Daily-life Physical Activity of Young Healthy Adults Associates with Function and Structure of the Hippocampus

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Daily-life physical activity of young healthy adults associates with function and structure of the hippocampus

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Abstract

Research on the impact of physical activity (PA) has shown that PA produces changes in the structure and function of a brain structure called the hippocampus. There are three main limitations in this research. First, the majority of the work has been carried out in elderly populations and as such, there is a paucity of research on the impact of PA on the brains of healthy young individuals. Second, whereas PA is typically assessed through controlled interventions, changes in the brain due to PA as performed during daily-life activities has not been explored. Finally, the hippocampus has a complex internal structure and the impact of PA on this internal structure is unclear. Here we examined how structural and functional aspects of the hippocampus are associated with habitual PA performed during work, leisure time and sports in the daily lives of young healthy adults. We found that PA performed during work time correlated with increased subicular volumes and with changed functional connectivity between a location in middle/posterior hippocampus and regions of the default mode network and between a location in anterior hippocampus and regions of the somatomotor network. No effects of PA performed during leisure time and sports were found. The results generalize the impact of PA to younger populations and show how PA performed in daily-life situations correlates with the precise internal structure of the hippocampus.

Keywords: Physical Activity; MRI; Functional Connectivity; Hippocampus; Subiculum; CA1

Introduction

It is now well-documented that the increasingly low Physical Activity (PA) and sedentary lifestyles in western societies are associated with compromised cognitive performance and mental health issues (Sormunen et al., 2017; Guthold et al., 2018; Gregory et al., 2012; Hills et al., 2011; Karege et al., 2002; Green et al., 2011; McMahon et al., 2017; O'Dougherty et al., 2012). Both animal and human studies have shown that PA affects a brain structure called the hippocampus (e.g., Vivar & van Praag, 2017; A. Thomas et al., 2012). For example, structural and resting-state functional Magnetic Resonance Imaging (sMRI and rsfMRI) studies have found that increased PA is associated with structural changes in hippocampal volumes (e.g., Frodl et al., 2019; A. G. Thomas et al., 2016), and with functional changes in the way that the hippocampus connects with other large-scale brain networks (Tao et al., 2016; Burdette et al., 2010). However, three main issues limit a more general interpretation of these results. First, although these studies have been instrumental in understanding the effects of PA on the brain, they have primarily studied PA in elderly populations and there is a lack of studies examing the effect of PA in young healthy adults. Second, PA is typically studied through controlled intervention programs. This means that the way that PA that is habitually performed during normal daily-life situations has not been explored. Finally, whereas previous studies show the impact of PA on the hippocampus as a whole, the way that PA affects the internal structure of the hippocampus remains poorly understood. Here we attempted to address these issues by studying how changes in hippocampal subfield volume and functional connectivity (FC) between hippocampus and other brain areas are related to habitual PA in a population of young healthy adults. To this end we performed a cross-sectional and data-driven multi-modal MRI study and assessed PA during work time, leisure time and sports.

Previous studies with both animals and humans have shown that PA produces structural changes in the hippocampus. For example, animal studies with rodents have found

that PA promotes neurogenesis, preservation of new neurons, angiogenesis and other molecular and cellular changes in the adult hippocampus (Vivar & van Praag, 2017; Kramer & Erickson, 2007; Bullitt et al., 2009; A. Thomas et al., 2012; So et al., 2017). In humans, most studies have examined structural changes in the hippocampus in groups of elderly participants. For example, such studies show that regular PA leads to better cognitive performance and increased hippocampal volumes (K. Erickson & Kramer, 2009; K. I. Erickson et al., 2011; A. Thomas et al., 2012; Jonasson et al., 2017; Makizako et al., 2015). Furthermore, rsfMRI studies examining functional connectivity in elderly have shown that PA produces changes in the way the hippocampus co-activates with other large-scale networks (e.g., Weng et al., 2017). Specifically, studies consistently find increased hippocampal connectivity to various default mode network areas such as anterior and posterior midline areas, as well as with motor areas (Tao et al., 2016; Ikuta et al., 2019; Prakash et al., 2011; Esteban-Cornejo et al., 2021; Voss, Erickson, et al., 2010; Voss, Prakash, et al., 2010; Voss et al., 2016; Burdette et al., 2010; Boraxbekk et al., 2016; Weng et al., 2017). For example, Voss, Prakash, et al. (2010) studied the effects of 3-times-per-week 1-year-long interventions for both aerobic and non-aerobic exercise in groups of elderly participants. They randomly assigned elderly participants to a program for aerobic walking exercise or a control program (toning, flexibility and balance). They found that after 12 months, the aerobic exercise group showed higher functional connectivity between regions of the default mode network than the non-aerobic exercise group.

Thus, although these studies show that PA leads to both structural (volume) and functional (FC) changes in the hippocampus in elderly participants, the impact of PA in young healthy adults remains poorly understood. Clearly, young adults also experience mental health issues and therefore understanding whether PA confers similar benefits for young adults is also important (McMahon et al., 2017; O'Dougherty et al., 2012; Sor-

munen et al., 2017). In addition, although the aforementioned studies have established the impact of PA on hippocampal structure as a whole, our understanding of how PA affects the internal structure of the hippocampus remains poor. Specifically, the hippocampus is not a homogeneous structure, and can be divided into subfields that vary in their cellular and molecular composition and in their anatomical connectivity (Andersen et al., 2007). However, studies have not found a consistent set of findings that reveal the impact of PA on the hippocampal subfields. For example, some studies have found that PA produced volume increases in the DG/CA3/CA4 (DG: Dentate Gyrus; CA: Cornu Ammonis) subfields (Frodl et al., 2019; Nauer et al., 2020), whereas others have found an impact on other subfields like the Subiculum (SUB) and CA1 (Frodl et al., 2019; Rosano et al., 2017; Nauer et al., 2020; Kern et al., 2021; Varma et al., 2016). In addition, Broadhouse et al. (2020) found that 18 months of exercise in patients with mild cognitive impairment halted volume reduction in SUB and reduced loss in CA1 and DG. Understanding why PA has such different effects on hippocampal structure is crucial in understanding the specific processes that benefit our brain health.

In terms of the functional connectivity of the hippocampus with the rest of the brain, most previous studies have examined how PA affected the relationship between the hippocampus and the default mode network (Tao et al., 2016; Ikuta et al., 2019; Prakash et al., 2011; Esteban-Cornejo et al., 2021; Voss, Erickson, et al., 2010; Voss, Prakash, et al., 2010; Voss et al., 2016; Burdette et al., 2010; Boraxbekk et al., 2016; Weng et al., 2017). However, it is well-known that the hippocampus co-activates with at least two different whole-brain resting-state networks (Ezama et al., 2021; Kahn et al., 2008; Ranganath & Ritchey, 2012; Vincent et al., 2006). For example, Ezama et al. (2021) found that during the resting-state, anterior sections of the hippocampus co-activated with brain regions typically associated with the somatomotor network, whereas middle/posterior sections of the hippocampus co-activated with brain regions typically

associated with the default mode network. Thus, whereas previous studies have shown that PA affects the connectivity between the hippocampus and the default mode network (Kronman et al., 2020; Stillman et al., 2018; Raichlen et al., 2016), how PA is associated to the connectivity between the hippocampus and the somatomotor networks remains unknown.

Here we assessed three types of habitual PA in a group of young healthy adults. For each participant, we obtained measures of PA during occupational time, sports and leisure time (Baecke et al., 1982). In addition, for each participant we collected structural and rsfMRI data that was preprocessed using Human Connectome Project minimnal preprocessing pipelines (Glasser et al., 2013; Dickie et al., 2019). We obtained volume estimates for the hippocampal subfields using automatic segmentation procedures (Iglesias et al., 2015). The functional connectivity analyses relied on an analysis approach previously developed in our laboratory (Ezama et al., 2021). We first performed Independent Component Analysis spatially restricted to the hippocampus (srICA; Blessing et al., 2016). We then calculated the functional connectivity of the independent components using a Dual Regression approach (Nickerson et al., 2017) and computed corresponding group-level maps. We then examined the correlation between these group level maps and existing reference resting-state networks (Yeo et al., 2011). Based on previous studies, we expected to find an anterior cluster of activity inside the hippocampus that was connected with the somatomotor network, and a middle/posterior cluster that was connected with the default mode network (e.g., Ezama et al., 2021; Kahn et al., 2008, 2008; Prakash et al., 2011; Ranganath & Ritchey, 2012; Buckner & DiNicola, 2019). In the final step of our analyses we tested whether the functional connectivity of the activation clusters detected inside the hippocampus and their associated resting-state networks were modulated by different levels of PA in work, sports and leisure-time. The analyses relied on regression models that took into account both variability by subject in terms of brain measures

(volume, functional connectivity) as well as brain morphology. We used linear regression models to assess whether hippocampal subfield volume was modulated by different levels of PA in the aforementioned contexts.

