Using sulcal and gyral measures of brain structure to investigate benefits of an active lifestyle.

Authors:

Ashley J. Lamont BSc (Hons)¹

Moyra E. Mortby PhD¹

Kaarin J. Anstey PhD¹

Perminder S. Sachdev MD, PhD, FRANZCP²

Nicolas Cherbuin PhD^{1*}

Affiliations:

¹ Centre for Research on Ageing, Health and Wellbeing, Australian National University,
Canberra, Australia

² Neuropsychiatric Institute, University of New South Wales, Sydney, Australia

***Correspondence:**

Nicolas Cherbuin, Centre for Research on Ageing, Health and Wellbeing, 63 Eggleston Road,
Australian National University, Canberra, ACT 0200, Australia

Tel: 0061253858; Fax: 0061258413; Email: nicolas.cherbuin@anu.edu.au

Word count: 3,756

Number of tables: 4

Number of figures: 3

Abstract

Background:

Physical activity is associated with brain and cognitive health in ageing. Higher levels of physical activity are linked to larger cerebral volumes, lower rates of atrophy, better cognitive function and less risk of cognitive decline and dementia. Neuroimaging studies have traditionally focused on volumetric brain tissue measures to test associations between factors of interest (e.g. physical activity) and brain structure. However, cortical sulci may provide additional information to these more standard measures.

Method:

Associations between physical activity, brain structure, and cognition were investigated in a large, community-based sample of cognitively healthy individuals (N=317) using both sulcal and volumetric measures.

Results:

Physical activity was associated with narrower width of the Left Superior Frontal Sulcus and the Right Central Sulcus, while volumetric measures showed no association with physical activity. In addition, Left Superior Frontal Sulcal width was associated with processing speed and executive function.

Discussion:

These findings suggest sulcal measures may be a sensitive index of physical activity related to cerebral health and cognitive function in healthy older individuals. Further research is required to confirm these findings and to examine how sulcal measures may be most effectively used in neuroimaging.

Introduction

It is well established that physical activity (PA) is associated with healthier brain structure (Erickson et al., 2010), better cognitive function (Colcombe et al., 2003), as well as a reduced risk of cognitive decline (Etgen et al., 2010; Muscari et al., 2010) and dementia (Ahlskog et al., 2011). The ageing process is associated with a decline in neurogenesis and an increase in neuroinflammation, which may result in reduced grey matter thickness (Kochunov et al., 2013). Suggested mechanisms contributing to the benefit of PA for cerebral health and cognitive function include: improved cardio-vascular health and cerebral perfusion, decreased chronic low-grade systemic inflammation, activation of anti-oxidant pathways that mitigate the impact of oxidative stress on the brain, and increased neuroplasticity (Anderson-Hanley et al., 2012; Gerecke et al., 2013; Kochunov et al., 2013; Muscari et al., 2010; Radak et al., 2008). In addition, PA provides a safe way (one not associated with increased cancer incidence) to upregulate adult stemcell neurogenesis pathways which has been demonstrated to lead to larger hippocampal volumes in older adults (Erickson et al., 2011).

Higher levels of PA are associated with improved attention, motor function, processing speed, executive function and memory both in intervention trials as well as animal studies (Angevaren et al., 2008; Colcombe et al., 2003; Smith et al., 2010; Stranahan et al., 2012; van Praag et al., 1999). Consistent findings have also been demonstrated in observational studies using cross-sectional and longitudinal designs (Bielak et al., 2007). In addition, research has also linked higher levels of PA with increased grey and white matter volumes in the parietal, prefrontal, and temporal cortex (Colcombe et al., 2006; Erickson et al., 2012; Erickson et al., 2010; Honea et al., 2009; Taubert et al., 2011). These brain regions also underlie executive function, working and episodic memory, and attention, and are implicated in cognitive decline and neurodegenerative disease prevalent in ageing (Colcombe et al., 2004; Erickson et al., 2009; Rosano et al., 2010). These findings have been supported by animal studies

demonstrating that PA induces increased neurogenesis and cell connectivity, in turn improving cognitive performance (van Praag et al., 1999).

To date, imaging research investigating risk and protective factors for cerebral health has focused on examining volumetric measures of brain structure (Lemaitre et al., 2012). Despite the value of such findings, these techniques have several limitations. First, volumetric techniques rely on the ability to accurately identify grey and white matter boundaries. However, grey-white matter signal contrast on MRI decreases with age and leads to increased variability of measurement, over-estimation of white and under-estimation of grey matter volumes thus resulting in reduced sensitivity of these measures in older adults (Kochunov et al., 2005; Lemaitre et al., 2012). Second, they may be less sensitive to more diffuse processes affecting cortical regions that do not necessarily follow clear anatomical boundaries or rely on sub-processes spread across adjoining gyri (Van Essen, 1997). Thirdly, many cerebral functions are affected concurrently by changes in both grey and white matter integrity which may not be optimally indexed by volumetric measures at the local level (Kochunov et al., 2005) .

