The effect of aerobic training at high intensity compared with moderate intensity on interoception in healthy adults : a Randomized control trial.

Final project

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ABSTRACT & KEYWORDS

BACKGROUND: Interoception is defined as the sense of physiological condition of the body. The interoception is divided in 3 dimensions: Interoceptive Accuracy, Interoceptive Sensibility and Interoceptive Awareness. High interoceptive ability and aerobic exercise are associated with high cardiovascular capability, structural and functional change in the neurological system. It is suggested that high intensity aerobic exercise will provide more health benefits. Aerobic exercise improves interoception, however, the most beneficial exercise intensity has not been determined. The aim of this study will be to determine the effects aerobic exercise at high versus moderate intensity on interoception.

METHOD: This study will be a triple-blind randomized control trial, multicenter. Healthy adult between 18 and 65 years-old living near the physiotherapist center will be included after answering no at every questions of the Physical Activity Readiness Questionnaire, presenting a systolic blood pressure <120 mmHg and <80mmHg in diastolic, normal Electrocardiogram, oxygen saturation >95% and giving their consent to participate. An independent researcher will randomly allocate subjects. The participants, physiotherapists in charge of the intervention and the assessors will be blind. The High-Intensity Training (HIT) group will practice 3 times per week during 8 weeks, 24 running sessions of 50 minutes on treadmill composed by 10 minutes of walking, 30 minutes of running at a Target Heart Rate (THR) > 70% and 10 minutes of walking. The Moderate-Intensity Training (MIT) group will practice 3 times per week during 8 weeks 24 running sessions of 50 minutes on a treadmill consisting of 10 minutes of walking, 30 minutes of running at a THR between 50% and 70% and 10 minutes of walking. The primary outcome is the Multidimensional Assessment of Interoceptive Awareness 2. The secondary outcomes are the Heartbeat Tracking Task, the Area Under the ROC curve using subjective confidence and the 6MWT. All outcomes will be assessed at baseline, 4 and 8 weeks. The statistical data will be analysed with ANOVA.

DISCUSSION: It is expected that high-intensity aerobic training improves more the 3 dimensions of interoception than moderate-intensity aerobic training.

KEYWORDS: Interoception, Aerobic exercise, Intensity, randomized-control trial.

INTRODUCTION

Introduced by Sherrington (1), Interoception is defined as the sense of physiological condition of the body. This definition created by Craig in 2002 (2) has, over the years, gained in popularity and its interpretation has also changed. Initially, the interoception was more restricted; it considered only the visceral sensation of the organs. Nowadays, interoception is described as the eight sensory system with a more inclusive definition, considering the internal sensation or perception of our own tissues. Garfinkel et al. have identified 3 dimensions of interoception (3).

The first dimension is the “sensibility”, referring to the subjective sensation of being self-sensitive of interoception or the self-perception of internal sensation. It is assessed with subjective self-report measures, the 2nd version Multidimensional Assessment of interoceptive awareness (MAIA 2) (4). The MAIA’s 2 Item have shown a good sensitivity to change, it has been validated for its use to assess the interoceptive dimension of the sensibility in clinical settings (5). A high interoceptive sensibility reflects that the patient can interpret and recognize the sensation of interoception.

The second dimension: The “Interoception accuracy” or sensitivity, is the objective accuracy in detecting internal stimuli. Two tests have been suggested to measure interoception accuracy, the Heartbeat discrimination task, which consists in presenting the subject with an external periodic signal (such as a light, a sound or a line), the participants will have to estimate if the signal are synchronized or not with their own cardiac rhythm (6). The second test, the Heartbeat Tracking Task (HTT), involves counting his own heart rate during 6 attempts lasting between 25 and 50 seconds without measuring his heart rate with his fingers (7). Despite a significant lack of validity (8, 9), for people with high interoceptive accuracy, the HTT shows a better correlation with the interoceptive awareness, moreover it is easily replicable and frequently used to assess interoception accuracy in research papers. Based on the previous arguments and building on current knowledge, HTT is the best test to objectively measure interoception accuracy. A good interoceptive accuracy means that the individual can correctly detect internal body sensation.

The last dimension of the interoception concept is the “interoceptive awareness”, it is a metacognition awareness of interoception accuracy. With metacognition being defined as the process of thinking about how we think. It can be assessed easily following the HTT by asking if the subject thinks that he is correctly or incorrectly assessing his number of heart rates. It is the relationship between objective performance and subjective awareness of

performance calculated with the area under the ROC curves representing the confidence in the precision (10). Lower the area is, higher the interoceptive awareness is, so the patients are confident about their own interoceptive sensation and think they have made a good measurement during the HTT.

Interoception is a concept exponentially studied, in biopsychosocial medicine, recent neuroanatomical and neurobiological studies have show that this interoceptive process comprises ascending neurological sensory signals from different organs of the body through specific afferent primary fibers (Aδ and C) of the vagal and spinal nerve (figure 1). These signals are integrated into the anterior insular cortex (11) and then into the anterior cingulate cortex (12). Similar findings have been found in children as young as the age of six years-old (13). The anterior cingulate cortex has a role of controlling, avoiding, and regulating painful emotions. An interoceptive dysfunction will therefore have a psychological effect, linked in particular to a fear of movement or to exacerbated pain. This will decrease the wellbeing of the patient and the outcome of the treatment.

