NeuroImage 223 (2020) 117359

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Exercise-induced changes in brain activity during memory encoding and retrieval after long-term bed rest

Anika Friedl-Werner[a,b], Katharina Brauns[a], Hanns-Christian Gunga[a], Simone Kühn[c,d], Alexander C. Stahn[a,e,*]

[a] Charité – Universitätsmedizin Berlin, a corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute of Physiology, Charitéplatz 1, CharitéCrossOver, Virchowweg 6, 10117 Berlin, Germany
[b] Université de Normandie, INSERM U 1075 COMETE, 14000 Caen, France
[c] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany
[d] Max-Planck-Institute for Human Development, Lise Meitner Group for Environmental Neuroscience, 14195 Berlin, Germany
[e] Unit of Experimental Psychiatry, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

ARTICLE INFO

Keywords:
Exercise
Bed rest
Pattern separation
Episodic memory

ABSTRACT

Episodic memory depends decisively on the hippocampus and the parahippocampal gyrus, brain structures that are also prone to exercise-induced neuroplasticity and cognitive improvement. We conducted a randomized controlled trial to investigate the effects of a high-intensity exercise program in twenty-two men resting in bed for 60 days on episodic memory and its neuronal basis. All participants were exposed to 60 days of uninterrupted bed rest. Eleven participants were additionally assigned to a high-intensity interval training that was performed five to six times weekly for 60 days. Episodic memory and its neural basis were determined four days prior to and on the 58th day of bed rest using functional magnetic resonance imaging (fMRI). We found increased BOLD signal in the left hippocampus and parahippocampal gyrus in the non-exercising group compared to the exercising bed rest group whereas the mnemonic performance did not differ significantly. These findings indicate a higher neuronal efficiency in the training group during memory encoding and retrieval and may suggest a dysfunctional mechanism in the non-exercising bed rest group induced by two months of physical inactivity. Our results provide further support for the modulating effects of physical exercise and adverse implications of a sedentary lifestyle and bedridden patients.

1. Introduction

Physical exercise is widely suggested as an effective, low-cost, non-pharmacological strategy for maintaining and improving physical and psychological health and well-being. There is increasing evidence that regular physical activity has also considerable neurobehavioral benefits across the lifespan. Recently, particular attention has been paid to the prefrontal cortex and the hippocampal formation and their associated cognitive functions such as executive control and declarative memory (Erickson, Leckie, & Weinstein, 2014; Firth et al. 2018). For instance, cross-sectional studies in preadolescents revealed that more physically fit children showed greater hippocampal volume and greater volume was accompanied with better performance in relational memory tasks (Chaddock et al., 2010; Chaddock, Hillman, Buck, & Cohen, 2011). Likewise, there is cross-sectional evidence suggesting that elderly people engaged in habitual exercise show less degenerative symptoms and perform better in spatial memory tasks than persons of the same age not engaged in exercise (Erickson et al., 2009; Erickson et al., 2010; Bugg & Head, 2011; Szabo et al., 2011). Longitudinal training studies in rodents (van Praag, Shubert, Zhao, & Gage, 2005; Lafenetre, 2010; (Wrann et al., 2013) and humans (Erickson et al., 2011) showed that regular physical activity can increase the concentrations of (neurotrophic) growth hormones, which are critical for hippocampal plasticity, learning, and memory formation. Changes in hippocampal volume were associated with changes in brain-derived neurotrophic factor (BDNF) (Erickson et al., 2011) as well as with changes in spatial (Erickson et al., 2011) and episodic memory (Hötting et al., 2012). These data highlight the positive neurobehavioral effects associated with regular physical activity.

Likewise, it can be speculated that a sedentary life-style may have adverse effects on hippocampal plasticity, learning, and memory formation. However, previous work investigating the effects of physical inactivity or immobilization has mainly been limited to structural brain changes in patients and the elderly (Liepert, Tegenthoff, & Malin, 1995; Lissek et al., 2009; Langer, Hänggi, Müller, Simmen, & Jäncke, 2012) or focused on functional changes in other brain regions such as the frontal and parietal lobes (Yuan et al., 2016) and on the (somatosensory) motor cortex (Cassady et al., 2016; Koppelmans et al., 2018). The majority of these studies have been cross-sectional in nature, questioning the causal relationship between physical inactivity and brain plasticity. For instance, it is well-known from animal studies that

* Corresponding author.
E-mail address: astahn@pennmedicine.upenn.edu (A.C. Stahn).

https://doi.org/10.1016/j.neuroimage.2020.117359
Received 7 May 2020; Received in revised form 17 July 2020; Accepted 3 September 2020
Available online 10 September 2020

environmental enrichment (Fabel et al., 2009) and social interaction (Djordjevic, Adzic, Djordjevic, & Radojcic, 2009; Murínová, Hlaváčová, Chmelová, & Riečanský, 2017) can also reinforce brain plasticity and memory function. These and other potential confounding factors have not been controlled for in human studies investigating the effects of physical (in)activity on the hippocampus and episodic memory formation.

To address this gap, we investigated the effects of an exercise program during two months of strict bed rest on memory-specific neuronal activity in humans using a randomized controlled trial study that standardized food, wake/sleep cycles, social interaction, and environmental enrichment. Healthy men undergoing two months of bed rest were randomly allocated to a control group and an exercise group that performed a high-intensity interval training. Both groups remained in bed rest throughout the entire study period. Using functional magnetic resonance imaging (fMRI) we determined neuronal activity during an episodic memory task that specifically targets the hippocampus and parahippocampal gyrus before and after two months of bed rest. Prolonged bed rest can be considered as a model to mimic accelerated physiological aging processes (Pavy-Le Traon, Heer, Narici, Rittweger, & Vernikos, 2007). Previous studies have shown that aging and cognitive decline are associated with hyperactive signaling of the hippocampus during episodic memory formation, which has been interpreted as a compensatory response (Hämäläinen et al., 2007; Miller et al., 2008a; Miller et al., 2008b; Nyberg et al. 2019; Yassa et al., 2010; Yassa, Mattfeld, Stark, & Stark, 2011). Consequently, we hypothesized that two months of bed rest would affect behavioral mnemonic performance and its neural basis, and that these changes were counteracted by the structured high-intensity interval training. In line with the above-mentioned studies assessing the effects of aging and cognitive decline, we expected that the maladaptive effects of prolonged physical inactivity would be evident as increases in hippocampal and parahippocampal neuronal signaling during mnemonic processing in the bed rest control group compared to the bed rest group that additionally performed the exercise program.

