

Featured Article

Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes

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Abstract

Introduction: There is a substantial interest in identifying interventions that can protect and buffer older adults from atrophy in the cortex and particularly, the hippocampus, a region important to memory. We report the 2-year effects of a randomized controlled trial of an intergenerational social health promotion program on older men's and women's brain volumes.

Methods: The Brain Health Study simultaneously enrolled, evaluated, and randomized 111 men and women (58 interventions; 53 controls) within the Baltimore Experience Corps Trial to evaluate the intervention impact on biomarkers of brain health at baseline and annual follow-ups during the 2-year trial exposure.

Results: Intention-to-treat analyses on cortical and hippocampal volumes for full and sex-stratified samples revealed program-specific increases in volumes that reached significance in men only (P 's $\leq .04$). Although men in the control arm exhibited age-related declines for 2 years, men in the Experience Corps arm showed a 0.7% to 1.6% increase in brain volumes. Women also exhibited modest intervention-specific gains of 0.3% to 0.54% by the second year of exposure that contrasted with declines of about 1% among women in the control group.

Discussion: These findings showed that purposeful activity embedded within a social health promotion program halted and, in men, reversed declines in brain volume in regions vulnerable to dementia.

Clinical Trial Registration: NCT0038.

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Keywords:

Randomized controlled trial; Brain aging; Social activity; Cognitive activity; Physical activity; Neuroimaging; Cortical volume; Hippocampus; MRI

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1. Introduction

Research over the last decade has shown that increased physical activity impacts cognitive aging and dementia risk [1]. Although the mechanisms related to the benefits of physical activity remain to be understood [2], evidence for physical exercise, particularly in enriched environments, suggests that exercise alters the functional and structural properties of the hippocampus, a brain region critical to learning and memory throughout the life course [2,3], vulnerable to aging [4,5], and implicated in risk for dementia [6]. In older adults, smaller and shrinking hippocampal volumes have been correlated with decline in memory performance and with increased risk for Alzheimer's disease (AD) [7–9]. Studies have reported an inverse association between self-reported physical activity and age-related decreases in mediotemporal lobe volume [10] and with reduced declines in hippocampal volume for 9 years [11]. In a 1-year, randomized controlled trial (RCT) of exercise in healthy older adults, walking led to a 2% increase in hippocampal volume relative to a 1% decrease in volume in the stretching and toning control group [12]. However, in comparison to exercise studies, neuroimaging studies examining how physical activity in the daily lives of older adults impacts brain volume have been limited [11,13,14].

Likewise, although a wealth of evidence shows that cognitive and social [15–17] activities reduce rates of cognitive decline and risk for dementia, similar evidence for their impact on rates of brain atrophy has been largely inferred from studies in younger adults [18], aging animal models [19–21], and indirectly from cognitive training interventions [22,23]. Animal studies of aging provide the most direct evidence that engagement in physical, cognitive, and social activity may yield measurable benefits in the hippocampus. A number of RCTs have emerged, integrating the findings given previously to examine whether multimodal, physical, cognitive, and social activity impacts cognition [24–26], but we are aware of no published large-scale, RCTs examining the impact of multimodal, real-world activity on brain volume and rates of age-related brain atrophy.

Experience Corps[®] (EC) represents one such model of multimodal activity embedded within a social health promotion model of high-intensity volunteer service. EC is a community-based program in which older adults volunteer in public schools to improve the academic performance of children in underserved urban areas by harnessing retired adults' time, skills, and wisdom to volunteer in teams in neighborhood elementary schools as mentors of children in grades Kindergarten through third grade for 15 hours a week over an academic year [27–32]. We demonstrated that, through service, volunteers showed increases in physical, cognitive, and social activities [28], suggesting the possibility that it might be a real world example of how increases in these activities might lead to better

cognitive health and reduced risk for dementia [33]. In a pilot trial, we therefore compared participants in the EC program to wait-list controls and found short-term gains in a component of executive functioning and memory, particularly among those with poor executive functioning at baseline [34]. A second, smaller functional magnetic resonance imaging study [35] in women extended these findings and showed increases in neural activity in prefrontal regions that support executive functions in EC participants vs. controls. These pilot results suggested the potential of real-world, activity-based interventions for increasing plasticity in age-vulnerable regions of the brain in older persons [35].

