Alzheimer Disease Alters the Relationship of Fitness With Brain Activation During the Stroop Task

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Background. Despite mounting evidence that physical activity has positive benefits for brain and cognitive health, there has been little characterization of the relationship between cardiorespiratory (CR) fitness and cognition-associated brain activity, measured by functional magnetic resonance imaging (fMRI). The lack of evidence is particularly glaring for diseases that degrade cognitive and functional performance such as Alzheimer disease (AD).

Objective. Describe the relationship between regional brain activation during cognitive tasks and fitness level in those with and without AD.

Design. Case-control, single observation

Methods. 34 individuals (18 without dementia, 16 in the earliest stages of AD) completed maximal exercise testing and performed a Stroop task during fMRI.

Results. CR fitness was inversely associated with anterior cingulate activation in the nondemented participants (r=-0.48, p=0.05), and unassociated with activation in those with AD (p>0.7). Weak associations of CR fitness and middle frontal cortex were noted.

Limitations. Wide age range and use of single task in fMRI rather than multiple tasks challenging different cognitive capacities.

Conclusions. The results offer further support of relationship between CR fitness and regional brain activation. However, this relationship may be attenuated by disease. Future work in this area may provide clinicians and researchers with interpretable and dependable regional fMRI biomarker signatures responsive to exercise intervention. They may also shed light on mechanisms by which exercise can support cognitive function.
Alzheimer disease (AD) is a pervasive disease typically associated with memory loss. However, executive dysfunction, including deficits in inhibition, attention allocation and response planning is common and may be one of the earliest manifestations of disease.\textsuperscript{1-5} Recognition and remediation of executive impairment in AD is particularly important as it is these cognitive faculties that underpin functional independence.\textsuperscript{6-9} Evidence suggests that both functional and exercise training, the domain of physical therapists, can positively impact ADL performance for those with AD.\textsuperscript{10-15} As the percentage of the population over 65 continues to grow, 1 in 8 Americans over 65 now has AD.\textsuperscript{16} Physical therapists are uniquely qualified to prescribe individualized aerobic exercise programs for clinical populations and will be increasingly called upon to provide exercise prescription for these individuals,\textsuperscript{17} which may support brain health and functional independence.

The hypothesis that exercise and CR fitness are associated with healthy brain aging and reduced AD progression is biologically plausible and supported by observational and epidemiological studies. Increased physical activity has been postulated to have a trophic effect on the brain, particularly the hippocampus. For instance, exercise is associated with increased brain-derived neurotrophic factor\textsuperscript{18} and other important neurochemicals\textsuperscript{19} supporting brain growth and survival. Exercise appears to stimulate neurogenesis\textsuperscript{20} as evidenced by increased counts of new neurons in adult animals on an exercise regimen. Exercise is also associated with enhanced neuronal survival\textsuperscript{21} and increased synaptic development and plasticity.\textsuperscript{22} Additionally, voluntary exercise may mediate the amyloid cascade by reducing the production of beta-amyloid and thus have a direct effect on AD pathophysiology.\textsuperscript{23}

In older adults without dementia, there is accumulating evidence that physical activity, such as walking, benefits overall brain health and executive function in particular.\textsuperscript{24-27} Fitness
has been associated with maintenance or increase in brain gray matter volume\textsuperscript{28-31} in normal aging. Further, regular physical activity may reduce risk of cognitive decline\textsuperscript{32,33} and delay dementia onset.\textsuperscript{34} In one report, researchers found greater activation in the right middle frontal cortex and better performance of more highly fit individuals when they engaged in a task assessing conflict resolution.\textsuperscript{25} In those who have already been diagnosed with dementia of various causes, meta-analysis of the small scale and methodologically diverse extant literature has found that exercise may have small effects physical function, cognition and behavior.\textsuperscript{35} We have reported that in AD, higher cardiorespiratory (CR) fitness levels are associated with increased whole brain,\textsuperscript{36} and hippocampal volume.\textsuperscript{37} We also found that lower CR fitness levels were associated with faster dementia progression over 2 years.\textsuperscript{31} However, a causal link between exercise and improved cognition, especially for the prevention or treatment of AD is far from established.\textsuperscript{38} Thus, the literature warrants a broad investigation of the association between CR fitness and cognitive health and its potential as a remediating factor for those in the early stages of the disease.