2. Methods

2.1. Study design

The experiment was performed as part of the European Space Agency (ESA) study “Reactive jumps in a sledge jump system as a countermeasure during long-term bed rest” (RSL). The study was conducted at the:envihab facility of the German Aerospace Center (DLR) in Cologne, Germany, and recorded on the German Clinical Trials Register (DRKS, registration number DRKS00012946, 18th of September 2017). The general study design is described elsewhere (Kramer et al., 2017a). Briefly, 23 young, healthy men underwent 60 days of six-degree head-down tilt bed rest (HDT). The baseline data collection (BDC-15 through BDC- 1) and subsequent recovery period (R+0 through R+14) lasted 15 days. On the first day of bed rest, eleven participants were randomly assigned to a high-intensity interval training (TRAIN). All participants underwent MRI scans four days prior to the bed rest commencing (BDC-4) and after 58 days of head-down tilt bed rest (HDT58). The experiment was approved by the Ethics Committee of the Northern Rhine Medical Association (Ärztekammer Nordrhein) in Düsseldorf, Germany and by the local Ethics Committee of the Charité - Universitätsmedizin Berlin, Germany. The study conformed to all standards of human research set out in the declaration of Helsinki. All participants were informed about the purpose, experimental procedures, and risks before giving their verbal and written informed consent.

2.2. Exercise training

The exercise training was performed in a supine position on a custom-built sledge jump system (Novotec Medical GmbH, Pforzheim, Germany) (Kramer et al., 2017a). All participants were familiarized with the correct jumping technique in nine 30 min sessions during the baseline data collection period. Four different training sessions consisting of varying numbers of countermovement jumps and hops were designed, and applied to TRAIN on 48 out of 60 days during the HDT phase, resulting in five to six training sessions per week (five sessions during the first two weeks of HDT and six sessions per week for the following six weeks of HDT). The force in the training device was increased gradually from 50% to 100% of participants’ body weight. The total training duration of one session did not exceed more than 17 min using an average training load between 80% and 90% of the body weight. Thus, the plyometric jump training can be considered as a short-duration high-intensity training that has been shown to successfully prevent musculoskeletal and cardiovascular deconditioning caused by 60 days of bed rest (Kramer et al., 2017b; Maggioni et al., 2018). All training sessions were scheduled in the afternoon from 2 pm to 6 pm. The timing of exercise sessions was kept constant within subjects. Visual feedback for jump height and peak force were provided via a monitor. Verbal feedback was given to the participants by an exercise physiologist to ensure correct execution during each session. All participants completed all scheduled training sessions. Maximum effort was not achieved in about 6% of all familiarization and training sessions due to headache, indisposition or minor discomfort (Kramer et al., 2017a). Further details about the training protocol and adherence are provided elsewhere (Kramer et al., 2017a).

2.3. Participants and recruitment process

Subject recruitment was supported by announcements in local and nationwide newspapers, internet, radio, poster advertisement, and DLR’s test participant archive. Short information was sent to all interested candidates, followed by a telephone screening. If interested, eligible participants received detailed information by email. Qualifying volunteers were invited to an information session, where the objectives, content, and risks of the experiment were explained in detail. Next, interested participants were medically and psychologically screened to ensure their compliance with all inclusion and exclusion criteria (Kramer et al., 2017a). The medical screening comprised a comprehensive anamnesis and physical examination, including an assessment of resting electrocardiogram (ECG), orthostatic tolerance, thrombosis risk, nicotine and substance abuse, the prevalence of infectious diseases, and cardiopulmonary fitness using graded exercise testing. The psychological screening was performed by a psychologist using questionnaires and a personal interview. Eligible participants underwent a dual energy X-ray absorptiometry (DEXA) scan to evaluate the bone mineral density of the femur and the lumbar vertebra column as a final criterion to be included in the study. Finally, twenty-seven volunteers passed the entire screening process and twenty-four of them were enrolled in the study. Twenty-three participants (29 ± 6 years, height: 181 ± 6 cm, weight: 77 ± 7 kg) completed the study. A detailed CONSORT flow diagram is displayed in Figure 1.

Because of medical reasons two subjects (one from each group) started their recovery on HDT 49 and HDT 50, respectively (instead of HDT60). MRI scanning for these participants was performed on the last day of their bed rest (i.e., HDT48 and HDT49 instead of HDT58). Due to an incomplete log file data set, one subject (TRAIN) had to be excluded from the data analysis. Both groups did not differ with respect to their age, height, weight, and BMI at baseline (two-tailed Student’s t-test: all $Ps > 0.3$). An overview of subjects’ group characteristics is displayed in Table 1.

2.4. MRI Scanning procedure

Magnetic resonance imaging was conducted on a 3 Tesla Siemens Biograph mMR (Siemens Healthcare, Erlangen, Germany), equipped with a 16-channel head coil. Functional images were acquired using a T2-weighted echo planar imaging (EPI) sequence sensitive to blood oxygen

