Running effects on cognition and plasticity (ReCaP): study protocol of a longitudinal examination of multimodal adaptations of marathon running

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Introduction

Over the past decades, research interest has grown on the beneficial and negative effects of different forms of physical activity (PA), with a focus on exercise-induced cardiovascular adaptions. Regular moderate PA reduces arterial blood pressure and the risk for hypertension (Dimeo et al., 2012). PA also improves insulin sensitivity and reduces the risk for diabetes mellitus (Ivy, 1997; Praet & van Loon, 2009). In various other disorders positive effects could be

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displayed (e.g. cancer) (Idorn & Thor Straten, 2017). Moreover, PA reduces all-cause mortality (Hu et al., 2005; Myers et al., 2004).

In contrast, a growing number of studies have reported potential negative effects of strenuous and prolonged exercise such as marathon running. A U-shaped association has been described between all-cause mortality and the running dose, with similar mortality rates between sedentary individuals and runners engaging in the most strenuous running programs (Schnohr, O'Keefe, Marott, Lange, & Jensen, 2015). Despite an awareness of the possible risks, more and more runners participated in running events like half-marathons /(ultra-) marathons over the past decades with an increasing amount of female participants and faster finishing times (Hoffman & Krouse, 2018; Knechtle & Nikolaidis, 2018). Multiple reports have been published about the complications of marathon running and strenuous exercise such as sudden cardiac death (Corrado et al., 2006; Kim et al., 2012; Maron & Pelliccia, 2006). The reasons for these incidents are still under discussion, but possible triggers could be arrhythmias due to structural cardiac changes with myocardial fibrosis and scars (Bisbal & Mont, 2012). The cardiovascular instability following exercise can be interpreted in the context of hemodynamic alterations (e.g. symptomatic hypotension and syncope) (Romero, Minson, & Halliwill, 2017). Moreover, changes in the autonomic nervous system or in the concentration of electrolytes are potential risk factors for adverse cardiovascular incidents (Walker, Calkins, & Nazarian, 2010). Increased levels of cardiac troponin (cTn) and inflammation have been reported in runners after marathon races, and represent potential signs of global structural damages (e.g. heart, muscles) (Da Ponte et al., 2018; Scherr et al., 2011). A review of 45 studies reported the effects of strenuous exercise on biomarkers, e.g. high sensitive troponin T (cTnT) or brain-derived neurotrophic factor (BNP), and on cardiac form and function. In this review, more than 50% of individuals had at least mildly increased cTnT concentrations after exercise. In addition, right ventricular impairment was observed by echocardiographic and MRI measurements, whereas left ventricular systolic function was unchanged. Only left ventricular diastolic function seemed to be impaired after exercise (Sedaghat-Hamedani et al., 2015).

Prior studies from our group investigated retinal circulation and found a significant increase in the arteriolar-to-venular ratio (AVR) due to larger arteriolar than venular dilatations immediately after marathon running (Pressler et al., 2011). These alterations returned to baseline values within 24 hours. Higher AVR was also observed among marathon runners compared to healthy but sedentary adults. Carotid intima-media thickness (IMT) is used as an index of cardiovascular risk, but despite concerns, one 3.8 year study was unable to show that regular marathon training and racing were linked to detrimental or beneficial IMT changes (Müller et al., 2017). Another study of 97 successful marathon runners assessed multiple vascular parameters including AVR, IMT, ankle-brachial index, augmentation index (AIx), pulse wave velocity (PWV) and reactive hyperaemia index. Normal values were reported for all measured parameters, indicating that running multiple marathons is not a risk factor for premature subclinical vascular impairment (Pressler et al., 2017). These results are in contrast to findings from other groups indicating a high prevalence of carotid and peripheral atherosclerosis in endurance runners (Kröger et al., 2011) A comparison between healthy controls and marathon runners demonstrated increased aortic stiffness and pressures in marathon runners (Vlachopoulos et al., 2010). In conclusion, acute post-marathon changes can be measured for multiple indices of vascular health, but the literature is inconsistent on the potential for adverse long-term effects.