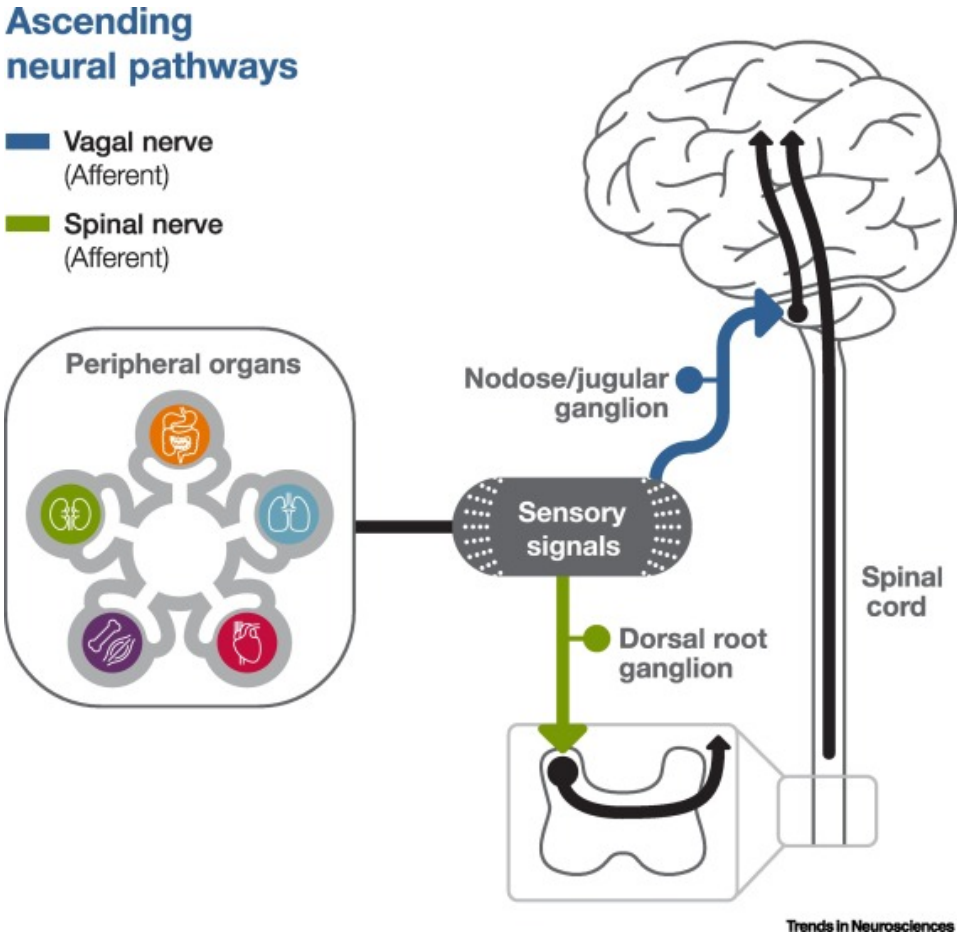


Figure 1 : **Illustrative Diagram of Sample Ascending Neural Pathways of Interoception.** (Chen et al. 2021)

Aerobic exercise (AE) or cardiovascular exercise is described as an exercise which uses oxygen to fulfill the metabolic demand of our body. After the phosphocreatine is exhausted, the carbohydrates take over to meet the energy needs of the body during exercise. Since glucose and glycogen can only be partially broken down to produce energy during exercise without oxygen, lactic acid is formed, preventing the muscles from functioning properly. After 10 minutes of exercise, the aerobic pathway takes over by improving the efficiency and effectiveness of the combustion of carbohydrates, amino acids, and fats, allowing the body to produce physical effort over a longer time without lactic acid.

AE has various effects on the physiology of the brain, in particular on anterior insular cortex and anterior cingulate cortex. It has been shown that a subject with higher aerobic capacity has a thicker gray matter in the anterior insular cortex, moreover the structural changes are associated with psychological benefits such as self-acceptance of physical area and subjective happiness (15). Several studies have shown that local gray matter volume of the anterior insular cortex has been correlated with better interoceptive accuracy, awareness (16). Interoceptive accuracy and sensibility are associated with an increased anterior insular cortex activation (11). AE increases the thickness of the anterior cingulate cortex (17) which influences cognitive functions such as motivation, decision making, learning or even cost-benefit calculation (18). Important in healthy adults, improving these functions will directly positively impact the quality of life, which will reduce the risk of injury (19) and increase cognitive (20) and physical performance (21, 22).

Glutamate is an excitatory neurotransmitter, when present in high concentration in the central nervous system, improves fundamental functions of neural cells such as plasticity, memory and neural development (23, 24). High glutamate concentration in the anterior cingulate cortex is associated with high interoceptive awareness (25) and has been found in subjects following AE. (26).