Methods

Participants

Thirty-two participants took part in the experiment. The data from one participant was discarded on the basis of quality control measures, and one on the basis of registration issues (see Supplementary Figure S1). In the final set of 30 participants, mean age was 23.9 yrs (sd = 7.8 yrs), and 27 % was male (see also Table 1). All participants were right-handed native Spanish speakers. Participants were recruited from two on-going studies in the laboratory. We ensured that participants did not have any neurological or psychiatric disorder. Participation in this experiment was completely voluntary and no reward was administered. The study was conducted in agreement with the declaration of Helsinki, and all participants provided informed consent in consonance with the protocol established by the Ethics Commission for Research of the University of La Laguna (Comité de Ética de la Investigación y Bienestar Animal).

Physical Activity assessment

Physical activity was assessed using a standardized questionnaire (Baecke et al., 1982). Assessment was performed in an on-line fashion using *Google forms*. All questionnaire data was obtained within one week after the MRI scans were performed. This questionnaire categorizes physical activity in three main divisions according to the context in which it occurs. Specifically, the questionnaire contains questions that intent to assess a person's physical activity during work, during sports, and during leisure time. The

questionnaire consisted of a total of 16 items, of which 8 items assessed physical activity during work, 4 items physical activity during sports and 4 items physical activity during leisure time. Questions were generally about the physical intensity, frequency and physical demand of the activities in all three contexts. All questions were answered on a 3 or 5 points Likert scale. Finally, following calculations provided by Baecke et al. (1982), individual participant's scores were converted into three separate indices that indicate the amount of physical activity during work (work index), during sports (sports index) and during leisure time (leisure index). Correlations between the three habitual PA indices in our sample are displayed in Table 2. Additional personal information, such as height, weight and age, was also requested on the Google form.

MRI data acquisition

Functional and structural data were acquired on a 3T General Electric Signa Excite MRI machine using a standard 8 channel head coil. Head motion was constrained by placing foam pads inside the coil, and earplugs were used to minimize the scanner noise. As participants were recruited from two different on-going studies in the laboratory, their functional data was acquired with two different imaging protocols, referred to here as dataset1 and dataset2. Dataset1 was acquired as part of a high spatial resolution study of the hippocampus. The protocol employed a partial zoomed FOV acquisition strategy as outlined in (Olman et al., 2009). For images in this dataset, 20 coronal slices focused on the hippocampus were acquired. Slice thickness was 2.4 mm with a 0.6 mm gap. The FOV was 192 x 96 mm, matrix size 128 x 64, resulting in 1.5 x 1.5 x 3 mm voxels. The TR was 1800 ms, TE 33 ms, and the flip angle 75°. In each run 200 volumes were collected and lasted 6 minutes. Dataset2 was a more standard whole-brain acquisition. For images in this dataset, 36 axial slices that covered the entire brain were acquired. Slice thickness was 3.7 mm with 0.3 mm gap. The FOV was 256 x 256 mm, matrix size

64 x 64 resulting in 4 mm isotropic voxels. The TR was 2.0 s, TE 40 ms and the flip angle 90°. In each run 440 volumes were collected and lasted around 15 minutes. Note that these obvious differences in dataset acquisition protocol result in signal intensity differences that we take into account in our statistical models reported below.

Finally, structural images were acquired using the same protocol in both datasets. Specifically, high resolution T1-weighted images were acquired for all the subjects using the same 3D FSPGR sequence: TI 650, TR of 6.8, and TE 1.4 ms, FA = 12°, 196 slices, slice thickness 1 mm, matrix 256 × 256, voxel size = 1 × 1 × 1 mm. Other images such as T2w and other functional runs were acquired but not analyzed here.

Preprocessing

Preprocessing of structural and functional data was performed using the Human Connectome Project (HCP) minimal preprocessing pipeline (v4.1.3) in Legacy Style Data mode (Glasser et al., 2013). For the preprocessing of the structural T1w images we used the pre-freesurfer, freesurfer and post-freesurfer batch scripts which we adapted to our specific situation (i.e., no T2w image, no readout distortion correction, 1mm MNI HCP templates, no gradient distortion correction, no conf2hires). The Freesurfer script relied on `freesurfer v6.0` (Dale et al., 1999). The post-freesurfer script was left at all default settings. Next, for the preprocessing of the fMRI datasets we used both the generic fMRI volume and generic fMRI surface batch scripts which were also adapted to our situation (i.e., first volume as reference, no susceptibility distortion correction, T1 dilated fMRI mask). Importantly, both dataset1 and dataset2 were resampled to the HCP standard MNI nonlinear space with 2 mm resolution (i.e., the parameter 'final fMRI resolution' was set to 2 mm for both datasets), resulting in aligned images in 2 mm MNI space between the two datasets. In addition, for the preprocessing of the partial FOV data from dataset1, the 'EPI2T1w' script was adapted to produce more accurate registrations

between the EPI and T1w images. Specifically, it was discovered that the original T1w images were more easily aligned with the partial FOV EPI data than the T1w images that were processed with FSL's robustFOV. Nevertheless, this registration procedure failed for one participant in dataset1 which was subsequently removed from the study.

Quality control of both the structural and functional data was performed by computing Euler's number from the freesurfer output (Rosen et al., 2018), and by computing for all functional data a composite score of head motion displacements from the six motion regressors (Jenkinson et al., 2002). Results of Quality Control are presented in Figure S2. As mentioned earlier, we removed one participant based on a large negative Euler number and a high head motion composite score. After completing the HCP pipeline, three additional preprocessing steps were performed on the functional data. First, all functional data from dataset2 was cleaned for head motion using `ICA-AROMA v0.3` with default options (Pruim et al., 2015). In addition, because ICA-AROMA did not work for the partial FOV data from dataset1, functional data from this dataset was cleaned manually using ICA. Next, all functional data was temporally filtered using high-pass filter at 2000 seconds. Finally, the white matter and CSF signals were regressed out of the functional data using participant-specific white-matter and CSF masks derived from the freesurfer wmparc atlas. All further analyses were performed on these 30 (1 run for 30 participants) cleaned datasets.

Analyses

Group creation

In the first main step of the analyses we created six groups based on individual participant's physical activity scores. Specifically, we created groups based on the work indices, on the sports indices and leisure time indices. We assigned participants to a particular group based on a median split, where one group contained participants with low physical

activity scores during a particular context and another group contained participants with high physical activity scores during a particular context. In short, three variables were created that corresponded to WorkIndex, SportsIndex and LeisureIndex. For distribution of the scores on these three variables and their median split see Figure S6.

Structural MRI data

To examine whether physical activity was associated with structural measures and to further examine which substructures of the hippocampus were related to physical activity we analyzed the effect of physical activity on the structure of the hippocampus. Specifically, we examined whether physical activity was associated with the volume of the hippocampal subfields. Hippocampal subregions were segmented using a tool based on a probabilistic atlas (Iglesias et al., 2015). Specifically we used the script `segmentHA_T1 v21` on the output produced by Freesurfer v6.0. The output of this script is a list of each hippocampal subfield with its estimated volume for each participant. In addition, the script lists the subfield volumes separately for the body and head of the hippocampus.

Substructures of the hippocampus proper included the Cornu Ammonis 1 (CA1), CA2/3, CA4, the Dentate Gyrus (DG), as well as the presubiculum (preSub) and subiculum (SUB). The molecular layer (ML) is generally not considered a subfield of the hippocampus proper but was included in these analyses for technical reasons. In particular, including the ML in the regression analyses (detailed below) ensures that variability in the volumes due to this structure is not assigned to other subfields. The CA1 segmented area included the CA1 pyramidal layer and the medial part of CA1, and did not include the hippocampal molecular layer. The segmentation procedure could not separate CA2 and CA3, thus these two subfields were labelled together as CA2/3. CA2/3 segmentation did not include the molecular layer either. CA4 label consisted of the hilus, the polymorphic and molecular layers of the DG. The segmentation called DG in this study consisted

of the granule cell layer of the DG. Finally, parasubiculum subfield was removed from the analysis because it was not sectioned into head and body by the segmentation software used.

We performed statistical analyses to assess whether volume of the hippocampal subfields is associated with PA in three habitual contexts. Specifically, we constructed a single large dataset that contained the volume estimates for all subfields in the body and head of the hippocampus and for all participants. We then ran a single statistical model that tested for the interaction between Group, Hippocampal Subfield and Hippocampal Section (i.e., body vs head). This model takes into account the variability between participants by including a random intercept for participants. In addition, we performed data inspection as well as model inspection to examine possible violations of model assumptions (see Figure S7). No serious problems were detected. The final model took the following form:

$$volume = Gender + Hemisphere + Group \times Subfield \times Section + random(participant), \quad (1)$$

where $Gender$ refers to a co-factor with two levels (male, female), $Hemisphere$ was a co-factor with two levels (left and right), $Group$ a factor that indicated whether a given participant had low or high physical activation, $Subfield$ a variable that denoted the different hippocampal subfields, and $Section$ a factor that denoted the location of the hippocampus (head, body, tail). Note that the variable participant age was not significant and therefore removed from the model. The dependent variable was the volume of a specific subfield that depended on the head, body and tail of the hippocampus.

In this model we were particularly interested in the triple interaction $Group \times$

$Subfield \times Section$ which tested the hypothesis that subfield volumes in different sections of the hippocampus would be correlated with the physical activity of the participants. However, note that in this model we were also interested in the lower order interaction $Group \times Subfield$ which simply revealed whether subfield volume would be related to phsyical activity independently of the particular section of the hippocampus. Again as before, note that this model allows for the estimation of participant-specific random variability which is not standard in analyses of brain structure (Kong et al., 2020).