In contrast, the effects of strenuous and long duration running on the central nervous system (CNS) have not been systematically evaluated. Exercise therapy is increasingly being used as a treatment for different neuropsychiatric diseases: a positive effect of regular exercise on symptom severity and onset of dementia has been demonstrated (Buchman et al., 2012; Hamer & Chida, 2009; Larson et al., 2006). A systematic review of 11 studies including 1497 patients with mild cognitive impairment indicated significant improvements in global cognitive ability and positive effects on memory (Zheng, Xia, Zhou, Tao, & Chen, 2016). Moreover, PA has beneficial effects on healthy ageing as supported by a recent review of 23 controlled and uncontrolled studies with 174114 participants (Daskalopoulou et al., 2017).

A meta-analysis of 10 exercise therapy trials with schizophrenia patients showed improved global cognition, working memory, social cognition and attention (Firth et al., 2017). Depressive symptoms may be responsive to exercise treatment or exercise in general, but these effects may be transitory (Krogh, Nordentoft, Sterne, & Lawlor, 2011). In summary, several studies highlighted the potential of exercise therapies to induce positive changes in various neuropsychiatric diseases and in healthy ageing, even though the examined interventions varied.

Neuropathological and neurophysiological studies explored possible mechanisms for the positive PA-CNS linkage including enlargement of hippocampal volume, enhanced neurogenesis, and increased cerebral blood flow (van Praag, Christie, Sejnowski, & Gage, 1999) (Brown et al., 2003; Pereira et al., 2007). A recent review provided an overview of these mechanisms and connected them with the upregulation of brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1) and Orexin A (Chieffi et al., 2017). Arterial compliance and peripheral biomarkers (e.g. cortisol) may also play important roles, and post-exercise training adaptions may occur on different levels (e.g. TMS, EEG or MRI) (Bullitt et al., 2010; Cirillo, Lavender, Ridding, & Semmler, 2009; Rojas Vega et al., 2006; Voss, Vivar, Kramer, & van Praag, 2013). There is a need for systematic and multimodal evaluations to improve scientific understanding in this area.

Few studies have investigated CNS adaptations to intensive, long duration exercise such as marathon running: one small-sample study with ultra-marathon runners showed relative post-race changes of inter-cellular volume and the potential for cerebral edema using brain magnetic resonance imaging (MRI) and various blood parameters (e.g. osmolality, hematocrit) (Zanchi et al., 2016). In contrast, MRI measurements of moderate exercise such as tai chi indicated beneficial effects on brain white matter (Yao et al., 2018). In a limited study with 9 participants, changes in the corticospinal excitability measured by transcranial magnetic stimulation (TMS) demonstrated peripheral fatigue and decreased motor-cortical excitability after running a marathon (Ross, Middleton, Shave, George, & Nowicky, 2007). Electroencephalography (EEG) was used to evaluate neuronal excitability and connectivity during marathon training, and showed a decrease in theta activity (4–6 Hz) and an increase of the slow alpha component and subtheta activity (6–8 Hz) (Honzák, Brodan, Frouz, Veselková, & Potůcek, 1985). In a study of 92 runners competing in a 168 km mountain ultramarathon, cognitive performance decreased during the race, especially in the early morning hours (Hurdiel et al., 2018).

A close relationship may exist between neuropsychiatric and cardiovascular parameters. Arterial stiffness is considered a sensitive predictor of cognitive impairment (Li, Lyu, Ren, An, & Dong, 2017). Other possible influencing factors of cognitive functioning include the glucose

supply to specific brain regions (Benton, 2001), inflammatory markers (Arfanakis et al., 2013) and impaired cerebral microvessel functionality (Silvestrini et al., 2006). Depressive symptoms among middle-aged participants are also associated with arterial stiffness (Onete et al., 2017). This finding provided a possible physiological explanation for the positive treatment effects of exercise therapy.

