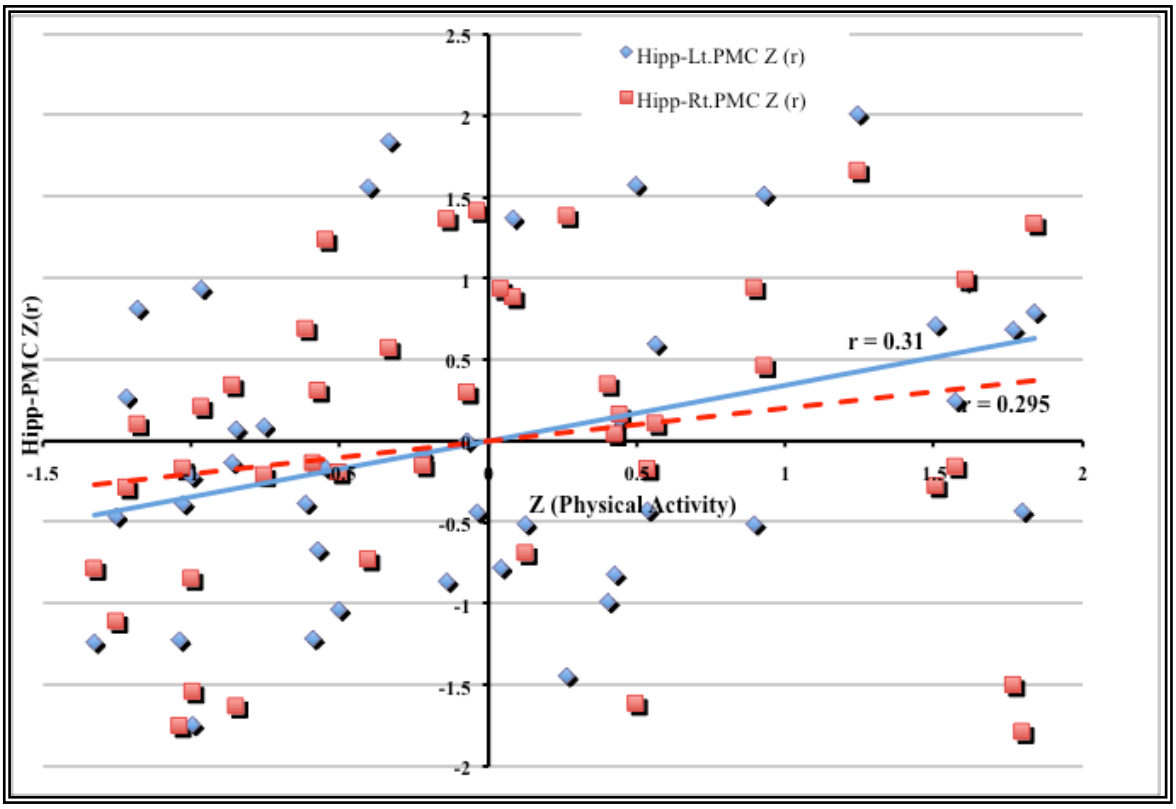
Supplementary Materials



Supplementary Figure 1: Presents scatter-plots of the correlation between standardized physical activity, and fisher transformed hippocampus-posteriomedial connection for the left (in blue) and right (in red) hippocampus after removing three outliers with physical activity data greater than 2 S.D. units.

METHODS

Functional and Structural MRI parameters

Participants were scanned at the Wright Center of Innovation on Ohio State campus using a 3T Philips full body scanner. High-resolution structural images were collected for each participant using a 3D Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE) protocol with 160 contiguous sagittal slices (TE/TR/TI 3.7/8.1/1005 ms), collected in an ascending fashion, parallel to the anterior and posterior commissures

using a spoiled gradient sequence (240 × 240 mm FOV; 1 mm thick slices, with a 1 × 1 x 1 mm in-plane resolution) with a flip angle of 8 degrees. Resting-state dataset was acquired following a fairly standard protocol in which participants were asked to lie down still on the scanner bed. Ambient light was minimized, and the participants were asked to lie with their eyes open, think of nothing in particular, and not fall asleep. These are standard resting state instructions that have been employed throughout the literature (Andrews-Hanna, Reidler, Huang & Buckner, 2010; Damoiseaux et al., 2008; Smith et al., 2009), resulting in robust characterization of the functional networks. For the functional resting-state scan, T2*-weighted echo planar images (EPIs) were acquired with the following sequence parameters: repetition time (TR)=2000 ms., echo time (TE)=24 ms., flip angle=80 degrees, number of slices = 38, voxel size = 3.44 mm isotropic. We acquired one six-minute functional scan, with 180 volumes.

