San Diego Performance-Based Skills Assessment

Figure 1. Flow of Subjects through the study

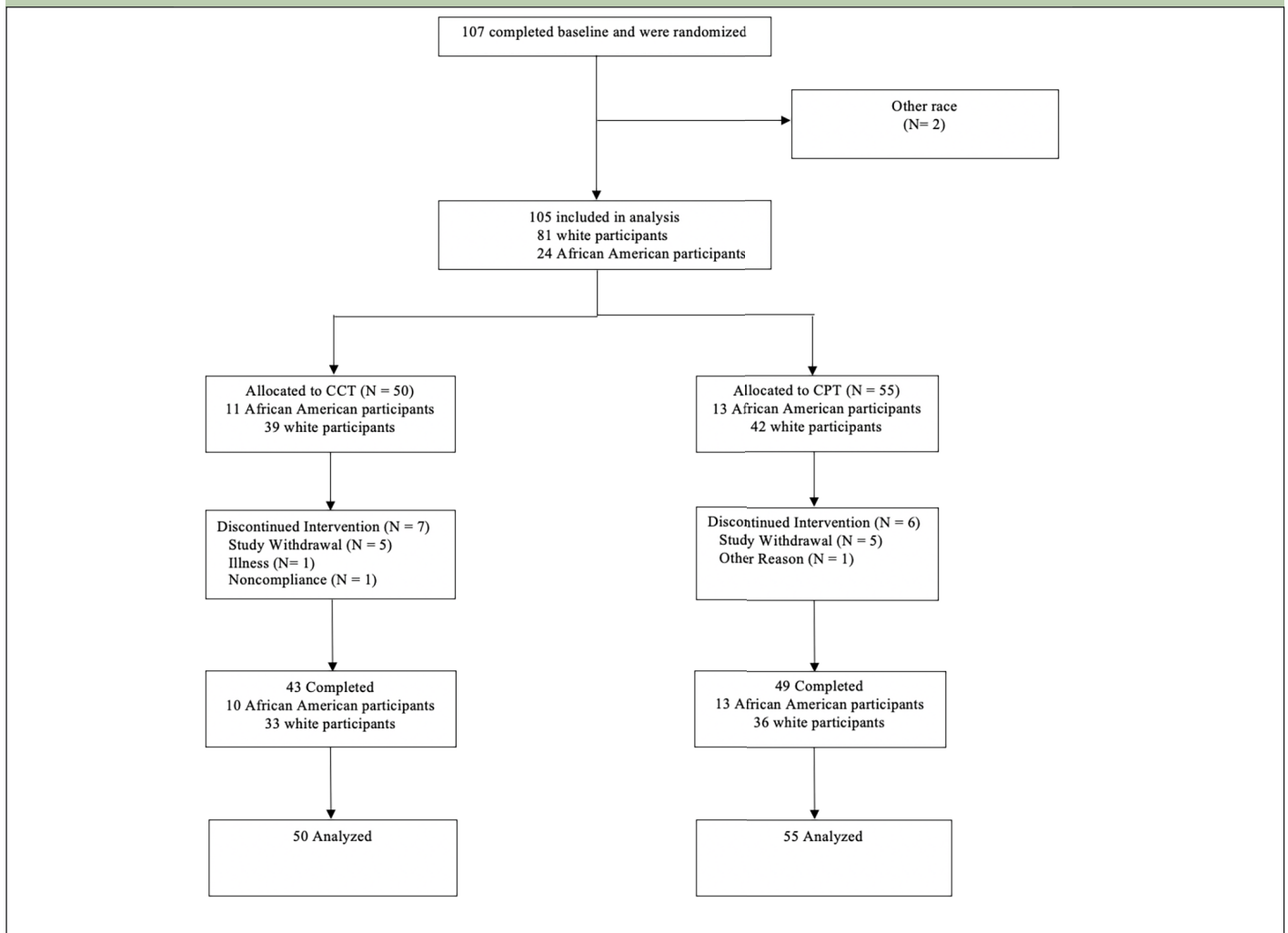
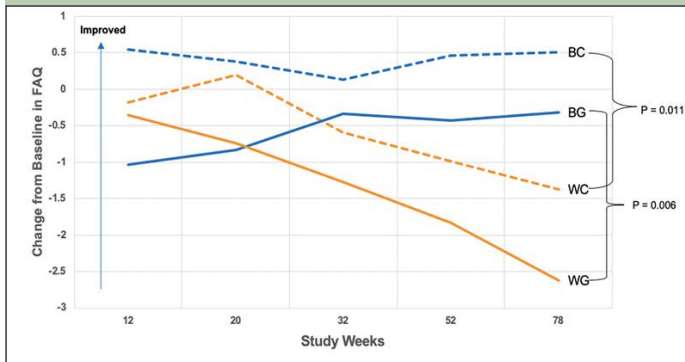