An alternative or potentially complementary approach to examining grey and white matter is the analysis of cortical sulci (Kochunov et al., 2005; Lemaitre et al., 2012). While cortical sulcal width increases with age (Kochunov et al., 2005), narrower sulcal width is associated with higher cognitive function (Liu et al., 2011). In addition, cortical sulcal depth reduces with age and pathological cognitive decline (e.g. Alzheimer's disease) (Im et al., 2008; Kochunov et al., 2005). Therefore, healthier sulci are characterised by narrower width and greater depth (Im et al., 2008; Liu et al., 2011). Examining characteristics of cortical sulci thus provides a sensitive representation of brain structure, which is not reliant on the discrimination of grey and white matter yet indexes atrophy in both (Kochunov et al., 2005),

is more sensitive to complex folding patterns of the brain surface (Lemaitre et al., 2012), and varies in association with age (Kochunov et al., 2005) and cognition (Liu et al., 2011).

The current study therefore aimed to 1) investigate whether the associations between a known predictor of cerebral health and integrity, namely physical activity, and brain structure can be detected with greater sensitivity using sulcal measures in place of or in addition to regional volumes using data from a large epidemiological cohort of older adults living in the community, and 2) assess whether the PA-related variability in brain measures, where present, is associated with cognitive function. It was predicted that greater levels of PA would be associated with deeper and narrower sulci, and with lower grey matter volumes in the adjoining areas. This effect was expected to be more prominent in the frontal lobe as this structure is known to be more sensitive to chronic disease and ageing processes and has previously been associated with PA (Colcombe et al., 2006). Moreover, it was predicted that where sulcal and/or volumetric measures were found to be related to PA, the regions identified would also be associated with cognitive function in domains known to be supported by these regions.

Methods

Participants

Participants were sampled from the Personality and Total Health Through Life (PATH) project, a large longitudinal study of ageing aimed at investigating the course of mood disorders, cognition, health and other individual characteristics across the lifespan (Anstey et al., 2011). It surveys 7,485 individuals in three age groups of 20-24, 40-44 and 60-64 years at baseline. Follow-up is every four years over a period of 20 years. PATH surveys residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, who were randomly recruited through the electoral roll (Anstey et al., 2011). Enrolment to vote is compulsory for

Australian citizens, making this cohort representative of the population. All participants provided written informed consent and the study was approved by the Australian National University Ethics Committee.

The present investigation is focused on older participants (60+ cohort) at the second assessment as brain scans were of higher quality for this wave and hence more amenable to processing with the Freesurfer software. Of the 2,551 randomly selected older PATH participants included in wave 1, 2,076 consented to be contacted regarding an MRI scan. Of these, a randomly selected subsample of 622 participants was offered an MRI scan and 478 (77%; 252 men) eventually underwent a brain scan. Of those with MRI scans, 102 were excluded from current analyses as they did not have a scan at wave 2. Participants were then excluded for stroke ($n=5$), epilepsy ($n=11$), Parkinson's disease ($n=20$), and missing PA data ($n=5$). A further 17 were excluded as their scan quality was insufficient for BrainVisa processing, leaving a final sample of 318. Selection is summarised in *Figure 1*. Participants did not differ significantly from the overall 60+ PATH cohort on age, gender, and PA but had significantly more years of education (14.25 vs. 13.83; $t(2,171)=-2.535$; $p=.011$). Participants' demographic characteristics are presented in *Table 1*.

Socio-demographic and Health Measures

Socio-demographic and health measures for race, years of education, alcohol consumption, smoking, and depression were assessed using self-report. Seated systolic and diastolic blood pressures were averaged over two measurements after a 5 minute rest. Body mass index (BMI) was based on subjects' self-report of weight and height and computed using the formula $\text{weight (kg)}/\text{height (m)}^2$. The Alcohol Use Disorder Identification Test (AUDIT) was used to assess alcohol intake (Saunders et al., 1993). For men, weekly alcohol consumption was categorized as light (1–13 units), moderate (14–27 units), hazardous (28–42

units) or harmful (>42 units). For women, weekly alcohol consumption was divided into light (1–7 units), moderate (8–13 units), hazardous (14–28 units) or harmful (>28 units) categories where a unit equates 10g of pure alcohol. Depression status was assessed with the Brief Patient Health Questionnaire (BPHQ) based on responses to ten questions assessing depressive symptomatology. Major and minor depression status was computed with a validated coding algorithm which has shown to have good psychometric characteristics against clinical diagnosis (Spitzer et al., 1999). Anti-depressive medication use was assessed by self-report.

Physical Activity (PA)

PA was assessed using self-report. Hours of average weekly PA were reported for three intensity categories: (1) mild (e.g. walking, weeding), (2) moderate (e.g. dancing, cycling) and (3) vigorous (e.g. running, squash). To provide an intensity-sensitive continuous score of PA, the three levels of PA were combined using a weighting system such that hours of mild PA were multiplied by 1, hours of moderate PA multiplied by 2, and hours of vigorous PA multiplied by 3. This scoring scheme was selected based on available evidence showing that moderate PA for typical activities (3-6 Metabolic Equivalents, METS) expands about twice as much energy as mild PA (~2 METS), while vigorous PA (10-11 METS) expands about three times as much energy as mild PA (Ainsworth et al., 2000; Jette et al., 1990).