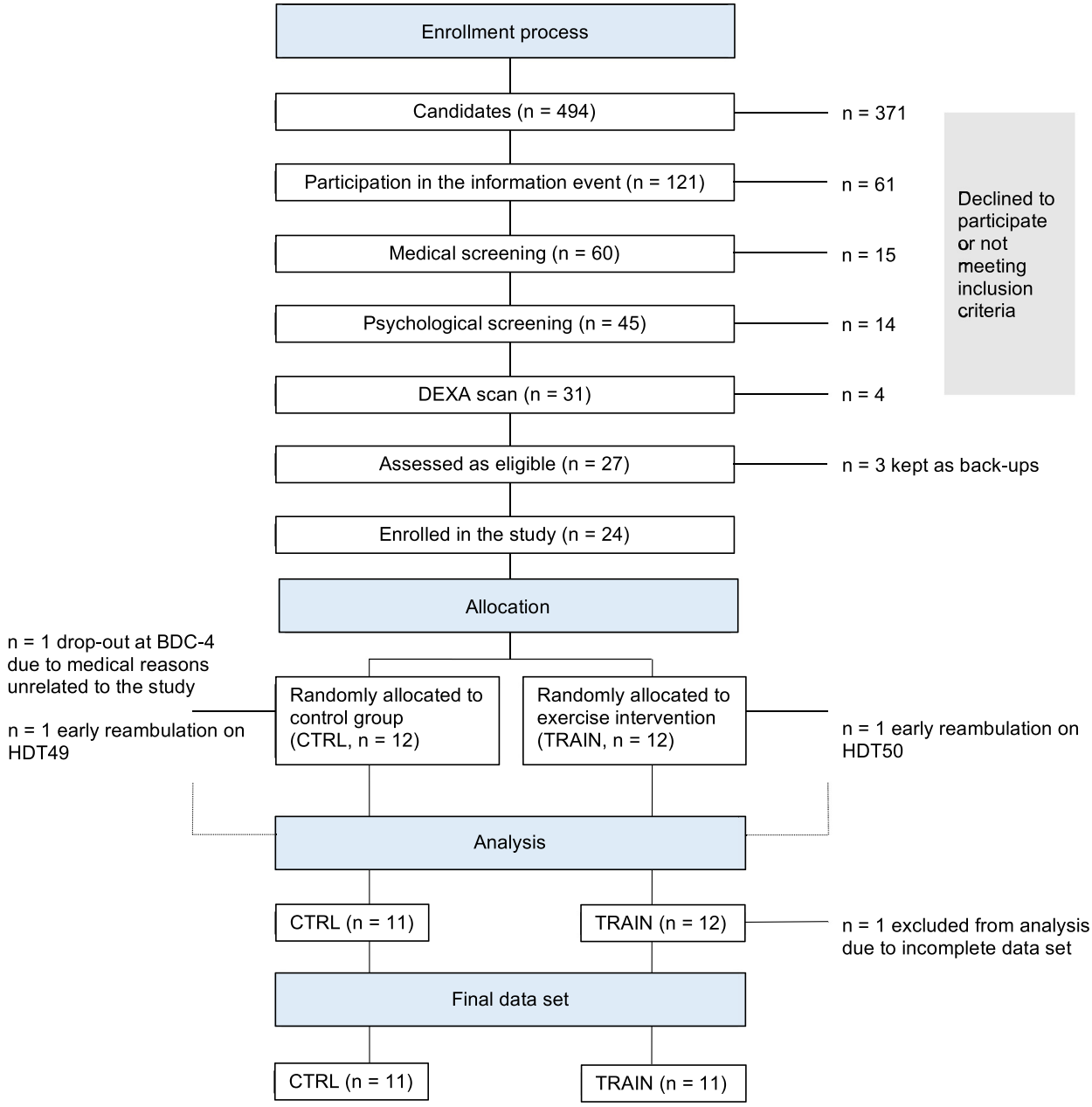

Fig. 1. CONSORT flow diagram. Overview of recruiting, enrollment, and analysis process.

Table 1
Subjects' group characteristics at baseline.*

Characteristic	CTRL (n = 11)	TRAIN (n = 11)	t_{20}	P
Age [years]	28.2 (5.7)	30.8 (6.2)	1.02	0.318
Height [cm]	180.6 (5.0)	181.6 (6.8)	0.39	0.699
Body Mass [kg]	76.2 (8.0)	77.9 (6.6)	0.54	0.593
BMI [kg/m^2]	23.4 (2.0)	23.6 (1.9)	0.24	0.812

* Data are means (SD); BMI, Body Mass Index; CTRL, bed rest control group; TRAIN, exercising bed rest group; t, t-statistics; P, p-value.

level dependent (BOLD) contrast (36 axial slices, interleaved slice order, time to repeat (TR) = 2000 ms, time to echo (TE) = 30 ms, field of view (FoV) read = 216 mm, FoV phase = 100%, flip angle = 80°, slice thickness = 3 mm, distance factor = 20%, voxel size: 3 mm × 3 mm × 3 mm). For anatomical reference, a three-dimensional volumetric T1-weighted Magnetization Prepared Rapid Acquisition of Gradient Echo (MPRAGE) sequence was acquired in a sagittal plane with the following parameters: voxel size: 1 mm × 1 mm × 1 mm; TR = 2500 ms, TE = 4.82 ms, inversion time = 1100 ms, FoV read = 256 mm, FoV phase = 100%, flip angle = 7°, and bandwidth = 140 Hz/Px. Scanning was always performed before noon between 8 am and 12 pm.

2.5. fMRI paradigm

Episodic memory was assessed using a continuous memory recognition task that was originally proposed by Kirwan & Stark (2007) and that was shown to reliably target the hippocampus (Bakker, Kirwan, Miller, & Stark, 2008; Kirwan et al., 2012; Ally, Hussey, Ko, & Molitor, 2013). A schematic overview of the fMRI paradigm is displayed in Fig. 2. Images of different objects were presented to the participants via a mirror system mounted on top of the head coil. Each picture was shown for 2000 ms with a randomized intertrial interval (ITI) of 2000 to 4000 ms. For each picture, participants had to indicate via a button press whether

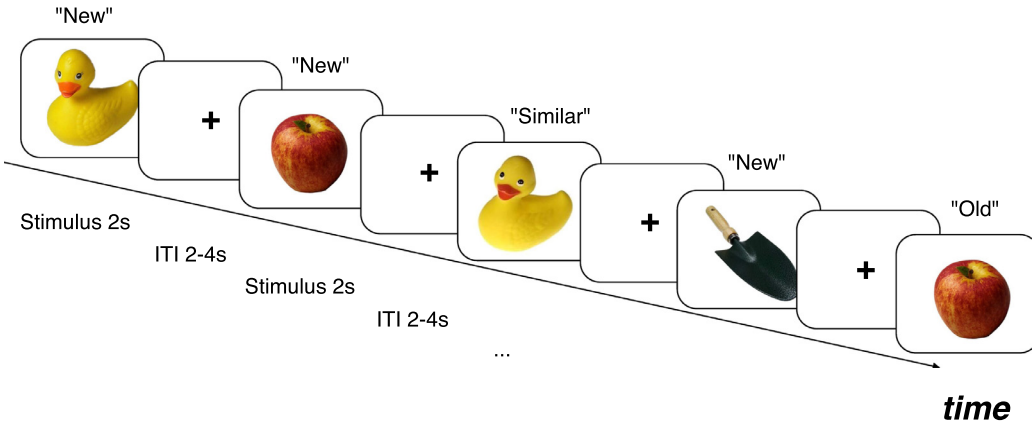

Fig. 2. fMRI paradigm for pattern separation task. A picture was presented for 2 s followed by an intertrial interval (ITI) of 2 to 4 s. Quotation marks above the picture indicate the correct response.

the presented object was “new” (novel condition), “old” (repetitive condition), or “similar”, though not identical to an object shown earlier in the run (lure condition). The experiment consisted of 216 trials administered in two blocks, each containing 108 items (16 similar pairs, 16 identical pairs and 44 unrelated novel stimuli) with an overall duration of approximately six minutes per run. To avoid that participants remembered the objects from pre- to posttest, one of two sets of stimuli were either presented on BDC-4 or HDT58. The order of the two sets was selected in a randomized counterbalanced fashion. Picture presentation and timing was controlled using Presentation® software (Version 18.1, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

2.6. Behavioral analysis

For each group and time point separately, the number of each stimulus type (novel, lure, repetition) in accordance with participants’ individual response (new, similar, old) was extracted from the data log file. We then calculated the percentage for each response type relative to the total number of trial type (i.e., number of correctly identified repeated stimuli as old relative to the total number of repeated stimuli). In order to distinguish between signal and noise that corrects for a possible response bias, we also determined separation bias (Yassa et al., 2010), also referred to as the lure discrimination index (Stark, Stevenson, Wu, Rutledge, & Stark, 2015) and recognition memory performance (Stark, Yassa, Lacy, & Stark, 2013).[1] The separation bias score was assessed as the percent of lure trials correctly identified as “similar” (Lure Correct Rejection) minus the percent of novel trials endorsed as “similar”. This approach corrects for a possible response bias toward exhibiting a tendency for the use of similar responses (Yassa et al., 2010). Recognition memory performance was operationalized as the percent of repetition trials correctly identified as “old” (Hits) minus the percent of novel trials endorsed as “old” (Stark et al., 2013). The behavioral response according to each trial type as well as the separation bias and recognition memory scores were subjected to mixed linear models to quantify the effects of *Time* (BDC-4, HDT58) and *Group* (CTRL, TRAIN), and their interaction. Details of the statistical model are provided in section 2.8 below.