Aerobic exercise may preferentially support executive function\textsuperscript{39} and there is considerable interest in exercise as a remediating intervention for AD.\textsuperscript{11} Further, fMRI may offer a sensitive means of capturing early exercise related neuroplasitic change in cognition.\textsuperscript{40,41} In prior cross-sectional analyses of cognitively healthy individuals, right frontal cortical activation was correlated with CR fitness during a task requiring resolution of conflicting stimuli.\textsuperscript{25,42} Higher CR fitness was associated with decreased activation in superior frontal, supramarginal, occipital and superior temporal gyri,\textsuperscript{42} and anterior cingulate cortex (ACC).\textsuperscript{25} Exercise intervention appears to enhance these relationships in a task dependent manner.\textsuperscript{25,43} The definitive measure of exercise effects on cognition would of course be improved cognitive
performance. However, frequently, there is a need in both research and clinical practice for additional biomarkers of intervention responsiveness. Neuroimaging may provide one measure of responsiveness to exercise intervention. Recently Kramer and colleagues highlighted the need for neuroimaging studies of the role of fitness on the performance of everyday tasks. Few imaging studies of executive neural activity have been performed in those with AD. In the available literature, differences in activation patterns with executive processes have been noted in those with mild cognitive impairment (MCI) and AD compared to nondemented controls. For example, Rosano and colleagues described increased activation in dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex of those with MCI during an executive task (prepotency of response). Similar regions were active in those with MCI when a Stroop task of attentional inhibition was performed. Another study found increased activation of frontal regions, especially the medial frontal cortex, in those with AD compared to nondemented and MCI subjects during a working memory task. The available evidence thus suggests that individuals with cognitive impairment activate additional fronto-parietal regions during executive tasks in comparison to their nondemented peers. However, it remains unclear if CR fitness is associated with brain activity during executive tasks in AD.

To our knowledge, there have been no reports of the relationship between CR fitness and executive activation in AD. Because fMRI signal appears to be altered by AD, the association of fitness and fMRI signal must be quantified before an intervention effect can be reliably interpreted. Therefore, we had participants with and without AD complete maximal exercise testing and a Stroop task during fMRI. We hypothesized that CR fitness would be associated with brain activity during stimulus conflict resolution (i.e. the Stroop interference task) in both those with AD and those without dementia specifically in the ACC and middle frontal (MidF)
regions. We also assessed the superior parietal lobule (SPL) as secondary region of attentional control modulated by CR fitness. The importance of the knowledge gained in this study is thus twofold: 1) it provides additional evidence towards our understanding of the fitness/brain function relationship, and it provides additional guidance toward the use of neuroimaging to evaluate therapeutic interventions.