The ReCaP study will examine marathon running-induced changes (both training and recovery periods) on behavioral, functional and morphological outcomes related to both the cardiovascular and central nervous systems. The 6-month period of this study will capture responses to normal exercise training and post-race recovery periods in comparison to the physiological stress imposed by the marathon race. This is the first study to provide a broad and multimodal evaluation of exercise-induced cardiovascular and central nervous system responses in marathon runners before, during, and after a competitive race.

Hypotheses of the study

The cognitive adaptions over the study period will correlate with adaptations of the vascular status.

Participants will show various adaptations during the marathon training period with improvements of neuronal and vascular parameters (e.g. neuronal or structural plasticity measured with TMS, EEG and MRI, vascular status including micro circulation) that will also be detectable during the follow-up period.

Immediately after a marathon, there will be a short-termed impairment of neuronal and cardiac parameters (as a consequence central fatigue and inflammation processes).

Baseline comparisons between marathon runners and sedentary controls will reveal better cardiac fitness, cognitive performance, increased neural plasticity in marathon runners.

Design and methods

ReCaP is a longitudinal observational study of marathon runners who were registered for the Munich Marathon on October 8th, 2017.

Participants and recruitment

A total of 100 participants were recruited by announcements in local newspapers, local running groups, and newsletters of the local organizer of the Munich marathon. Furthermore, participants of prior marathon studies from our group (Grabs, Nieman, Haller, Halle, & Scherr, 2014; Scherr et al., 2012) were contacted. Participants were recruited between May and August 2017. All participants received compensation after the second completed visit. During the study period, various activities were offered for the runners in order to maintain participation until the last follow-up visit (e.g. nutrition counselling, group workout).

Inclusion criteria were an age range between 18 and 60 years, successful registration for the Munich Marathon 2017, completion of at least one half-marathon, sufficient German language skills and written informed consent. Exclusion criteria were relevant neurological, cardiac or psychiatric diseases, pregnancy and cannabis abuse. Further exclusion criteria for runners who participated in the sub study with MRI scans or TMS

were a history of seizures or metal parts in their body. Eligibility screening and provision of informed consent were performed before the first measurements on visit T-1 by a study group member.

The sedentary control group with a total of 46 participants was recruited via announcements in local newspapers and other channels (e.g. social media) until March 2018. A sedentary lifestyle was defined as less than 25 minutes of physical activity per day (Cabrera de León et al., 2007).

Ethics and registration

The study proceedings agreed with Good Clinical Practice guidelines, the guiding principles of the Declaration of Helsinki 2008 and local laws and regulations. The study protocol was approved by the ethics committees of both the Ludwig-Maximilians University Munich (approval reference number 17–148) and the Technical University Munich (approval reference number 218/17 S). The study was registered at https://www.drks.de/(DRKS-ID: DRKS00012496). For all participants, an insurance was provided by Ecclesia Mildenberger Hospital GmbH. All participants provided written informed consent prior to inclusion in the study.

Study timeline

The study timeline is presented in Figure 1. The first visit (visit −1) was performed 10 to 12 weeks prior to the marathon, as most marathon training schedules recommend approx. 10 weeks of intensive training (Treff et al., 2017; Voight, Roberts, Lunos, & Chow, 2011). In the 1 to 2 weeks prior to the marathon, after the intensive training period and in the tapering phase, the second visit was undertaken (visit 0). Visit 1 was performed immediately after the marathon (all measurements within 2 hours after the marathon). Visit 2 contained two measurement time points (2.1 und 2.2) at 24 hours and 72 hours post-marathon to capture responses to the short-term recovery period. The EEG and TMS measurements were conducted within 7 days post marathon, the MRI scans within 14 days. Follow-up examinations for the long-term recovery period took place in January 2018, three months after the marathon. Table 1 displays the different study visits with a listing of the examinations and investigated parameters.

Figure 1. Study timeline.

Table 1. Study visits with a listing of the examinations and investigated parameters.

