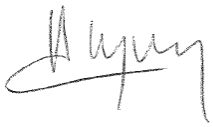
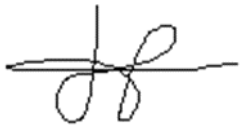
EXPERIMENTAL TRIAL STUDY PROTOCOL

Title of the project

Differences in brain activation between individuals with a different level of mental fatigue susceptibility: an fMRI study

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Protocol log:

Version 3, date: 22/01/24

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1. Introduction

Mental fatigue (MF) can be defined as *"a psychobiological state that arises during prolonged demanding cognitive activity of any kind, and results in an acute feeling of tiredness, a decreased performance capacity and/or a difference in brain activation"(1-4)*. It can ensue after only limited amounts of cognitive work (which includes driving a vehicle (5)) in healthy individuals and can bring about an increased risk of error in professions such as surgeons (6) and air traffic controllers (7)**.** It is also an important part of many neurological diseases (such as multiple sclerosis and Parkinson (8)). Because of the high prevalence of MF, a multitude of studies have assessed how MF can impact different kinds of human performance (9). These studies have shown that MF negatively affects important aspects of both cognitive (e.g. attention (10) and planning (11)) and physical performance (e.g. endurance (12, 13) and sport-specific psychomotor performance (1)). Because of its effects, some researchers have formulated theoretical mechanisms of the effect of MF on physical performance (14). These mechanisms are all primarily connected to the brain, as traditional peripheral measures such as heart rate remain non influenced by MF (14). They are speculated to be linked to dopaminergic circuits and adenosine accumulation in the prefrontal cortex (15, 16), but remain theoretical and debated (14, 17).

A recent systematic review of our team argues that the next big step in MF research might be the interindividual variability in the effects of MF on both physical as well as cognitive performance (18). Multiple research papers have shown a large range of responses between individuals who are mentally fatigued, which might also be connected to differences in individual factors, such as age, sex and training level (18). If it is possible to connect these factors to changes in responses to MF, we will gain further insights into the mechanisms of this complex phenomenon, which are still up for debate. However, another way we might be able to investigate why these differences occur is by measuring brain structure and activity in individuals with different levels of MF susceptibility (i.e. the amount of MF a person suffers from and the influence it has on that person's performance). Since MF primarily happens in the brain, directly measuring brain activity should be the first step to uncovering its mechanisms.

There are multiple ways that we might be able to investigate this notion, such as electroencephalography (EEG) (19, 20) and functional near infrared spectroscopy (fNIRS) (21, 22). However, the method that gives the greatest amount of spatial resolution is functional magnetic resonance imaging (fMRI) (23). Therefore, multiple researchers have focused on this specific method in mental fatigue related research (24-26). These investigations have revealed that there are different brain regions that are either activated, such as the default mode network (e.g. angular gyrus), or disactivated, such as the cognitive control network (e.g. dorsolateral prefrontal cortex) because of mental fatigue, greatly improving our understanding of its mechanisms (26). However, these studies are still scarce, and there are still a lot of steps that can be taken to provide new perspectives to existing research. For example, no studies, to the best of our knowledge, have investigated the brain activity of participants while they were performing the cognitively demanding task, such as the Stroop task. Moreover, most studies have limited themselves

to one specific fMRI technique, mostly basic blood oxygen level dependent (BOLD) measurements. However, for this study we will be using a recently introduced imaging sequence by General Electrics, combining both BOLD and ASL measurements. Conventional simultaneous acquisition of blood oxygenation-level dependent (BOLD) and arterial spin labeling (ASL) sequences typically captures two echoes: one sensitive to perfusion and another sensitive to BOLD response (27). The suggested approach enables the capture of images for ASL contrast shortly after the ASL labeling pulse and post-inversion delay (28, 29). Subsequently, it facilitates the acquisition of images with a longer TE to enhance BOLD contrast (28, 29). This will be the first study using simultaneous BOLD and ASL measurements in the onset of MF research (27, 29).

Objective and hypotheses

The objective of the present study is to investigate the differences in brain structure and activation during and after a cognitively demanding task in individuals with different levels of MF susceptibility using fMRI. Based on the high amount of variability in MF effects, we suspect a difference between individuals with different levels of MF susceptibility which will represent itself in a change in brain activation or deactivation in the different brain networks associated with MF.

2. Materials & methods

The following protocol was made in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) of 2013 (30). We intend to register the present trial at the Clinicaltrials.gov registry.