The vagus nerve has been shown to be directly implicated in the afferent information of the interoceptive signal, by stimulating the vagus nerve, participants increased their interoceptive sensitivity and sensibility (27). Studies found that vagus nerve activity increases after AE cessation (28), a high vagus activity is strongly correlated with aerobic capacity (29). The vagus nerve has an important role in cardiovascular activity. When activated, it reduces the heart rate (30) and it determines our ability to exercise (29). Interestingly, a study evaluating the interoceptive accuracy on dancers shows a significant difference on HTT in dancers compared with the control group (not dancers). Between the two groups, only the hours of training per week, the experiences in the art, the numbers of years of experience in the dances and the resting heart rate differentiate from the control

group. Knowing that the questionnaires relating to the psychological and emotional evaluation of the subjects did not show any significant differences, the study suggests that the resting heart rate may be associated with interoceptive accuracy (31).

Depending on the intensity of AE chosen, the effects on the physiology and health can be different. The central and peripheral adaptation and the peak oxygen uptake is associated with high-intensity training (32). High-intensity training improves bone mineral density (33), and symptoms related to non-specific chronic low-back pain compared with moderate-intensity (34), however, high-intensity AE has not been better at improving body composition (35, 36) than moderate-intensity AE.

The intensity of AE seems to have a different effect on the cardiovascular system. The aerobic capacity, measured with the % of VO2 maximum, improves significantly after higher-intensity exercise when volume is controlled in healthy adults (37). Evidence suggests that the effect of training on the resting heart rate is higher after high-intensity AE compared with low-intensity AE (38) as well as vagus nerve activity appears to be greater following high-intensity aerobic activity (29).

Concerning the structural and functional change in the brain related to AE at different intensity, moderate-intensity aerobic training increases gray matter volume and thickness of the anterior cingulate cortex (17). No studies have investigated the effects of high-intensity aerobic training on the anterior cingulate cortex compared with moderate-intensity aerobic training, however evidence suggests that following a high-intensity training, the concentration of glutamate in the anterior cingulate cortex increases (26). The functional connectivity of the anterior insular cortex increases significantly more after a high-intensity exercise compared with low-intensity exercise (39).

Based on the evidence cited above, high-intensity aerobic exercise will affect the cardiovascular system and the structure and function of the brain, which will increase the interoceptive ability of patients.

Knowledge gap :

Interestingly, interoception abilities have similarities with the benefits of practicing aerobic exercises: Higher BMI is associated with a deficit of interoception (40), AE assists in weight management and weight loss (41); Subjects with chronic pain present a low interoceptive accuracy, and interoceptive accuracy correlates with symptoms severity specific disorder (42), AE have been shown to decrease chronic pain in long term (43); subject with Low back pain present lower interoceptive awareness (44, 45), AE improves the

condition of low back pain (46); Patient with depressive disorder have lower Interoceptive accuracy (47), however, AE decreases the symptoms of depression (48); AE has been found to improve reaction time (49) and patients with a high interoceptive awareness have a greater motor reactivity (50).

In 2017, a study investigated the effects of a meditation and aerobic exercise program on interoceptive awareness. Participants in this program showed significant improvement in their MAIA scores after 12 weeks of training (51). At the time of writing the protocol, only one study has investigated the effect of AE solely on interoception. After 2 months of aerobic exercise at 50% of the Heart rate reserve, at a frequency of 3 sessions per week, the healthy subject significantly improved their interoceptive accuracy (52).

Current literature suggests an effect of aerobic exercise on interoception, however, it would be important to determine an intensity of AE for which interoception increases the most in order to get a more holistic rehabilitation, more suitable for patients. For that, this trial will try to support or refute the evidence, as well as to determine an optimal intensity of training to increase interoception.

The aim of this study will be to assess the effects of high versus moderate intensity aerobic exercise on the three dimensions of interoception.

HYPOTHESIS

Null hypothesis: High-intensity aerobic training has an equal effect on interoception sensibility compared with moderate-intensity aerobic training in healthy adults.

Alternative hypothesis: High-intensity aerobic training has a better effect on interoception sensibility compared with moderate-intensity aerobic training.