	Study period				
Timepoint	*T − 1*	*T0*	*T1*	*T2* (including 24 and 72 hrs post marathon)	*T3*
Eligibility screen	X				
Informed consent	X				
Clinical examinations	X				
MMPI	X				
Resting ECG	X	X			X
Cardiopulmonary exercise testing (CPXT)	X	X			
Echocardiography	X	X			
IMT	X				
PWC	X	X	X	X	X
AIx	X	X	X	X	X
AV − Ratio, CRAE, CRVE	X	X	X	X	X
Vital signs	X	X	X	X	X
EEG	X	X		X	X
TMS + NIBS	X	X		X	X
Sublinguar IM	X	X	X	X	
MRI	X	X		X	X
MRI including contrast medium	X				X
Anthropometry	X	X	X	X	X
Blood sample, saliva sample	X	X	X	X	X
Urine sample	X				
Stool sample	X	X		X	
Heart rate during marathon			X		
Cognitive tasks	X	X	X	X	X
PANAS/BDI/OHQ	X	X	X	X	X
GAF/HAMD	X	X		X	X
EAI, BIS-11	X				
FFS	X	X	X	X	X
McGill Pain Questionnaire	X	X	X	X	X
Food and stool diary	X	X	X	X	X
Training diary	X	X			
IPAQ	X				X

MMPI: Minnesota Multiphasic Personality Inventory; ECG: electrocardiography; IMT: intima-media thickness; PWC: pulse wave curve; AIx: augmentation index; AV-Ratio: arteriolar-to-venular ratio; CRAE, CRVE: central retinal arteriolar and venular equivalents; EEG: electroencephalography; TMS: transcranial magnetic stimulation; NIBS: non-invasive brain stimulation; sublinguar IM: intravital microscopy; MRI: magnetic-resonance imaging; PANAS: Positive and Negative Affect Schedule; BDI: Beck Depression Inventory, OHQ: Oxford Happiness Questionnaire, GAF: global assessment of functioning; HAMD: Hamilton Depression Scale; EAI: exercise addiction inventory; BIS-11: Barratt Impulsiveness Scale; FFS: Fatigue Severity Scale; IPAQ: International Physical Activity Questionnaire. Cognitive tasks included n-back, TMT A/B, CRT.

Modes of measurement

Table 2 shows the specific modes of measurements and the detailed outcome parameters.

Examinations of the cardiovascular system and physical activity

Transthoracic echocardiography (IE33, Philips, Amsterdam, The Netherlands; standard 2D parasternal short- and long-axis images and apical 2-, 3- and 4-chamber views) was performed during end-expiratory apnea in a left lateral decubitus position by experienced echocardiographers in accordance to current recommendations (Lang et al., 2015).

Intima-media-thickness (IMT) was assessed by carotid ultrasound with an 11MHz transducer with a software for automated analysis (IE33; Qlab, Philips, Amsterdam, The Netherlands) as described previously (Naqvi & Lee, 2014). Briefly, two measurements were performed at end-diastole from antero- and posterolateral views on both sides, 1 cm proximal to the bifurcation with calculation of the average value as the mean of left and right IMT.

Table 2. Modes of measurement and time points.

Mode of measurement	Outcome parameters
Anthropometry	e.g. body fat percentage, blood pressure, height, weight, BMI
Resting- and exercise electrocardiogram	e.g. heart rate, duration of intervals
Cardiopulmonary exercise testing (CPET)	e.g. maximum oxygen uptake (VO2max)
Ultrasound (echocardiography, carotid ultrasound)	Functional and morphological parameters (e.g. left- and right-ventricular dimensions and function, diastolic left-ventricular function, IMT)
MRI	Cerebral MRI (T1, T2 FLAIR, DTI, field mapping, resting state fMRI), cardiac MRI (structural, functional, LGE, T1-mapping), hepatic fat quantification
EEG	Brain electric activity and functional connectivity (resting state)
TMS	Excitability and plasticity
Blood sample	Inflammatory markers, cardiac and muscular parameters, neurotrophic parameters (e.g. BDNF), proteomics
Cognition	Working memory, visual attention, impulsivity, decision making
Retinal vessel analysis, analysis of pulse wave velocity and wave reflection analysis	Parameters of macro- and microvasculature (e.g. retinal microcirculation AVR, CRAE, CRVE and circulation in the bigger vessels AIx, PWV)
Sublinguar IM	PVD, PPV, TVD, number of vessel crossings
Microbiome analyses	Microbiome diversity