3.1. Research design, timeline and setting

We will adopt a randomized, single-blinded, placebo controlled, counter-balanced, cross-over design, where participants will be instructed to return on three separate occasions (familiarization, intervention an control trial) (figure 1). The experiment will consist of three consecutive trials performed in the radiology department of the academic hospital (Kinderziekenhuis, UZ Brussel, Dikke-Beuklaan 128, 1090 Jette (Brussels)) and the MFYS exercise lab (BLITS, VUB campus Etterbeek, Boulevard General Jaques 271, 1050 Elsene (Brussels)). Trained staff (pre-doctoral researchers and trained master students) will be present during the experimental trials. The familiarization, the experimental and the control trial will be separated by at least five days to ensure full recovery. The experimental/control trials will be conducted at around the same time of day in as similar conditions as possible.

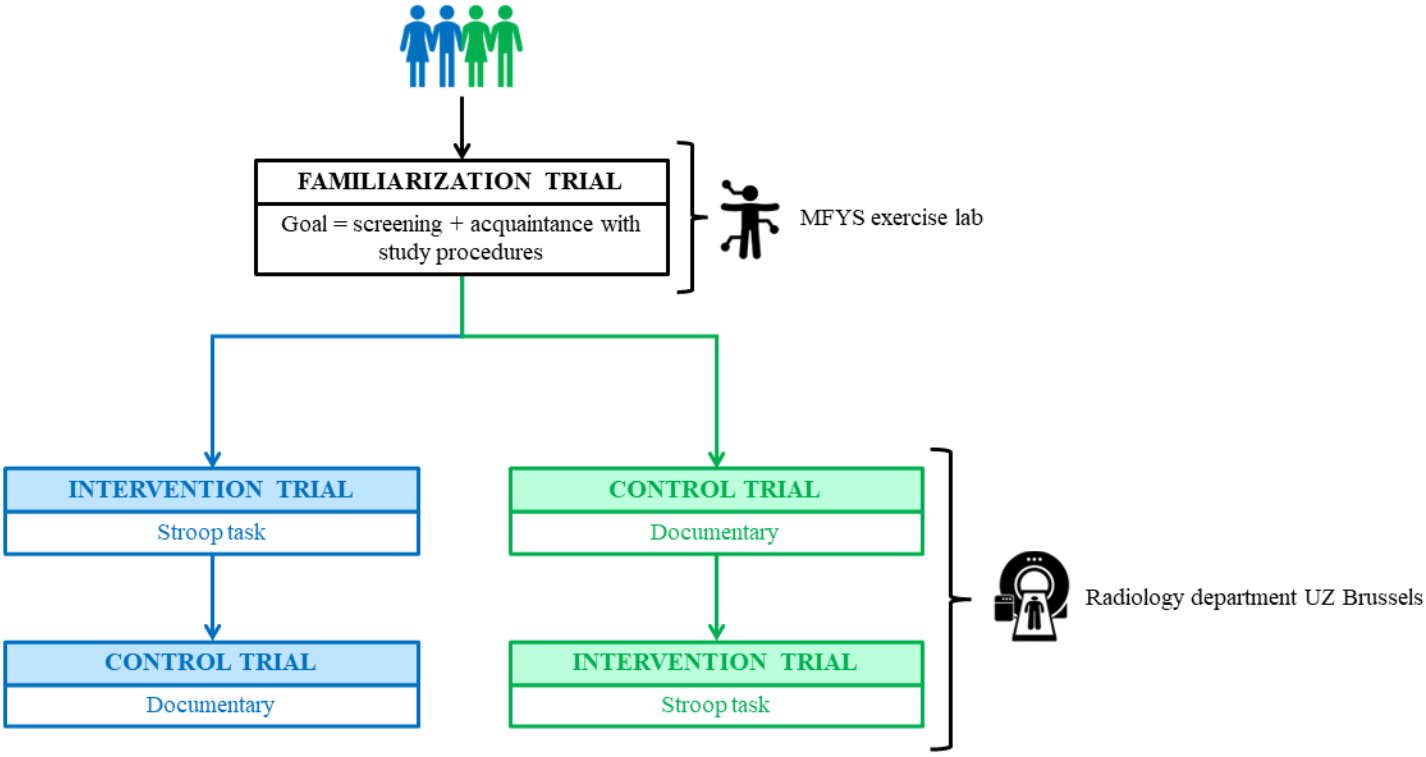


Figure 1: overview of the experimental design of the proposed protocol

3.2. Subject eligibility criteria and recruitment

2.2.1 Inclusion

- Healthy (no neurological, cardiovascular or musculoskeletal disorders of any kind)
- Male or female from age 18 to 50
- Right-handed
- No medication
- Non-smoker

