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Higher neural demands on stimulus processing after prolonged hospitalization can be mitigated by a cognitively stimulating environment

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Abstract: Prolonged periods of complete physical inactivity or bed rest trigger various alterations in the functional and metabolic levels of the human body. However, bed rest-related adaptations of the central nervous system are less known and thoroughly studied. The aim of this study was to investigate brain electrophysiological changes using event-related potentials (ERPs) after 14 days of bed rest and 12 consecutive sessions of computerized cognitive training (CCT). Sixteen older (M_{age}= 60 years) healthy volunteers were randomly divided into a CCT treatment group and an active control group. All participants performed ERP measurements based on the foveal visual presentation of a circle on a black background before and after bed rest. After 14 days of bed rest, participants in the control group showed increased peak P1 amplitude (p = .012), decreased P1 latency (p = .024), and increased P2 amplitude (p = .036), while the CCT group also showed decreased P1 latency (p = .023) and decreased P2 latency (p = .049). Our results suggest that, even from a central adaptation perspective, prolonged periods of physical inactivity or bed rest trigger additional neural recruitment and should therefore be minimized, and that CCT may serve as a tool to mitigate this. Future research should focus on other aspects of central nervous system adaptation following periods of immobilization/hospitalization to improve our knowledge of influence of physical inactivity and its effects on cortical activity and to develop appropriate countermeasures to mitigate functional dysregulation.

Keywords: bed rest immobilization, aging, electroencephalography (EEG), computerized cognitive training, event-related potential (ERP)

Kognitivno spodbudno okolje lahko ublaži višje nevronske potrebe za procesiranje vidnih dražljajev po večdnevni hospitalizaciji

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Povzetek: Dolgotrajna obdobja popolne gibalne neaktivnosti ali horizontalnega ležanja sprožijo v človeškem telesu različne spremembe na funkcionalni in metabolni ravni. Prilagoditve centralnega živčnega sistema, povezane s horizontalnim ležanjem, so manj poznane in še ne dovolj preučene. Namen te raziskave je bil oceniti možganske elektrofiziološke spremembe z uporabo metode z dogodkom povezanih potencialov (ERP) po 14-dnevnem horizontalnem ležanju in 12 zaporednih vadbah računalniškega kognitivnega treninga (RKT). Šestnajst starejših ($M_{starost}$= 60 let) zdravih prostovoljcev je bilo naključno razdeljenih v intervencijo RKT in aktivno kontrolno skupino. Vsi udeleženci so izvajali meritve ERP pred in po horizontalnem ležanju na podlagi fovealne vidne predstavitve kroga na črni podlagi. Po 14-dnevnem horizontalnem ležanju je analiza ERP pokazala povečano amplitudo P1 (p = ,012), zmanjšano latenco P1 (p = ,024) in povečano amplitudo P2 (p = ,036) pri kontrolni skupini, medtem ko sta se v skupini RKT latenci P1 (p = ,023) in P2 skrajšali (p = ,049). Naši rezultati kažejo, da daljša obdobja gibalne neaktivnosti ali horizontalnega ležanja sprožijo, tudi z vidika centralne prilagoditve, dodatno rekrutacijo nevronov, zato je treba taka obdobja zmanjšati na najmanjšo možno mero. Ugotovljeno je bilo tudi, da lahko RKT služi kot orodje za ublažitev upada. Prihodnje raziskave bi se morale osredotočiti še na druge vidike prilagajanja centralnega živčnega sistema po obdobjih imobilizacije/hospitalizacije, da bi izboljšali razumevanje posledic gibalne neaktivnosti in njenih učinkov na kortikalno aktivnost ter razvili ustrezne protiukrepe za blaženje funkcionalne disregulacije.