The pilot findings, mentioned previously, were among the data that served as the basis for a large-scale RCT entitled the Baltimore Experience Corps Trial (BECT) [32] and a simultaneous nested Brain Health Substudy (BHS). The BHS was designed to extend the results observed in pilot studies of primarily [34], and solely [35], female volunteer samples by recruiting a sufficient number of men to allow for the formal evaluation of mechanistic benefits of volunteer service to men and women [36,37], given sex differences in brain morphology and risk for age-related neuropathologies, including AD [38–40] and vascular dementia [41], and given sex differences in the association between exercise and neurocognition [9].

Here, we evaluated the effectiveness of 2 years of exposure to Experience Corps, a productive social engagement intervention, on brain volume in a subset of participants randomized to the BHS within the BECT. The BECT represents an effort to design meaningful, socially valuable roles for older adults that will: (1) attract and engage a larger proportion of older adults; (2) demonstrate the benefits of an aging society by helping a younger generation (i.e., improving elementary school education); and (3) serve as a vehicle for enhancing physical, cognitive, and social activity in sociodemographically diverse populations [28] to thereby promote neurocognitive health among those at greatest risk for health disparities [28,42]. Here, we evaluated whether the Experience Corps program mitigated, or even reversed, rates of age-related brain atrophy, as measured by cortical and hippocampal volumes.

2. Methods

2.1. Participants

The BECT is a sex-stratified RCT designed to evaluate the effectiveness of the Experience Corps[®] (EC) high-intensity, senior service volunteer program on the health of older adults, the school's climate, and children. The trial is described in greater detail elsewhere [32]. Briefly, the EC Baltimore program in elementary schools is designed to support both the academic success of children in grades kindergarten through third grade and to promote the health of older volunteers by increasing their physical, social, and cognitive activity. The nested BHS simultaneously recruited eligible

participants before randomization to evaluate the benefits of the program on their brain and biological health. From January 2006 to December 2009, 702 eligible participants were randomized to either the EC program or referred to a low-activity control. Simultaneously, 123 individuals were enrolled in the BHS. Eligibility criteria included: (1) being 60 years of age or older; (2) English speaking; (3) clearance on the criminal background check; (3) minimum sixth grade reading level on the Wide Range Achievement Test [43], and; (4) Mini-Mental State Examination (MMSE) score ≥ 24 [32,44]. Additional criteria for enrollment in the BHS have been described previously [35] and included: (1) right-hand dominance; (2) being free of a pacemaker or other ferrous metals in the body; and (3) no history of brain cancer, brain aneurism or stroke in the prior year. Self-reported health was assessed on a scale of 1 (Excellent) to 5 (Poor) and participants reported if their doctor told them they had hypertension or diabetes. As noted previously, the BHS stratified randomization by sex to allow for stratified comparisons.

During BECT randomization, 123 participants were invited to enroll in the nested BHS, as detailed in the Consolidated Standards of Reporting Trials (CONSORT) (Fig. 1). The final baseline sample included 111 participants. Excluded participants did not vary significantly from included participants in age, MMSE, sex, or education ($P_s > .05$). Additionally, BHS participants did not differ significantly from participants in the larger BECT in age, MMSE, self-reported health, and education ($P_s > .05$). BHS study visits were conducted at baseline, 12- and 24-month follow-ups in conjunction with the BECT. The study

was approved by the Johns Hopkins Institutional Review Board and all participants provided written, informed consent.

2.1.1. Intervention

Experience Corps volunteers received 5 days (30 hours) of formal training conducted by the staff of the Greater Homewood Community Corporation, the community-based partner in trial and program implementation. Training includes lecture, discussion, exercises, role plays, and handouts designed to provide necessary skills in (a) orientation to the school environment; (b) working with today's children, and their needs; (c) overview of roles for volunteers in the school; (d) basic skills necessary to perform roles; and (e) what they can and cannot do as EC volunteers in schools (i.e., they do not run a class, either with or in the absence of a teacher, and their roles are to meet major unmet needs for children's success). A secondary purpose of training is to promote a sense of community among volunteers, assign them into teams who will work in a school together, and to train them in teamwork. Training culminates in a formal graduation ceremony attended by local dignitaries. Those randomized to the wait-list control arm were referred to the Baltimore City Commission on Aging and Retirement Education for other low-activity volunteer opportunities in Baltimore City; these were selected to be of short duration and of low time demand, such as volunteering at health fairs, city festivals, and senior center events. Controls were wait-listed for participation in EC after 2 years, if interested.