Functional MRI data

The main goal of this analysis was to examine how different levels of habitual physical activity were linked to differences in functional connectivity between specific areas of the hippocampus and the rest of the brain. To this end, there were three main steps in the analyses. In the first step, we relied on an approach called spatially-restricted group Independent Component Analysis (ICA)(ICA Blessing et al., 2016; McKeown et al., 1998) combined with Dual Regression (Nickerson et al., 2017). First, the hippocampus was segmented from each individual participant's fMRI data in MNI space using a participant-specific bilateral hippocampal mask derived from the freesurfer aparc+aseg atlas (Desikan et al., 2006). This resulted in 30 4D fMRI datasets (one for each participant) that contained signal changes only in the bilateral hippocampal area. We then performed group spatial-ICA on the concatenation of all 30 datasets using `FSL Melodic v3.15`. This resulted in the detection of hippocampal clusters that may or may not reflect true BOLD signal activity. We refer to such locations as "hotspots". We obtained most clearly interpretable results with 4 dimensions, although we also report the results for 3 and 5 dimensions in the Supplementary Materials (see Figures S3-5). Next, we computed functional connectivity from the estimated time courses and associated each hippocampal hotspot and the rest of the brain using the Dual Regression technique (Nickerson et al.,

2017). Group level maps were also computed using `FSL randomise`. These group level maps did not serve any other purpose than to classify each detected hotspot as true BOLD signal or noise. The final outcome of this procedure were participant-specific Z value maps for each hippocampal hotspot, where each voxel in the map indicated the degree to which it was functionally connected with the specific hippocampal hotspot. In line with other studies, we refer to these maps as co-activity maps (Sourty et al., 2015).

The main difference between this approach and a standard seed based approach is that instead of placing seeds in arbitrary locations inside the hippocampus, the ICA procedure finds clusters of voxels inside the hippocampus that show activity during the resting-state (Blessing et al., 2016; Formisano et al., 2004; Vincent et al., 2006; Kahn et al., 2008; Qin et al., 2016). It can therefore be ensured that functional connectivity is computed from locations inside the hippocampus that are actually active during the scanning session.

The final main step of the analyses tested how functional connectivity between each hippocampal hotspot and the rest of the brain was affected by differences in physical activity. Specifically, we relied on an approach in which Z values averaged across voxels in specific atlas regions were compared between groups. These atlas regions were obtained from each individual participant's aparc+aseg freesurfer atlas. The main advantage of this approach is that the atlas regions are defined in terms of the unique morphology of each individual participant's brain and therefore avoid problems with variability in brain morphology typically associated with voxel-based group analyses (e.g., Anticevic et al., 2008; Van Essen et al., 2012). Note that this approach should be differentiated from surface-based approaches in which volumetric fMRI activity is projected to the cortical surface (Fischl et al., 2004; Glasser et al., 2013). Statistical modeling of these data examined the triple interaction between Group, Brain region, and Hippocampal hotspot. The main mixed effect regression model that was tested in our analyses was:

$$Z\_value = Hemisphere + Group \times Brain\_Region \times Hotspot + random(participant) + random(dataset), \quad (2)$$

where $Hemisphere$ was a co-factor with two levels (left and right), $Group$ a factor that indicated whether a given participant had low or high physical activation, $brain\_region$ a variable that denoted the different areas of the aparc+aseg atlas available in the current dataset, $Hotspot$ a factor that referred to the number of ICs classified as signal. Importantly, three separate models were constructed where the $Group$ variable either referred to low and high Work, Leisure, or Sports index. In addition, note that the model included random effects terms for the variables participant and dataset. These latter variables were included to take into account the random variance associated between different participants and the different datasets (see Figure S5).

As before, in this model we were particularly interested in the triple interaction term between $Group \times Brain\_Region \times Hotspot$, which tests if the different co-activity values observed for brain regions between the different IC clusters would depend on the group. In other words, this interaction tested whether connectivity between different hippocampal hotspots and the rest of the brain was associated with level of physical activity. Note there are also lower order interactions with the variable Group in this model (i.e., $Group \times Brain\_Region$ and $Group \times Hotspot$) which we do not further examine.

Again as before, we employed model specification that relied on model justification and model inspection (Zellner et al., 2001). Specifically, each variable in the model was justified by model comparisons using ANOVA tests. In addition, violations of basic model assumptions were assessed by plotting distribution and residual plots (see Figures S5 and

S6). Variables for Gender and Age did not have significant effects and were therefore excluded from the model. Note that random slopes for any of the main effects lead to indeterminate models. Note also that the inclusion of a participant random intercept enables the estimation of participant specific variability which has been shown to lead to more accurate parameter estimates (Westfall et al., 2016; Barr et al., 2013).

All mixed effect modeling relied on `R v3.6.3` using the package `lme4 v4.1.1`. We will report results from our analyses using type III ANOVA estimates obtained directly from our mixed effect models using the package `lmerTest v3.1` using the Satterthwaite's method to extract the p values (Kuznetsova et al., 2017), and results from individual comparisons that are also directly extracted from the mixed effect models using the package `emmeans v1.4.6`. All individual comparisons examined the effect of Group by Brain region and by Hippocampal hotspot and were corrected for multiple comparisons using the Bonferroni correction.

Results

Structural data

The regression analyses for Work Index using equation 1 as a model revealed an interaction between Subfield and Work Index Group, suggesting that volumes of the hippocampal subfields depended on the group. Note that there were no significant interactions for the Leisure and Sports Index analyses (see Table 3 for a full overview of the statistics from all three regression models). Further exploration of this interaction using pairwise comparisons of the high versus the low group for each subfield revealed that there were significantly increased volume estimates for the pre-subiculum and subiculum subfields ($p < 0.05$) and a trend in the CA1 subfield ($p = 0.07$) in the high Work Index group versus the low Work Index group (see Figure 1 for a graphical overview).

Functional MRI data

The spatially restricted group ICA with four dimensions revealed four clear hotspots in the different locations of the hippocampus. Of these four, two hotspots, IC0 and IC3, were clearly interpretable as BOLD signal. The other two independent components can be seen in the SI. As can be observed in Figures 2 and 3, IC0 and IC3 represented hotspots in a middle/posterior location and in an anterior location of the hippocampus, respectively. In particular, IC0 was located along the middle/posterior section of the hippocampus and is connected strongly with isthmus cingulate, parahippocampal gyrus, putamen, lateral orbitofrontal cortex, and several lateral temporal regions. By contrast, IC3 was located in an anterior section of the hippocampus and connected with anterior regions like the amygdala and the nucleus accumbens (see Supplementary Table S1). Please also note that analyses with fewer dimensions or more dimensions did not lead to more interpretable results (see Figures S2-4).

Impact of PA on hippocampal connectivity

The results above indicate that during the resting-state, there were two locations inside the hippocampus that co-activated with two whole-brain networks. Specifically, the hotspot in middle/posterior sctions of the hippocampus (IC0) co-activated with regions of the default mode network, whereas the hotspot located an anterior sections of the hippocampus (IC3) co-activated with regions of the somatomotor network. Subsequent analyses examined the extent to which these two whole-brain resting-state networks were related to the various types of physical activity. For Work Index, the regression analyses described in equation 2 revealed a critical triple interaction between Group, Brain Region and Hotspot ($F(31,3353) = 3.51$, $p < 0.0001$), suggesting that areas of the two whole-brain networks that co-activated with IC0 and IC3 were differentially related to Work Index. For Leisure Index or Sports Index this triple interaction was not signifi-

cant (see Table 4 for a full overview of the statistics from all three regression models). Posthoc analyses that further explored the triple interaction for Work Index revealed the set of cortical and subcortical areas that revealed differences in co-activity between high and low levels of Work Index. Specifically, we found that increased Work Index increased connectivity between the middle/posterior hippocampal hotspot and various posterior midline regions (isthmus cingulate, posterior cingulate cortex, rostral anterior cingulate), lateral and medial orbitofrontal cortex, insula, parahippocampus, as well as lateral temporal areas (STS, transverse temporal cortex). In addition, we found that increased Work Index increased connectivity between the anterior hippocampal hotspot and nucleus accumbens and ventral diencephalon, and decreased connectivity between the anterior hippocampal hotspot and various primary and secondary motor regions (rostral/caudal middle frontal gyrus, pre/postcentral gyrus, pars tri/oppercularis) as well as supramarginal gyrus and caudal anterior cingulate. (see Table 5 for an overview of all areas, and Figures 5 and 4 for a graphical overview).