MRI Data Acquisition

Participants were imaged using a 1.5-tesla Phillips Gyroscan scanner (Phillips Medical Systems, Best, Netherlands). 3-D structural T1-weighted images were acquired in coronal orientation using a Fast Field Echo (FFE) sequence with the following parameters: repetition time (TR)/echo time (TE) = 28.005/2.64ms; flip angle = 30°; matrix size = 256 X 256; field

of view (FOV) = 260 X 260mm; slice thickness = 2.0mm and mid-slice to mid-slice distance = 1.0mm, providing over-contiguous coronal slices and an in-plane spatial resolution of 1.016 X 1.016 X 1.016mm/pixel.

Image Processing

All images were processed using FreeSurfer (<http://freesurfer.net>) (Fischl, 2012) and BrainVisa software (<http://brainvisa.info/>) (Shokouhi et al., 2011). FreeSurfer enables automatic parcellation of cortical surface volumes using T1-weighted images (Dale et al., 1999). Briefly, magnetic field inhomogeneities are corrected and after removal of non-brain tissue skull-stripped images are segmented into grey and white matter. Sub-cortical structures are segmented. Cutting planes are computed, separating cerebral hemispheres and disconnecting subcortical structures. A preliminary segmentation is then generated and interior holes filled, producing a single filled volume for each cortical hemisphere. The resulting volume is covered with a triangular tessellation and deformed to produce an accurate and smooth representation of the grey and white matter interface as well as the pial surface. Finally, regional structures are segmented and volumes extracted according to the FreeSurfer atlas (Dale et al., 1999; Desikan et al., 2006).

The three-dimensional cortical surface produced in FreeSurfer is then imported into BrainVisa. Using the program pipelines, a model of cortical sulci is automatically produced for each participant. This process includes: 1) cortical surface extraction in which a three-dimensional representation of the cortical surface is produced; 2) gyral and sulcal regions are differentiated from each other and segmented; 3) an anisotropic geodesic distance map of the different depths of sulcal regions is computed; and 4) anisotropic skeletons – representations of the shape or “hull” of identified sulci - is extracted. Based on these steps, BrainVisa

produces an integrated map combining all measurable cortical sulci with labels extracted from a brain atlas (i.e. labels identified in FreeSurfer) (Kochunov et al., 2012).

For each sulcus two measurements were considered in the present study: average depth and width. According to Kochunov et al. (Kochunov et al., 2005), sulcal depth is characterised by the distance from the pial surface of surrounding gyral areas to the deepest point in the sulcus. This measurement is repeated at all points along the length of the sulcus and is measured perpendicular to the trajectory of the sulcal axis (the path followed by the base of the sulcus), then averaged over all measurements to provide a measure of average depth. Sulcal width is the mean distance from one gyral area to that opposite and is computed based on the volume of the cerebrospinal fluid filling the sulcus divided by the surface of the sulcal mesh (computed in BrainVisa).

Regions of interest

Consistent with previous research which showed sulcal width to be associated with cognitive function (i.e. Kochunov et al., 2010; Kochunov et al., 2009; Liu et al., 2011), this study examined the same regions of interest including the Central, Intraparietal, Superior Frontal, and Superior Temporal Sulci. In addition, the Inferior Frontal Sulcus was selected as a secondary measure in the frontal lobes, as age-related atrophy in the frontal lobe is particularly pronounced (Fox and Schott, 2004). Independent measures of mean depth and width were assessed in both the left and right hemispheres for these five sulci (*Figure 2*). Matching the selected sulci the following surrounding gyral volumes were also examined: 1) for the Central Sulcus: precentral and postcentral gyri; 2) for the Intraparietal Sulcus: superior parietal and inferior parietal gyri; 3) for the Superior Frontal Sulcus: superior frontal, and rostral and caudal middle frontal gyri; 4) for the Superior Temporal Sulcus: superior temporal and middle temporal gyri; and 5) for the Inferior Temporal Sulcus: rostral middle gyrus and

pars triangularis. In addition, as ageing processes and PA are known to have some global effects total brain volume and the volume of the hippocampus were also investigated.

Neuropsychological tests

Executive function and processing speed were assessed using the *Symbol Digit Modalities Test* (SDMT) (Strauss et al., 2006) and the *Trail Making Test Part B* (TMT-B) (Reitan and Wolfson, 1985). The SDMT was scored as the number of correct matches identified as corresponding with the symbols and digits in the stimulus code. TMT-B was scored as the amount of time taken to complete the task. Processing speed was measured independently using the *Trail Making Test Part A* (TMT-A) (Reitan and Wolfson, 1985) and the Purdue Pegboard both hands task (Tiffin and Asher, 1948). TMT-A was scored as the amount of time taken to complete the task. Purdue Pegboard was scored as the number of pairs of pins placed into the pegboard device within the allocated time. Working memory was assessed using the *Digits-Span Backwards Task* (Pisoni et al., 2011), scored as the total number of digit sequences correctly repeated in reverse order. The first list of the *California Verbal Learning Test* (Rannikko et al., 2012) was used for both immediate and delayed recall measures, scored as the number of words correctly recalled from the administered list. The *Spot-the-Word task* (STW)(Mackinnon and Christensen, 2007) was used as a measure of verbal intelligence, scored as the number of words correctly identified by the participant. Finally, a composite cognitive measure was computed by summing all individual cognitive test z-scores. For this measure scores on TMT-A and TMT-B were reverse-scored.