Table 2. Effect of Race on ADAS-Cog-11 Outcomes

Visit	Race 1	Treatment 1	Race 2	Treatment 2	Adj LS Mean Difference adj. \pm SE	P
Week 78	African American	CPT ¹	white	CPT	-0.13 \pm 1.16	0.910
Week 78	African American	CCT ²	African American	CPT	-1.81 \pm 1.49	0.226
Week 78	African American	CCT	white	CCT	-0.54 \pm 1.32	0.681
Week 78	white	CCT	white	CPT	-1.40 \pm 0.82	0.089

1. CPT, crossword puzzle training; 2. CCT, computerized cognitive training. LS mean differences are depicting baseline minus week 78. None of the comparisons were significant. Please see text for details.

Figure 2. Effect of Race on Functional (FAQ) Outcome by Treatment

BC = African American participants randomized to CPT; BG = African American participants randomized to CCT; WC = white participants randomized to CPT; WG = white participants randomized to CCT. The horizontal axis illustrates study time points going from Week 12 to Week 78, and the vertical axis depicts the mean change on the FAQ from baseline to Week 78, with a higher value on the y-axis meaning improvement. At week 78, BC had a higher mean change in FAQ scores than WC. Similarly, BG experienced a greater improvement in FAQ than WG at week 78.

Cognitive and Functional Outcomes

The cognitive outcome – change in ADAS-Cog score from baseline to week 78 – did not differ significantly between treatments within each race cohort ($p=0.226$ for African Americans, $p=0.089$ for white), nor between races within each treatment group ($p=0.910$ for CPT; $p=0.681$ for CCT; Table 2). There was an effect of race on the change in FAQ from baseline to week 78. Irrespective of treatment intervention, African American participants' FAQ scores were consistent over the course of the study, with notable improvement from week 32 to week 78. Conversely, white participants worsened substantially, with statistically significant differences between the two cohorts at weeks 52 and 78 ($P = 0.009$, $P = 0.0002$, respectively). Within the CCT cohort, FAQ scores for African American participants improved between baseline and week 78, compared to white participants randomized to CCT (Figure 2, Table 3). This difference was also notable in the CPT cohort (Figure 2, Table 3). Within the white cohort, the CCT group worsened more than CPT patients (Table 3). There was no effect of race on the UPSA.

MRI Outcomes

There was no effect of race on the MRI outcomes. Regarding hippocampal volume change, there were no significant between African American and white participants. Within the white cohort, participants randomized to CCT exhibited a greater decrease in hippocampal volume than those in the CPT intervention from baseline to week 78 (Table 4). Similarly, there was no effect of race on cortical thickness. Within the white cohort, those randomized to CCT showed a greater decrease in cortical thickness from baseline to week 78 than those randomized to CPT (Table 4).

Discussion

To our knowledge, this is the first study to examine the effects of race on the cognitive, functional, and MRI outcomes in a randomized trial of MCI subjects engaging in either CCT or CPT. We did not find an effect of race on the cognitive or MRI outcomes but found that African American participants showed greater functional improvements on an informant-reported scale (FAQ) over the 78 weeks compared to white participants. Combined with our prior finding of the beneficial effects of crossword puzzle training (18), these initial data suggest that African Americans are likely to benefit at least as much as Caucasians from such training.