Discussion

In the current study we examined how various types of PA performed in the daily life of young adults were related to the structure and function of the internal hippocampus. To this end we obtained measures of the amount of PA during work, sports and leisure time as well as structural and resting-state functional MRI data measures from a set of 30 participants. We found that increased PA during work time was associated with higher volumes in the subiculum and presubiculum subfields. There was also a trend for increased volume in the CA1 subfield. PA during sports and leisure time did not show any association with hippocampal subfield volumes. In addition, functional connectivity analyses in the same group revealed that PA performed during work was strongly asso-

ciated with connectivity between two locations in the hippocampus and two large-scale brain networks. Specifically, increased PA performed during work was linked to increased connectivity between a middle/posterior location in the hippocampus and regions of the default mode network. In addition, increased PA performed during work was linked to increased connectivity between an anterior location in the hippocampus and the nucleus accumbens and ventral diencephalon, and decreased connectivity between this anterior location in the hippocampus and areas of the somatomotor network.

Our observation that PA relates to the volume of the CA1 and subicular complex subfields finds resonance in previous studies. For example, Kern et al. (2021) studied the relationship between cardiorespiratory fitness, as defined by VO_2max measures, and hippocampal subfields volumes in elderly participants. They found that VO_2max measures were associated with increased subicular volume of elderly women. Similarly, Varma et al. (2016) found that the total walking PA measured for a week was positively associated with increasing surface area of the subiculum, again in elderly women. In addition, results from Broadhouse et al. (2020) suggest that PA has a larger impact on subicular volume than CA1 and DG subfields volumes in elderly patients with mild cognitive impairment. Various other studies displayed different results. For instance, Rosano et al. (2017) found that PA intervention increased volume of all CA subfields in older participants. In addition, Frodl et al. (2019) and Nauer et al. (2020) found that middle aged and young adults had increased CA4/DG and DG/CA3 volumes to various PA interventions. A common characteristic to these three different results is the use of PA interventions in contrast with the passive measurements of daily PA in Kern et al. (2021) and Varma et al. (2015). A possible explanation is that PA interventions could have acute effects in some structures, while the daily PA, assessed through VO_2max, measured daily walking activity and questionnaires, may have another nature of changes that are reflected in the subiculum. Future studies should look at effects of measured daily PA in contrast

with the effects of PA interventions. Furthermore, previous studies did not differentiate the subiculum and presubiculum and we found individual effects in these two structures. This should be further assessed in subsequent research.

Regarding the functional connectivity results, in line with previous results, we found that during the resting-state there are two activity clusters inside the hippocampus that correlated with the default mode network and the somatomotor network (e.g., Ezama et al., 2021; Kahn et al., 2008; Qin et al., 2016). In addition, our results show that the connectivity between these two activity clusters and resting-state networks is linked to PA in complex ways. Specifically, we found that PA is linked to increased connectivity between the middle/posterior hippocampal activation cluster and regions of the default mode network. This is in accordance with many previous results reported in the literature (Tao et al., 2016; Ikuta et al., 2019; Prakash et al., 2011; Esteban-Cornejo et al., 2021; Voss, Erickson, et al., 2010; Voss, Prakash, et al., 2010; Voss et al., 2016; Burdette et al., 2010; Boraxbekk et al., 2016; Weng et al., 2017). In addition, we found that PA is associated with a decreased connectivity between an anterior hippocampal activation cluster and areas typically involved in the somatomotor network. Specifically, we found that increased PA during work time was linked to increased connectivity between this anterior cluster and the nucleus accumbens and ventral diencephalon, and that increased PA during work was linked to decreased connectivity between the anterior cluster and areas of the somatomotor network like the precentral gyrus. Such decreases in connectivity due to PA have been reported in previous studies where Stillman et al. (2018) found that PA decreased co-activity between the anterior hippocampus and the right superior frontal gyrus. Although these findings remain to be further established, they are illustrative of the complex impact of PA on the brain. Overall, the results reported here indicate the precise locations along the hippocampal long axis that are connected to variations in habitual PA and show how PA is associated with differences in the func-

tional connectivity between specific hippocampal clusters and two known resting-state networks.

Taking the structural and functional data together, the results reported here suggest that PA is associated with structural changes in the subiculum and CA1 subfields, and with functional changes in middle/posterior and anterior hippocampal clusters related to the default mode and somatomotor network, respectively. These observations make sense in light of previous high-spatial resolution functional connectivity studies (Ezama et al., 2021; Dalton et al., 2019; de Flores et al., 2017). These studies have shown that regions of the default mode network reliably co-activate with the presubiculum and subiculum subfields of the middle/posterior hippocampus, and that regions of the somatomotor network co-activate with the CA1 and CA3 regions of the anterior hippocampus. Thus, the current findings of changes in the structure of the presubiculum, subiculum and CA1 subfield along with functional changes in the connectivity with the default mode and somatomotor network therefore further integrate the special relationship of the presubiculum, subiculum and CA1 subfields in the default mode and somatomotor networks. Future studies that combine high spatial resolution functional connectivity with measures of PA may be used to further confirm this role.

One interesting aspect of our results is that we found structural and functional changes in the hippocampus when PA was performed during work, but not during leisure time or sports. One possible reason for this state of affairs has to do with the frequency that the various daily life occupations are carried out. Specifically, work time may involve in most cases at least eight hours per day, five days a week. Previous research has shown the hippocampal volume sensitivity to specific occupational activities. One example is the classical study on the hippocampal volume of the taxi drivers in London (Maguire et al., 2003). Hippocampal volume differences were associated to the spatial cognitive task performed continuously during the working time of the taxi drivers. Greater hip-

pocampal volumes have also been linked to supervisory and managerial roles during the occupational time (Suo et al., 2012). Smaller hippocampal volumes, however, have been found in people that have higher loads of physical stress (e.g., physically dangerous activities) in their working activities (Burzynska et al., 2020). By contrast, the leisure and sports activities are carried out in a more sporadic fashion. Although obvious future studies need to confirm this issue, we speculate that the frequency with which PA is carried out has important consequences for brain health.

A limitation to our study is the lack of information in our sample to disclose more specific aspects of the physical activity performed during occupational time that exert the herein reported effects. As it has been previously commented, the current is an exploratory study on a subject that has not been previously studied. Thus, it needs subsequent efforts in the direction of better understanding aspects of occupational physical activity involved in these effects to our hippocampal structure and function and, in general, to our brains. Another aspect that should be explored in the near future is whether there is any interaction between individual's PA in different habitual contexts in producing the brain changes reported. Although our study focuses on a young and healthy population, our results find agreement with structural and functional connectivity results reported in different age groups. This may mean that there are some general effects to the brain across the lifespan and given a variety of PA-related measures. However, further research is needed to understand the relationship between the PA-related measures and occupational PA to understand why this and no other habitual PA is related to these changes.

To sum up, previous research on PA had shown that PA produces changes in the structure and function of the hippocampus (K. Erickson & Kramer, 2009; A. Thomas et al., 2012; Tao et al., 2016; Ikuta et al., 2019; Esteban-Cornejo et al., 2021; Voss, Erickson, et al., 2010; Boraxbekk et al., 2016; Kern et al., 2021) but had barely addressed whether

such findings generalize to young adults, whether they are found for PA performed in daily life and how they relate to the internal structure of the hippocampus. Here we observed that PA performed during daily work is related to structural changes in the presubiculum, subiculum and CA1 subfields in the hippocampus, and to changes in the functional connectivity between a middle/posterior hippocampal cluster and regions of the default mode network as well as between an anterior cluster and regions of the somatomotor network. Our results shed light onto the specific relationship between PA performed during occupational time and significant structural and large-scale functional connectivity changes to this structure. The hippocampus and its functional connectivity systems are crucial in memory and other important cognitive functions. Furthermore, these hippocampal characteristics are altered in severe neuropsychiatric diseases that have a dramatic incidence worldwide. Given the increasingly sedentary nature of many jobs, better strategies must be found to reduce the impact of sedentarism in workers mental health. Identifying the specific aspects of occupational physical activity are the most relevant to these changes should be key to achieve this.

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Conflict of interest

The authors declare no competing interests.

Author contributions

SS and NJ designed the study, analysed the data and wrote the paper. SS and LE acquired the data.

Data accessibility

The article's supporting data will be provided upon reasonable request.

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Tables

Table 1: Description of the sample

PA index	Group	N	Gender(male)	t-test	Mean age (SD)	t-test
WI	H	15	9	p = 0.481	27.9 (9.1)	p = 0.015
	L	15	7		21.2 (3.1)	
SI	H	14	7	p = 0.743	25.5 (8.0)	p = 0.537
	L	16	9		23.8 (7.3)	
LI	H	10	6	p = 0.622	24.5 (8.8)	p = 0.976
	L	20	10		24.6 (7.0)	

Table 2: Correlations between the three dependent variables.

	Workindex	Sportindex	Leisureindex
Workindex	1.00	0.01	0.08
Sportindex	0.01	1.00	0.33
Leisureindex	0.08	0.33	1.00

Table 3: Full ANOVA tables from the regression modeling of the structural data that examined effects of Work Index, Leisure Index and Sports Index.