Method

Participants

Forty participants, both with and without AD, age 60-85 were recruited as a sample of convenience from a registry of individuals with an interest in participating in research at the University of Kansas Alzheimer’s Disease Center. Participants for this case-control study were recruited from Nov 2009 through May 2011. Inclusion criteria were normal cognition or impaired cognition possibly or probably related to AD based on a clinical evaluation within the prior 6 months, independent ambulation without an assistive device and an informant regularly in contact with the participant (> 3 days/week) able to be present at the clinical evaluation. Exclusion criteria were neurological disorders other than AD that have the potential to impair cognition (e.g., Parkinson’s disease, stroke, etc.), insulin-dependent diabetes mellitus, a recent history (< 3 years) of cardiovascular or pulmonary disease, significant orthopedic issues that could limit performance on the maximal exercise test, clinically significant depressive symptoms (Geriatric Depression Scale score >4), abnormalities in B12 or thyroid function that may account for cognitive symptoms, use of psychoactive and investigational medications, any MRI exclusion and significant visual or auditory impairment. Informed consent was obtained from all participants before enrollment into the study.
All participants first underwent a clinical evaluation as part of the Alzheimer’s Disease Center Registry and additional measures such as the Mini-Mental State Examination and Geriatric Depression Scale. Participants were offered the opportunity to enroll at that time. All but 2 participants had a CDR within 2 months of starting the exercise testing or MRI. These 2 participants were enrolled from inquiries they made to the Center regarding ongoing studies and had undergone a clinical evaluation and CDR in the last 6 months. Once enrolled, MRI and CR Fitness assessment visits were scheduled within 2 weeks of each other without regard to order, based on lab and participant availability.

**Clinical Evaluation**

Dementia status and diagnosis of AD was based on clinical evaluation by trained clinicians. The assessment included a semi-structured interview with the participant and the informant. AD diagnosis was determined by a single clinician based on established diagnostic criteria. Dementia severity was determined using the Clinical Dementia Rating (CDR) scale. Medications, past medical history, education, demographic information and family history were collected. Dementia severity was determined using the Clinical Dementia Rating (CDR) scale. A Global CDR score is derived from individual ratings in each domain such that CDR 0 indicates no dementia, CDR 0.5 indicates very mild, CDR 1 indicates mild, CDR 2 indicates moderate, and CDR 3 indicates severe dementia. Individuals with AD met criteria for very mild or mild dementia (Global CDR 0.5 or 1.0). All participants were community dwelling.

**CR Fitness Assessment**

Prior to testing, the Physical Performance Test (PPT) was administered to index
physical function and to allow study staff to subjectively assess potential ability during the maximal exercise test. We have previously shown that maximal exercise testing is reliable and feasible in populations with AD.\textsuperscript{59,60} While our lab has no hard rule for PPT scores that would raise concerns about exercise testing performance, the PPT items allow study staff to observe the participant’s power, agility, gait, balance and ability to follow commands. Study staff had no concerns about any participant’s ability to satisfactorily complete testing.

CR fitness was assessed as peak oxygen consumption ($\text{VO}_2$ peak; ml*kg$^{-1}$*min$^{-1}$) during a symptom-limited, graded treadmill test using a modified Bruce protocol designed for older adults.\textsuperscript{61} Maximal exercise testing has been shown to be reliable in those with early-stage AD.\textsuperscript{59} Individuals were instructed to abstain from consuming food and caffeine 3 hours prior the scheduled test. Calibration procedures were performed on the metabolic cart before each test according to the manufacturer specifications. An exercise physiologist familiarized each participant with the exercise equipment, testing protocol and explained the Borg Rating of Perceived Exertion (RPE) Scale. Participants began walking at a pace of 1.7 miles per hour at 0% incline. At each 2-minute interval, the grade, speed or both was increased. Participants were attached to a 12-lead electrocardiograph to continuously monitor heart rate and rhythm. A 2-way, non-rebreathing valve, headgear, mouthpiece and nose clip were worn to collect expired air. Blood pressure and RPE were acquired during the last 30 seconds of each stage. Expired gases were collected continuously and oxygen uptake and carbon dioxide production was averaged at 15-second intervals (Parvomedics, Sandy, UT). The exercise test was terminated if the participant reached volitional exhaustion or met absolute test termination criteria according to ACSM guidelines.\textsuperscript{62} CR fitness was indexed as $\text{VO}_2$ peak, the highest oxygen consumption value achieved during the test.
**Stroop Task During MRI**

Structural MRI was obtained using a Siemens 3.0 Tesla Allegra MRI scanner. High-resolution T1 images were collected for anatomic localization and co-registration (MP-RAGE: 1.3 x 0.9 x 1.0mm voxels, TR/TE=2300/3.05ms, 8° flip angle, FOV=240mm, 208 slices). Functional imaging data were collected as axial echo-planar images using a single-shot, blipped gradient, echo-planar pulse sequence (3 x 3 x 3.5mm, 0.5 mm gap, TR/TE=2000/30ms, 90° flip angle, FOV=192mm, 34 slices, 337 volumes). Foam pads were placed around the participant’s head to reduce movement.