Ključne besede: imobilizacija, staranje, elektroencefalografija (EEG), računalniški kognitivni trening, z dogodkom povezani potenciali

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Due to its nature, hospitalization or prolonged bed rest can lead to impaired mobility or loss of autonomy, rehospitalization, and/or increased risk of mortality (Goh et al., 2018; Ponzetto et al., 2003). A growing body of evidence suggests that prolonged periods of physical inactivity or bed rest trigger significant negative functional and metabolic changes in the human body (Pisot et al., 2016). These effects are most evident in the decreased functioning of cardiovascular (Perhonen et al., 2001; Traon et al., 1998), skeletal (LeBlanc et al., 2007; Rittweger et al., 2009) and neuromuscular (Grogorieva & Kozlovskaia, 1987; Mulavara et al., 2018; Pisot et al., 2008) systems of human body, with some evidence of potential deficits on brain structure (Li et al., 2015) and functioning (Ioseliani et al., 1985; Lipnicki & Gunga, 2009; Marusic et al., 2014).

Evidence regarding brain changes after prolonged bed rest are scarce. Although bed rest models were introduced in the 1960s to simulate acute adaptations to a microgravity environment (Adams et al., 2003), their effects on the human organism appear to be similar to those that occur after periods of physical inactivity, sedentary lifestyles, immobilization, and even space flight (Marusic et al., 2014; Pavy-Le Traon et al., 2007). Bed rest has also been used as a model for age-related changes, more specifically for an accelerated form of the ageing process (Timiras, 1994; Vernikos & Schneider, 2009).

Studies examining brain structural changes after prolonged (70 days) head-down tilt bed rest revealed specific gray matter modifications in sensorimotor brain regions (Koppelmans et al., 2017). In particular, a focal increase in gray matter volume was found in posterior parietal regions and a decrease in frontal regions. A shorter, 30-day head-down tilt bed rest reduced gray matter volumes mainly in the bilateral frontal lobes, temporal poles, insula, parahippocampal gyrus and right hippocampus (Li et al., 2015). Decreases in gray matter volume were also accompanied by some increases, which could represent neuroanatomical adaptations and/or redistribution of fluid (Koppelmans et al., 2017; Li et al., 2015). From the perspective of brain electrocortical activity, as measured by electroencephalography (EEG), prolonged periods of bed rest most likely represent signs of cortical inhibition (Marusic et al., 2014), but other EEG approaches such as event-related potentials (ERPs) have rarely been used besides measuring fluctuations in EEG frequencies.

The early perceptual processes of static visual stimuli are commonly studied with so-called visual evoked potentials (VEPs) and represent a non-invasive technique that provides information about early functional changes in the visual pathway and visual cortex of the brain (for a review see Kuba et al., 2007). Foveal presentation of a static stimulus elicits a three-phase waveform composed of P1, N1, and P2 components, presumably reflecting early processing of luminance pattern changes (Bach & Ullrich, 1997; Kubová et al., 1995) and subsequent pattern recognition. It has been suggested that P1 and N1 are involved in “gain control” of sensory processing (Hillyard et al., 1998). Studies assessing P2 claim that this component indexes working memory (Finnigan et al., 2011; Lefebvre et al., 2005), stimulus salience (Riis et al., 2009), and stimulus evaluation (Potts, 2004), while others claim that P2 plays a significant role in top-down cognitive control (Karamacoska et al., 2019; Lai et al., 2020).

To date, there are no ERP/VEP data associated with prolonged physical inactivity. However, research findings on age effects on early VEP P1, N1, and P2 components may be of particular interest if we hypothesize that bed rest could be used as a model for accelerated aging. Aging studies using early VEP components revealed that increased peak P1 amplitude with prolonged P1 latencies were observed in aged individuals compared to their younger counterparts (De Sanctis et al., 2008; Falkenstein et al., 2006; Yordanova et al., 2004). Zalar et al. (2015) reported that older participants showed increased P1 amplitude compared to young participants, while their P2 amplitude was reduced. In addition, increased N1 amplitudes and prolonged P2 latencies were also found in aging (Goodin et al., 1978; Iragui et al., 1993; Pfefferbaum et al., 1979, 1980).

We hypothesized that bed rest-induced negative adaptations of early perceptual processes could be detected after 14 days of complete physical inactivity and that a computerized cognitive training (CCT) intervention, specifically targeting the hippocampus and frontal areas (Marusic et al., 2018), could help mitigate them.