	NumDF	DenDF	F value	Pr(>F)
Gender	1	27	7.89	0.0091
Hemisphere	1	29	17.67	0.0002
Section	1	754	2518.21	< 0.0001
Subfield	6	754	2399.71	< 0.0001
WorkIndexGroup	1	27	2.20	0.1493
Sect:Subfield	6	754	1825.63	< 0.0001
Sect:WIGroup	1	754	8.23	0.0042
Subfield:WIGroup	6	754	4.07	0.0005
Sect:Subfield:WIGroup	6	754	1.07	0.3791
Gender	1	27	9.27	0.0051
Hemisphere	1	29	17.67	0.0002
Section	1	754	2017.09	< 0.0001
Subfield	6	754	1943.74	< 0.0001
LeisureIndexGroup	1	27	0.64	0.4319
Sect:Subfield	6	754	1460.21	< 0.0001
Sect:LIGroup	1	754	0.31	0.5780
Subfield:LIGroup	6	754	0.95	0.4592
Sect:Subfield:LIGroup	6	754	0.63	0.7052
Gender	1	27	8.56	0.0069
Hemisphere	1	29	17.67	0.0002
Section	1	754	2412.74	< 0.0001
Subfield	6	754	2271.05	< 0.0001
SportsIndexGroup	1	27	0.11	0.7482
Sect:Subfield	6	754	1730.38	< 0.0001
Sect:SIGroup	1	754	3.52	0.0610
Subfield:SIGroup	6	754	1.06	0.3879
Sect:Subfield:SIGroup	6	754	0.32	0.9269

Table 4: Full ANOVA tables from the regression modeling of the functional connectivity data that examined effects of Work Index, Leisure Index and Sports Index. Note dependent variable in Work Index model was log-transformed.

	NumDF	DenDF	F value	Pr(>F)
Hemisphere	1	3353.84	8.00	0.0047
WorkIndexGroup	1	26.59	1.45	0.2385
Region	31	3353.05	12.51	< 0.0001
IC	1	27.76	17.06	0.0003
WIGroup:Region	31	3353.06	6.35	< 0.0001
WIGroup:IC	1	27.76	13.89	0.0009
Region:IC	31	3353.09	5.54	< 0.0001
WIGroup:Region:IC	31	3353.09	3.51	< 0.0001
Hemisphere	1	3603.03	4.93	0.0264
LeisureIndexGroup	1	27.05	0.46	0.5015
Region	31	3603.02	7.89	< 0.0001
IC	1	3603.01	121.49	< 0.0001
LIGroup:Region	31	3603.02	0.92	0.5884
LIGroup:IC	1	3603.01	0.01	0.9050
Region:IC	31	3603.01	4.31	< 0.0001
LIGroup:Region:IC	31	3603.01	1.05	0.3885
Hemisphere	1	3603.03	4.94	0.0263
SportsIndexGroup	1	27.05	0.29	0.5976
Region	31	3603.03	8.92	< 0.0001
IC	1	3603.01	129.01	< 0.0001
SIGroup:Region	31	3603.03	2.29	0.0001
SIGroup:IC	1	3603.01	28.91	< 0.0001
Region:IC	31	3603.01	3.76	< 0.0001
SIGroup:Region:IC	31	3603.01	0.76	0.8294

Table 5: Overview of pairwise individual comparisons of the effects of work index on each cortical and subcortical area that showed co-activity with the two hotspots inside the hippocampus

Region	Z-ratio	IC	p-value
iCing	4.65	IC0	3.398E-06
Ptm	4.07	IC0	4.753E-05
Hipp	3.76	IC0	1.685E-04
pCC	3.39	IC0	6.864E-04
VentralDC	3.27	IC0	1.067E-03
STS	2.97	IC0	2.974E-03
lOF	2.40	IC0	1.642E-02
mOF	2.34	IC0	1.911E-02
parHipp	2.30	IC0	2.164E-02
insula	2.25	IC0	2.469E-02
transTemp	2.22	IC0	2.621E-02
rACC	2.21	IC0	2.729E-02
Thalamus	2.08	IC0	3.733E-02
Accumbens	2.03	IC0	4.251E-02
Accumbens	2.92	IC3	3.516E-03
Hipp	2.57	IC3	1.028E-02
VentralDC	2.08	IC3	3.732E-02
preCent	-2.16	IC3	3.100E-02
cACC	-2.25	IC3	2.421E-02
parsOpp	-2.27	IC3	2.334E-02
postCent	-2.52	IC3	1.172E-02
parsTri	-2.65	IC3	8.118E-03
rMF	-2.75	IC3	5.910E-03
supraMar	-3.12	IC3	1.836E-03
cdMF	-3.60	IC3	3.151E-04

Figures

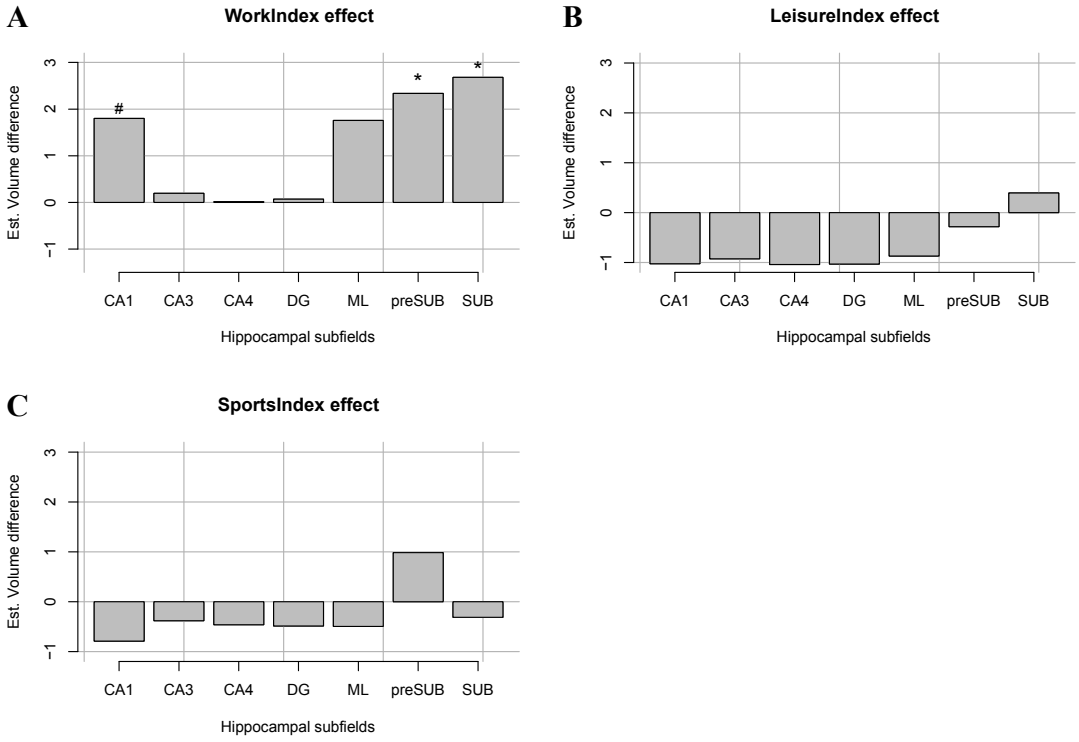


Figure 1: Estimated volume difference between high and low index of occupational PA (A), leisure-time PA (B) and sports time PA (C) per each hippocampal formation segment (CA1, CA3, CA4, DG, ML, preSUB and SUB). '*' indicates that a volume difference was significant between high and low PA groups for a certain PA context and hippocampal formation structure.

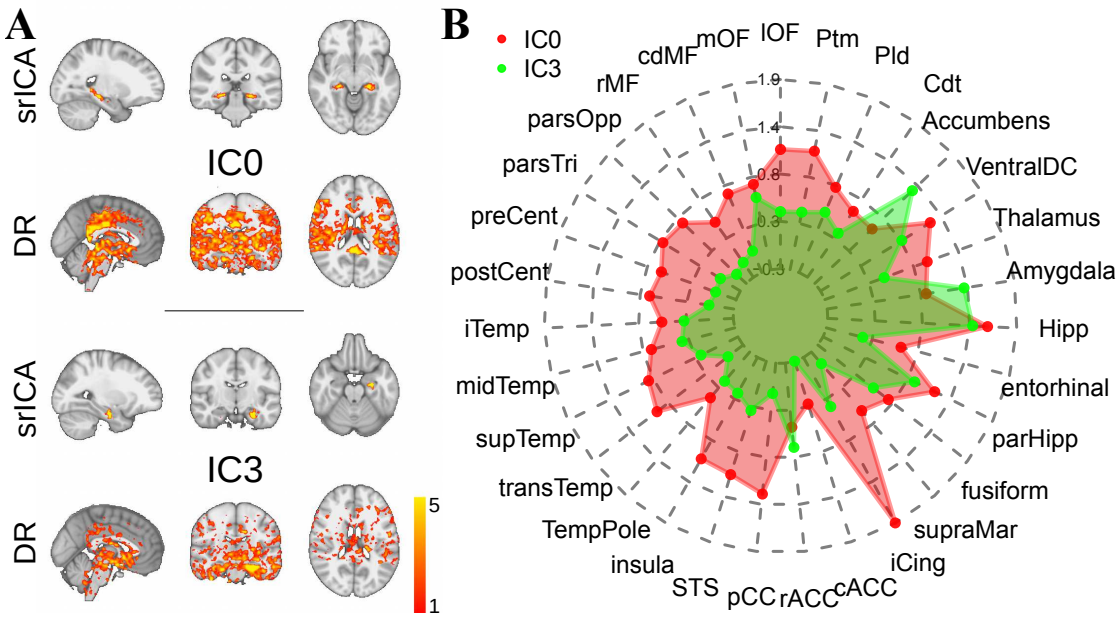


Figure 2: Hippocampal independent components and their large-scale co-activation networks. In panel A, upper rows, we see the components IC0 and IC3 resulting from spatially restricted ICA to the hippocampus, and in panel A, lower rows, their corresponding FC maps that were calculated through a Dual Regression. Co-activation is indicated in Z-values that are represented in the color gradient bar from red, low, to yellow, high. Panel B reveals the co-activation coefficients of IC0 (in red) and IC3 (in green) with the rest of the brain. Note how IC0 and IC3 show contrastive co-activity with different whole-brain networks.