2.7. fMRI Analyses

2.7.1. Image preprocessing

fMRI data were preprocessed and analyzed using SPM12 software (Wellcome Department of Cognitive Neurology, London, UK) running on Matlab R2015b. The first four volumes of all EPI series were excluded from the analysis to allow the magnetization to reach a dynamic equilibrium. Data processing started with slice time correction and realignment of the EPI datasets. A mean image of EPI volumes was created to which individual volumes were spatially realigned by means of rigid body transformations. The individual structural image of each subject was co-registered with the mean image of the respective EPI series. The structural images were normalized to the Montreal Neurological Institute (MNI) template and normalization parameters were applied to the EPI images to ensure an anatomically informed normalization. A commonly applied filter of 8 mm FWHM (full-width at half maximum) was used to smooth the images. Low-frequency drifts in the time domain were removed by modelling the time series for each voxel by a set of discrete cosine functions to which a cut-off of 128 seconds was applied.

2.7.2. Subject-level analyses

Region of interest model. The subject-level statistical analyses were performed using general linear models (GLM) within the SPM-framework. The model was based on the first-level model reported by Kirwan and Stark (2007) using the following conditions: 1) *Hits* (repeated stimuli correctly called “old”; 2) *Lure Correct Rejection* (lure stimuli correctly identified as “similar”); 3) *Lure False Alarms* (lure stimuli called “old”); 4) *Miss* (repeated or lure stimuli called “new”); 5) *Subsequent Hits* (first time presentation of a repetition stimuli that was later correctly identified as “old”); 6) *Subsequent Lure Correct Rejection* (first time presentation of a lure stimuli that was later correctly identified as “similar”); 7) *Subsequent Lure False Alarms* (first time presentation of a lure stimuli that was later incorrectly identified as “old”); 8) *Subsequent Misses* (first time presentation of a repetition or lure stimuli that was later incorrectly labeled as “new”); 9) *Foils* (stimuli that have only been shown once and not in the same or similar way again and have been classified as “new”); and 10) *Other* (foils and first presentations that were incorrectly labeled as “old” or “similar”). Vectors of onsets for each of the above-mentioned event types for each participant and each point in time were convolved with the canonical hemodynamic response function (HRF) and the temporal derivative. Both session runs that have been administered at one point in time were modeled in the same GLM. Furthermore, the six movement regressors obtained from the realignment step were

[1] Typically, d’ prime is used as a sensitivity index to distinguish between signal and noise that corrects for a possible response bias in two-item response paradigms. For instance, in a yes/no discrimination paradigm giving the same answer for all trials yields 100% correct for one item, and 0% for the other (Pallier, 2002). The current task, however, was characterized by a three-choice serial reaction time task, requiring a slightly different analysis approach, taking into account three alternative responses. We here follow the suggestions to determine separation bias and recognition memory score for the pattern separation paradigm as outlined by Stark and colleagues (Stark, Yassa, Lacy, & Stark, 2013; Stark, Stevenson, Wu, Rutledge, & Stark, 2015; Yassa et al., 2010).

entered into the GLM. After model estimation, this model was used for the region of interest analysis (ROI).

To verify if the regions of the medial temporal lobe were engaged in the task, we additionally computed a contrast on our first-level GLM from the ROI analysis were the average activity in *Hits* is greater than the average in *Lure Correct Rejection* and *Foils* (*Hits* > *Lure CR* = *Foils*) and a contrast where average activity in *Lure Correct Rejection* is greater than the average activity in *Hits* and *Foils* (*Lure CR* > *Hits* = *Foils)*. These contrasts were computed for all participants during their baseline assessment (BDC-4) before they were assigned to any intervention. The resulting contrast images were used for group-level statistics within the SPM-framework.

Whole-brain model. For whole-brain data we modeled a second GLM on a subject-level, but limited the analyses to conditions with correct responses, i.e., *Foils, Hits,* and *Lure Correct Rejections* (Pidgeon & Morcom, 2016). We computed *t*-contrasts for pattern separation and pattern completion as follows: Pattern separation was defined as the contrast where average activity in *Lure Correct Rejection* is the same as in *Foils* and greater than the average activity in *Hits* (*Lure CR* = *Foils* > *Hits*), and pattern completion was defined as the contrast where average activity in *Foils* was greater than in *Hits* and *Lure Correct Rejection* (*Foils* > *Hits* = *Lure CR*) (Pidgeon & Morcom, 2016). The resulting contrast images were used for further whole brain analysis on a group level.

2.7.3. Group-level analyses

Region of interest analysis. Anatomical regions of interests were determined a priori based on 1) regions that have been shown to be vulnerable to physical exercise, and 2) regions that have been reported previously to be involved in the task that we used. Previous work on the effects of physical exercise suggests that the hippocampus is significantly affected by regular exercise (Erickson et al., 2011; Firth et al., 2018). The pattern separation paradigm used in the present study distinctly activates the hippocampus and parahippocampal gyri (Kirwan & Stark, 2007; Bakker et al., 2008). Hence, we retrieved BOLD signal change in bilateral hippocampus and parahippocampal gyrus from the Automated Anatomical Labeling (AAL) Atlas (Tzourio-Mazoyer et al., 2002). This subject-level design matrix was used to extract the mean percent signal changes for each subject, each condition, and each point in time. Given that blood oxygenation peaks 4 to 6 seconds post-stimulus (Poldrack, Mumford & Nichols, 2011; Chen, Shen & Truong, 2016), we extracted the mean percent signal change covering a time window of 4 to 6 seconds after stimulus onset for each of the four regions of interest (left and right hippocampus and left and right parahippocampal gyrus) using the MarsBaR toolbox (http://marsbar.sourceforge.net/) (Brett, Anton, Valabregue, & Poline, 2002). Differences in mean percent signal change of hippocampal and parahippocampal activation were analyzed using mixed linear models (see also statistical models in section 2.8 for details). To validate the paradigm on the group-level, the contrast images for the contrasts *Hits* > *Lure CR* = *Foils* and *Lure CR* > *Hits* = *Foils* that had been computed across all participants during the baseline assessment prior to the intervention (BDC-4) were subjected to a one-sample *t*-test within the SPM-framework to verify which regions were engaged during the retrieval of repetitive and lure stimuli. The results were corrected using a family wise error rate (FWE).