OBJECTIVES

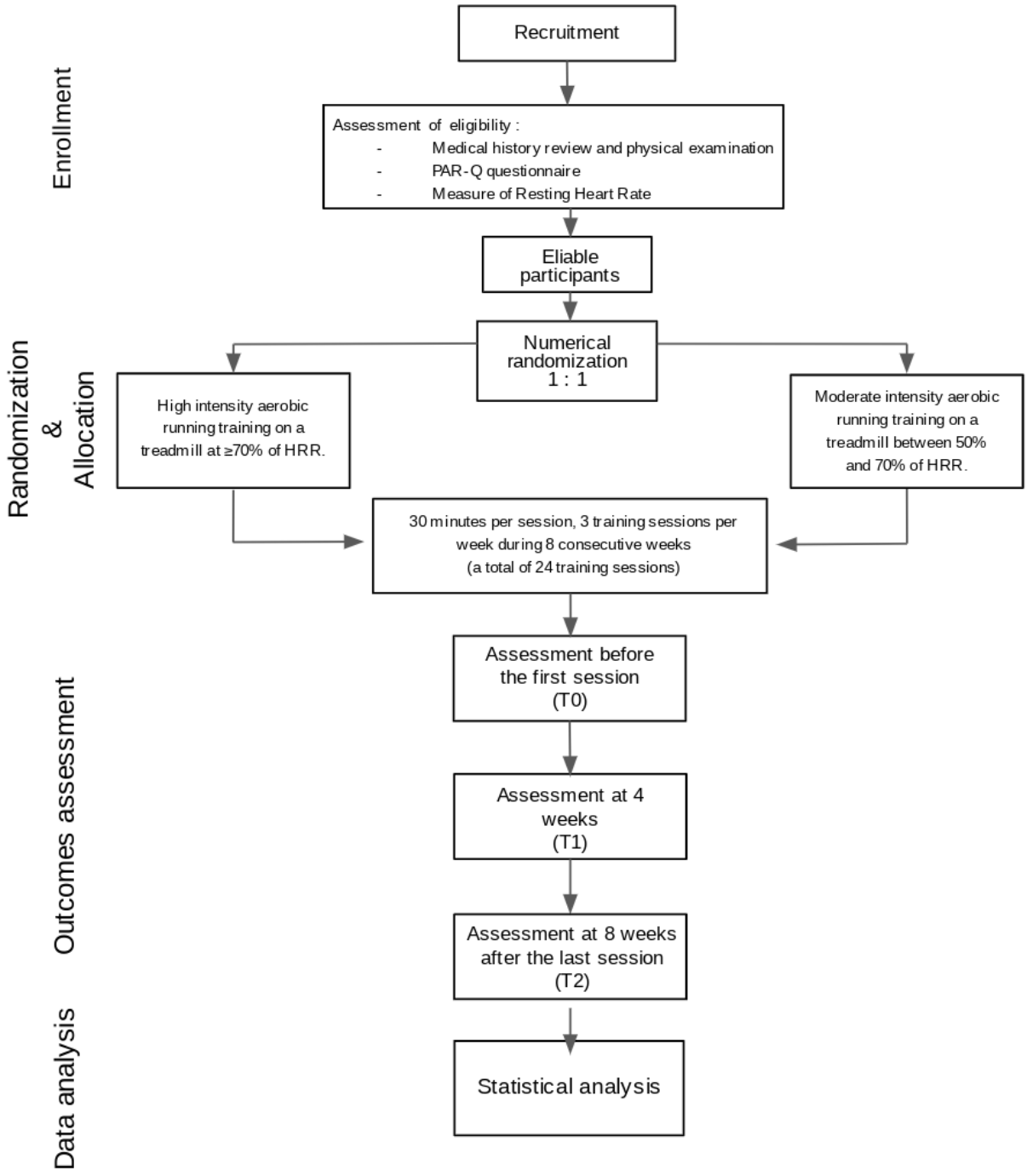
The main objective is to determine the effect of aerobic training at high-intensity versus moderate-intensity aerobic training on interoceptive sensibility on healthy adults. The secondary objectives are to determine the effect of high-intensity versus moderate-intensity aerobic training on interoceptive sensitivity on healthy adults and to determine the effect of high-intensity versus moderate-intensity aerobic training on interoceptive awareness on healthy adults.

STUDY DESIGN

The aim of the proposed study is to conduct a triple-blind randomized control trial with two parallel groups with an allocation ratio of 1:1. Group 1 will be submitted to a High Intensity Training (HIT) and the group 2 to a Moderate Intensity Training (MIT). The trial will be a multi-center study, with 2 centers for the intervention and one 1 for the assessment of the outcomes.

The SPIRIT guidelines will be followed to construct this study.

FLOW DIAGRAM OF THE STUDY DESIGN



ELIGIBILITY CRITERIA

Inclusion criteria :

- Men and Women of 18 - 65y
- Blood pressure <120 mmHg in Systolic and <80mmHg in diastolic
- Normal ECG
- Oxygen saturation : >95%
- Living in London at less than 30 minutes of the two Physiotherapist's centers
- Physical Activity Readiness Questionnaire : Answer NO at every questions

Exclusion criteria :

- Pregnant women
- Amputation
- Psychological disorder
- English speaker
- Subject having no time to do sport 3 times a week
- Subject missing the first appointment
- Subject missing more than 2 sessions
- Subject not having signed the informed consent (Annexe 4)

SAMPLE SIZE

The sample size calculation will be based on the Minimal Clinically Important Difference (MCID) or Minimal Important Difference (MID) of the main outcome, the Multidimensional Assessment on interoceptive awareness versions 2 (MAIA 2). Only one study has determined the MID (5) . The MID using the distribution-based methods for each unique item differs from 0.38 (not-distracting) from 0.61 (trusting) point. To determine the sample size, it will therefore include in the calculi the highest MID of the Items, which is 0.61.