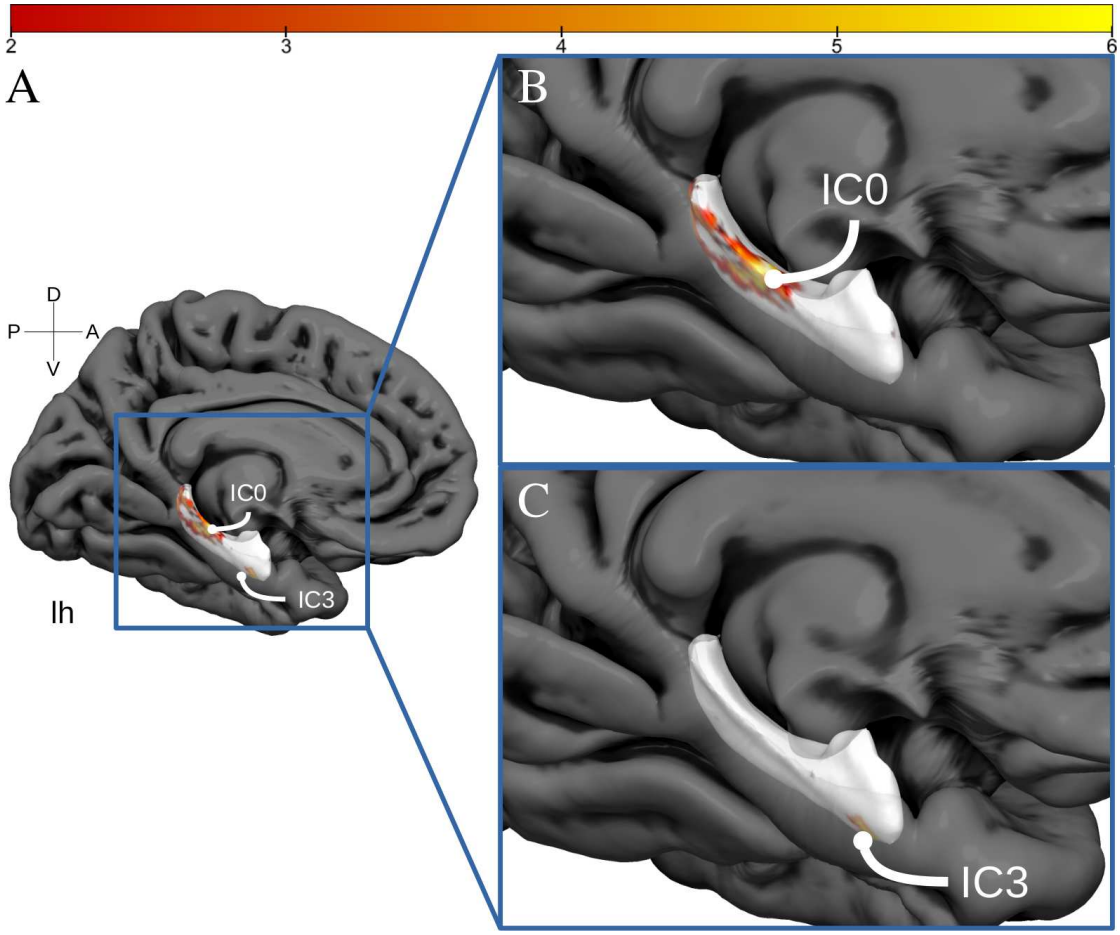


Figure 3: Hippocampal activation clusters projected to a surface representation of the left hippocampus. In A we see a medial view of the left hemisphere of fsaverage. In B we see a zoomed view of this hemisphere and the IC0 projected to the hippocampal surface. IC0 is displayed as a middle-posterior activation cluster. In C we see the IC3 projected to the same zoomed hippocampal surface.

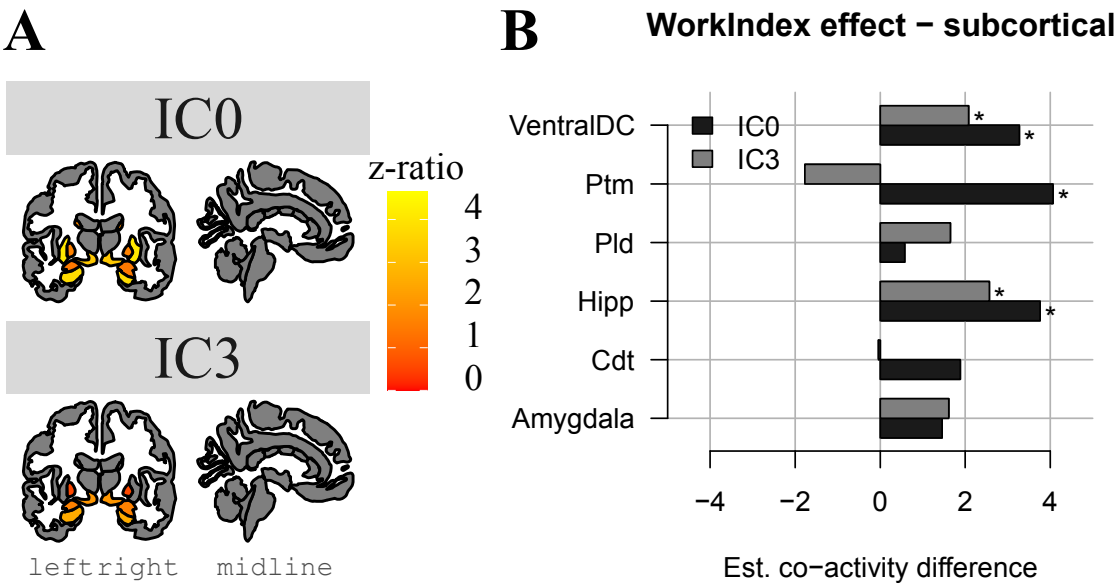


Figure 4: Changes in hippocampal FC to subcortical structures in high PA compared to low PA during work. In A we see a representation of the increased z-ratio, co-activation values, of the subcortical structures with hippocampal activation clusters IC0 (in the upper part) and IC3 (in the lower part). Z-values are represented with a gradient of color on subcortical parcellations in coronal and sagital views of the brain (left to right). In B we see the the same co-activation changes in a bar plot, in which we can compare the changes between IC0 and IC3.

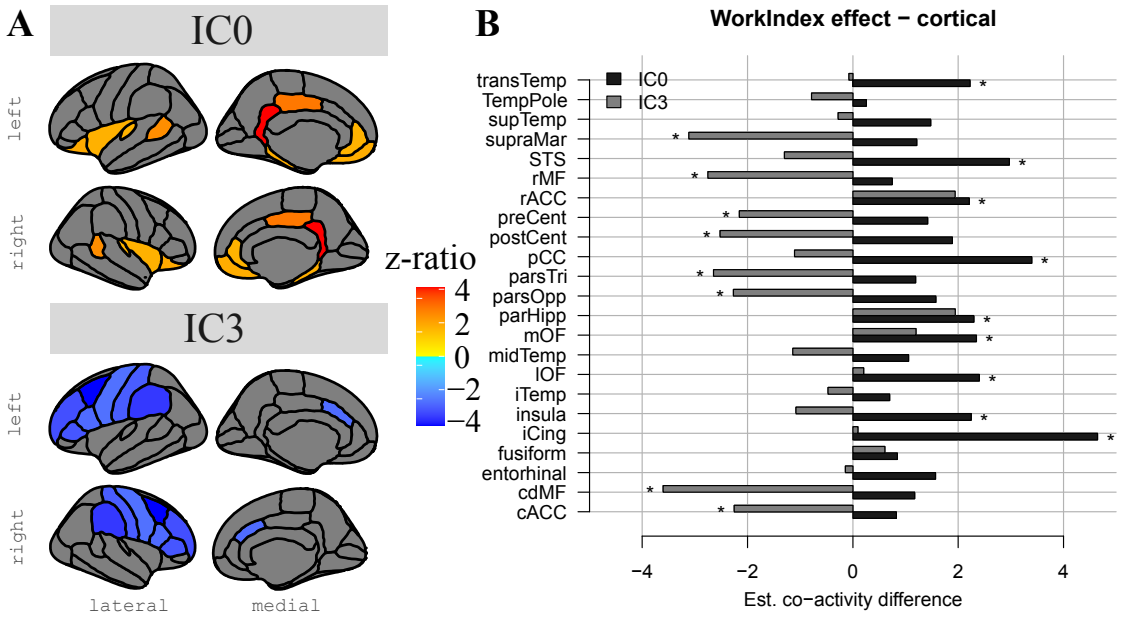


Figure 5: Changes in hippocampal FC to cortical structures in high compared to low PA during work. In A we see a representation of the differences in hippocampal-cortical co-activation between high and low PA during work. Co-activation is expressed in z-ratios as displayed on the color gradient bar. Co-activation with IC0 is represented in the upper part and co-activation with IC3, in the lower part. Lateral and medial surfaces are displayed from left to right. In B there is a bar plot representation of the same comparison between co-activation values in high and low occupational PA, but this time we can visually compare hippocampal-cortical coactivation in IC0 and in IC3.