Whole-brain analyses. The contrast images of the pattern separation and completion contrasts that had been acquired on a subject-level were used in a flexible factorial design within the SPM framework with *Subject* as a random factor, and *Time* and *Group* as fixed factors. Contrasts for main and interaction effects were computed and results were corrected for multiple comparisons using a family wise error rate (FWE).

2.8. Statistical analysis

Behavioral data and mean percent BOLD signal change for our *a priori* regions of interest, i.e., bilateral hippocampus and parahippocampal gyrus were analyzed by linear mixed models. To assess the effects of bed rest and the exercise intervention on percent responses classified as new, similar or old, we performed mixed models with *Group* (CTRL, TRAIN), *Time* (BDC-4, HDT58), and their interaction as fixed factors, and *Subject* as a random factor. The inclusion of *Stimulus Type* (novel, lure, repetition) as an additional factor did not allow precise estimations of the variance-covariance matrices. Hence, we ran separate mixed models for each stimulus (novel, lure, repetition) and response type (new, similar, old). Mean percent BOLD signal change was assessed for hippocampus and parahippocampal gyrus in two separate models. In each model, we entered *Time* (BDC-4, HDT58), *Group* (TRAIN, CTRL), *Laterality* (Left, Right), *Condition* (Encoding, Retrieval), and *Stimulus Type* (Lure, Repetition). Covariance matrices were determined by restricted maximum likelihood (REML) estimation. P-values were obtained by using Satterthwaite's approximation for denominator degrees of freedom. Pre-planned contrasts were used to quantify the interaction between *Time* and *Group* by *Laterality* crossed with *Condition* and *Stimulus Type* for BOLD signal change. Contrasts were adjusted using a false discovery rate (FDR) procedure treating each region of interest (left and right hippocampus and parahippocampal gyrus) as one family of four comparisons each (two comparisons for *Condition* x two comparisons for *Stimulus Type*) (Benjamini & Hochberg, 1995). Effect sizes were reported as Cohen's *d* and 95% confidence intervals. For imaging data, a false coverage statement rate (FCR) was computed using a Matlab script (Groppe, 2020) to construct multiple comparison corrected confidence intervals that correspond to the FDR-adjusted p-values (Benjamini & Yekutieli, 2005). The level of significance was set at = 0.05 (two-sided) for all tests. All statistical analyses and graphical illustrations were carried out using the software package R version 3.5.2 (R Core Team, 2018).

3. Results

3.1. Validation of the fMRI paradigm

All participants demonstrated high accuracy in correctly identifying novel (> 93%) and repetitive stimuli (> 90%), whereas lure stimuli were harder to classify correctly (between 43% to 51% for BDC-4). A detailed summary of the descriptive statistics is provided in the Supplementary Material (Table S1). To verify which regions were engaged in the paradigm, we assessed brain activations during the contrasts *Hits* > *Lure CR* = *Foils* and *Lure CR* > *Hits* = *Foils* at the first point in time (BDC-4) for all participants (n = 22). Clusters that were significantly activated for the contrast *Hits* > *Lure CR* = *Foils* were the left fusiform gyrus, left hippocampus, left MTG (for all 3 clusters $P_{FWE\text{-}corr.} = 0.033$), and bilateral precuneus ($P_{FWE\text{-}corr.} < 0.001$) as well as bilateral cerebellum ($P_{FWE\text{-}corr.} = 0.029$ for right and $P_{FWE\text{-}corr.} = 0.002$ for left cerebellum). For the contrast *Lure CR* > *Hits* = *Foils*, we observed significant activations in bilateral precuneus ($P_{FWE\text{-}corr.} < 0.001$), left hippocampus ($P_{FWE\text{-}corr.} = 0.042$), and bilateral cerebellum ($P_{FWE\text{-}corr.} = 0.027$ for right and $P_{FWE\text{-}corr.} = 0.026$ for left cerebellum). Both, the behavioral performance and the regions activated at BDC-4 are very similar to the results reported previously confirming the validity of the paradigm (Hämäläinen et al., 2007; Kirwan & Stark, 2007; Pidgeon & Morcom, 2011).

3.2. Behavioral findings

Figure 3 shows frequency of the responses given to each stimulus type for the contrast between HDT58 and BDC-4. Both groups showed a significant improvement in the discrimination of lure items by identifying them more often as "similar" and less as "old" on HDT58 (all *P*s < 0.05). Numerically, TRAIN also improved in the recognition of repetition trials ($t_{20} = 0.46$, $P = 0.654$, $d = 0.19$, [-0.65, 1.03]), whereas CTRL showed a small decrease from HDT58 to BDC-4 ($t_{20} = -0.76$, $P = 0.457$, $d = -0.32$, [-1.16, 0.52]). There was neither a significant main effect for *Group* nor a *Group* x *Time* interaction in any of the behavioral

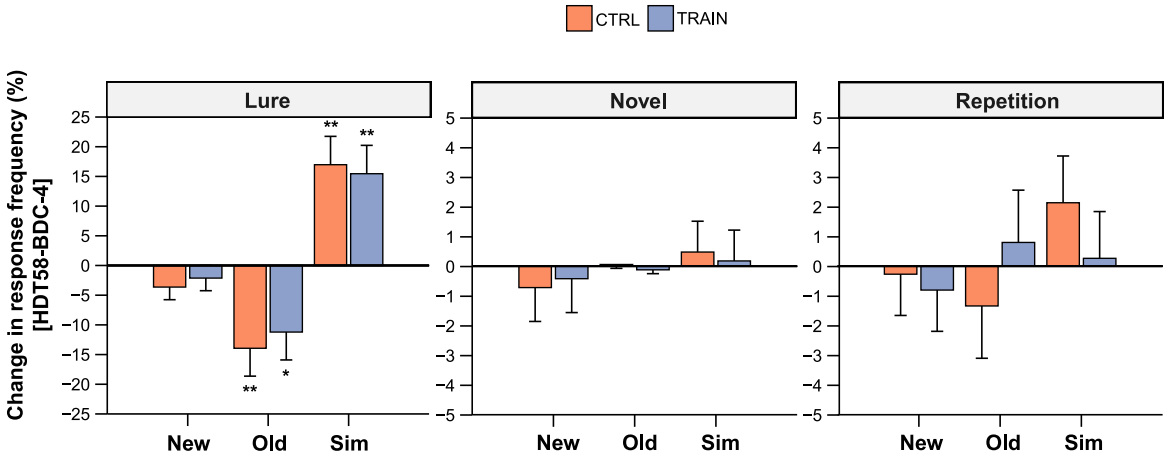

Fig. 3. Changes in response frequency from baseline (HDT58 vs. BDC-4) by *Stimulus Type* (lure, novel and repeated stimuli), *Group* (TRAIN, CTRL), and *Response* (items classified as new, old, or similar). Data are marginal means and standard errors. CTRL, bed rest control group; TRAIN, exercising bed rest group. N = 11 for each group respectively. * $P < 0.05$, ** $P < 0.01$ compared to BDC-4.

conditions (all *Ps* > 0.124). Detailed statistical results are provided in Supplementary Material (Table S2 and S3).