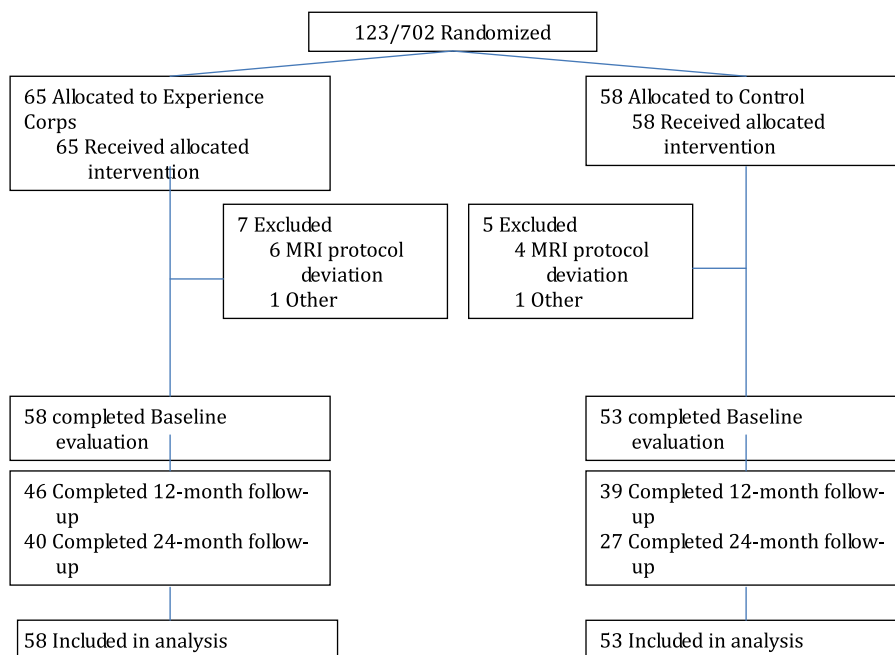


Fig. 1. CONSORT diagram summarizing Baltimore Experience Corps Trial participants' randomization into the Brain Health Substudy.

2.2. Brain magnetic resonance imaging acquisition

Magnetic resonance imaging (MRI) scans were collected at baseline and at two subsequent annual visits (12- and 24-month follow-ups). All high-resolution T1-weighted brain MRI data were collected on a 3.0T Phillips scanner (Best, the Netherlands) using magnetization-prepared rapid gradient echo (MP-RAGE) with repetition time (TR) = 8 ms, TE = 3.6 ms, matrix size = 256 × 256, and the field of view = 256 × 256 mm. Two hundred slices were contiguous with slice thickness of 1 mm. All images were processed using Free Surfer version 5.1.0 [45], a program which allows for longitudinal analysis and offers good test-retest reliability [46,47]. Details of the procedures are published elsewhere [48,49]. Preprocessing included motion correction, nonuniform intensity normalization, and automated removal of nonbrain tissue. All processed images were visually inspected and manually corrected, as needed, by blinded reviewers. Interrater reliability for images requiring manual correction was high (interclass correlations >0.95) for cortical volume, or the sum of cortical white and gray matter volumes, and bilateral hippocampal volumes. Both measures were adjusted for intracranial volume (ICV) and reported in mm³.

To assess changes in brain volumes, we used Free Surfer [46] to incorporate within-subject correlations across observations. All time points were first processed cross-sectionally, as described previously. Then, an unbiased template image [50] was created from three time points using robust, inverse consistent registration [48]. This template image served as an initial estimate for the segmentation and surface reconstruction and all follow-up measurements were registered to this template to ensure unbiased analysis, thereby reducing variability and increasing the stability of all longitudinal analyses [46].