BMI: body mass index; MR: magnetic resonance imaging; DTI: diffusion tensor imaging; LGE: late gadolinium enhancement; EEG: electroencephalography; TMS: transcranial magnetic stimulation; BDNF: brain derived neurotrophic factor; AVR: arterio-venous ratio; CRAE; CRVE: central retinal arteriolar and venular equivalents; AIx augmentation index; PWV: pulse wave velocity; Sublinguar IM: Sublinguar intravital microscopy; IMT: intima-media thickness; PVD: Perfused vessel density; PPV: perfused proportion of vessels; TVD: total vessel density

For wave reflection analysis we used applanation tonometry with a validated system (SphygmoCor Xcel, AtCor Medical Pty Ltd, Sydney, Australia) as described previously in detail (Laurent et al., 2006). Shortly, central blood pressure wave was estimated from the pressure wave of the radial artery by a generalized transfer function. Calibration of radial artery pressure waves was performed using non-invasively measured systolic and diastolic blood pressures measured in the brachial artery. Subsequently, we calculated the following parameters: central blood pressure (systolic and diastolic), pulse pressure (calculated as difference between central systolic and diastolic blood pressure), augmentation pressure (AP; pressure added to the incident wave by the reflected pulse wave), and augmentation index (AIx; ratio between augmentation and pulse pressure); the latter represented the key outcome parameter of this technique.

The vessels of the fundus oculi were analyzed with a non-mydriatic, noninvasive fundus camera using the Static Retinal Vessel Analyzer (SVA-T, Imedos Systems UG, Jena, Germany). For each participant, two valid images from the right and left eye with a centered papilla were recorded and analyzed as previously described (Pressler et al., 2011). Briefly, the images were subdivided into ring zones where the arterioles and venules were labeled with special analysis software (Vesselmap 2, Visualis, Imedos Systems UG, Jena, Germany) in the outer ring zone. The central retinal arteriolar and venular equivalents (CRAE, CRVE) were calculated as described previously (Hubbard et al., 1999). Additionally, the ratio of average vessel diameter of both vessel types was calculated (the arteriolar-to-venular ratio, AVR).

Sublingual microcirculation was visualized by the application of intravital blood flow microscopy with the Sidestream Darkfield (SDF) technology (Microscan Microscope, Microvision Medical, Amsterdam, The Netherlands) (Jung, Fritzenwanger, Lauten, Figulla, & Ferrari, 2010). Analysis of the imagery data was subsequently performed offline with a video-analysis that entailed the application of the dedicated Automated Vascular Analysis (AVA) software (AVA, Version 4.3 C). The targets standardized were perfused vessel density (PVD) and the perfused proportion of vessels (PPV) as well as the total vessel density (TVD) as standard variables. Additionally, we assessed the number of vessel crossings. Concomitantly, vital signs (blood pressure, heart rate and oxygen saturation) of each test subject were documented. The cuff of the blood pressure device (Welch Allyn Connex Pro BP 3400 digital blood pressure device, Skaneateles Falls, New York, USA) was placed on the right upper arm of the participant whereas the pulse oximeter (Pulox PO-300, Nividion GmbH, Cologne, Germany) was placed on the participant's left index finger.

The physical activity level was assessed with the International Physical Activity Questionnaire (IPAQ) at the first visit. The questionnaire provides a detailed overview of the physical activity in the working environment, in the household, in leisure time and in the physical training. Each participant filled out precise training diaries for the training period in between Visit −1 and 0. Food intake, and sensation of fatigue and pain were documented in the three day period prior to each visit with food diaries, and the McGill Pain Score and Fatigue Severity Score.