OUTCOMES

Primary outcomes :

The main outcome of the study is the interoceptive sensibility using the Multidimensional Assessment on interoceptive awareness versions 2 (MAIA 2). MAIA 2 comprises 37 questions divided into 8 items (Annexe 1): noticing, not distracting, not-worrying, attention regulation, emotional awareness, self regulation, body listening and trusting. Subjects need to indicate how often each statement applies to them in daily life by scoring from 0 to 5, with 0 representing never and 5 always. For example, in the noticing's item: I notice when I am uncomfortable in my body: if the subject notices his body frequently but not always he can circle 4. The average of each item will be calculated between 0 and 5. The higher the total score is, the more the subject has a high interoceptive sensibility.

Secondary outcomes :

The interoceptive sensitivity will be assessed with the Heartbeat Tracking Task (HTT). Before starting the assessment, the investigator should tell the participants "Without manually checking, can you silently count each heartbeat you feel in your body from the time you hear "start" to when you hear "stop". 6 trials will be done randomly using 6 different time-windows (25, 30, 35, 40, 45 and 50s). For each trial, an accuracy score will be given with the following formula :

$$1 - (|nbeatsreal - nbeatsreported|)/((nbeatsreal + nbeatsreported)/2)$$

The 6 resulting scores will be averaged for each subject to determine a total HTT score. Closer the average will be from 1, higher the interoceptive sensitivity will be. ((Schandry, 1981))

Interoceptive awareness will be assessed with the Area Under ROC Curve (AUC) at the end of each trial of the HTT by asking the subject "Do you know whether you are accurately or inaccurately assessing your heart-timing?". The judgment of confidence will be made using a visual analogue scale (VAS) of 10cm (Annexe 2). If the subject chooses 0cm this will mean that the subject answered randomly during the HTT and inversely if he chooses 10cm it will mean that he has complete confidence in his perception of heartbeat. The interoceptive awareness will be calculated using receiver operating characteristic (ROC) curve analysis (50). The area under the ROC curve will define the level of

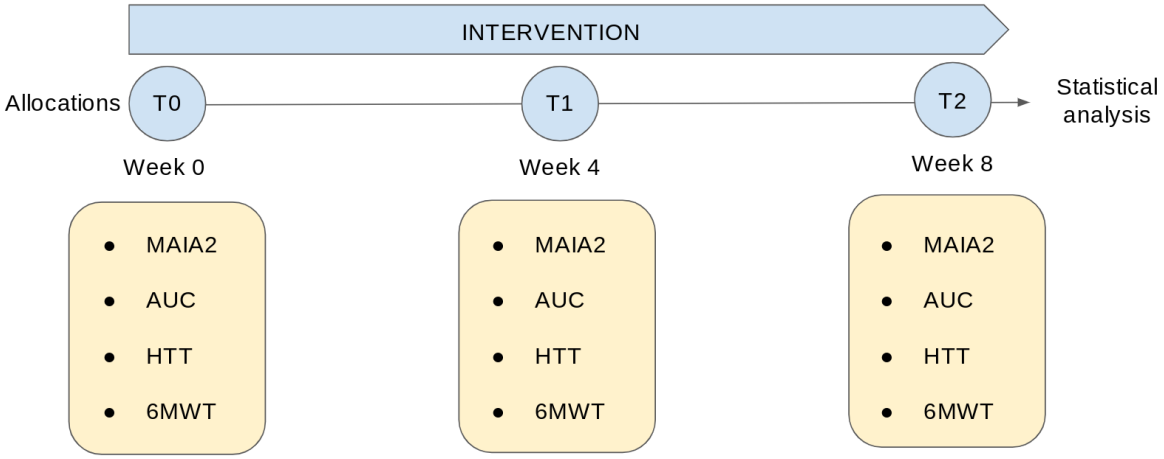
interoceptive awareness, a large area will represent low interoceptive awareness and a low area will mean a high interoceptive awareness.

The 6 Minutes Walking Test (6MWT) is a well-known physical endurance test, widely used in research and clinical settings. During this assessment, the participant needs to walk for 6minutes on a straight 30m track. The subject will have to walk as fast as possible for 6 minutes. The investigators have an important role in this test. They need to follow strict guidelines (Annexe 3) explaining the goal of the test and encouraging the patient every minute by saying: At 1 minute: “You are doing well. You have 5 minutes to go.” At 2 minute: “Keep up the good work. You have 4 minutes to go.” At 3rd minute: “You are doing well. You are halfway done.” At 4th minute: Keep up the good work. You have only 2 minutes left.” At 5th minute: You are doing well. You have only 1 minute to go.” At 6th minute: Please stop where you are.”. The result will be expressed in meters and the aim of this test will be to evaluate the change of performance throughout the complete study.