2.3. Memory measure

Verbal memory was measured by the Rey Auditory Verbal Learning Test (RAVLT) [51]. The RAVLT is widely used to measure memory in older adults [52] with good validity and reliability [53,54]. The RAVLT is comprised of a list-learning test, an interference test, and recall tests. Participants were read and recalled words from a 15-word list, five consecutive times. The target list was followed by one learning trial of an interference list and then recall of the original target list (short delay).

2.4. Statistical analysis

At baseline, intervention and control groups were comparable in age, MMSE, years of education, self-reported health, and MRI volumes (Table 1) (P s > .05). Men and women were comparable on the variables, mentioned previously. Women in the EC program tended to report more hours (615) than men in the program (459.4) but this group difference was not significant (P > .10), due in part, to vari-

Table 1

Baseline characteristics of Brain Health Study participants by intervention status

Characteristics	Intervention	Control	Total
	(n = 58)	(n = 53)	(n = 111)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	67.7 (6.2)	66.7 (5.9)	67.2 (6.1)
Sex (% male)	27.6	30.2	28.8
MMSE	28.4 (1.4)	28.3 (1.5)	28.3 (1.5)
score (max = 30)			
RAVLT short delay	6.6 (2.9)	6.5 (2.6)	6.6 (2.7)
(max = 15)			
Ethnic group (%)			
African American and Other	91.4	96.2	93.7
White	8.6	3.8	6.3
Education (yrs)	14.1 (2.9)	13.5 (2.6)	13.8 (2.8)
Self-reported health	2.4 (0.8)	2.5 (0.9)	2.5 (0.8)
(1 = excellent; 5 = poor)			
Total exposure hours	562.8 (466.5)	0	
Brain volumes (adjusted for ICV)			
Cortical volume (mm ³)	937,214.9	929,501.9	933,532.13
Hippocampal volume (mm ³)	6636.2	6563.8	6601.63

Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; ICV, intracranial volume.

NOTE. There were no significant differences between groups (at P < .05), with the exception of exposure.

ation. The primary MRI outcomes were cortical volume and hippocampal volume. Total hippocampal volume was obtained by summing volumes for the left and right hemispheres.

All analyses were performed using an intention-to-treat (ITT) design. Mixed effects models with random intercept were adjusted for covariates, ICV, age, centered at the mean age of 67 years, and education, given previous evidence that these variables have strong associations with brain and cognitive aging. Time of follow-up and intervention status (EC vs. control) were treated as categorical variables, with time equal to zero at baseline and controls as the reference group. All analyses were completed for the full and sex-stratified samples. Volume estimates at 12- and 24-month follow-ups were computed with least squares means, and percent change in volumes at 12- and 24-month follow-ups between intervention and control groups were calculated from these least square means. To examine whether intervention-specific changes in brain volume were correlated with behavioral change in memory over 24 months of exposure, we calculated 24-month difference scores for brain volumes and RAVLT short delay recall. Linear scatter plots and Pearson correlations were conducted stratifying by intervention status. All analyses were conducted in SAS version 9.3 and intervention results were generated using MIXED procedure (SAS Institute, Inc, Cary, NC).

Table 2
Mean percent change in brain volumes over 12- and 24-month intervals by intervention status

Percent change in brain volume	Men				Women			
	Control		Intervention		Control		Intervention	
	12 months—baseline	24 months—baseline	12 months—baseline	24 months—baseline	12 months—baseline	24 months—baseline	12 months—baseline	24 months—baseline
Cortex	0.20%	-0.14%	-0.55%	0.67%*	-0.37%	-1.19%	0.02%	-0.54%
Hippocampus	0.34%	-3.52%	0.77%	1.56%*	-0.11%	-1.09%	-0.25%	-0.29%

All models were adjusted for age (centered at 67), education, and intracranial volume.

*Differences significant at $P < .05$ in models.

3. Results

Participant characteristics are presented in Table 1. Of the 111 participants included in this analysis, 58 were randomized to the EC intervention group and 53 to the control group. In aggregate, participants were about 67.2 years of age, 72.2% female, 93% African American, reported good health, and had 13.8 years of education (= some college). Eight EC and 12 control participants did not contribute follow-up data for various reasons, including: failing a criminal background check, death, moving out of state, dropping out of the trial, health, and poor MRI data quality. These participants were not significantly different at baseline from those retained in mean age, sex, racial distribution, MMSE, education, or brain volumes ($P_s > .05$).