Statistical Analyses

Statistical analyses were computed using IBM SPSS Statistics 20.0. Using volumetric and sulcal measures (computed in FreeSurfer and BrainVisa respectively), hierarchical regression

analyses were performed to examine the associations between PA and brain structure controlling for age, gender, and education. Sulcal characteristics and matching regional volumes were separately entered as dependent variables into hierarchical regression analyses with age, gender, and education (block 1), and PA (block 2) entered as independent variables. To determine whether PA-related brain structures were associated with cognitive function known to be supported by the investigated areas, further hierarchical regressions were conducted. Scores for individual cognitive measures were separately entered as dependent variables in hierarchical regression analyses with age, gender, and education (block 1), and sulcal measures (block 2) entered as independent variables.

Results

Descriptive analyses demonstrated that the selected sample was well-educated, cognitively healthy Caucasian older adults (Table 1). Participants had an average of 14.25 years of education, a greater number than required to complete the final year of high school in Australia. Scores on the Mini-Mental State Exam averaged 29.37, suggesting a largely unimpaired sample. On average, participants reported an average 7.94 hours of mild activity (e.g. walking, weeding), 3.57 hours of moderate activity (e.g. dancing, cycling), and 0.9 hours of vigorous activity (e.g. running, squash) each week.

Bivariate correlations between physical activity and socio-demographic measures are as follows: age ($r=.019$; $p=.735$); gender ($r=.140$; $p=.013$); education ($r=.044$; $p=.431$); MMSE ($r=-.158$; $p=.005$); and BMI ($r=-.105$; $p=.064$). Bivariate correlations between physical activity and cognitive measures are as follows: digits backwards ($r=-.071$; $p=.210$); Purdue Pegboard ($r=-.127$; $p=.024$); SDMT ($r=-.063$; $p=.260$); TMT-A ($r=.044$; $p=.433$); TMT-B ($r=.065$; $p=.249$); immediate recall ($r=-.014$; $p=.797$); delayed recall ($r=.004$; $p=.947$); and Spot-the-Word ($r=-.079$; $p=.164$).

Tables 2 and 3 present the association between PA, sulcal width and depth, and gyral grey matter volume. Hierarchical regression analyses controlling for age, gender, and education showed higher PA to be associated with narrower width of the **Left Superior Frontal Sulcus** ($\Delta R^2 = .015$; $p = .027$), the **Left Central Sulcus** ($\Delta R^2 = .016$; $p = .025$) and the **Right Central Sulcus** ($\Delta R^2 = .024$; $p = .006$) (Table 2). No significant associations were found between PA and sulcal depth or between PA and any of the volumetric measures (Table 3). In addition, to remove bias in selecting covariates these analyses were repeated using all covariates reported in sample characteristics. They produced essentially the same results (Supplementary Tables 1 and 2). Also, because some participants with missing data on the PA measure were excluded from the main analyses, further sensitivity analyses including these participants with imputed their PA measures were conducted. They too produced essentially the same results (not shown).

To determine whether PA-related sulcal characteristics were associated with cognitive functions supported by cerebral regions adjoining the sulci further analyses were conducted. Table 4 presents the association between PA-related sulcal measures and cognitive function. Greater width of the **Left Superior Frontal Sulcus** was found to be associated with poorer performance on **TMT-B** ($\Delta R^2 = .014$; $p = .036$) and greater width of the **Left Central Sulcus** was associated with poorer performance on the **delayed recall** task ($\Delta R^2 = .011$; $p = .050$).

Discussion

This study aimed to determine whether the effect of a known contributor to brain health - physical activity (PA) - could be more effectively assessed by complementing traditional analyses, including regional volumes, with measures of sulcal characteristics. The main findings showed that: 1) higher levels of PA were associated with narrower width of the Left Superior Frontal and Right Central Sulci but not with cortical volumes in adjoining gyral

areas, and 2) narrower width of the Left Superior Frontal Sulcus was also associated with better cognitive performance.

These findings support the view that sulcal measures and specifically sulcal width can be more sensitive than volumetric gyral measures at indexing variance associated with PA. The detected associations between higher levels of PA and narrower width of the Left Superior Frontal Sulcus (frontal lobe), Left Central Sulcus (parietal lobe), and the Right Central Sulcus (parietal lobe) are of particular interest as age-related cerebral atrophy is most pronounced in the frontal and parietal lobes (Fox and Schott, 2004). These findings further add to the available evidence and suggests that higher levels of PA may be protective against age related changes in subtle brain structure indexed by sulcal characteristics but not yet detectable in gyral volumes.