The mechanism(s) underlying the effect of race on functional outcomes is unknown. Our findings that African American participants received greater functional benefits (on FAQ) than Caucasians from computerized cognitive training appears concordant with a prior trial that also showed greater improvements of IADLs in African American participants (26) - suggesting they may represent a true differential functional benefit. Our observation of racial differences in outcomes on the informant-based FAQ but not on the performance-based UPSA as well as the worsening seen in Caucasians was unexpected. A study of 4284 MCI participants and their informants from the National Alzheimer's Coordinating Center Uniform Data Set found that FAQ scores were rated lowest (less impaired) among Black/African American informants as compared to all other racial/ethnic groups (31). This study also found that FAQ scores were higher among informants with higher levels of

Table 3. Effect of Race on FAQ Outcomes

Visit	Race 1	Treatment 1	Race 2	Treatment 2	Adj LS Mean Difference adj. \pm SE	P
Week 78	African Americans	CPT ¹	white	CPT	1.88 \pm 0.73	0.011*
Week 78	African Americans	CCT ²	African Americans	CPT	-0.83 \pm 0.94	0.378
Week 78	African Americans	CCT	white	CCT	2.30 \pm 0.83	0.006*
Week 78	white	CCT	white	CPT	-1.25 \pm 0.52	0.017*

1. CPT, crossword puzzle training; 2. CCT, computerized cognitive training. LS mean differences are depicting baseline minus week 78. Within the CPT cohort, African Americans showed significant improvement in FAQ outcomes at week 78 than white participants. At week 78, white participants randomized to CPT significantly improved on FAQ outcomes than white individuals randomized to CCT.

Table 4. Changes in Hippocampal Volume and Cortical Thickness across race and study intervention at week 78

Variable	Race 1	Treatment 1	Race 2	Treatment 2	Adj LS Mean Difference adj. \pm SE	P
Hippocampal Volume	African American	CCT ¹	African American	CPT ²	18.138 \pm 33.942	0.593
	African American	CCT	white	CCT	-19.80 \pm 30.792	0.520
	African American	CPT	white	CPT	6.374 \pm 27.614	0.817
	white	CCT	white	CPT	44.311 \pm 20.604	0.032*
Cortical Thickness	African American	CCT	African American	CPT	0.013 \pm 0.020	0.511
	African American	CCT	white	CCT	-0.012 \pm 0.018	0.498
	African American	CPT	white	CPT	0.002 \pm 0.017	0.909
	white	CCT	white	CPT	0.027 \pm 0.012	0.027*

¹CCT, computerized cognitive training; ²CPT, crossword puzzle training. LS mean differences are depicting baseline minus week 78. There was no effect of race on hippocampal volume. However, within the white cohort, those randomized to CPT had significant improvements in hippocampal volume and cortical thickness at week 78 than those randomized to CCT.

education (31). Another study found that black caregivers generally overrated, and white caregivers underrated, their care recipient's cognitive ability (32). Hence, in addition to true differences, there is also the possibility of an informant bias by race and educational level.

Overall, these findings must be interpreted as preliminary, as the two ethnic groups in the sample were not equivalent in size, and at baseline, the proportion of EMCI was numerically (but not statistically) higher in African American participants than in white participants. Additionally, we did not have enough statistical power to test other moderator variables by race such as engagement, socioeconomic status, genetics, or medical comorbidities. Further studies in larger samples are needed to replicate and elucidate possible mechanisms.

The strengths of our study are the use of data from prospective clinical trial, rigorous selection of study subjects, relatively low attrition rates, long study duration of 78-weeks, use of well-validated outcomes measures and study design comparing two cognitive training strategies in wide use by older adults. Limitations including the relatively small sample size, failure to study other races, exploratory nature of analyses and the lack of a control condition. Hence, our findings must be interpreted in this context and must be viewed as preliminary pending replication.

To summarize, this is the first study to examine the effect of race on cognitive, functional, and imaging

outcomes in MCI participants following two types of computerized cognitive training. Our study suggests that African Americans are likely to receive at least as much benefit as white participants and highlights the need to further study underrepresented people in AD preventive trials.

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Competing interest: DPD has received research grants from the National Institute on Aging and the Alzheimer's Association and has served as a consultant on scientific advisory boards to Acadia, Corium, Genentech, TauRx, and a DSMB for BioXcel. PMD has received research grants from the National Institute on Aging, DARPA, DOD, ONR, Salix, Avanir, Avid, Cure Alzheimer's Fund, Karen L. Wrenn Trust, Steve Aoki Foundation, and advisory fees from Apollo, Brain Forum, Clearview, Lumos, Neuroglee, Otsuka, Verily, Vitakey, Sermo, Lilly, Nutricia, and Transposon. PMD is a co-inventor on patents for the diagnosis or treatment of Alzheimer disease and a patent for infection detection. PMD owns shares in several biotechnology companies whose products are not discussed here. Other authors have received grant support from NIH and report no other competing interests. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org. A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Ethical standards: The study was approved by all site IRBs and all subjects gave written informed consent.

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