At baseline, older age was significantly associated with smaller cortical volume, as expected. Specifically, each additional year of age was associated with 140,704 mm³ smaller cortical volume ($P < .001$). A similar relationship was observed in the hippocampus where each additional year of age was associated with a 4583 mm³ reduction in volume ($P < .0001$). Education was not associated with baseline brain volumes ($P_s > .15$).

3.1. Intervention effects

Effects of time at 12- and 24-month follow-ups were modeled relative to reference baseline volumes in full and sex stratified models. ITT analyses in the full sample revealed no significant intervention effects for either cortical or hippocampal volumes at either 12- or 24-month follow-ups ($P_s > .10$; data not shown), with an effect size of 0.54 (based on a two-tailed test with 80% power). The effect size of 0.54 signifies that the mean regional brain volume of the intervention group was greater than that of about 70% of those in the control group. In analyses stratified by sex, shown in Table 2, men showed intervention-specific gains in cortical (0.67%) and hippocampal (1.56%) volumes by 24 months, whereas male controls showed expected age-related declines of -0.14% to 3.52%. Both differences were significant ($P_s = .04$) with effect sizes over 1.0. Residualized mean hippocampal volumes by intervention status are graphed (Fig. 2A). In women (Fig. 2B), intervention-related gains emerged at 24 months, but did not reach statis-

tical significance ($P > .10$) with effect sizes of 0.64 to 0.66. Specifically, by 24 months, women in the intervention group showed marginally less age-related declines (0.29%–0.54%) than female controls (1.09%–1.19%).

3.2. Correlating intervention-specific changes in cortical and hippocampal volumes with intervention-specific changes in memory

Using linear scatter plots, we examined whether intervention-specific differences from baseline to 24 months in cortical and hippocampal volumes were correlated with intervention-specific differences in short-delay recall on the RAVLT over the same period. For the intervention group only, the 24-month difference in recall was positively correlated with the 24-month difference in cortical volume (Fig. 3; $r = 0.39$; $P = .02$). A positive correlation was also observed for hippocampal volume but did not reach significance ($P > .10$; data not presented) due, in part, to this

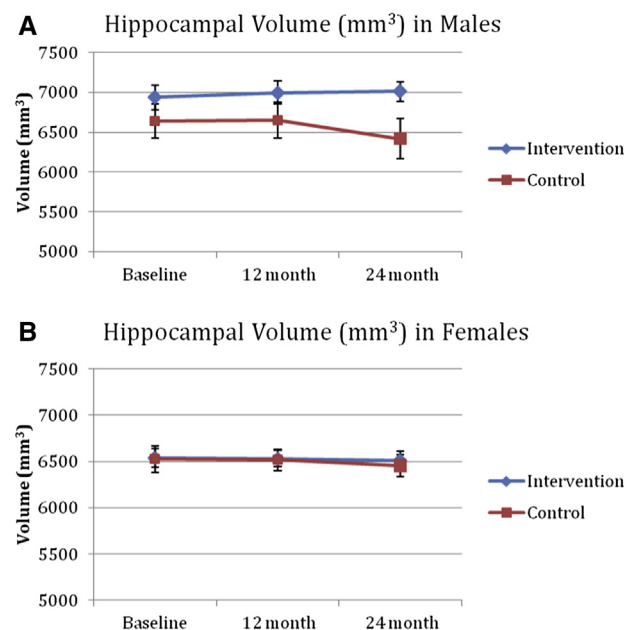


Fig. 2. Annual changes over 24 months in total hippocampal volume for (A) men and (B) women by intervention status.