Data Analyses

Behavioral Analyses

Recognition data collected for the Item and Relational Memory task was analyzed using PASW 18.0. In order to minimize response bias, a *d'* index based on the accuracy scores was calculated for face recognition, scene recognition, and face-scene recognition. All responses to the recognition trials were classified as a hit, miss, correction rejection, false alarm or a no response. A "hit" was defined as correctly identifying a previously studied item as old, whereas a "miss" was defined as incorrectly identifying a previously studied item as new. A "correct rejection" was defined as correctly identifying a newly presented item as new, whereas a "false alarm" was defined as incorrectly identifying a newly

studied item as old. In order to calculate the *d'* index, we added a constant of 0.05 to all responses, and *d'* was defined by subtracting the z-score of the false alarms from the z-score of the hits (with chance performance represented by a d' score of 0). *d'* index was calculated separately for the face recognition trials, scene recognition trials, and the face-scene recognition trials and used in all subsequent analyses.

Image Analyses

Structural MRI preprocessing and FIRST segmentation – All structural data was analyzed using FSL 4.1.4 (Smith et al., 2004, Woolrich, Behrens, Beckmann, Jenkinson, & Smith 2004). The high-resolution T1 images were used firstly, to compute the spatial transformation from the mean functional EPI image for the resting state functional scan to the high-resolution MPRAGE image, and the transformation from the MPRAGE image to the standard MNI (Montreal Neurological Institute) template. These transformations were then concatenated into a single transformation (Jenkinson, Bannister, Brady, & Smith 2002), and applied to the parameter estimates derived from the connectivity analyses to achieve a common spatial coordinate system for mixed-effects analyses.

Secondly, these high-resolution images were used for segmenting each participant's left and right hippocampus using FMRIB's Integrated Registration and Segmentation Tool (FIRST, Patenaude, Smith, Kennedy, & Jenkinson, 2007, 2008) to generate individual-level seeds for seed-based connectivity analyses. FIRST is a model-based, sub-cortical segmentation and registration tool utilizing a Bayesian framework, which has been reliably used in previous studies to segment sub-cortical structures, including the hippocampus, to study individual differences (Chaddock et al., 2010;

Erickson et al., 2009). The shape and appearance models used in FIRST are based on 336 manually segmented brain images from pathological and healthy populations provided by the Center for Morphometric Analysis, MGH, Boston, which are parameterized as surface meshes and modeled as a point distribution model.

The procedure involves a two-stage affine registration of the high-resolution T1 image to a standard space MNI template with 1-mm resolution, with the first stage being the cortical registration of the T1 images to the standard template, and the second stage involving a sub-cortical mask so as to exclude voxels outside the sub-cortical regions. This was followed by segmentation of the left and right hippocampus using 30 modes of variation, and boundary correction to avoid overlap of sub-cortical structures based on a statistical probability (*z-score* > 3.00, $p < 0.001$). The final segmented image resulted in masks for the left and right hippocampus, comprising of the dentate gyrus, the ammonic subfields (CA 1-4), the prosubiculum, and the subiculum for each individual participant.

Preprocessing for seed-based functional connectivity analyses – For seed-based connectivity analyses, we employed fMRIB's software library (FSL version 4.1.4, Smith et al., 2004). The following pre-statistics processing was applied to the resting-state EPI data before the analyses: rigid body motion correction using MCFLIRT (Jenkinson et al., 2002), removal of non-brain structures using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 6.0-mm, grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor, and temporal filtering to restrict the bandwidth of the fMRI signal to $.008 < f < .060$ Hz.

To remove the potential influence of participant movement, and signal from the white matter and CSF on low-frequency spontaneous oscillations, we regressed out the

timeseries of these variables from the preprocessed data. Specifically, for each participant, we first regressed out the six motion parameters computed by rigid body translation and rotation in preprocessing (Jenkinson et al., 2002). Second, employing FMRIB's Automatic Segmentation Tool (FAST), we segmented the T1 image into masks of gray matter, white matter, and cerebrospinal fluid (CSF) probability maps. The white matter, and CSF maps were then used as masks to extract mean timeseries data, which was then regressed out from the preprocessed data to generate a 4D residual functional dataset, independent of the confound of these nuisance variables.

RESULTS

Brain-Behavior Associations

All associations between physical activity and the strength of functional connectivity between the hippocampus and regions of interest were examined using non-parametric partial correlations, after removing variance associated with age, education, gender, and disease duration. In here, physical activity was found to be associated with a greater functional connectivity between the left hippocampus-PMC connection and right hippocampus-PMC connection. Three of the forty-five participants had physical activity scores that exceeded 2 S.D. units and thus to ensure that the observed results were not driven primarily by the effects of the outliers, we removed these three participants and the correlation between physical activity and increased connectivity remained statistically significant (pr = 0.31 for left Hipp.-PMC connection and pr=0.295 for right Hipp.-PMC connection). These results are graphically displayed in Supplementary Figure 1.

References

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