The data collection will be done at the hospital St Thomas at T0, T1 and T2. The subjects will be asked to fill the MAIA 2. Then the participants will be taken to a quiet room to do the HTT and estimate their level of confidence on their own measure. Once the tests are completed, subjects will be required to perform the 6MWT. Because of a learning effect when performing the test, two measurements will be taken during T0 (at least 15 minutes apart between each measurement to recover). The assessors will have to fill a paper with all the measures, the name of the assessor and the identification number (Annexe 4). The paper will be kept in a safe and secure place in the St Thomas Hospital.

Each data collection sheet will be digitized and saved in the hospital's database following each assessment to avoid any loss of data. It will be given to the data analyst after the last measurement (T2) in order to analyze the results.

ASSESSMENT



ETHICS

The ethical committee of the St. Thomas hospital will evaluate the trial. The development of this project will follow the rules of good clinical practice, the principles set in the Helsinki Declaration (World Medical Association, 1989). An informed consent will be requested for all study participants and signed during the first meeting with the researcher after an explanation of the risk of adverse events during the intervention and assessment. The participation at this trial is voluntary, and the patient has the right to withdraw at any time. (Annexe 4: Informed consent)

RECRUITMENT

The center responsible for the study is the St. Thomas Hospital, two physiotherapists from the rehabilitation center will carry the assessments out in the Hospital.

The intervention will be done in two different physiotherapist's offices associated with the St Thomas Hospital. To be eligible, the physiotherapist's office must have a treadmill equipped with a cardiac sensor. Two meetings with the physiotherapists in charge of the intervention will be held: the first one will be scheduled before the beginning of the study to confirm that the center has the material resources and the ability to supervise a group of 3 patients on treadmills. The second meeting will be held after the allocation, the aim will be to share with

the physiotherapists in charge of the intervention the basic knowledge about aerobic and running exercise, the investigator will give him the identity number and the THR of each subject allocated in his center. In case of doubt or technical problem, they must inform the principal investigator.

The subjects will be recruited via flyers present at the reception of the primary care and at the entrance of several gyms associated with the hospital. During the first call, we will confirm the eligibility criteria and propose a meeting with the investigators at the St Thomas Hospital in order to do a medical check and sign the informed consent. We need to give a minimum of information to the subject to not compromise the blinding.

RANDOMIZATION

An independent researcher will be in charge of the allocation. This researcher will copy on an Excel spreadsheet the name, surname and email of the subjects and the software will create a random identification number (dialed by 6 digits) and allocate each subject in one of the 2 groups with an allocation ratio of 1:1. Then, the participant will receive an email with their identification numbers, the address of the physiotherapy center and the scheduled sessions for the complete study. The physiotherapists will receive an email with all the identification numbers of the subjects and their scheduled sessions allocated to them. The identification numbers will be helpful to blind the data analyst and the assessor and to protect the privacy of the personal data of the subjects.

BLINDING

The trial will be triple-blinded: the participants, the physiotherapists in charge of the intervention and the data assessors will be blind from the allocation and study hypothesis.

The participant will not be informed of the presence of another group, as each office will have a different group. They will also be blind from the study hypothesis, they will only know that they have to run at a defined intensity.

The four physiotherapists in charge of the intervention will neither know another group, and they will not know the hypothesis and aim of the study.

Two physiotherapists in charge of assessing the outcomes from the sector of rehabilitation of the St Thomas hospital will be blind from the subject allocations and the study hypothesis.

INTERVENTION

First study group :
High-intensity running on a treadmill in healthy adult (HIT)

Explanation of the intervention :

What ?

The sessions will be split into 3 phases: Warm-up, Running and Resting.
The warm-up will comprise walking for 10 minutes at a maximum speed of 5 km/h on the treadmill with an inclination of 0°.
Then, the patient will have to run for 30 minutes with an inclination of 0° on a treadmill. The intensity will be defined with a Target Heart Rate (THR) at over 70% of Maximal Heart Rate (48). The Target Heart Rate (THR) will be estimated for each subject during the medical checking before the beginning of the training program with the Karvonen formula of the THR (49):

$$TargetHeartRate(THR) = (HeartRateMax(HRM) - HeartRateRest(HRRest)) * \%Intensity(\%I) + HRRestwithHRM = 220 - Subject'sage$$

According to the intensity set previously, the THR's formula for the HIT group will be :

$$THR(HIT) \geq ((220 - Subject'sage) - HRRest) * 0.7 - HRRest$$

During the first session, the physiotherapists will have to explain the basic knowledge about the running technique, how the treadmill works, and the THR(HIT) of the subject. The subjects will have to run at an intensity, so there will be no increase in workload during the entire procedure. The resting phase will be like the warm-up one, the participant will have to walk at a maximum speed of 5 km/h on the treadmill with an inclination of 0° to decrease the heart rate before finishing the session and therefore avoid adverse events during 10 minutes.

Who provided :

The provider of the training sessions will be 2 physiotherapists from the center A. They need to know how the equipment works and how to improve running technique and the recovery to decrease the risk of injury.