Methods

Participants

A total of 16 men (M_{age} = 60 years, *SD* = 3 years; $M_{body\ mass\ index}$ = 26.2 kg/m^2, *SD* = 4.5 kg/m^2) volunteered to participate in the project “*Bed Rest Study – PANGeA, Valdoltra 2012*”. Participants were recruited through public advertisement of the project, newspaper advertisements and word-of-mouth recommendation from three coastal towns in Slovenia. They underwent 14 days of horizontal bed rest with a supervised 28-day recovery period with an extensive battery of functional and cognitive assessments. All participants were right-handed, had normal or corrected-to-normal vision, and had no cardiovascular, neurological, or psychiatric disease. All procedures were performed in accordance with the Declaration of Helsinki and approved by the Republic of Slovenia National Medical Ethics Committee (KME 103/04/12). Written informed consent was obtained from all participants before the bed rest experiment. Participants were financially compensated for the time spent on the bed rest study and the subsequent rehabilitation period.

The educational level of the majority (10/16) was at a secondary level (gymnasium or vocational secondary school: 12 years of education), three participants had 16 years of education (college or university diploma), and three of them had lower than secondary level degree. With regard to computer use, 5 participants reported not using it at all (1 from the CCT group and 4 from the control group), while the other 11 participants used it daily or often, approximately 2 hours per day, mainly for the purpose of information search, e-mailing and e-banking.

Participants were medically screened prior to inclusion in the study with an interview, routine blood and urine analysis, and a fitness battery test. Exclusion criteria were: regular alcohol consumption; ferromagnetic implants; history of deep vein thrombosis with D-dimer < 500 μg·L-1; acute or chronic skeletal, neuromuscular, metabolic and cardiovascular disease condition; pulmonary embolism; a Short Physical Performance Battery score < 9; and a VO_2 max < 21 ml/kg/min.

Study design

This bed rest study was a controlled, longitudinal, interventional study. To achieve the aims of the study (simulate prolonged physical inactivity), participants were required to lie in bed continuously for 14 days. During bed rest, they were only allowed to turn on all sides of their bodies, or place no more than two pillows under their head, and they were not allowed to stand up, sit on the bed, or raise their arms above the level of their heads. Hospital staff regularly checked the physical condition of the participants and took them to the bathroom with their beds for personal hygiene. They received the usual hospital meals three times a day at 7.30 am, 12 noon and 6 pm. The bedrooms (3–4 persons per room) were air-conditioned and the room temperature was kept comfortably below 25 °C. During bed rest, the study participants were allowed to read books and newspapers, use the Internet, watch TV and listen to the radio, and communicate freely with each other.

Eight participants were randomly selected for CCT (CCT group), while the other eight served as active controls (Control group). In separate rooms, the CCT group performed cognitive training for approximately 50 minutes daily, while the control group watched documentaries at the same time and for the same duration. The bed rest study was conducted at Orthopaedic Hospital Valdoltra, Ankaran, Slovenia.

Procedure

Computerized cognitive training. For virtual navigation training we used virtual maze navigation task which was previously described in Marusic et al. (2015) and Marusic et al. (2018). Participants in the CCT group were asked to navigate through virtual mazes with the use of a joystick for approximately 50 minutes on each of the 12 consecutive days of bed rest. The cognitive training was adaptive in terms of increasing difficulty; if a participant completed a virtual maze twice in a row without making a mistake, they were administered a maze with a higher level of difficulty. Although the number of seven-intersection virtual mazes completed at the end of the training period varied depending on how quickly each participant reached criterion in each virtual maze, all participants who completed the cognitive training finished at least four of the seven-intersection mazes. As described in Marusic et al. (2018), the use of a spatial navigation-based computerized intervention was expected to target multiple network-linked brain areas that support critical cognitive abilities that often decline with aging and dementia, such as working memory, attention, and spatial orientation, optimizing the possibility of generalizing the results of CCT. The sustained attention and decision making required to navigate the virtual maze, and the constant updating of working memory due to traversing a series of intersections in the virtual maze, could be reflected in the neurophysiological changes measured by the ERP method.