Results for the separation bias and the recognition memory score were similar to changes observed for discriminating lure and repetition trials (see Supplementary Material Figure S1). We also observed an increase in the separation bias score in both groups ($F_{1,20} = 26.16$, $P < 0.001$ for *Time*). This is in line with the improvement in discriminating lure trials, given that the separation bias score was calculated as the difference between the probability of identifying a lure item as "similar" and the probability of identifying a novel foil item as "similar". Numerically, TRAIN showed a higher and CTRL a lower recognition memory score that, however, did not reach statistical significance (*Group* x *Time*, $F_{1,20} = 0.89$, $P = 0.358$). Detailed statistical results are provided in Supplementary Material Table S4.

3.3. fMRI results

3.3.1. Region of interest analysis

After two months of bed rest, increases in BOLD signal were observed in CTRL for all mnemonic conditions, whereas the signal in TRAIN decreased (Fig. 4). Pre-planned contrasts revealed that the decrease in BOLD signal within TRAIN was significant for five out of eight conditions in the left hemisphere (all *Ps* < 0.05). A detailed summary of the simple effects of *Time* by *Laterality* (Left, Right) and *Condition* (Encoding, Retrieval) and *Stimulus Type* (Lure, Repetition) for each group separately and for all main and interaction effects of the multilevel analysis is provided in Supplementary Material Table S5, S6, and S7. We also observed a significant interaction between *Group* and *Time* in the left hemisphere for the retrieval process of lure stimuli (hippocampus: $P = 0.035$, $d = -1.12$ [-2.27, 0.04]); parahippocampal gyrus: $P = 0.012$, $d = -1.23$ [(-2.14, -0.30]). Furthermore, a significant interaction of *Group* x *Time* during correct encoding and retrieval of repetition stimuli was found in the left parahippocampal gyrus ($P = 0.019$, $d = -1.01$[-1.89, -0.11]; $P = 0.018$, $d = -1.05$ [-1.93, -0.14], respectively). A nearly significant interaction was observed for the left hippocampus during encoding of lure items ($P = 0.054$, $d = -0.95$ [-2.07, 0.19]) and for the right parahippocampal gyrus during retrieval of lures ($P = 0.056$, $d = -1.05$). There were no other significant main or interaction effects (all *Ps* > 0.215). Details of these analysis are provided in Supplementary Material Table S8.

3.3.2. Whole-brain analysis

Greater activation on HDT58 compared to BDC-4 for the pattern separation contrast [BDC-4 (*Lure CR* = *Foils* > *Hits*)] vs. [HDT58 (*Lure CR* = *Foils* > *Hits*)] was observed in the right occipital pole (R OCP), right middle temporal gyrus (R MTG), frontal pole, right fusiform gyrus (R FuG), and left inferior temporal gyrus (L ITG) for CTRL ($P < 0.001$, clusterwise FWE-corrected ($P < 0.05$)). Notably, only the right OCP survived the FWE-cluster correction (Fig. 5). Higher activation was also seen in the right superior parietal lobule in TRAIN, but did not reach the level of significance. There was no *Group* x *Time* interaction for the pattern separation contrast.

Regions showing decreased activation for the pattern completion contrast [BDC-4 (*Foils* > *Hits* = *Lure CR*)] vs. [HDT58 (*Foils* > *Hits* = *Lure CR*)] involved bilateral precentral gyrus, bilateral insular cortex, and right middle temporal gyrus for CTRL and left superior temporal gyrus (L STG) and left occipital fusiform gyrus (L OFuG) for TRAIN. Only the bilateral precentral gyrus survived FWE-cluster correction. A *Group* x *Time* interaction that did not reached statistical significance was observed in the right precentral gyrus. A detailed overview of the regions that showed changes in the pattern separation and completion contrast from BDC-4 to HDT58 and exceeded the threshold of 20 voxels is provided in the Supplementary Material Table S9 and S10.

4. Discussion

We investigated the effects of long-term bed rest on episodic memory performance and its neural basis and whether a high-intensity jump training can mitigate the effects of physical inactivity on the neural underpinnings of memory functioning. After two months of bed rest, we found increases in BOLD signal during memory encoding and retrieval in the hippocampal formation in CTRL compared to TRAIN, suggesting a modulating effect of the exercise intervention. The strongest effects of exercise were observed in the left hemisphere. This is in line with recent research summarizing the effects of regular physical activity on the hippocampus. In a meta-analysis of 14 longitudinal studies, Firth et al. (2018) reported significantly larger effects for the left hippocampus (Hedge's *g* [95% CI] = 0.265 [0.090, 0.441], $P = 0.003$) compared to the right hippocampus (Hedge's *g* [95% CI] = 0.164, [-0.010, 0.339], $P = 0.065$).

Increased brain activity during pattern separation has been observed in the elderly compared to young adults (Yassa et al., 2011), as well as in patients with mild cognitive impairment (MCI) compared to healthy controls (Hämäläinen et al., 2007; Yassa et al., 2010). Bed rest is a classical model to simulate some of the physiological adaptations associated with spaceflight (Pavy-Le Traon et al., 2007). Given that the physiological responses to spaceflight reflect an accelerated aging process (McGuire et al., 2001; Vernikos & Schneider, 2010), bed