In another study of sulcal characteristics and cognitive function, Liu et al. (Liu et al., 2011) showed Left Superior Frontal Sulcal width to be associated with processing speed, while no associations were found between Right Central Sulcal width and cognition. In accordance, the current study demonstrated an association between narrower width of the Left Superior Frontal Sulcus and better processing speed, and no association between Right Central Sulcal width and cognition. However, in addition to these findings, the current study also found narrower Left Superior Frontal Sulcus width to be associated with better executive function and narrower Left Central Sulcus width to be associated with better episodic memory. Hence, these findings further support the notion that sulcal characteristics are not only sensitive measures of brain structure, but that the variance they share with PA is also associated with cognitive ability. These results are consistent with research showing that PA is associated with both grey (Erickson et al., 2010) and white matter (Colcombe et al., 2003) integrity and suggest that because sulcal width is likely to be influenced by both grey and white matter variance, change in sulcal width may become detectable earlier than that of

other volumetric measures. Future research needs to confirm this interpretation and to more systematically investigate the associations between volumetric measures, sulcal characteristics, contributors to cerebral health, and cognitive performance in order to determine whether the effects presented here are generalisable to other domains.

It is unclear why sulcal depth was not associated with PA. It may be that as certain brain regions (e.g. frontal lobe) shrink the combined decrease in grey and white matter leads to gyri spreading in a fan-like fashion which may produce much more sulcal widening than shallowing. This speculation will require further investigation, particularly focusing on the parallel trajectories of volumetric tissue volume and sulcal characteristics as well as on more holistic models of brain shape configuration changes (e.g. how the brain sags following atrophy and/or disconnection of specific regions with age – processes which are poorly understood).

This study has a number of limitations but also several strengths. First, while PATH is a population representative study in which participants were randomly selected into the neuroimaging sub-study from the larger population-representative cohort, it may not be completely representative of the population at large. Additional exclusion based on technical and statistical rationale may again lessen the representativeness of the selected sample. Second, while the use of a narrow age cohort avoids some biases due to cohort effect and therefore allows for more sensitive detection of associations between PA, sulcal characteristics and cognitive performance, it also makes it more difficult to generalize the current findings to other age groups. Third, PA was assessed using self-report measures which may be susceptible to biases not found with objective measures. Fourth, the PA measure utilised was not as precise as measures which assign METS units to individual activities and which have been used in other investigations. Finally, cognitive measures used are designed to be informative to broad cognitive domains. It is possible that more specific

cognitive measures may correlate more strongly with individual sulci. Despite these limitations, this study is characterized by significant strengths. First, its large sample size and narrow age range makes this study significantly more representative of the population than other neuroimaging studies which traditionally include much larger age ranges in convenience samples (Lemaitre et al., 2012). Second, while traditional imaging methods (e.g. volumetric measures) are considered somewhat limited in older populations, the current use of sulcal characteristics as a measure of brain structure was found to be sensitive and appropriate in the current sample.

In conclusion, the present findings bring more evidence supporting the importance of physical activity as a contributor to cerebral health. Moreover, they suggest that PA effects on brain structure may be detected earlier when sulcal width is included as a marker of cerebral integrity.

References

- Ahlskog, J.E., Geda, Y.E., Graff-Radford, N.R., Petersen, R.C., 2011. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clinic Proceedings* 86, 876-884.
- Ainsworth, B.E., Haskell, W.L., Whitt, M.C., Irwin, M.L., Swartz, A.M., Strath, S.J., O'Brien, W.L., Bassett, D.R., Jr., Schmitz, K.H., Emplaincourt, P.O., Jacobs, D.R., Jr., Leon, A.S., 2000. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 32, S498-504.
- Anderson-Hanley, C., Arciero, P.J., Brickman, A.M., Nimon, J.P., Okuma, N., Westen, S.C., Merz, M.E., Pence, B.D., Woods, J.A., Kramer, A.F., Zimmerman, E.A., 2012. Exergaming and older adult cognition: a cluster randomized clinical trial. *American Journal of Preventive Medicine* 42, 109-119.
- Angevaren, M., Aufdemkampe, G., Verhaar, H.J., Aleman, A., Vanhees, L., 2008. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews*, CD005381.
- Anstey, K.J., Christensen, H., Butterworth, P., Easteal, S., Mackinnon, A., Jacomb, T., Maxwell, K., Rodgers, B., Windsor, T., Cherbuin, N., Jorm, A.F., 2011. Cohort Profile: The PATH through life project. *International Journal of Epidemiology*.
- Bielak, A.A., Hughes, T.F., Small, B.J., Dixon, R.A., 2007. It's never too late to engage in lifestyle activities: significant concurrent but not change relationships between lifestyle activities and cognitive speed. *J Gerontol B Psychol Sci Soc Sci* 62, P331-339.
- Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., Kramer, A.F., 2003. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci* 58, 176-180.
- Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D.X., Hu, L., Kramer, A.F., 2006. Aerobic exercise training increases brain volume in aging humans. *Journals of Gerontology: Series A* 61, 1166-1170.
- Colcombe, S.J., Kramer, A.F., Erickson, K.I., Scalf, P., McAuley, E., Cohen, N.J., Webb, A., Jerome, G.J., Marquez, D.X., Elavsky, S., 2004. Cardiovascular fitness, cortical plasticity, and aging. *PNAS* 101, 3316-3321.
- Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage* 9, 179-194.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* 31, 968-980.