2.2.2 Exclusion

- Suffering from a chronic health condition (could be neurological, cardiovascular, internal and musculoskeletal)
- Participants with color-blindness
- Participating in any concomitant care or research trials
- History of suffering from any mental/psychiatric disorders (31)
    - Suffering from a higher risk of burn out, indicated by a total score of ≥ 2.59 on the Burn out assessment tool (BAT) (32)
    - Suffering from high general fatigue, indicated by a score of >57 on the Multidimensional fatigue inventory (MFI) (33)

  - Suffering from depression, indicated by a score of >16 on the Beck depression inventory-II (BDI-II) (34)
- Use of medication
- Use of caffeine and heavy efforts 24 hours prior to each trial
- Not eating a standardized meal, the evening before and the morning of each trial
- Claustrophobia
- Participants with iron teeth implants, braces or iron string behind the teeth
- Participants with a non-MRI compatible implant.

2.2.3 Recruitment

First and foremost, to address one of the primary research questions, participants will first be recruited from an existing subject pool that was included in a previous experimental study by the participating research group (BUN 1432022000084, EC-2022-114). These participants will fill a similar screening questionnaire as last time, and be subject to screening criteria. Recruitment for follow up trials will be done through email. If participants do not answer or decline the invitation, another participant will be contacted. They will be selected randomly based on the previous measurements. Participants will be verbally notified of the possibility of invitation for these follow up measurements at the end of the last trial. The subject pool will then be enlarged by the inclusion of new participants until the researchers can get to the required number of participants. Subjects will be recruited through word of mouth advertising, flyers, the use of social media, contacting the subject pool with the research groups MFYS and VIPER, etc. Participants will also be asked to fill in a questionnaire that assesses availability and compatibility for the project. Eligible and available participants will then be contacted to schedule their first session (familiarization trial). Before arriving for the first appointment, the questionnaires mentioned above (i.e. CBI, MFI and BDI-II) will also be administered online (with RedCap).

3.3 Experimental procedure and intervention/control task

Data of questionnaires will be collected and managed using REDCap (Research Electronic Data Capture) hosted at UZ Brussel (35, 36). REDCap is a secure web-based application including compliance with the general data protection regulation (GDPR).

The familiarization trial will consist of one visit to the MFYS exercise lab, to give participants a basic briefing of the study and to acquaint them with basic study procedures. When participants arrive, they will first be given a thorough explanation of the study, along with all risks and rights that they are entitled to. Participants will also read and sign the informed consent form, giving permission to the research to proceed with the study. Before starting the actual familiarization, participants will be required to fill in the international physical activity questionnaire-sort form (IPAQ-SF) and a female physiology questionnaire. Both of these factors will be used as covariates in the present study, as both have the

potential to alter brain activity and structure (37, 38). Then, participants will be able to perform all tasks and questionnaires that will be administered during the intervention/control trial, including the Stroop max task, Go NoGo task, M-VAS, A-VAS, B-VAS, BRUMS, KSS, SIMS and NASA-TLX4. At the end, participants will be scheduled for the subsequent measurements.

Before beginning the intervention/control trial, which will all take place in the radiology department of the UZ Brussels (MRI 3, zone F, level -1), participants will first need to fill in a pretest checklist, to check adherence to pretest protocol. After this, participants will be subjected to the first collection of questionnaires, which are the Brunnel mood scale (BRUMS), the Karolinska sleepiness scale (KSS) and the visual analogue scale for the subjective level of mental fatigue (M-VAS), and will perform a baseline cognitive task (i.e. the GoNoGo task). After these baseline assessments, the respiratory band and ECG device will be fixed on the body of the participant, and they will take place in the MRI scanner. The intervention/control trial consists of a MF inducing task (Stroop task or an emotionally neutral documentary), which is both preceded and followed by a cognitive test (Go-NoGo task). Participants will enter the MRI scanner to complete the 6-minute Go-NoGo task at baseline. Following this, they will start the 48-minute MF inducing task (Stroop task or emotionally neutral documentary). The screen will be positioned at the participants feet and viewed via a mirror mounted on the head coil. Immediately afterwards, participants will be required to perform the 6-minute Go-NoGo task once again, in the MRI scanner. After this task, participants will be able to exit the scanner and will be required to fill in a last set of questionnaires (i.e. BRUMS, KSS, M-VAS, A-VAS, B-VAS, situational motivation scale (SIMS), The National Aeronautics and Space Administration Task Load Index (NASA-TLX4)). The MRI protocol consists of a quick anatomical scan (~6 minutes), which is necessary for positioning the subsequent scans. Afterwards, a BOLD (Blood Oxygen Level Dependent) scan and an ASL (Arterial Spin Labeling) scan will be taken simultaneously during the execution of the Stroop task and Go-NoGo tasks. This BOLD/ASL scan will allow us to visualize brain activation and cerebral blood flow during both tasks. See figure 2 for an overview of the experimental trials.