Electroencephalographic (EEG) measurements. Scalp electroencephalographic (EEG) activity was recorded using Brain Products GmbH equipment, with 64-channel ActiCap, modified according to the International 10–20 System. The FCz and AFz electrodes were used as reference and ground electrodes, respectively. During EEG measurements, low-pass and high-pass filters were set to 70 Hz and 0.1 Hz, respectively, and were used only for online visualization. The cutoff frequencies for these filters were set to 3 dB down; the roll off was 12 dB per octave on both sides. Impedances were kept below 10 kΩ for each channel and balanced across all channels within a 5 kΩ range. The sampling rate was 2000 Hz with a resolution of 32-bits. Due to process optimizations, the EEG data were then resampled from 2000 Hz to 500 Hz.

Participants' EEG was recorded before the start of the study and immediately after 14 days of bed rest while sitting in a neutral position. After baseline measurement with eyes open (3 min) and closed (3 min), participants were instructed to observe 200 visual stimuli presented every 1000 ms on a 17-inch flat panel LCD monitor (resolution 1280 x 1024, response time 25 ms, refresh rate 60 Hz) located approximately 50 cm in front of them. The visual stimuli were created with custom software coded in C using the Allegro function library and compiled with MinGW software. They were presented in the center of a monitor (duration 300 ms, intensity 50 cd/m^2, viewing angle 1° horizontal/1.5° vertical) located in front of the subject's eyes. The interstimulus interval was 1000 ms, corresponding to 300 ms of stimulus occurrence and 700 ms of blank screen. Participants were asked to perform finger tapping, synchronizing their index finger movements as closely as possible to the visual stimuli.

All data were analyzed using the EEGLAB toolbox (Delorme & Makeig, 2004). Initially offline visual inspection of the EEG data was performed to identify and remove segments contaminated by either excessive noise, saturation, or lack of EEG activity.

A high-pass (0.5 Hz) and low-pass filter (cut-off frequency 40 Hz, roll-off 6 dB/octave) were applied to the EEG data, and then independent component analysis (ICA) was used to remove eye blinks. Visual evoked potentials (VEPs) were segmented from –200 to +800 ms, with baseline set from –200 to 0 ms. Using the "pop_autorej" function for automatic epoch selection, epochs exceeding a threshold of 100 μV were removed and then visually inspected. In all cases, at least 120 stimulus epochs were averaged. Visual modality was assessed across occipital sites on the scalp, with an average of electrodes O1, O2, and Oz. The following analyses were performed: (i) P1 was detected as the most positive peak (amplitude and latency) in the range of 80–150 ms after stimulus presentation, (ii) N1 was the most negative peak (amplitude and latency) in the range of 120–200 ms, and (iii) P2 was the first positive peak (amplitude and latency) after 200 ms.

Statistical analysis. Data were analyzed using IBM SPSS Statistics 26.0 software for Windows. Normality of the distribution of parameters was tested using Shapiro-

Wilk's test and visually with Q-Q plots as well as histograms. Baseline differences between the two groups were assessed with a nonparametric Mann-Whitney test, whereas pre-post differences were evaluated with the nonparametric Wilcoxon test. Results with *p*-values < .05 were considered statistically significant.

Results

For baseline (pre-bed rest) characteristics of stimulus-related processes, the Mann-Whitney test showed no significant changes between the two groups for peak P1 amplitude (U = 18.0, Z = –1.47, p = .161) and latency (U = 30.5, Z = –0.16, p = .878), N1 amplitude (U = 28.0, Z = –0.42, p = .721) and latency (U = 27.5, Z = –0.47, p = .645), and P2 amplitude (U = 16.0, Z = –1.68, p = .105) and latency (U = 30.5, Z = –0.16, p = .878).

Results from the CCT group comparing changes before and after bed rest showed a significant reduction in P1 latency (mean delta = –3.25 ms, Z = –2.27, p = .023) and P2 latency (mean delta = –4.75 ms, Z = –1.97, p = .049), whereas no significant changes were observed for P1 amplitude (p = .327), N1 amplitude (p = .484), N1 latency (p = .320), and P2 amplitude (p = .889) (Figure 1, panel A).