One run of the Stroop Word/Arrow task was performed following anatomical imaging. The Stroop Word/Arrow task\(^3\) assesses response inhibition and selective attention. Each stimulus consists of a word (RIGHT or LEFT) and an arrow (← or →), stacked one above the other at the center of the screen. The stacking order was random. The four event conditions were generated by crossing stimulus attention (Word vs. Arrow) and congruency (Congruent vs. Incongruent) factors. The event conditions were equally represented in a rapid event-related paradigm, designed for maximal efficiency using efMRI (Chris Rorden, http://www.mccauslandcenter.sc.edu/CRNL/tools/fmrisim). The task was synchronized to MRI acquisition. Stimuli were back-projected onto a translucent plate and viewed on an adjustable mirror mounted above the participant’s head.

Participants were initially instructed to pay attention and respond to the direction indicated by the word using the left or right index finger on a button box (Current Designs, Inc. Philadelphia PA.). After each block of 10 trials (12 blocks total), an instruction was presented to attend to a new stimulus object (Word or Arrow). Congruency conditions and relevant stimulus
location were randomized but balanced over trials. Trials were separated by a random, interstimulus interval of 5 to 7 seconds.

Functional images were preprocessed using Analysis of Functional NeuroImages software. The first 4 functional volumes of the time series were discarded to allow the magnetic field to stabilize. Datasets for each individual were first processed using the standard uber_subject.py pipeline settings with an 8mm³ full-width half-maximum smoothing kernel. We modeled activation for each participant using four event condition onsets convolved with the gamma function, the six motion parameters and 3rd order polynomials, censoring TRs with > 1mm of motion. Resulting contrasts of Incongruent events > Congruent events [0.5 0.5 -0.5 -0.5] were then passed to the group analysis.

Structural images were aligned to a standard template in Talairach space as part of the uber_subject.py pipeline. Additionally, structural images were divided by tissue type and region using Freesurfer. The standard Freesurfer processing pipeline, recon_all, separates the anatomical image into individualized regions based on gyral and sulcal structure and tissue type.

**Data Analysis**

Published estimates of sample size for fMRI experiments with a conservative random effect model and moderate effects sizes, indicate that 80% power can be achieved using a threshold of 0.002 with approximately 20 participants per group. Thirty-four individuals were included in the final analysis. Four individuals with AD were excluded with accuracy on the Stroop task below 66%. One individual with AD experienced a fall in the home prior to exercise testing and withdrew. One individual without AD declined to participate in the MRI after
consenting.

For our primary hypothesis, we found the median percent signal change in our *a priori* hypothesized regions of interest (ROI) constructed using the Freesurfer segments.\textsuperscript{65, 66} We extracted the median percent signal change values from the following regions of the Destrieux Atlas: left and right middle frontal gyri, superior parietal lobule, anterior cingulate gyri and sulci, and precentral gyri as a control region. We then calculated dPSC as the difference in median percent signal change between conditions (Incongruent – Congruent).

We assessed group differences in demographics and task performance with appropriate tests (ANOVA, Pearson Chi-square, Mann-Whitney). To test our primary hypothesis that CR fitness would be associated with greater ROI activation we correlated dPSC difference with CR fitness (VO$_2$ peak ml*kg$^{-1}$*min$^{-1}$), correcting for age using partial correlation. We also tested dPSC against the response time cost of incongruency. Tolerance of Type I error was set at $\alpha=0.05$. Statistical analyses were performed using SPSS 20 (IBM Corp, Armonk, NY).