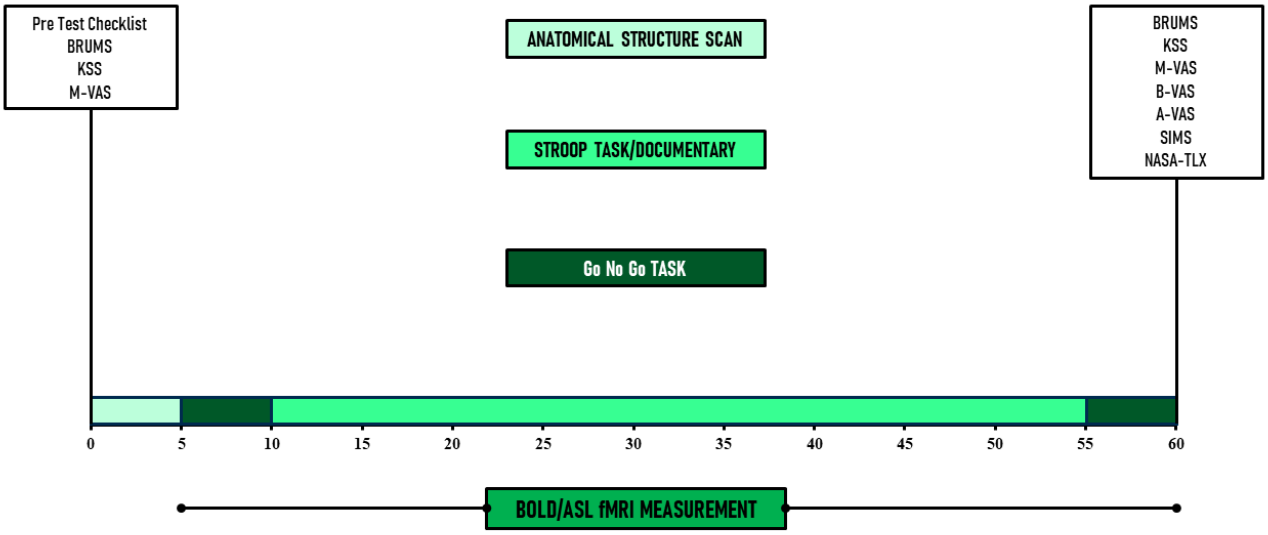


Figure 2: overview of the experimental/control trial

3.3.1. Mental fatigue task

A modified Stroop task (39, 40), of approximately 50 min, will be used as the mentally fatiguing task. In this task, four coloured words (“rood”, “blauw”, “groen” and “geel”) will be presented one at a time on a computer screen. The participants will be required to indicate the colour of the word, ignoring the meaning of the word itself. If, however, the ink colour of the word is red, the button to be pressed will be the button linked to the real meaning of the word. The word presented and its ink colour will be randomly selected by a computer (50% incongruent (colour different from presented word), 50% congruent (colour the same as presented word)), with all congruent and incongruent word-colour combinations being equally common. Each word will be presented on the computer screen in the fMRI in 34 point font for 1000 ms with a changing inter-stimulus interval of 1100, 1500 and 1900 ms. Subjects will be instructed to respond as quickly and accurately as possible using the controllers provided in the MRI scanner. Because of the analysis performed in the fMRI machine, we will use a block protocol in the present task. This means that different blocks of incongruent and congruent stimuli will be conducted in a steady 1:1 sequence. 1 block consists of 36 stimuli (12 combination possibilities with 3 changing interstimulus times), with a duration of about 1 min 30 for every block. Within each block, all stimuli will be randomly selected. The analysis of the MRI scanner will be conducted during the first minute of each block, with a pause of 10 seconds with no stimuli presented before the start of the next block. In total, 44 blocks (22 blocks of incongruent stimuli, 22 blocks of congruent stimuli) will be performed to get to a total duration of 51.3 minutes (see also figure 3).