The control group showed a significant increase in P1 amplitude (mean delta = +1.10 µV, Z = –2.52, p = .012), a decrease in P1 latency (mean delta = –2.50 ms, Z = –2.26, p = .024), and an increase in P2 amplitude (mean delta = +0.82 µV, Z = –2.10, p = .036) at the end of bed rest. In contrast, there were no significant changes in N1 amplitude (p = .484), N1 latency (p = .611), and P2 latency (p = .161) (Figure 1, panel C).

The VEPs are further supported by topographic maps of the post-pre difference for the CCT and control groups (Figure 1, panel B and panel D, respectively), showing the post-pre differences in the P1, N1, and P2 components in the parieto-occipital region. As expected from the grand waveforms, the post-pre differences were more pronounced for the control group than for the CCT participants.

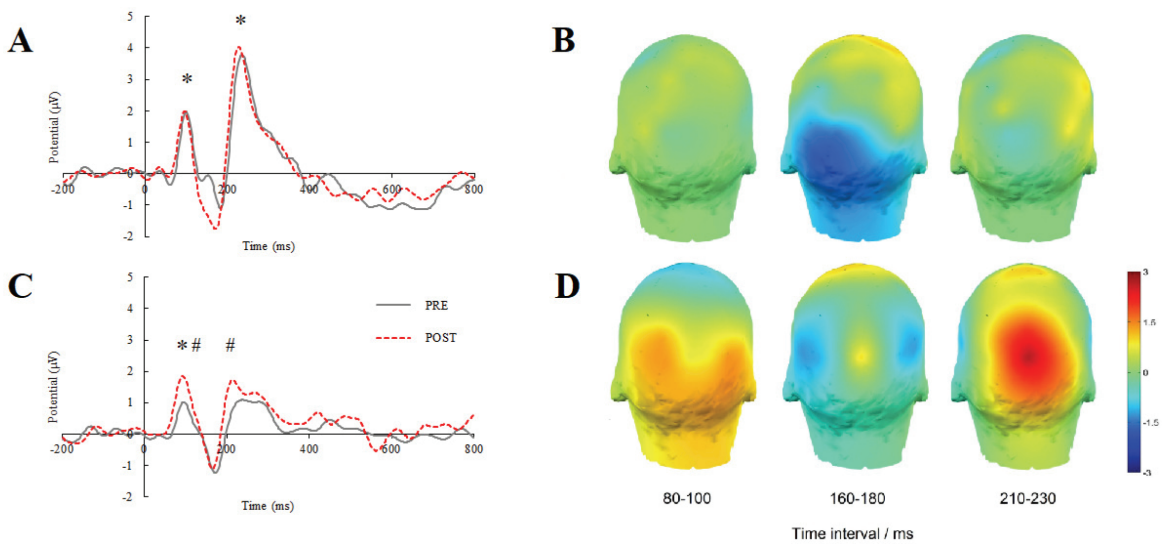
Discussion

The first aim of this study was to assess central adaptations of the brain in older adult population after completing fourteen days of complete physical inactivity/bed rest that might be reflected as changes in early perceptual processes of visual stimuli. In addition, our second aim was to assess whether cognitive intervention might be helpful in mitigating and/or preventing physical inactivity-related negative adaptations.

Our results showed that fourteen days of bed rest triggers specific central adaptations detectable with an electroencephalographic assessment tool (EEG/ERP). We found a significant increase in the maximum P1 peak amplitude only in control subjects. In contrast, an unchanging peak P1 component was found in the CCT group that completed twelve consecutive sessions of the CCT intervention during the bed rest period. Increased peak P1 amplitude may reflect a higher level of activation needed after bed rest to compensate for the same speed and intensity of early perceptual processing (Amenedo & Díaz, 1998). This finding is comparable with aging studies, which examined age-related changes in stimulus processing and reported enhanced peak of P1 component in older vs. younger participants (De Sanctis

Figure 1

Visual Evoked Potentials for CCT (A) and Control Group (C), and Topographic Maps of Post-Pre Difference for CCT (B) and Control Group (D)



Notes: The solid gray line represents the data from pre-bed rest, while the dashed red line represents post-bed rest data. * marks a significant decrease in latency at the end of bed rest. # marks a significant increase in amplitude at the end of bed rest. The topographic maps are shown from posterior view.

et al., 2008; Falkenstein et al., 2006; Yordanova et al., 2004; Zalar et al., 2015). Interestingly, P1 latency was significantly reduced in both groups, with a higher effect size observed in the CCT group. Shorter P1 latencies in both groups at the end of bed rest possibly reflect a practice effect and/or higher attentional levels to the forthcoming stimulus, which may modulate the processing of visual information, reflected in shorter P1 latencies (Schuller & Rossion, 2001).