We then assessed group differences in imaging space (i.e. AFNI 3dttest++), including age and VO$_2$ peak as covariates. First, we assessed the main effect of incongruency (Incongruent $>$ Congruent) pooling all subjects. We then compared group activation patterns. Finally, we specifically assessed the effect of incongruency with regard to CR fitness within each group separately. Because AD-associated atrophy can result in spurious findings we inclusively masked all imaging analyses using a binary mask of voxels representing gray matter in at least 50% of the AD group. A voxel-wise threshold of $p<0.001$ uncorrected and cluster size (k) of 10 voxels or greater was set for these analyses.\textsuperscript{68}

*Data Management*
Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Kansas. Imaging data were archived on the Extensible Neuroimaging Archive Toolkit (XNAT version 1.5). Statistical analysis was performed using SPSS 20 (IBM Corp, Armonk, New York).

Role of the Funding Source

Portions of this work were supported by the following grants from the National Institutes of Health: R01AG033673, R01AG034614, KL2TR000119, and UL1TR00001. Dr Vidoni was supported by a New Investigator Fellowship Training Initiative Award from the Foundation for Physical Therapy during this study. Dr Vidoni and Dr Burns are supported by the University of Kansas Alzheimer's Disease Center (P30AG035982). Dr Honea is supported by National Institutes of Health grant K01AG035042.

Results

All participants were community dwelling and independently ambulating without an assistive device. The groups (Nondemented, AD) did not differ in age, VO₂ peak, sex, or performance on the Stroop task. The groups were different in MMSE, PPT, and Global CDR, as expected. We also saw an increased response time for incongruent stimuli across all subjects. Table 1 includes demographic and performance data for the groups.

We saw no difference between left and right dPSC in ACC and MidF and therefore averaged dPSC sides for the analyses. Our primary hypothesis was that higher CR fitness would be associated with greater activation in the ACC and MidF across all individuals. However, when we correlated VO₂ peak with ACC dPSC corrected for age we found group differences in
the relationship of fitness level and activity (Figure 1A). In the AD group, VO$_2$ peak was not associated with dPSC in any ROI (p>0.7). The nondemented group (ND) showed a significant inverse relationship in the ACC, with higher CR fitness level associated with a lower dPSC in the ACC ($r=-0.48, p=0.05$; Figure 1A). No other ROIs were significantly associated with VO$_2$ peak in the nondemented group.

We also compared dPSC to the response time cost of stimulus incongruency. In the AD group, response time cost was again not associated with dPSC in any ROI (p>0.3). However, the ND group displayed a positive relationship in the MidF ($r=0.57, p=0.02$), and SPL ($r=0.48, p=0.05$), with greater response time cost associated with increased dPSC. No other regions approached significance in the nondemented group (p>0.13).

We next performed our whole brain imaging analysis. First, we assessed the main effect of Incongruency > Congruency pooling all subjects. Bilateral MidF, and bilateral inferior frontal gyri showed increased activation, even after controlling for age and VO$_2$ peak, demonstrating our paradigm elicited activation comparable to previous studies (Table 2A, Figure 1B). No differences were detected between groups, although there were trends (p<0.005 uncorrected, k>=10) for greater activation by the ND group in the left precentral gyrus (BA 4 and 6) and right precuneus (BA 7)(Table 2B). No region showed a significant CR fitness by group interaction.

To explore CR fitness-related brain activation beyond our a-priori defined ROIs, we regressed CR fitness against whole brain contrast maps in each group separately. In the AD group, CR fitness was unrelated to regional activation although there was a trend for decreased activation to be associated with higher CR fitness in the right inferior temporal gyrus (p<0.005, k=5; Table 2C). Likewise, in the nondemented group, no regions were significantly associated with CR fitness. However, there was a trend in the ND group for those with higher CR fitness to
demonstrate increased activation in left MidF gyrus (BA 9, p<0.005 uncorrected, k=7; Table 2D; Figure 1C).