Neurophysiological and neuropsychological examinations

For each participant and each visit, mood and other behavioral parameters and demographics were documented via questionnaires containing Beck Depression Inventory (BDI), Hamilton Depression Scale (HAMD), global assessment of functioning (GAF), Oxford Happiness Questionnaire (OHQ), Positive and Negative Affect Schedule (PANAS). Baseline

values of personality aspects were assessed with the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) and the level of sports addiction was detected with the Exercise Addiction Inventory (EAI).

Neurocognitive tasks included a computer-based continuous performance working memory task (n-back) with three different loads for working memory, the trail making test A and B (TMT A/B) for visual attention and working memory, computer-based reaction time (CRT) assessments, and the d2-test for concentration and attention.

TMS (The Magstim Company Ltd, UK) of the left primary motor-cortex was used to evaluate cortical excitability with single-pulse (RMT, S1mV, MEP) and paired pulse-measures (SICI, ICF) (Di Lazzaro et al., 1998; Kujirai et al., 1993; Ziemann, 2004). Cortical plasticity was measured by anodal and cathodal tDCS (NeuroConn GmbH, Ilmenau, Germany) (Nitsche & Paulus, 2000, 2001, 2011) applied to the left primary motor cortex and changes in plasticity were changes in MEPs before and after stimulation. Resting EEG was recorded for six minutes with a 32-channel Acti-Cap System (Brain Products, Gilching, Germany). The measurements allow analyses of neuronal electrical activity changes using spectral power analysis and standardized low-resolution tomography (sLORETA) (Pascual-Marqui, 2002). Offline EEG-analysis was performed with the Brain Vision Analyzer 2.0 software (Brain Products, Gilching, Germany).

MRI scans, laboratory measurements

MR imaging of the brain included the following sequences: isotropic 3D-T1-weighed MPRAGE sequence, isotropic 3D-T2 FLAIR sequence, Diffusions Tensor Imaging (DTI), fieldmaps, a resting state functional MR imaging sequence (blood oxygenation level dependent (BOLD)). Cardiac MR imaging included an MR-based assessment of cardiac dimensions and function, a structural T1-mapping, late gadolinium enhancement at baseline and after the marathon. In addition, a Dixon sequence was acquired for the quantification of liver fat.

Laboratory measurements included parameters of inflammation (e.g. C-reactive Protein (CRP) and Interleukin 6 (IL-6), leukocyte count), cardiac and muscular parameters (e.g. Troponin T, Creatine Kinase (CK)), neurotrophic parameters (e.g. BDNF), and proteomics.

Several studies indicated a close relationship between physical activity and gut microbiome (Barton et al., 2017). Even though rising evidence for an association between gut microbiome and cardiovascular and cognitive function parameters exists (e.g. atherosclerosis (Serino, Blasco-Baque, Nicolas, & Burcelin, 2014) (Gareau, 2014)), no studies have investigated the longitudinal changes in correlation to different forms of endurance exercise.

Microbiome diversity was examined before the training period, before the marathon and after the marathon.

Sample size calculation and statistical analysis, missing data

This study included several biological, physiological and clinical measures with varying sample sizes as part of our cohort. A power analysis was made to define the minimum sample size required for a given analysis. For all calculations repeated measures ANOVA for one group (marathon runners) was assumed as the analysis method. The parameter of interest was the within-subject factor time. A significance level of $\alpha = 0.005$ (corrected for multiple testing), a power of $1\text{-}\beta = 0.8$, correlations between measures of $r = 0.5$ and 4

measures per variable were assumed, resulting in required sample sizes of n = 16 for large effects (f = 0.4), n = 27 for medium effects (f = 0.3) and n = 57 for small effects (f = 0.2). Microbiome was assessed only at three time-points, but even for a conservative f = 0.25, n = 45 participants would be sufficient to analyze within-subject differences over time.