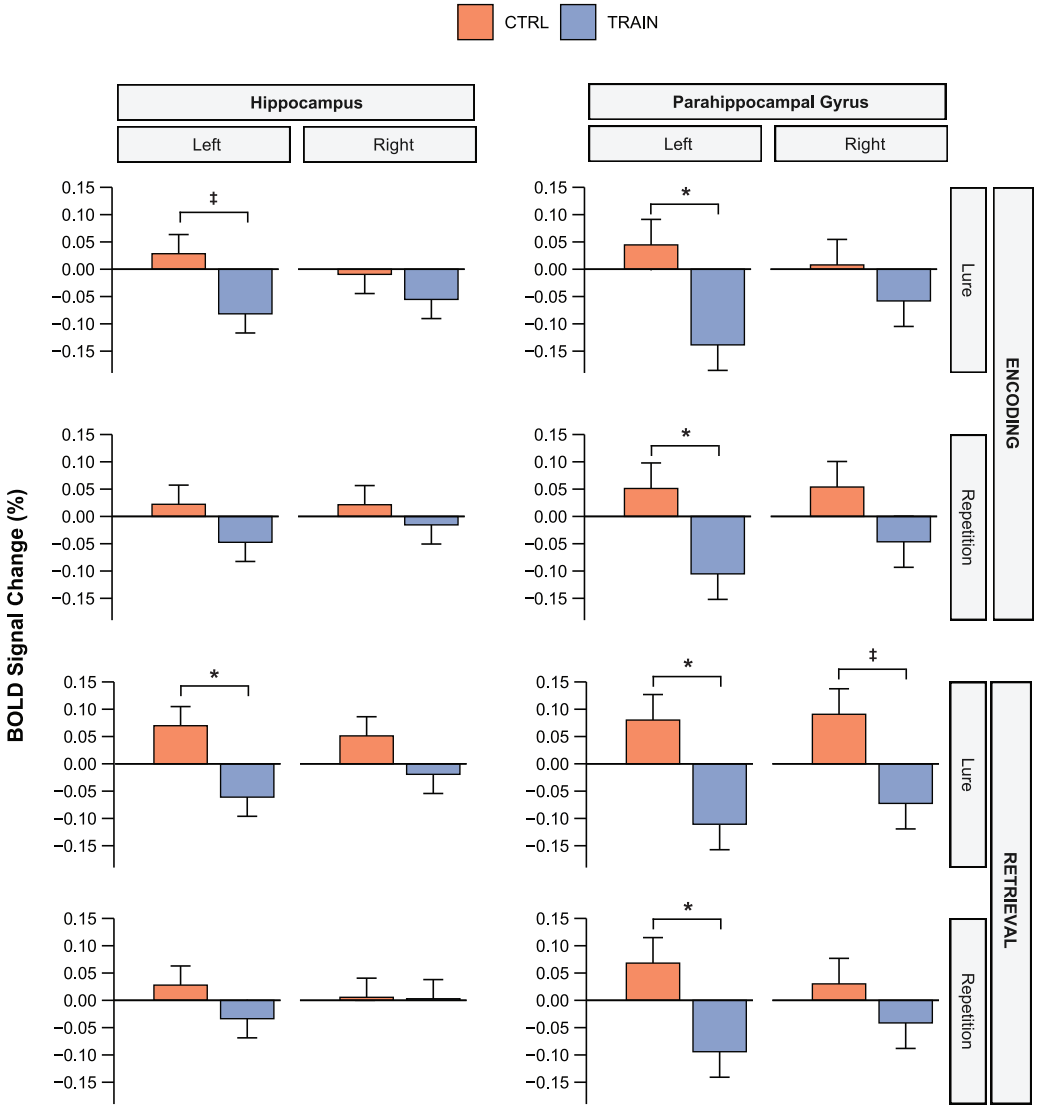

Fig. 4. BOLD signal change during memory encoding and retrieval of lure and repetition stimuli for bilateral hippocampus and parahippocampal gyrus. Data are marginal means and standard errors for the interaction of *Group* (TRAIN, CTRL) x *Time* (BDC-4, HDT58) by *Laterality* (Left, Right) crossed with *Condition* (Encoding, Retrieval) and *Stimulus Type* (Lure, Repetition). CTRL, bed rest control group; TRAIN, exercising bed rest group. N = 11 for each group respectively. * $P < 0.05$, ‡ interaction was close to statistical significance with $P = 0.054$ for left hippocampus during encoding of lure stimuli and $P = 0.056$ for right parahippocampal gyrus during retrieval of lure stimuli.

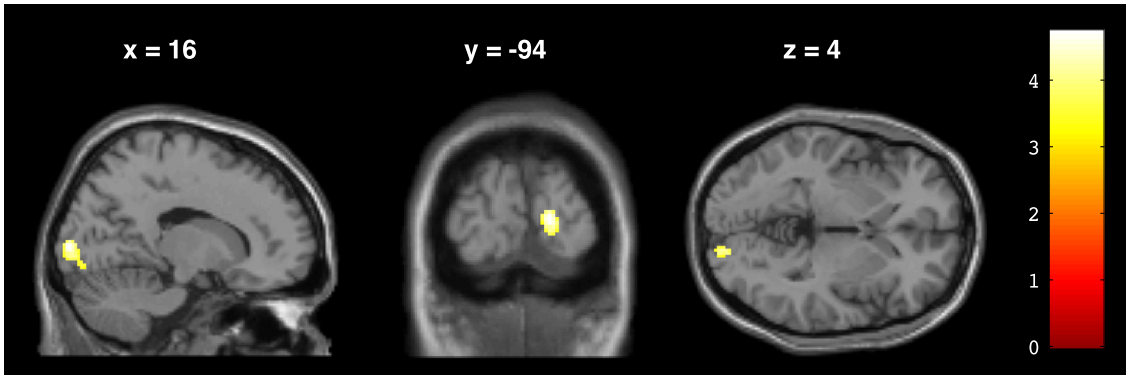

Fig. 5. Right occipital pole showing increased activation during pattern separation in CTRL. SPMs for the contrast [BDC-4 (*Lure CR = Foils > Hits*)] vs. [HDT58 (*Lure CR = Foils > Hits*)] averaged over 11 CTRL subjects mapped onto an MNI template ($P < 0.001$, clusterwise FWE-corrected ($P < 0.05$)).

rest can also be considered as a unique model to better understand the effects of premature physiological aging. In this regard, our findings of increased brain activation in CTRL could be interpreted as a consequence of bed rest-induced accelerated aging. This is also supported by findings from Miller and colleagues (Miller et al., 2008a), showing a very similar response in the elderly. Specifically, they observed greater hippocampal activity during the encoding process in low-performing older adults and explained this phenomenon as a compensatory response (Miller et al., 2008a). In another study Miller and colleagues also demonstrated that greater hippocampal activation during memory encoding predicted the rate of cognitive decline (Miller et al., 2008b). Additional evidence comes from Yassa et al. (2010) who found an inverse relationship between hyperactivity in the dentate gyrus and CA3 region and behavioral performance, suggesting that the increase in brain activity resulted from dysfunctional encoding mechanisms. Conflicting results have been reported in a precedent study by Small and colleagues (Small, Perera, DeLaPaz, Mayeux, & Stern, 1999) who found reduced activation in all hippocampal subfields in Alzheimer patients compared to healthy elder controls. Sperling speculated that hyperactivation occurs in very early stages of MCI as a compensatory response to maintain memory performance but at a later stage the hippocampus fails, resulting in decreased activation (Sperling, 2007). In a longitudinal study Nyberg and colleagues (2019) have observed both during encoding, an age-related hypoactivity in the anterior hippocampus, and hyperactivity in the anterior and posterior hippocampus in elderly having lower memory performance and a higher dementia risk. The authors suggested that hippocampal hyperactivity is not a response per se to normal aging but rather a pathological sign of neurocognitive disorders (Nyberg et al. 2019). The same group also assumed that hippocampal atrophy and memory decline induces functional reorganization in the prefrontal cortex (Pudas et al., 2018) and elevated functional connectivity between PFC and anterior hippocampus (Nyberg et al. 2019).