Discussion

The results of this study reflect a complex relationship between CR fitness, cognitive performance and AD. To our knowledge only one other study has compared fitness and functional imaging markers of cognition in those with cognitive impairment, and none have specifically assessed CR fitness or executive function. We focused on ROIs that are commonly activated during Stroop tasks. We found that CR fitness was associated with increased activation during Stroop interference, echoing prior findings of a fitness / brain activation association in those without dementia. However this relationship was not present in those with AD. This disease-related mitigation of the CR fitness / fMRI signal suggests that fMRI could be used to monitor exercise intervention response. That is, if exercise interventions in those with AD resulted in a “normalization” of the CR fitness / brain activation association similar to nondemented older adults, it would suggest a positive response to the intervention, especially if coupled to behavioral improvement.

Fitness and Brain Activity During the Stroop Task

Both increased and decreased regional activation have now been reported to be associated with CR fitness. The conflicting reports may reflect differences in functional task, age of participants or analysis methodology. For example, both Colcombe et al. and Voelcker-Rehage et al. report right MidF activation to be positively associated with CR fitness during a task requiring resolution of conflicting stimuli. However, Voelcker-Rehage also reported that
individuals with increased CR fitness had decreased activation in superior frontal and MidF cortex.\textsuperscript{42} Colcombe also reported an inverse relationship in the ACC, whereas Voelcker-Rehage found no relationship. Our results, albeit some at a trend level, are consistent with the findings of Colcombe et al.;\textsuperscript{25} increased MidF and SPL and decreased ACC activation are associated with CR fitness during an executive task.

Executive function encompasses a broad set of cognitive functions that few measures can fully quantify. We chose to use a well-known task paradigm (Stroop Interference) that specifically tests the executive functions of selective attention and conflict resolution. These executive functions are highly applicable to functional independence. For example, one must rely heavily on selective attention and conflict resolution when evaluating the many directional arrows on roadway signs when driving on the highway. Though our results cannot speak to a CR fitness relationship to other executive functions, such as working memory or scheduling, or to ecologically valid activities such as driving, they do support further investigation of the executive faculties and activities.

\textbf{Does AD Modulate the Fitness-Brain Activity Relationship?}

CR fitness and brain activation associations evident in those without dementia were not evident in the AD group. We noted that bilateral MidF activation was increased with greater task difficulty across participants. However, we saw no group based differences and the increased activation was unrelated to CR fitness in the AD group. Notably absent was an association between CR fitness and decreased ACC activation. Based on these results, we suggest that AD alters or overrides the relationship of CR fitness with brain function. We readily acknowledge that absence of evidence is not evidence of absence of a relationship. However, we were
particularly careful to account for various confounding factors that might influence this association discussed in our Limitations section. Thus, our results likely reflect a diminished fitness effect associated with AD.

This does not preclude the possibility that exercise training could entrain a more typical relationship and positively alter brain activation, especially in the ACC. Indeed, there is preliminary evidence that exercise may support functional plastic change in the earliest stages of AD. In that randomized controlled trial, resistance training in individuals with mild cognitive impairment improved performance on both the Stroop task and an associative memory task. Increased activity in lingual and temporal regions was positively correlated with improved memory task performance in those that resistance trained.