Erickson, K.I., Miller, D.L., Weinstein, A.M., Akl, S.L., Banducci, S., 2012. Physical activity and brain plasticity in late adulthood: a conceptual and comprehensive review. *Ageing Research* 3, 34-47.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Hu, L., Morris, K.S., White, S.M., Wojcicki, T.R., McAuley, E., Kramer, A.F., 2009. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus* 19, 1030-1039.

Erickson, K.I., Raji, C.A., Lopez, O.L., Becker, J.T., Rosano, C., Newman, A.B., Gach, H.M., Thompson, P.M., Ho, A.J., Kuller, L.H., 2010. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology* 75, 1415-1422.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences* 108, 3017-3022.

Etgen, T., Sander, D., Huntgeburth, U., Poppert, H., Forstl, H., Bickel, H., 2010. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. *Archives of Internal Medicine* 170, 186-193.

Fischl, B., 2012. FreeSurfer. *NeuroImage*.

Fox, N.C., Schott, J.M., 2004. Imaging cerebral atrophy: normal ageing to Alzheimer's disease. *Lancet* 363, 392-394.

Gerecke, K.M., Kolobova, A., Allen, S., Fawer, J.L., 2013. Exercise protects against chronic restraint stress-induced oxidative stress in the cortex and hippocampus. *Brain Res* 8993, 027.

Honea, R.A., Thomas, G.P., Harsha, A., Anderson, H.S., Donnelly, J.E., Brooks, W.M., Burns, J.M., 2009. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. *Alzheimer Dis Assoc Disord* 23, 188-197.

Im, K., Lee, J.-M., Seo, S.W., Kim, S.H., Kim, S.I., Na, D.L., 2008. Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer's disease. *NeuroImage* 43, 103-113.

Jette, M., Sidney, K., Blumchen, G., 1990. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 13, 555-565.

Kochunov, P., Charlesworth, J., Winkler, A., Hong, L.E., Nichols, T.E., Curran, J.E., Sprooten, E., Jahanshad, N., Thompson, P.M., Johnson, M.P., Kent, J.W., Jr., Landman, B.A., Mitchell, B., Cole, S.A., Dyer, T.D., Moses, E.K., Goring, H.H., Almasy, L., Duggirala, R., Olvera, R.L., Glahn, D.C., Blangero, J., 2013. Transcriptomics of cortical gray matter thickness decline during normal aging. *NeuroImage* 82, 273-283.

Kochunov, P., Coyle, T., Lancaster, J., Robin, D.A., Hardies, J., Kochunov, V., Bartzokis, G., Stanley, J., Royall, D., Schlosser, A.E., Null, M., Fox, P.T., 2010. Processing speed is correlated with cerebral health markers in the frontal lobes as quantified by neuroimaging. *NeuroImage* 49, 1190-1199.

Kochunov, P., Mangin, J.F., Coyle, T., Lancaster, J., Thompson, P., Riviere, D., Cointepas, Y., Regis, J., Schlosser, A., Royall, D.R., Zilles, K., Mazziotta, J., Toga, A., Fox, P.T., 2005. Age-related morphology trends of cortical sulci. *Human Brain Mapping* 26, 210-220.

Kochunov, P., Robin, D.A., Royall, D.R., Coyle, T., Lancaster, J., Kochunov, V., Schlosser, A.E., Fox, P.T., 2009. Can structural MRI indices of cerebral integrity track cognitive trends in executive control function during normal maturation and adulthood? *Human Brain Mapping* 30, 2581-2594.

Kochunov, P., Rogers, W., Mangin, J.F., Lancaster, J., 2012. A library of cortical morphology analysis tools to study development, aging and genetics of cerebral cortex. *Neuroinformatics* 10, 81-96.

Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? *Neurobiology of Aging* 33, 617 e611-619.

Liu, T., Wen, W., Zhu, W., Kochan, N.A., Trollor, J.N., Reppermund, S., Jin, J.S., Luo, S., Brodaty, H., Sachdev, P.S., 2011. The relationship between cortical sulcal variability and cognitive performance in the elderly. *NeuroImage* 56, 865-873.

Mackinnon, A., Christensen, H., 2007. An investigation of the measurement properties of the Spot-the-Word test in a community sample. *Psychol Assess* 19, 459-468.

Muscari, A., Giannoni, C., Pierpaoli, L., Berzigotti, A., Maietta, P., Foschi, E., Ravaioli, C., Poggiopollini, G., Bianchi, G., Magalotti, D., Tentoni, C., Zoli, M., 2010. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. *International Journal of Geriatric Psychiatry* 25, 1055-1064.