In the present study, differences in brain activity between groups were not paralleled by changes in behavioral performance. Participants most often identified novel, lure, and repetition stimuli correctly as new, similar, and old showing the highest accuracy in novel and repetition items. Lure items were harder to classify and only correctly identified in 43% to 66% of all lure trials. Very similar performances on novel, lure and repetitive trials have been reported in previous studies (Hämäläinen et al., 2007; Kirwan & Stark, 2007) confirming the validity of the paradigm in the present study. Notably, we observed an improvement in the ability of discriminating lure trials on HDT58 compared to BDC-4 in both groups that may be the result of additional test-enhanced learning effects that occurred independently of the intervention. It can only be speculated whether the discrepancy between neuronal activity and mnemonic performance is due to a reduced neuronal efficiency in CTRL (i.e., that maintaining behavioral performance requires a higher neural demand) or that bed rest induced dysfunctional mechanisms in neuronal coupling, which were counteracted by the exercise intervention. In addition to our *a priori* hypothesis anticipating changes in hippocampus and parahippocampal gyrus, we also explored whole-brain BOLD signal changes during pattern separation and completion from BDC-4 to HDT58. We observed a significant increase in the right occipital pole during pattern separation in participants that did not undergo the training intervention. Occipital, parietal, and temporal regions have been reported previously to contribute to pattern separation (Pidgeon & Morcom, 2016) and memory retrieval (Jonker et al., 2018). It is also possible that these activations reflect other processes associated with the encoding of the stimuli. For instance, Sestieri, Shulman, & Corbetta (2017) noted that such activations could be related to perceptual attention. Our data also suggested a stronger decrease in CTRL for bilateral precentral gyrus. However, the interaction between *Group* and *Time* was not significant. It is possible that this activation is likely to be attributed to bed rest (Cassady et al., 2016). Cassady and colleagues reported that the intrinsic connectivity contrast (ICC) of the precentral gyrus is increased after 70 days of bed rest (Cassady et al., 2016). We therefore assume that the observed cluster is unrelated to our fMRI paradigm and a result of prolonged bed rest per se.

Key strengths of this study are the highly-standardized conditions and environment of the experimental and control group. In contrast to previous ambulatory training studies (Erickson et al., 2011; Ruscheweyh et al., 2011; Hötting et al., 2012), we were able to standardize various critical factors that are known to affect neurobehavioral measures, including the social environment, leisure time activities, nutrition, sleep, and day and night cycles. Over three months, including the 60 days of bed rest, sleep, diet, light exposure, environmental conditions, and physical activity were strictly regulated and standardized (Kramer et al., 2017a). Social interactions were limited to staff, other participants, and individual personal phone calls only. Thus, the differences in neuronal activity observed in the study can likely be exclusively attributed to the result of the exercise intervention. It should also be noted that the exercise intensity and target population of the current project differed compared to previous studies.

Our exercise group followed a short but intensive jump training protocol and completed 48 sessions within two months. For example, this was the same amount of sessions over a course of six months in the study by Hötting et al. (2012). Moreover, a large part of the existing body of research focuses on older adults with a mean age >60 years (e.g., Erickson et al., 2011; Ruscheweyh et al., 2011; Jonasson et al., 2016). Only very few studies with a similar cohort following a comparable study design have been reported so far and none of these studies particularly targeted the function of the hippocampus (Koppelmans et al., 2013; Rao et al., 2014; Zhou et al., 2014; Yuan et al., 2016). In these studies, 45 days of bed rest led to altered functional connectivity in the left anterior insula and dorsal anterior cingulate cortex (Zhou et al., 2014) as well as to greater activation in the ventromedial prefrontal cortex during risky decision making (Rao et al., 2014). Another research group reported increased brain activity in frontal and parietal regions that were accompanied with slower reaction times (Yuan et al., 2016) and detrimental effects on functional connectivity in motor and somatosensory brain areas after 70 days of bed rest (Cassady et al., 2016; Koppelmans et al., 2017; Koppelmans et al., 2018). The authors concluded from the observed increased brain activation that more neurocognitive control is required during bed rest for dual-task execution (Yuan et al., 2016). The results of the present study confirm these findings for episodic memory and its neural basis, and provide novel insights into the effects of physical activity on mitigating the effects of bed rest on brain function.

4.1. Limitations

Although the study was highly standardized, our findings are subject to a few limitations. The overall experimental protocol was defined by the study sponsor, including inclusion and exclusion criteria as well as sample size. These restricted criteria have resulted in a highly selective sample of young, healthy men. Accordingly, caution must be applied with respect to the generalizability of the findings to women, the aging population, and patients. Further research is needed to investigate bed rest induced changes in mnemonic processing and their neural basis in different populations. We also acknowledge that the present study lacks a non-resting control group. Albeit, the challenges in controlling for diet, sleep, social contacts, and physical activity levels in ambulatory controls, such data could also provide important information to better understand the effects of long-duration immobilization.

5. Conclusion

The current study assessed the effects of long-term bed rest on episodic memory and its neural correlates and the efficacy of a regular high-intensity exercise to mitigate adverse neurobehavioral effects. With the same mnemonic performance, we found an elevated BOLD

signal in the non-exercising bed rest group compared to the exercising bed rest group. It cannot be conclusively decided whether this is a compensatory response or the result of an underlying dysfunctional mechanism. Our findings show, however, that high-intensity exercise modulates neuronal activity and may counteract hyperactive signaling in the hippocampal formation. Further research is needed to elucidate sex-specific effects of the high-intensity exercise program on hippocampal activation, and explore the potential of these programs to preserve brain function in the aging population.

Funding

The project was supported by the European Space Agency (ESA) and by the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt; DLR) through grants 50WB1525 and 50WB1519 awarded to ACS.

CRediT authorship contribution statement

Anika Friedl-Werner: Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Katharina Brauns:** Project administration, Investigation, Data curation, Writing - review & editing. **Hanns-Christian Gunga:** Writing - review & editing. **Simone Kühn:** Methodology, Software, Formal analysis, Writing - review & editing. **Alexander C. Stahn:** Conceptualization, Supervision, Project administration, Funding acquisition, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing.

Acknowledgements

The authors thank the European Space Agency for providing the opportunity to participate in this study, Ulrich Limper, Edwin Mulder, and Alexandra Noppe from DLR for their medical, technical, and administrative support in implementing the study protocol as well as Darius Gerlach, Kerstin Kempter, and Annette von Wächter for MRI acquisition.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117359.

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