**Strengths and Limitations**

The fMRI signal can change with age and disease. With this in mind, we were careful to test a priori hypotheses and relied on several strategies recommended to account for age-related signal change. We focused our imaging analyses on a comparison of two conditions, rather than task performance to a no-task baseline, and employed percent signal change, which is relative to the individual. Thus we analyzed an interaction of condition and diagnosis rather than a main effect of diagnosis, an important distinction that resolves some concerns regarding disease related hemodynamic differences. Because age and CR fitness are correlated, our assessment using age, a covariate of no interest, is conservative. Prior studies have not controlled for age, which may explain some differences in our study. Tighter age groups would alleviate this problem but decrease generalizability to the wide age range of AD onset. A second limitation to our study is that we cannot rule out that our group without AD was not in the
preclinical stages of AD through biomarker assessment. However, we are confident that our nondemented cohort represents a group without cognitive impairment based on a thorough clinical interview that includes corroboration with someone who knows the participant well. Finally, we stress that this is a cross-sectional assessment, and thus cannot inform our understanding of any causal relationship between CR fitness and brain function. As we’ve noted, future randomized controlled studies can build upon these observational findings and investigate causal or intervention effects of exercise.

**Conclusions**

Taken together, the results of this study supports previous findings that suggest that in nondemented individuals, greater cardiorespiratory fitness is associated with increased middle frontal and decreased anterior cingulate activation during tasks that tax attention and conflict resolution, two executive functions. We know of no prior studies that have examined the relationship between CR fitness and executive function using fMRI in early-stage AD. This gap in the literature remains despite evidence that fitness supports executive cognitive performance in nondemented aging. The present study provides further evidence that these regions are appropriate candidates for monitoring functional neuroplastic response to exercise in both those without dementia and those in the earliest stages of AD. If CR fitness is ultimately shown to support executive function in those with AD, it may have significant implications as an adjunct therapy for maintaining functional independence. Physical therapists could incorporate both functional and aerobic training in their plans of care for those in the early stages of AD to maximize IADL performance and independence. Future work in this area should focus on provide clinicians and researchers with interpretable and dependable regional fMRI biomarker
signatures responsive to exercise intervention. Additionally, follow-up study should emphasize exploration of mechanisms by which exercise can support cognitive function.
Dr Vidoni, Dr Savage, and Dr Burns provided concept/idea/research design and project management. Dr Vidoni, Mr. Gayed, Dr Savage, and Mr Hobbs provided writing. Dr Vidoni provided data collection. Dr Vidoni, Mr. Gayed, Dr Honea, Dr Savage, and Mr Hobbs provided data analysis. Dr Vidoni and Dr Burns provided fund procurement, study participants, facilities/equipment, and institutional liaisons. Dr Savage and Dr Burns provided consultation (including review of manuscript before submission).

Portions of this work were supported by the following grants from the National Institutes of Health: R01AG033673, R01AG034614, KL2TR000119, and UL1TR00001. Dr Vidoni was supported by a New Investigator Fellowship Training Initiative Award from the Foundation for Physical Therapy during this study. Dr Vidoni and Dr Burns are supported by the University of Kansas Alzheimer's Disease Center (P30AG035982). Dr Honea is supported by National Institutes of Health grant K01AG035042.

References


28. Colcombe SJ, Erickson KI, Raz N, et al. Aerobic Fitness Reduces Brain Tissue Loss in


55. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the


Table 1. Demographic and performance measures for each group. Statistical test results are present for each measure.

<table>
<thead>
<tr>
<th>Measure</th>
<th>ND (n=18)</th>
<th>AD (n=16)</th>
<th>sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.2 (7.2)</td>
<td>74.9 (7.4)</td>
<td>F=1.22, p=0.28</td>
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<tr>
<td>Gender (% Female)</td>
<td>50</td>
<td>44</td>
<td>X=0.133, p=0.72</td>
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<tr>
<td>Physical Performance Test</td>
<td>33 (1.8)</td>
<td>28.9 (4.7)</td>
<td>F=12.2, p=0.001</td>
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<td>CR Fitness (ml/kg/min)</td>
<td>23.7 (6.1)</td>
<td>20.5 (4.8)</td>
<td>F=2.8, p=0.10</td>
</tr>
<tr>
<td>Global Clinical Dementia Rating</td>
<td>0 [0]</td>
<td>.63 [0.5 - 1]</td>
<td>N/A</td>
</tr>
<tr>
<td>Mini-Mental State Exam</td>
<td>29.2 [27 - 30]</td>
<td>26.8 [24 - 30]</td>
<td>U=40.5, p&lt;0.001</td>
</tr>
<tr>
<td>Median Response Time for Congruent Stimuli in fMRI (ms)</td>
<td>940 (213)</td>
<td>991 (171)</td>
<td>Main effect of Condition F=31.7(1,22), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Main effect of Dementia F=0.6(1,21), p&gt;0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interaction F=0.7, p&gt;0.1</td>
</tr>
<tr>
<td>Median Response Time for Incongruent Stimuli in fMRI (ms)</td>
<td>1075 (204)</td>
<td>1103 (195)</td>
<td></td>
</tr>
</tbody>
</table>