Pisoni, D.B., Kronenberger, W.G., Roman, A.S., Geers, A.E., 2011. Measures of digit span and verbal rehearsal speed in deaf children after more than 10 years of cochlear implantation. *Ear and hearing* 32, 60S-74S.

Radak, Z., Chung, H.Y., Goto, S., 2008. Systemic adaptation to oxidative challenge induced by regular exercise. *Free Radic Biol Med.* 44, 153-159. doi: 110.1016/j.freeradbiomed.2007.1001.1029. Epub 2007 Jan 1023.

Rannikko, I., Paavola, L., Haapea, M., Huhtaniska, S., Miettunen, J., Veijola, J., Murray, G.K., Barnes, A., Wahlberg, K.E., Isohanni, M., Jaaskelainen, E., 2012. Verbal learning and memory and their associations with brain morphology and illness course in schizophrenia spectrum psychoses. *J Clin Exp Neuropsychol.*

Reitan, R.M., Wolfson, D., 1985. Rehabilitation of the Brain-Damaged Adult. *The Journal of Nervous and Mental Disease* 173, 379.

Rosano, C., Venkatraman, V.K., Guralnik, J., Newman, A.B., Glynn, N.W., Launer, L., Taylor, C.A., Williamson, J., Studenski, S., Pahor, M., Aizenstein, H., 2010. Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. *J Gerontol A Biol Sci Med Sci* 65, 639-647.

Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R., Grant, M., 1993. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 88, 791-804.

Shokouhi, M., Barnes, A., Suckling, J., Moorhead, T.W., Brennan, D., Job, D., Lymer, K., Dazzan, P., Reis Marques, T., Mackay, C., McKie, S., Williams, S.C., Lawrie, S.M., Deakin, B., Williams, S.R., Condon, B., 2011. Assessment of the impact of the scanner-related factors on brain morphometry analysis with Brainvisa. *BMC Medical Imaging* 11, 23.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Browndyke, J.N., Sherwood, A., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomatic Medicine* 72, 239-252.

Spitzer, R.L., Kroenke, K., Williams, J.B., 1999. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. Jama* 282, 1737-1744.

Stranahan, A.M., Martin, B., Maudsley, S., 2012. Anti-inflammatory effects of physical activity in relationship to improved cognitive status in humans and mouse models of Alzheimer's disease. *Curr Alzheimer Res* 9, 86-92.

- Strauss, E., Sherman, E.M.S., Spreen, O., 2006. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, 3rd Edition ed. Oxford University Press, New York.
- Taubert, M., Lohmann, G., Margulies, D.S., Villringer, A., Ragert, P., 2011. Long-term effects of motor training on resting-state networks and underlying brain structure. *NeuroImage* 57, 1492-1498.
- Tiffin, J., Asher, E.J., 1948. The Purdue Pegboard: norms and studies of reliability and validity. *Journal of applied psychology* 32, 234.
- Van Essen, D.C., 1997. A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 385, 313-318.
- van Praag, H., Christie, B.R., Sejnowski, T.J., Gage, F.H., 1999. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences* 96, 13427-13431.

Table 1: Sample characteristics

Characteristics	Overall Sample (N = 317)
Age, years (SD)	66.48 (1.43)
Range	64-70
Male, N (%)	172 (54.09)
Education, years (SD)	14.25 (2.70)
MMSE, score (SD)	29.37 (1.11)
BMI, score (SD)	26.49 (4.31)
Physical activity score (SD)	2.54 (0.93)
Hours of mild physical activity (SD)	7.94 (8.66)
Hours of moderate physical activity (SD)	3.57 (4.82)
Hours of vigorous physical activity (SD)	0.90 (2.48)
Alcohol Consumption	
Abstain/occasional, N (%)	75 (23.6)
Light/medium, N (%)	227 (71.4)
Hazardous/harmful, N (%)	16 (5.0)
Smoke	
History or Current, N (%)	134 (42.1)
Depression	
Anti-depressive medication, N (%)	19 (6.0)
BPHQ Minor Depression, N (%)	14 (4.4)
BPHQ Major Depression, N (%)	6 (1.9)
Cognitive Test Performance	
Digits backwards, mean (SD)	5.33 (2.08)
Purdue Pegboard, mean (SD)	10.73 (1.81)
Symbol Digit Modalities	50.84 (8.54)
Trails A, mean (SD)	32.84 (9.08)
Trails B, mean (SD)	76.69 (26.66)
Immediate recall, mean (SD)	7.22 (1.95)
Delayed recall, mean (SD)	6.35 (2.28)
Spot-the-word, mean (SD)	53.39 (5.39)

Table 2: Relationships between physical activity and sulcal characteristics

Region	Width		Depth	
	ΔR^2	β	ΔR^2	β
Left intraparietal	<.001	.001	<.001	.014
Right intraparietal	.002	-.044	.001	.036
Left superior frontal	.015*	-.125	.003	.050
Right superior frontal	.007	-.085	.001	.036
Left inferior frontal	<.001	-.003	.002	.046
Right inferior frontal	<.001	.005	.001	.031
Left superior temporal	<.001	-.015	.002	-.045
Right superior temporal	.002	.048	.002	.042
Left central	.016*	-.126	<.001	.021
Right central	.024**	-.156	.003	.054

* $p < .05$; ** $p < .01$. Hierarchical regression analysis between physical activity and sulcal characteristics (width and depth) controlling for age, gender, and education.