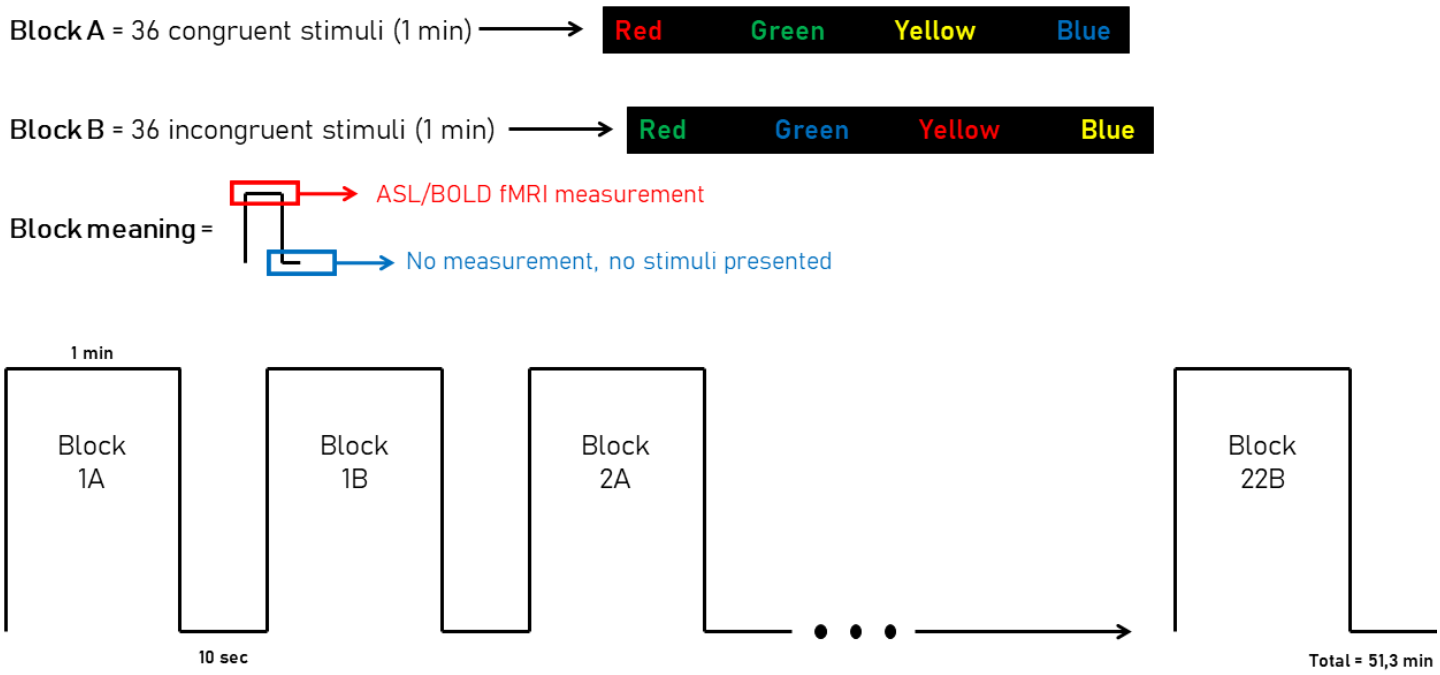


Figure 3: overview of the Stroop task model

The level of the Stroop task will be determined by the performance on a max task that will be conducted during familiarization. During this trial, participants will first start with a warm up session, with the short Stroop task with a stimulus duration of 1500 ms. After this, participants will be given a harder task to determine their Stroop task level (starting at a stimulus presentation time of 1100 ms). Subjects need to aim for an accuracy level of 85% or higher before they can proceed to a harder tasks. There are three attempts per level, and five second attempts in total. During this task, the participants will be lying down with a controller in both of their hands and a screen positioned right above their head, to stimulate the environment of the MRI scanner as close as possible.

3.3.2. Control task

In the control task subjects will have to watch a documentary of about 50 min in the MRI scanner. In order to avoid under- and over-arousal (which can both impact performance (41)), participants will have the opportunity to choose between several documentaries. The participants will also receive a list of the available documentaries (based on selections from Disney+) during the familiarization trial so that the trial can go as smoothly as possible.

3.4 Primary outcome measures

3.4.1 Cognitive performance during the Stroop task

To assess performance on the Stroop task, both ACC and reaction time (RT) will be collected and averaged every block. The goal of the experiment is also to assess the Stroop effect, and to connect this

effect with possible changes in brain activity. Therefore, we will also average the ACC and RT separately for the congruent and incongruent stimuli, in total and within every block.