Number enclosed in ( ) are 1 standard deviation. Numbers enclosed in [ ] are ranges. Global Clinical Dementia Rating is by definition different between groups and therefore not formally tested.
Table 2. Regions of increased activation in the Incongruent vs. Congruent stimulus conditions. Locations derived from the Talairach-Tournoux Atlas.

A. Main effect of Incongruency > Congruency across all participants regardless of dementia

<table>
<thead>
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<th>Location</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Middle Frontal Gyrus (BA 9)*</td>
<td>32</td>
<td>50</td>
<td>-14</td>
<td>36</td>
</tr>
<tr>
<td>Right Middle Frontal Gyrus (BA 9)*</td>
<td>19</td>
<td>-47</td>
<td>-14</td>
<td>33</td>
</tr>
<tr>
<td>Left Inferior/Middle Frontal Gyri (BA 47)*</td>
<td>11</td>
<td>-47</td>
<td>-44</td>
<td>3</td>
</tr>
<tr>
<td>Right Inferior/Middle Frontal Gyri (BA 46)*</td>
<td>11</td>
<td>26</td>
<td>-29</td>
<td>-10</td>
</tr>
</tbody>
</table>

B. Group differences (ND > AD) in increased activation during Incongruent stimuli

<table>
<thead>
<tr>
<th>Location</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Precuneus (BA 6 &amp; 7)^</td>
<td>20</td>
<td>-8</td>
<td>47</td>
<td>57</td>
</tr>
<tr>
<td>Left Precentral Gyrus (BA 4 &amp; 6)^</td>
<td>13</td>
<td>38</td>
<td>23</td>
<td>63</td>
</tr>
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C. AD increased activation associated with greater VO$_2$ peak

<table>
<thead>
<tr>
<th>Location</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
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</thead>
<tbody>
<tr>
<td>Right Inferior Temporal Gyrus^</td>
<td>5</td>
<td>-50</td>
<td>20</td>
<td>-22</td>
</tr>
</tbody>
</table>

D. ND increased activation associated with greater VO$_2$ peak

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<tr>
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</thead>
<tbody>
<tr>
<td>Left Middle Frontal Gyrus (BA 9)^</td>
<td>7</td>
<td>32</td>
<td>-23</td>
<td>36</td>
</tr>
</tbody>
</table>

* significant at voxelwise p<0.001 uncorrected, k>9
^ trends toward significance at voxelwise p<0.005
Figure 1. AD modulates the relationship of CR Fitness and bilateral anterior cingulate (ACC) difference in percent signal change (dPSC). Nondemented individuals (open circles, dashed line) with greater CR fitness (x-axis, toward the right) showed less difference in activation ($r=-0.48$, $p=0.05$). Individuals with AD (filled circles, solid line) showed no such relationship ($p=0.77$).

Figure 2. A) Across subjects, stimulus incongruency increased activation in bilateral middle frontal cortex ($p<0.001$, $k>10$). B) We found a trend ($p<0.005$, $k=7$) for increased activation to be associated with greater VO$_2$ peak in the left middle frontal gyrus in the ND group only. The color bar represents dPSC. All displayed voxels are members of significant clusters overlaid on an average anatomical image of all AD participants.