Figures

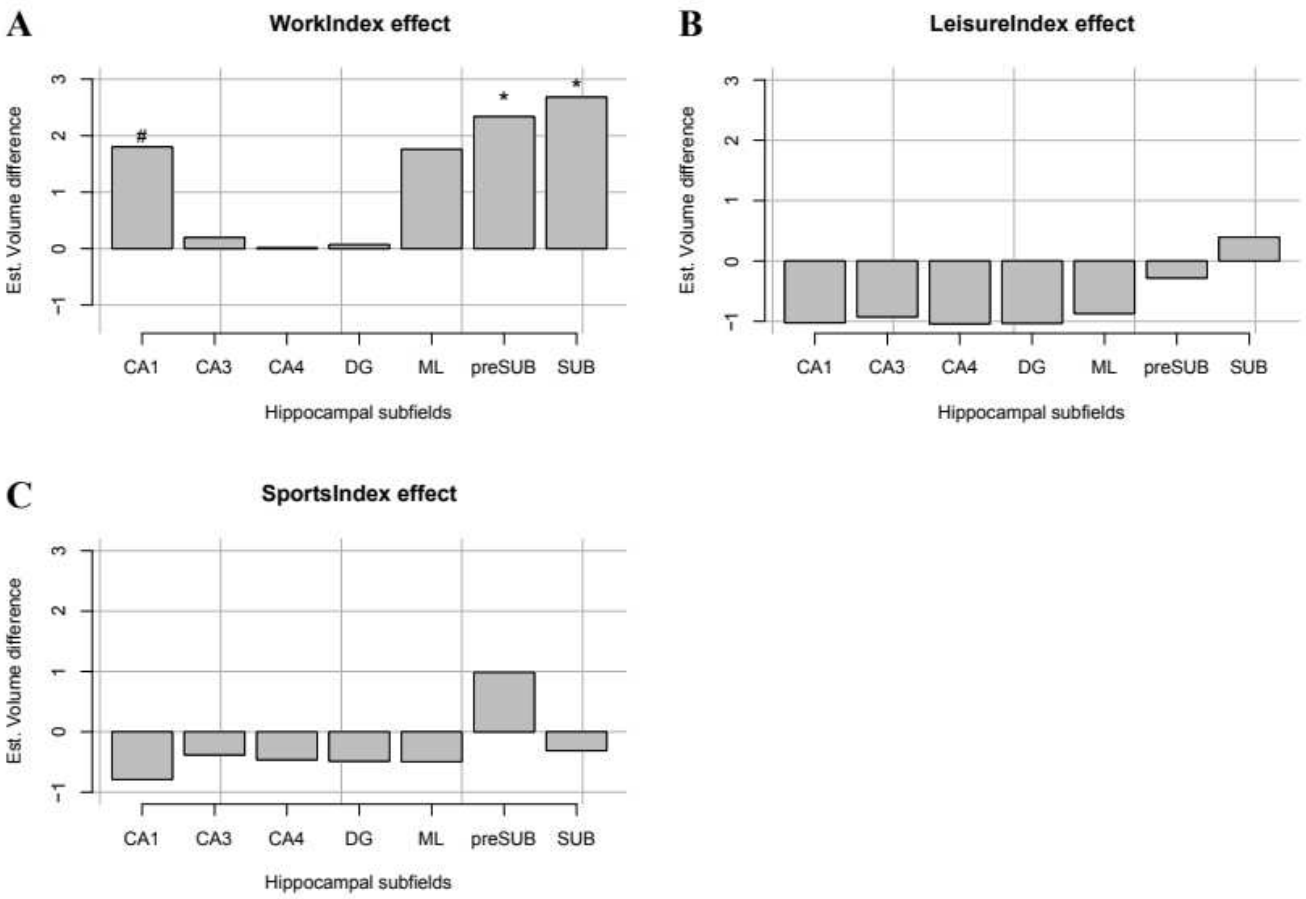
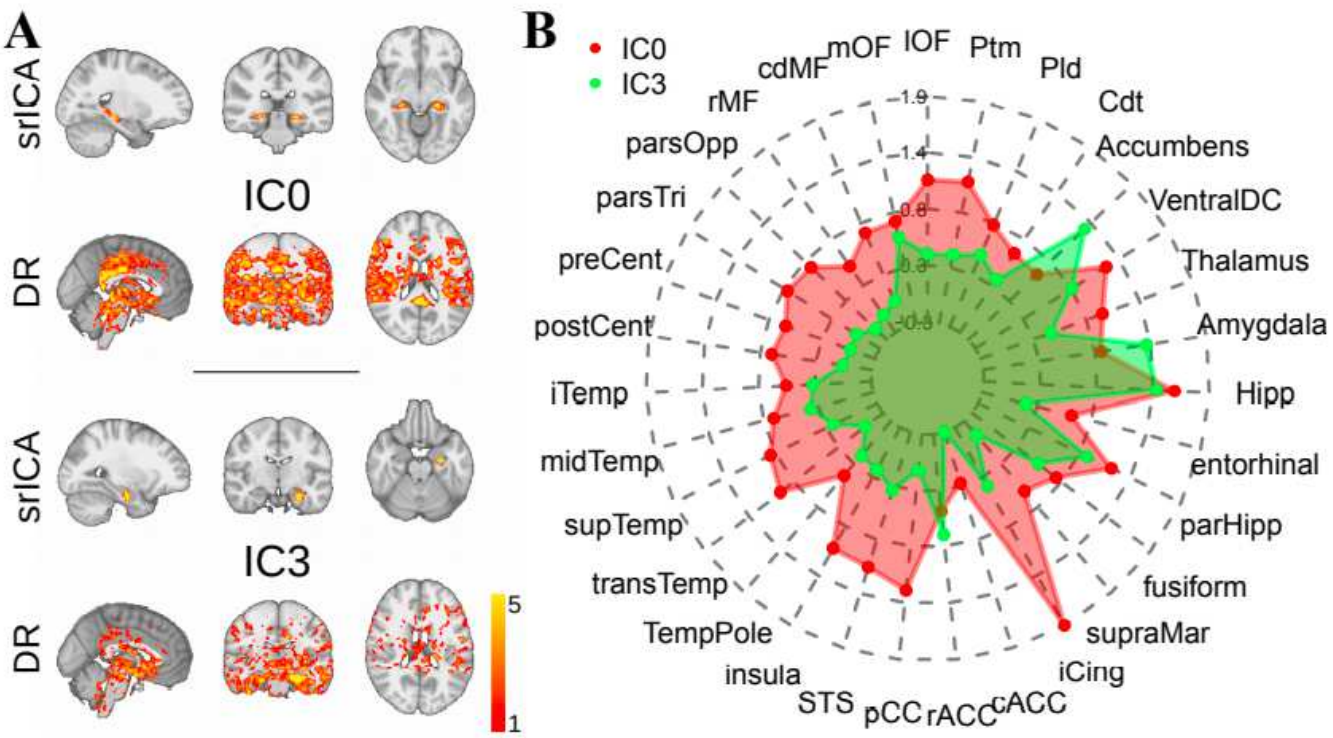


Figure 1

Estimated volume difference between high and low index of occupational PA (A), leisure-time PA (B) and sports time PA (C) per each hippocampal formation segment (CA1, CA3, CA4, DG, ML, preSUB and SUB). '*' indicates that a volume difference was significant between high and low PA groups for a certain PA context and hippocampal formation structure.