3.4.2 Cognitive performance during the Go/NoGo task

Cognitive performance will be assessed using a task based on the go/no-go paradigm primarily suggested by Guo et al. (42) and Kato et al. (43). Participants are to react to different stimuli displayed on a computer screen in the MRI scanner, preceded by a screen with general instructions (similar to the Stroop task). Two different stimuli were present at the same time: a Go or NoGo stimuli, and a left or right stimuli (meaning that four combinations are possible: GoRight, GoLeft, NoGoRight and NoGoLeft). If a Go stimuli is presented, participants are instructed to react to the left or right stimuli with the corresponding arrows. However, if a NoGo stimulus is presented, participants are instructed to refrain from reacting to the either the left or right stimuli. This proposed paradigm measures attention, response inhibition and working memory, executive functions who are all consistently negatively impacted by MF (10, 42, 44, 45). Stimuli will be presented for 500 ms, with a varying interstimulus time between 1100 and 1700 ms. Outcomes for Go trials include RT and ACC, while the sole outcome for NoGo trials is ACC. The ratio of Go/NoGo trials will be 80 to 20 respectively. Since the trials feature seven different interstimulus times, 1 cycle of trials consists of 56 Go and 14 NoGo trials. 3 cycles will be performed, resulting in a task duration of about 6.5 minutes.

3.4.3. fMRI measurements

Functional magnetic resonance imaging will allow us to measure brain activity by detecting changes in blood flow and oxygenation in different areas of the brain. This is accomplished by tracking the hemodynamic response, which is the relationship between neural activity and blood flow (46, 47). Essentially, fMRI will provide us a way to observe which parts of the brain are activated during the Stroop task and the Go-NoGo task.

3.5. Secondary outcome Measures

3.5.1. Questionnaires performed during familiarization

Physical activity. The international physical activity questionnaire short form (IPAQ-SF) will assess the overall physical activity habits of the participant. The IPAQ-SF consists of 7 questions, assessing amount and level of intensity of physical activity in the last 7 days, and represents good reliability and validity (48, 49). The questionnaire takes approximately 2-3 min to complete.

Female Physiology. A self-made questionnaire will be administered to all female participants with the following topics: (hormonal) contraception use, days since last period, regularity of period, presence of peri and post-menopausal symptoms and days since last pregnancy.

3.5.2. Questionnaires during the trial

Mood. The Brunel Mood Scale (BRUMS) will be used to indicate mood, and serve as a control measure for both arousal as well as boredom . It will be assessed before and after each trial. This scale is based on the Profile of Mood States, and was validated using a multi-sample confirmatory factor analysis (50-52). It features 24 mood descriptors (divided into 6 subscales (i.e. anger, confusion, depression, fatigue, tension and vigor)), where participants have to give a value for every mood on a 5-point Likert scale (i.e. 0=not at all to 4 = extremely) responding to the question: "how do you feel right now?" (51). It supports an adequate internal consistency and test-retest reliability (51). Moreover, it has been used in multiple MF studies and can accurately be used as a possible confounder variable (53, 54).

Subjective workload. Subjective workload will be measured the 4 item version of The National Aeronautics and Space Administration Task Load Index (NASA-TLX-4). The 4 item version of the NASA-TLX scale is a scale specifically designed to assess the single factor of "mental strain", as opposed to the original 6 item scale that is more a measure of general workload (55, 56). Details about the original questionnaire are described by Hart and Staveland, 1988 (57). The NASA-TLX-4 is composed of four subscales (i.e. mental demand, temporal demand, effort and frustration) and, since its task specific, will be taken after finishing the 60-min intervention/control task and after both cognitive performance outcomes (55, 56). Further information on validation can be found in Hernandez et al. (55).

Situational motivation. The Situational Motivation Scale (SIMS) was created to assess concepts of intrinsic motivation, identified regulation, external regulation or amotivation and will be conducted at the end of every trial. This 7-point scale goes from 1 = 'corresponds not at all' to 7 = 'corresponds exactly'. The SIMS has previously been used in the onset of MF research (58) and its validity has been determined (59).

Subjective feeling of Mental Fatigue. The M-VAS-scale (0-10cm) will be taken at the start and the end of the trial (60). It will assess how mentally fatigued the subject is feeling (100 point VAS scale), and ranges from 'not at all' to 'completely exhausted'. The validity and reliability of a visual analogue scale to assess general fatigue was demonstrated by Lee et al. (61), and this type of scale has been shown to be one of the most sensitive assessments of MF (62).

Sleepiness. The Karolinska Sleepiness Scale (KSS) will be conducted at the start of every trial. This 10-point scale measures the subjective level of sleepiness and goes from 1 = 'extremely alert' to 10 = 'extremely sleepy, falls asleep all the time'. It is an often used scale in sleepiness research (63), Kaida et al. (64) stated that this scale has a high validity in measuring sleepiness.