Table 3: Associations between physical activity and grey matter volumes

Gyrus	Left		Right	
	ΔR^2	β	ΔR^2	β
Precentral	<.001	.013	<.001	.013
Postcentral	<.001	.013	<.001	.013
Superior Parietal	<.001	.011	<.001	.013
Inferior Parietal	<.001	.014	<.001	.013
Superior Frontal	<.001	.012	<.001	.011
Rostral Middle Frontal	<.001	.012	<.001	.012
Caudal Middle Frontal	<.001	.012	<.001	.013
Superior Temporal	<.001	.013	<.001	.013
Middle Temporal	<.001	.013	<.001	.013
Pars Triangularis	<.001	.012	<.001	.013
Hippocampus	<.001	.013	<.001	.013
Total brain volume	<.001	.007		

* $p < .05$. Hierarchical regression analysis between physical activity and regional volumes controlling for age, gender, and education.

Table 4: Associations between brain structure and cognitive scores

	Left Superior Frontal Sulcal Width		Left Central Sulcal Width		Right Central Sulcal Width	
	ΔR^2	β	ΔR^2	β	ΔR^2	β
Digits back	<.001	-.017	.001	-.025	<.001	.004
Purdue both	<.001	.016	.002	-.044	<.001	-.003
SDMT	.002	-.048	.004	-.065	.006	-.079
TMT-A	.002	.044	.002	.043	.002	.039
TMT-B	.013*	.116	.001	.038	.001	-.024
Immediate recall	.003	-.058	.010	-.099	.009	-.096
Delayed recall	.004	-.062	.011*	-.106	.008	-.092
STW	.001	.025	.001	.027	.004	.061

* $p < .05$. Hierarchical regression analysis between brain structure and cognition controlling for age, gender, and education. SDMT: Symbol Digit Modalities Test, TMT – A: Trail Making Test part A, TMT – B: Trail Making Test part B, STW: Spot-the-Word task.

Figures

Figure 1: Sample inclusion

Figure 2: Sulci examined highlighted on the left cortical surface of one participant. Image in a) axial and b) sagittal orientation.
 Legend: red – Superior Frontal Sulcus; purple – Inferior Frontal Sulcus; Yellow; Central Sulcus; green = Intraparietal Sulcus; blue – Superior Temporal Sulcus.

Figure 3: Regional volumes examined highlighted on the left cortical surface of one participant.

Image in a) axial and b) sagittal orientation.

Legend: Light green – Superior Frontal Region; purple – Rostral Middle Frontal Region; deep red – Caudal Middle Frontal Region; light blue – Pars Triangularis; dark blue – Precentral Region; light red – Postcentral Region; pink – Superior Parietal Region; dark green – Inferior Parietal Region; yellow – Superior Temporal Region; orange – Inferior Temporal Region.

Supplementary Table 1: Relationships between physical activity and sulcal characteristics

Region	Width		Depth	
	ΔR^2	β	ΔR^2	β
Left intraparietal	<.001	.016	<.001	-.002
Right intraparietal	.001	-.039	.001	.035
Left superior frontal	.017*	-.132	.004	.061
Right superior frontal	.007	-.087	.001	.033
Left inferior frontal	<.001	-.011	.004	.062
Right inferior frontal	<.001	-.003	.002	.033
Left superior temporal	<.001	.004	.004	-.062
Right superior temporal	.003	.058	.002	.044
Left central	.015*	-.122	.001	.026
Right central	.023**	-.160	.004	.065

* $p < .05$; ** $p < .01$. Hierarchical regression analysis between physical activity and sulcal characteristics (width and depth) controlling for age, gender, education, systolic and diastolic blood pressure, smoking history, alcohol consumption, depression, and body mass index.

Supplementary Table 2: Associations between physical activity and grey matter volumes

Gyrus	Left		Right	
	ΔR^2	β	ΔR^2	β
Precentral	<.001	-.026	<.001	-.026
Postcentral	<.001	-.025	<.001	-.026
Superior Parietal	<.001	-.027	<.001	-.026
Inferior Parietal	<.001	-.025	<.001	-.026
Superior Frontal	<.001	-.027	<.001	-.028
Rostral Middle Frontal	<.001	-.026	<.001	-.027
Caudal Middle Frontal	<.001	-.026	<.001	-.026
Superior Temporal	<.001	-.025	<.001	-.026
Middle Temporal	<.001	-.026	<.001	-.025
Pars Triangularis	<.001	-.026	<.001	-.026
Hippocampus	<.001	-.025	<.001	-.025
Total brain volume	<.001	.023		

* $p < .05$. Hierarchical regression analysis between physical activity and regional volumes controlling for age, gender, education, systolic and diastolic blood pressure, smoking history, alcohol consumption, depression, and body mass index.