Assuming a drop-out rate of 40% over the 6 months study duration, the total minimum sample size required for this project was calculated as 95 marathon runners that have to be included to result in the required sample size of n = 57. For all sample size calculations, G*Power 3.1.9 was used (Faul, Erdfelder, Lang, & Buchner, 2007).

Data entry and availability of data

All participants were assigned a pseudonym during the trial in order to protect confidentiality. Data was acquired on paper-CRF and transferred to local e-CRF. The transfer was be done by two independent study group members. The datasets generated and/or analyzed during the current study are not publicly available due to individual privacy of the participants but are available from the corresponding author on reasonable request.

Results will be presented to participants via twitter (@recapstudie), selected publications will be submitted with open access option.

Discussion

To the best of our knowledge, this is the first study to evaluate the effects of endurance exercise on the combination of both neurophysiological and cardiovascular adaptions in a longitudinal design.

With this novel approach, we will be able to identify the interaction of both systems. Our hypothesis is that the cognitive adaptions over the study period (as displayed by n-back, TMT A/B, d2 and CRT) will correlate with adaptations of the vascular status (AVR, AIx, AP, CRAE, CRVE, PWC, IMT). Using imaging/neurophysiological methods (MRI, TMS, EEG, sublinguar IM), we will be able to show various adaptations during the marathon training period with possible improvements of neuronal and vascular parameters (e.g. neuronal or structural plasticity). Immediately after the marathon, these adaptions could show impairments as a consequence to central fatigue and inflammation processes.

Prior studies used either exercise therapy with low-to moderate intensities and with different types and durations (Daskalopoulou et al., 2017; Firth et al., 2017; Zheng et al., 2016) or solely investigated the effects of high-intensity exercise, e.g. marathon running, on one or two modalities (Honzák et al., 1985; Kröger et al., 2011; Pressler et al., 2011; Ross et al., 2007; Vlachopoulos et al., 2010; Zanchi et al., 2016). Moreover, interpretation of data from studies investigating the health-related effects of physical activity is limited by the wide range of potential exercise workloads, related lifestyle interventions, and interactions with health professionals. In the small number of studies examining neuronal responses to extreme forms of endurance exercise such as marathon running, recovery periods were often not included in the design, limiting the usefulness of the data. Only limited knowledge is currently available regarding the magnitude and duration of CNS and behavioral responses to heavy exertion, and potential adverse changes in cerebral blood flow, hippocampal volume, and neurogenesis (Cass, 2017).

In our design, we included a baseline-measurement prior to the start of 10–12 weeks of extensive and documented endurance training and a second measurement after the training period/in the tapering phase. The acute effects of the marathon and the short- and long-term recovery period were measured with four different visits. This enabled us to differentiate between the different types of physical load.

To evaluate exercise-specific differences at baseline, we recruited a healthy, but sedentary control group. The multimodal assessment with laboratory measurements, multimodal MRI scans, neurophysiological, vessel-analysis methods and neurocognitive measurements, allowed broad insights into exercise-induced cardiovascular system and CNS responses.

Conclusion

We expect to significantly improve our understanding of the interactions between cardiovascular and neurophysiological outcomes to varying exercise workloads in athletes. A chief goal is to explore underlying mechanisms to these interactions, providing data-driven insights into the development of more tailored clinical therapeutic strategies.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics approval and consent to participate

The study proceedings agreed with Good Clinical Practice guidelines, the guiding principles of the Declaration of Helsinki 2008, and local laws and regulations. The study protocol was approved by the ethics committees of both the Ludwig-Maximilians University Munich (approval reference number 17-148) and the Technical University Munich (approval reference number 218/17 S). Possible amendments will have to be agreed by both ethics committees. The study was registered the WHO international clinical trials registry platform under the main ID DRKS00012496. The full trial protocol is available from the corresponding author. For all participants, insurance was provided by Ecclesia Mildenberger Hospital GmbH. All participants provided written informed consent prior to inclusion in the study.

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