Subjective feeling of boredom. To assess the feeling of boredom the question "How boring did you find the performed task?" will be asked, the subjects will have to answer on a visual analogue scale that ranges from 'not at all' to 'completely bored'. This visual analogue scale for boredom (B-VAS) will be taken after the trial. The validity and reliability of a general visual analogue scale has already been determined (61), and the B-VAS has also already been used in MF research (65).

Subjective measure of attention. The A-VAS scale will be taken at the end of each trial to assess how well subjects could stay attentive. The question "How well could you keep your attention on the task?" will be asked and the subjects will have to answer on a visual analogue scale that goes from 0 = "not at all" to 100 = "perfect". The A-VAS scale has previously been used in MF research (24).

3.5.2. Physiological Measurements during the trial

Respiratory Rate will be assessed with a belt (i.e., a metal wire that is coiled in a spiral form and that is part of the 3T MRI scanner) that monitored respiratory-related chest wall motion. **Heart rate** will be assessed using a VCG device. Heart rate and RR will be measured throughout the participants' time in the scanner. Data will be averaged over each task and for every block of the Stroop task.

3. Sample size, recruitment and retention interventions

A sample size calculation based on the measurements of Persson et al. (2013) (66) (η_p^2 = 0.19), determined that we need about 26-30 participants to include in the present trial (α = 0.05, power = 0.85, taken into account a dropout of 10% with 2 groups (one very susceptible, and one not so susceptible to mental fatigue)).

Data collected from participants that dropped out will be deleted and not taken into account in further analysis. Dropout will be reduced by minimizing the time between the different sessions and using additional reminders. During the trial, the inclusion criteria of participants will be narrowed to make sure that equal and subsequently contrasting groups can be constructed based on the individual factors (e.g. sex ratio should be 50/50).

4. Assignment of treatment order and allocation concealment

All participants are required to perform both the intervention and the control procedure. Treatment order (MF or CON) will be randomized by using a web-based computer program (www.randomization.com) to determine treatment order.

We will inform the participants in a way that explains the study as an investigation of the cerebrovascular responses during different cognitive activities. We will strive to induce equal expectations for all the participants in both the experimental and the control trials concerning the influence of the cognitive task on the cognitive and visuomotor performance task. At the end of the last trial we will ask a standardized

question to follow up on their thoughts about the objective of the study. Allocation will not be concealed to trial personnel (outcome assessors and intervention/control providers), since they are in charge of providing participants with the right cognitive task in the middle of the trial. The allocation of participants to specific treatment orders and the generation of these orders will all be performed by Jelle Habay and Manon Roose. Treatment allocation will only be reported to participants on specific request (which is always allowed, regardless of the nature of the request), with these specific participants will be excluded from further analysis when the request is granted.

5. Statistical analysis

The person responsible for carrying out the statistical analyses will be Jelle Habay (Human Physiology Research Group, Vrije Universiteit Brussel, Brussels, Belgium) and Manon Roose (Human Physiology Research Group, Vrije Universiteit Brussel, Brussels, Belgium; and Department of Radiology, UZ-Brussel, Vrije Universiteit Brussel, Brussels, Belgium). All statistical tests will be conducted in R (version 4.1.2.). All data will be presented as means ± standard deviation (SD). Normality will be checked using the Shapiro-Wilk test, and visually confirmed with histograms. If data is not normally distributed, log and squared data transformations will be performed. If data is still not normally distributed, non-parametrical equivalents will be used instead. The Mauchly's test will be used to verify for sphericity. However, if sphericity cannot be assumed, the Greenhouse-Geisser procedure will be used to correct the significance of F-values. Effect of MF on cognitive performance will be performed by a 2 (time) x 2 (condition) repeated measures ANOVA. The same base statistical procedure will be used to examine changes in manipulation checks and other psychological, physiological and subjective measures during the trial.

5.1. Processing and analysis of the MRI measurements

All fMRI data will be processed and analyzed using Statistical Parametric Mapping (SPM12) in Matlab R2022b. The following steps summarize the analysis of the individual fMRI (BOLD) scans that will be recorded while the participants perform the Stroop task and the Go-NoGo task (i.e., the mentally fatiguing and the cognitive task).

Step 1: Raw fMRI (BOLD) data will be motion and slice time corrected, normalised to the standard anatomical space (EPI cortex 155 (2022) 30 e4 5 35 MNI template), smoothed using an 8-mm isotropic kernel and high-pass filtered.

Step 2: The anatomical 3D scan will be segmented (white and grey matter and cerebrospinal fluid) and normalised to the standard anatomical space (T1MNI template) to eventually be used as anatomical underlay for the results.