How :

The running sessions will be applied face-to-face in a group of 3 subjects maximum due to the sanitary condition. One physiotherapist will be in charge of 3 patients.

Where :

The HIT group will be allocated to one Physiotherapist's center located less than 30 minutes from the hospital of St Thomas of London. The treadmill will be in a ventilated room with a temperature set between 20° and 25° C. The patients will have at their disposal lockers, a cloakroom, and drinking water.

When and how much :

Participants will have to come 3 times a week during 8 weeks at the center for 24 running sessions. Patients will be able to miss at least 2 sessions among the 24, each session will last between 50 and 60 minutes. The sessions should be spaced at least one day off and the schedule will be adjusted according to the patient and the physiotherapist. The investigators will ask the subjects not to engage in physical activity outside the study in order to increase the reliability and validity of the results.

Comparison study group :

Moderate-intensity running on a treadmill in healthy adult (MIT)

Explanation of the intervention :

What ?

Sessions will also be split in 3 phases: Warm-up, running and resting.

The warm-up will comprise walking for 10 minutes at a maximum speed of 5 km/h on the treadmill with an inclination of 0°. The running phase will last 30 minutes with an inclination of 0° on a treadmill. The intensity will be defined with a Target Heart Rate (THR) between 50% and 70% of maximal Heart Rate Resting and the Karvonen formula for the MIT group will be:

$$THR(MIT) > ((220 - Subject'sage) - HRRest) * 0.5 - HRRest$$
$$THR(MIT) < ((220 - Subject'sage) - HRRest) * 0.7 - HRRest$$

Patients of the MIT group will have the same treadmill as the HIT group to monitor their own heartbeat. The basic knowledge about the running technique, how the treadmill works and their individual THR(MIT) will be given during the first session.Since it will require subjects to run at a preset heart rate, there will be no workload progression throughout the study.

Then, as the Warm-up phase, the subjects will be required to walk for 10 minutes at a maximum speed of 5km/h to restore heart rate at rest and finish the session. The inclination will be set at 0°.

Who provided :

The 2 physiotherapists of the center B will be in charge of the intervention, they will need to know how the equipment works and have the basic knowledge about the good running technique and recovery.

How :

The running sessions will be applied face-to-face in a group of 3 subjects maximum due to the sanitary condition supervised by one physiotherapist.

Where :

The MIT group will be allocated to one Physiotherapist's center localized at less than 30 minutes to the hospital of St Thomas of London. Like the HIT group, the treadmill will be in

a ventilated room with a temperature set between 20° and 25° C. The patients will have at their disposal lockers, a cloakroom, and drinking water.

When and how much :

Participants will have to come 3 times a week during 8 weeks at the center for 24 running sessions. The patients will be able to miss at least 2 sessions among the 24, each session will last between 50 and 60 minutes. The sessions should be spaced at least one day off and the schedule will be adjusted according to the patient and the physiotherapist. There will be no difference in the frequency and duration of sessions between the two groups. To increase the reliability and validity of the results, the investigators will ask the subjects not to engage in physical activity outside the study.

STATISTICAL ANALYSIS

The objective of the study is to determine the effect of aerobic exercise at high versus low intensity on interoception. The effect of aerobic exercise will be measured with the 6MWT and the 3 dimensions of Interoception will be assessed with the MAIA 2 (sensibility), HTT (sensitivity), AUC (Awareness).
The data of the MAIA 2, HTT, AUC and 6MWT will be continuous and normally distributed. The data analyst will express them in mean and standard deviation. He will compare the 2 groups at 3 different time points with the mean score of the MAIA 2 and 6MWT using ANOVA to determine the effect of HIT versus MIT on the interoceptive sensibility. The effect of HIT versus MIT on interoceptive sensitivity will be determined by comparing the groups with the mean score of HTT and 6MWT at 3 different times points using ANOVA. To determine the effect of HIT vs MIT on interoceptive awareness, the data analyst will use ANOVA by comparing the 2 groups at 3 different time points with the mean of the AUC and the 6MWT of the subjects.

CALENDAR

	Study Period				
	Enrollment	Allocation	Baseline	Mid intervention	End Intervention
TIME-POINT	-T1	0	T0	T1	T2
ENROLLMENT					
Eligibility screening	X				
Medical history and physical examination	X				
HRrest measurement	X				
Informed consent	X				
ALLOCATION		X			
INTERVENTION					
Intervention HIT group					
Intervention MIT group					
ASSESSMENT					
MAIA 2			X	X	X
HTT			X	X	X
AUC			X	X	X
6MWT			X	X	X

Figure : **Calendar** : Resting Heart Rate (HRrest), High Intensity Training (HIT); Moderate Intensity Training (MIT), Multidimensional Assessment on interoceptive awareness versions 2 (MAIA 2), Heartbeat Tracking Task (HTT), Area Under ROC Curve (AUC), 6 Minutes Walking Test (6MWT).

ROLE OF THE INVESTIGATORS

10 professionals will take part in this study: 6 physiotherapists, 2 doctors, 1 independent researcher and 1 statistician.