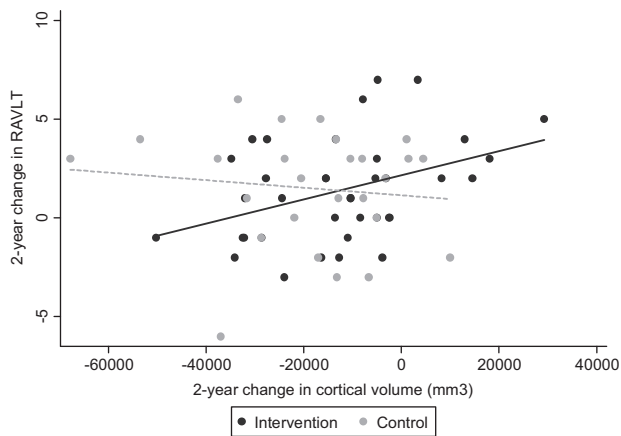


Fig. 3. Correlation between 24-month difference in Rey Auditory Verbal Learning Test short delay and 24-month difference in cortical volume by intervention status.

region's small size and the corresponding small annual rates of decline expected over 2 years among nondemented older adults [55].

4. Discussion

Results from the BHS revealed program-specific increases in cortical and hippocampal volumes by the second year that were greater in men than in women. These results suggest that multimodal activity embedded within a social health promotion program forestalled and possibly reversed age-related declines in annual rates of atrophy that typically range from 0.8% to 2.0% [55,56]. Whereas men in the control arm exhibited these expected declines over 2 years, men in the Experience Corps arm showed a 0.7% to 1.6% increase in brain volumes. This 2-year gain corresponds to an approximate 3-year reversal in brain aging. Women in Experience Corps also exhibited modest gains of 0.3% to 0.54% by the second year of exposure that contrasted with approximately 1.15% declines among women in the control group. In both men and women in the Experience Corps arm, 2-year changes in cortical volume were positively correlated with 2-year improvements in memory. These results were achieved in a sample of older adults that reflected the Baltimore City community, including minorities and a variety of socioeconomic and educational backgrounds. Together, these findings are the first from a RCT of a multimodal activity intervention to show age-related brain plasticity, providing support for the brain reserve hypothesis [57]. They suggest that those men randomized to Experience Corps maintained brain volumes with increasing age, and even exhibited modest increases in brain volumes relative to the control group, a finding consistent with that observed for exercise.

Furthermore, these results were achieved through a community-based, social health promotion program embedded within a novel, complex, and changing school environment. We hypothesize that this complexity provided

a key source of the program's strengths in exercising many abilities that can directly impact markers of brain health (for review, see [17]). It is therefore possible that programs that combine physical, cognitive, and social engagement, like Experience Corps, can serve to buffer age-related changes in brain and cognitive aging.

Duration of engagement beyond 1 year led to additional benefits in the maintenance, and even, increases in brain structure. If this intervention had concluded in under a year, as most cognitive interventions do, we would not have been able to assess the duration-dependent brain benefits. The 2-year effects indicate that measurable and statistically meaningful changes in brain volume accrued over time. We speculate that intervention-related benefits may continue to accrue postexposure perhaps by changing behaviors and motives that lead to sustained increases in social, cognitive, and physical activity in daily life.

Experience Corps increased multimodal activity through a social health promotion program that involved intergenerational transfer of wisdom and knowledge, raising the question of whether the desire to give back to a younger generation simply served as a motivator to increase and sustain volunteer activity or whether it offered more synergistic benefits related to the rewards associated with achieving these developmental goals [58]. In focus groups with program volunteers, they reported experiencing rewards through their perceived positive impact on children, a sense of renewed purpose postretirement, social bonds formed with peers and teachers (networks), and through self discovery of their own learning and teaching potential [59]. It is therefore possible that these perceived benefits played an important role.

Older women as a group did not show the same magnitude of intervention-related gains in brain volumes as men. We consider several possible explanations, in turn. First, Experience Corps was hypothesized to promote novelty and social engagement, but may not have been as novel for women as for men given that women's roles over the life course often involve teaching and care-giving with peers and children. Second, women in the BHS were more socioeconomically disadvantaged than men (less education, lower income). Socioeconomic disadvantage is associated with greater age-related cognitive decline and impairment [60]. The third reason for sex differences may be related to older women's elevated risk for physical and mobility difficulties [61] and tendency to be less physically active than older men [62,63], particularly among African-American women, who comprised the majority of the sample. While Experience Corps has been shown to increase physical activity in older African-American women through daily transit to and from and within schools [27], this alone may not have been sufficient to engender brain benefits observed through exercise. However, cross-sectional examination suggests that even modestly greater rates of daily walking activity are associated with larger hippocampal volumes among older women independent of moderate to vigorous-intensity activity [64]. The role of daily walking activity remains to be understood

for its relationship to neurocognitive health. We will evaluate the role of daily walking activity among men and women in mediating intervention-related benefits.