Step 3: Denoising with quadratic detrending, high-pass filtering and CompCor.

Step 4: A general linear model will be used to fit a model containing the onsets of the incongruent and neutral trials, each convolved with the haemodynamic response function and a constant (to model the mean signal), to the data. Based on the fitting results, contrast (incongruent > neutral) maps will be generated for the Stroop tasks and the Go-NoGo tasks of each participant.

A standardized processing procedure will be used for the ASL fMRI data.

6. Data storage and management

6.1. Data storage:

The persons responsible for data management and preservation are Prof. Dr. Bart Roelands, Jelle Habay and Manon Roose. The project will exclusively generate new data. Following data types and their content are applicable:

- Questionnaires: A-VAS, KSS, Pretest checklist, M-VAS, B-VAS, SIMS and NASA-TLX
- Physiological data: fMRI neurovascular and anatomical data, heart rate and cardiological electrical activity, and respiratory rate.
- Behavioural data: cognitive performance on Stroop and Go No Go task

During the trial, data will be saved on the VUB share point, which has a build in back up. An external back up will be available in the form of an external HDD provided by the MFYS department. After the trial, data will be anonymized where possible and stored in the VUB university archive. An exclusive identity code will be assigned to each participant. The identity of the individual for the exclusive code will only be known by the research team. As the data consists of special categories it will not be stored on any external archives (= restricted access). Option to access the database will require a data use agreement. The stored data will remain unchanged and be identified by the researcher ORCID and article DOI. Transfer of data will only be done if essential. All manual files and written data will be stored in locked filing cabinets.

All anonymized data will be stored for up to 25 years to allow for access before publication and may be required at a later date for further analysis and auditing.

6.2. Data management:

The person responsible for all data management of the present study will be Manon Roose (manon.marie.roose@vub.be) and Jelle Habay (jelle.habay@vub.be).

The data protection officer of the VUB (dpo@vub.be) will be notified of our study.

Data in the present study will be managed confidentially, conform the Algemene Verordening Gegevensbescherming (GDPR) of 27 April 2016. Participating in this study means that the participant agrees that the investigators gather data of the participant, data that will be used to conduct the investigation and eventually will result in the publications in scientific journals and presentations at conferences. The participant will always have the right to ask the investigators which data he/she has gathered on them and for what this data is used in light of the investigation. The participant retains the right to look into this data and to ask for corrections in the occasion this data would contain errors. The participant also retains the right to stop his/her participation in the study at any moment.

In order to control the quality of the present study, it is possible the medical file of the participants is consulted. If so, this will be done by qualified personnel who are bound to professional secrecy, e.g. representatives of the ethical committee or an extern auditing bureau. This can only take place under strict conditions, under the responsibility of the investigator and under his supervision. The encrypted data can also be passed through the Belgium government or another regulatory authority or the ethical committee.

7. Ethics and dissemination

The study will be submitted to the commission of medical ethics at the University Hospital of the Vrije Universiteit Brussel.

All alterations of the present protocol, if accepted, will be communicated to the commission of medical ethics through the use of amendments. All of these amendments will be submitted through the DycoFlow system, and subjected to approval by the commission. The proposed changes will only be implemented if they are approved by the mentioned commission.

The approval of subjects to participate in the present trial will be collected using an informed consent which will be designed using a template of the UZBrussel and utilised informed consents from accepted studies at the MFYS research lab. Drs. Jelle Habay and Dra. Manon Roose will be responsible for providing participants with all required information of the present trial, and making sure that they correctly fill in the afore mentioned forms.

As personal information is branded by the EU as sensitive, data will be anonymized as soon as possible. Participants will receive a code corresponding to their inclusion order, and the file that relates these codes to their personal information will be encrypted. During the course of the entire PhD's of Drs. Jelle habay and Dra. Manon Roose the data will only be stored with personal access, on a personal cloud server and an external HDD. After the completion of this PhD, almost all data will be shared with the research lab through a network attached storage, except for the personal data file, which will remain stored on the external HDD. For further details on the preservation of personal data, one can consult the detailed data management plan.

The submitters of the present protocol proposal declare no financial or other conflicts of interest.

Trial results will be communicated to the general public through the publication of disseminated manuscripts published in scientific journals, and through conference presentations/posters. Authorship of these papers and presentations will only be granted to researchers that performed a substantial contribution to the scientific article. Public access will be granted to the entire protocol through the Clinicaltrials.gov registry. The statistical code and dataset will only be shared upon reasonable request, and the responsible data managers reserve the right to refuse such requests.

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