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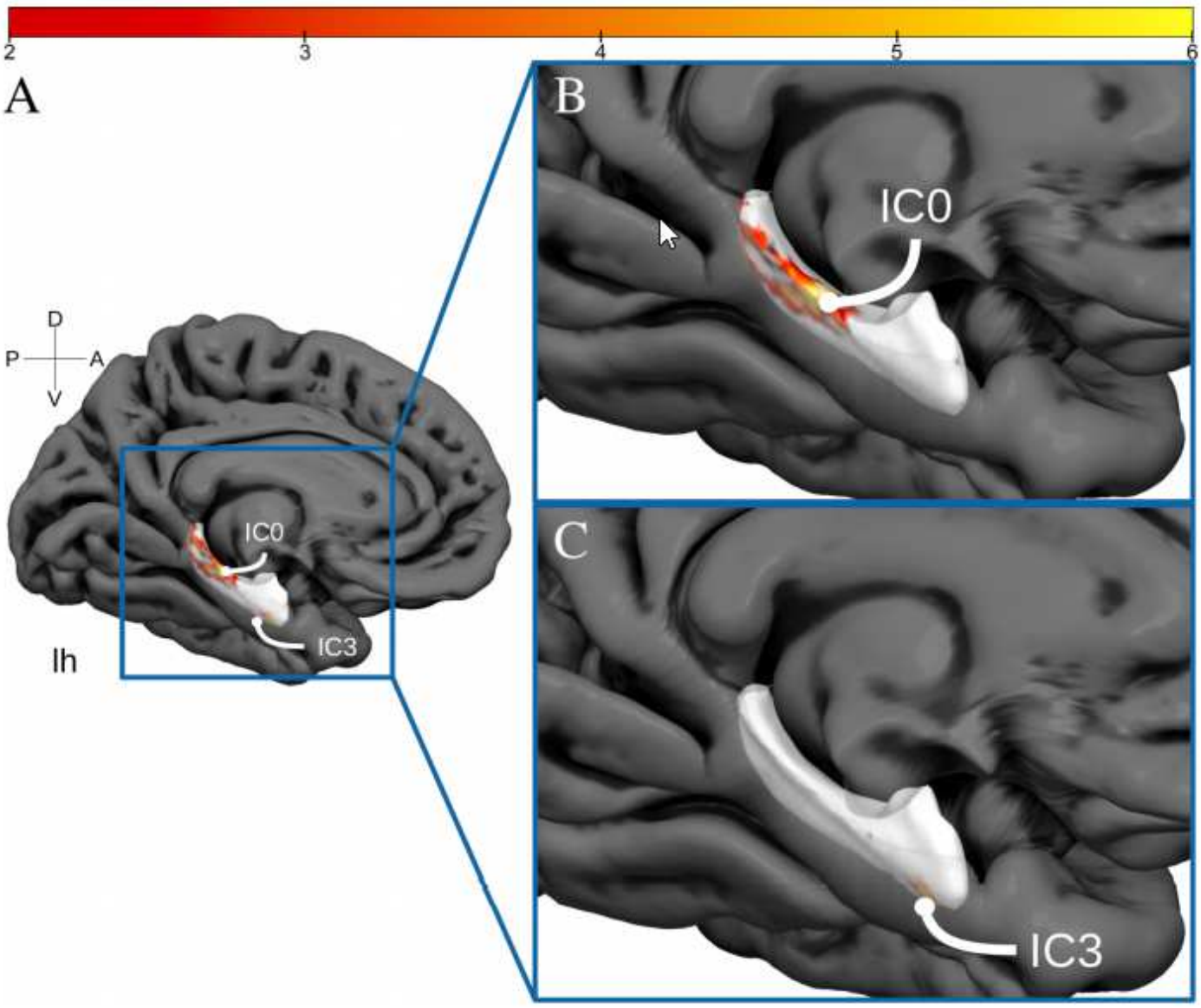

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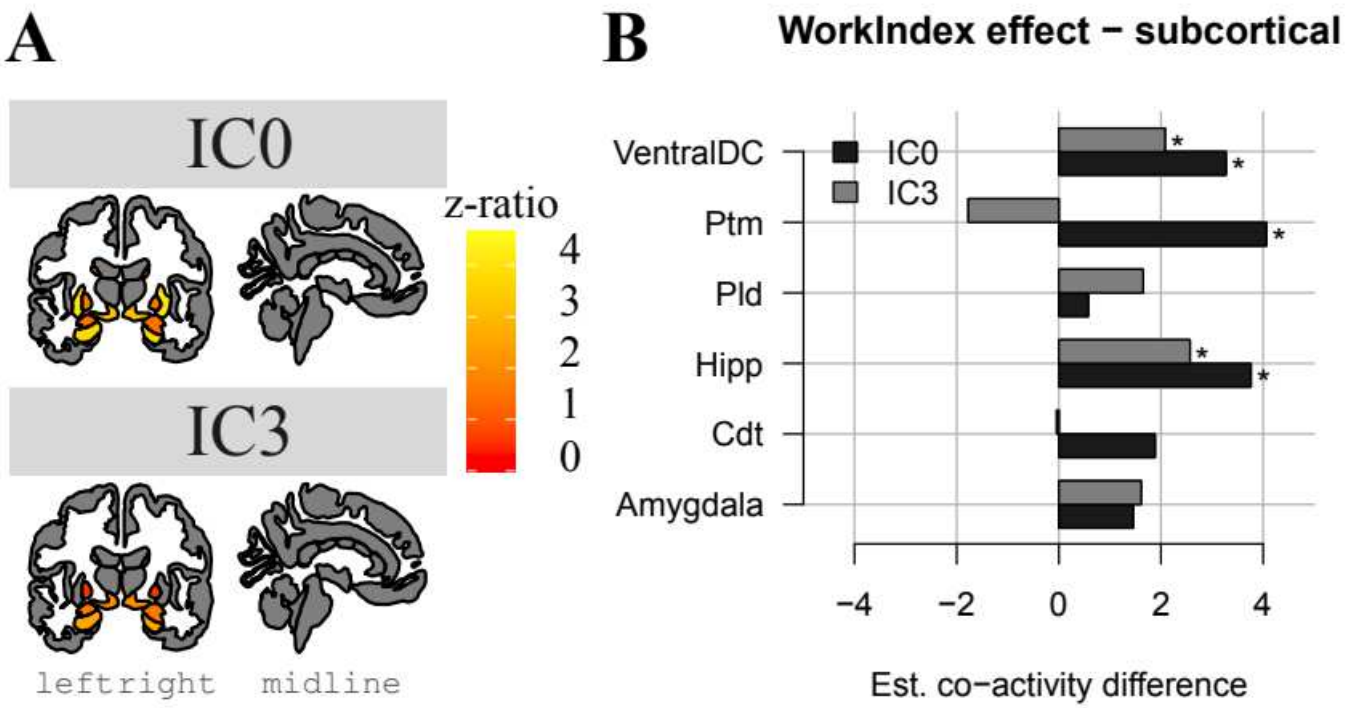

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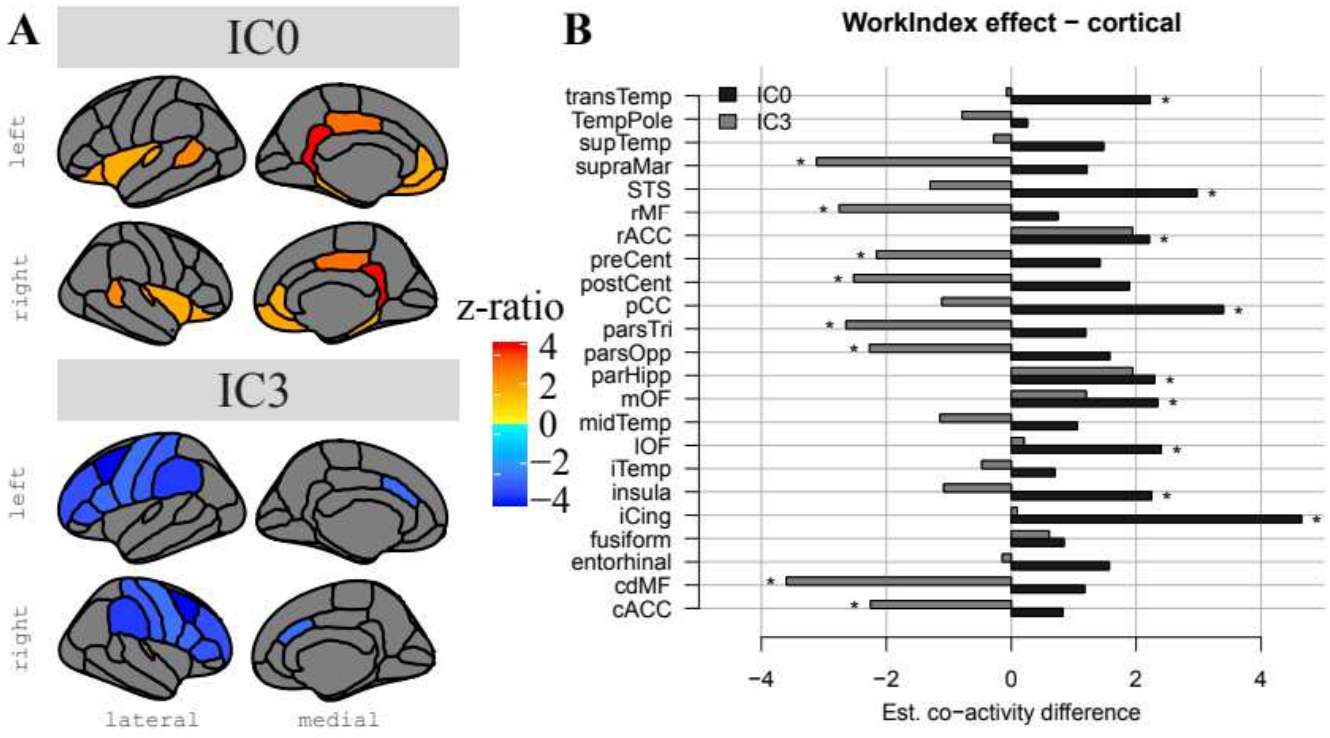

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Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.pdf