Study limitations are largely related to the effects of variable exposures and attrition over 2 years on the power to observe Experience Corps program benefits. This power restriction likely led to an underestimation of program benefits. In addition, the implementation of this real-world intervention precluded our ability to parse and measure intervention-specific effects of cognitive, social, and physical activity for their independent contributions. Future efforts will address this limitation through the use of accelerometry, global positioning system (GPS), and real-time survey methods. Strengths of this study include the 2-year exposure period, which is longer than prior randomized trials of cognitive training and exercise, a period that allowed us to observe cumulative, duration-dependent effects on brain health. Second, the rationale and incorporation of MRI into this trial was evidence-based and cost-effective because it built on prior pilot trial data [35], and, cooccurred simultaneously with randomization in the larger trial according to the same ITT design thereby mitigating selection bias and ensuring a representative subsample from the trial with which to examine mechanisms. Third, this trial addressed a limitation of prior studies of aging and lifestyle that are observational and thus, unable to disentangle selection bias associated with other healthful behaviors and with already high levels of cognitive ability. Fourth, direct examination of brain volume and atrophy provides useful intermediate biomarkers of program impact on cognitive aging [65] and risk for dementia that suggest longer-term benefits to Experience Corps volunteers postexposure in delaying dementia onset and possibly, mortality risk. Finally, this mechanistic study nested within an RCT sets a precedent by examining the impact of multimodal, real-world activity yoked to volunteer service, the success of which offers promise for the large-scale promotion of brain health in older adults, particularly among those at elevated sociodemographic risk for health disparities.

5. Conclusion

This is the first study, to our knowledge, to incorporate neuroimaging into an RCT to directly assess the impact of a multimodal social engagement program on markers of brain health in older adults. We observed increases in cortical and hippocampal volumes by the second year that reached significance only in men. In women and men in the intervention group, 2-year increases in cortical volume were positively correlated with improvements in memory. These results await replication and continued follow-up postexposure will allow us to examine whether programs like this can delay memory declines and risk of dementia. Broadly, these findings offer new directions for embedding healthy and generative activity into everyday life.

Acknowledgments

The authors would like to extend their appreciation and thanks to the Baltimore Experience Corps Trial (BECT) Brain Health Substudy (BHS) study participants for their critical contributions to this research. Recruitment and baseline evaluation was supported by the Johns Hopkins Neurobehavioral Research Unit and a supplement to the National Institute on Aging (BSR grant P01 AG027735-03). Follow-up evaluation, data cleaning, and analysis were supported by the Alzheimer's Drug Discovery Foundation. Dr. Kuo's data analysis was supported by the Johns Hopkins Epidemiology and Biostatistics of Aging Research Fellowship (NIA T32AG000247).

Author Contributions: Drs Carlson and Kuo had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: No other disclosures were reported.

RESEARCH IN CONTEXT

1. Systematic review: Previous observational studies have shown that physical, cognitive, and social activities are associated with reduced rates of cognitive decline and dementia in older adults. However, these studies are prone to selection bias and interventions have yet to evaluate the impact of lifestyle activities on biomarkers of brain health related to risk for dementia. This study addressed prior limitations through a randomized controlled trial assessing the impact of volunteer service as a vehicle for enhancing physical, cognitive, and social activity in sociodemographically diverse older adults on cortical and hippocampal volumes in healthy older adults over 2 years.
2. Interpretation: Activity embedded within a social health promotion program, entitled Experience Corps, to improve academic achievement among elementary school children vs. activity solely for personal health promotion led to maintenance and, in men, increases in biomarkers of brain health implicated in risk for dementia. With ongoing exposure over 2 years, benefits continued to accrue.
3. Future directions: Continued follow-up postexposure will allow us to examine whether social programs like Experience Corps can delay memory declines and risk of dementia. Broadly, these findings offer new directions for embedding healthful and generative activity into everyday life.

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