The other two significant results were observed for P2 amplitude, which was increased only in the control group, and for P2 latency, which was significantly reduced only in the CCT group after the end of bed rest. Because the CCT intervention included the spatial navigation task, we hypothesized that multiple network-linked brain areas were stimulated and thus a preventive effect would be observed in parameters related to higher-order cognitive functions. More specifically, the observed reduced P2 latency might therefore reflect the generalization of the CCT intervention to other cognitive functions, in particular the improvement of working memory (Finnigan et al., 2011; Lefebvre et al., 2005), although this component has also been previously associated with stimulus salience (Riis et al., 2009) and stimulus evaluation (Potts, 2004). However, our finger-tapping synchronization task cannot be classified as a complex cognitive-motor task, it mainly required sustained attention and working memory. The increase in amplitudes can be attributed to a compensatory process in the control group that enabled them to finger tap correctly. Other bed rest studies addressing VEPs lack or focus on other paradigms and later ERP components (e.g., P3; Brauns et al., 2019). Considering bed rest as a model for an accelerated form of aging (Timiras, 1994; Vernikos & Schneider, 2009), results on aging studies and P2 latency parameters are mixed; some studies have shown increased P2 latencies (Goodin et al., 1978; Iragui et al., 1993; Pfefferbaum et al., 1979, 1980), whereas others have reported no significant age-related changes (Amenedo & Díaz, 1998, 1999; Zalar et al., 2015).

The present study confirms previously observed results, which demonstrate that CCT can serve as an effective tool to counteract prolonged physical inactivity-induced adaptations. Our group has previously reported positive transfer of CCT intervention to specifically trained as well as specifically untrained cognitive functions (Marusic et al., 2018), as well as to a distal untrained domain such as complex dual-task locomotion (Marusic et al., 2015). In addition, we found that it positively affects plasma brain-derived neurotrophic factor (Passaro et al., 2017) and to some extent also vascular function (Goswami et al., 2015).

Our study was conducted in a highly controlled environment (hospital setting). However, several limitations need to be mentioned. Future studies could replicate our findings on a bigger sample sizes as well as conduct both interventions (bed rest and cognitive training) in different age and gender groups. Here we need to emphasize that we were very constrained with respect to the sample size, age and gender composition. Sample size was primarily limited due to the high costs of bed rest study, allowing us to only include 16 older adult participants. With respect to the age and gender composition, the instructions and decision of the Republic of Slovenia National Medical Ethics Committee limited us to recruiting only men younger than 65 years of age. The committee based its decision on the lack of any published research investigating the effects of extended bed rest with older people. However, none of our participants developed any serious medical conditions after 14 days of bed rest, suggesting that older participants could be recruited and participate safely in future bedrest studies.

Conclusions and future directions

Our study emphasizes that two weeks of highly controlled hospitalization elicits significant changes in early perceptual processes of visual stimuli in a healthy population of older adult males. After 14 days of bed rest, an additional neural recruitment indexed by increased P1 and P2 amplitude was observed only in control subjects, which can be interpreted as a compensatory mechanism of the brain to consistently process the same amount of information. To the opposite, the mentally active group did not (from the central point of view) show the need for additional recruitment. In other words, CCT maintained visual processing at the same level throughout two weeks of bed rest. These findings have direct application for the need of CCT in hospitalized patients after injury/surgery or the sedentary elderly in general since we have observed above described maintenance of early visual processing during two weeks of complete physical inactivity. Future research should focus on other aspects of central nervous system adaptation, particularly functional dysregulation of the motor cortex and causes of behavioral slowing that occur after periods of immobilization, hospitalization, or physical inactivity in general.

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