The doctors will be in charge of the recruitment of the patient. They will need to call the patients to confirm the eligibility criteria. Once the criteria are met, they will organize an appointment to perform a medical check-up, measure the heart rate of the patient at rest as well as have the informed consent signed.

The independent researcher will be in charge of the anonymization and of the allocation randomized in the two different centers.

Four Physiotherapists will be in charge of the intervention, two physiotherapists per group and per center. They will have to instruct the patient about the utilization of the materials and the best running technique. They will have to monitor that participants are performing well at their individual THR. The physiotherapists will also be able, at the request of the patients, to practice a massage session per week in order to reduce muscular tensions. They will have to schedule the sessions to fit as better as possible the schedule of the subjects.

Two physiotherapists from the sector of rehabilitation of the St Thomas hospital will be in charge of the outcomes assessment. They will need to complete the paper dedicated to the collection of data. They will be blind from the participants' allocation.

The statistician will be based at the hospital St Thomas of London. He will receive and analyze the data after the last assessment.

LIMITATION

The major limitation of the trial is the outcomes. Interoception being a new emerging concept, few studies have investigated the best way to measure it. The MAIA 2 was created in 2018, there are few studies on the validity and reliability of questionnaires on healthy populations. The self reported questionnaires have advantages and inherently disadvantages, subjects may not understand or misunderstand questions. They may also not respond truthfully, wanting to affect the result as much as possible. They may overestimate his interoceptive sensitivity with the MAIA 2. In addition, it is difficult to collect objective data on interoception; the evaluation of interoceptive sensitivity with HTT showed

low validity, being based only on the sensitivity of the heart. The patient can have the expectation or the knowledge of his own heartbeat at rest.

Another limitation of this study is the compliance of the participants. Asking a subject to run 3 times a week for 8 weeks can be perceived as boring and very repetitive. Physiotherapists will need to organize an optimal training environment. The physiotherapists should inform the researchers when he perceives a decrease in motivation so that a phone meeting can be considered to increase the subject's adherence.

The lack of study relating to interoception and physical activity can be seen as a limitation. It will need further research to confirm the correlation by explaining how aerobic physical activity affects interoception and if running on a treadmill is the best physical exercise to improve the 3 dimensions of interoception.

RESOURCES

The resources will differ in function of the places :

Both Physiotherapist’s centers will need to have at least 3 treadmills, drinking water, lockers and cloakrooms.

The St Thomas hospital will need to have papers to print the informed consent, questionnaires and the paper with the result of the data. To conduct the assessment and the enrollment, they will need to have a quiet room with an auscultation table with roll paper, an echocardiography machine, transducer, sphygmomanometer, stethoscope, a pulse oximeter, a flat ground of a length of 30 meters, a chronometer and pencils.

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ANNEXES

Annexe 1: MAIA 2

Multidimensional Assessment of Interoceptive Awareness

Version 2
(MAIA-2)
(2018)

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Multidimensional Assessment of Interoceptive Awareness (Version 2)

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Scoring Instructions

Take the average of the items on each scale.
Note: (R): reverse-score (5 – x) items 5, 6, 7, 8, 9 and 10 on Not-Distracting, and items 11, 12 and 15 on Not-Worrying.

1. **Noticing:** Awareness of uncomfortable, comfortable, and neutral body sensations
   Q1_____ + Q2_____ + Q3_____ + Q4_____ / 4 = _____
2. **Not-Distracting:** Tendency not to ignore or distract oneself from sensations of pain or discomfort
   Q5(R)____ + Q6(R)____+ Q7(R)____+ Q8(R)____+Q9(R)____+Q10(R) / 6 = _____
3. **Not-Worrying:** Tendency not to worry or experience emotional distress with sensations of pain or discomfort
   Q11(R)_____ + Q12(R)_____ + Q13_____ + Q14_____ + Q15 (R) / 5 = _____
4. **Attention Regulation:** Ability to sustain and control attention to body sensations
   Q16_____ + Q17_____ + Q18_____ + Q19_____ + Q20_____ + Q21_____ + Q22_____ / 7 = _____
5. **Emotional Awareness:** Awareness of the connection between body sensations and emotional states
   Q23_____ + Q24_____ + Q25_____ + Q26_____ + Q27_____ / 5 = _____
6. **Self-Regulation:** Ability to regulate distress by attention to body sensations
   Q28_____ + Q29_____ + Q30_____ + Q31_____ / 4= _____
7. **Body Listening:** Active listening to the body for insight
   Q32_____ + Q33_____ + Q34_____ / 3= _____
8. **Trusting:** Experience of one's body as safe and trustworthy
   Q35_____ + Q36_____ + Q37_____ / 3= _____

Below you will find a list of statements. Please indicate how often each statement applies to you generally in daily life.

	Circle one number on each line					
	Never					Always
1. When I am tense I notice where the tension is located in my body.	0	1	2	3	4	5
2. I notice when I am uncomfortable in my body.	0	1	2	3	4	5
3. I notice where in my body I am comfortable.	0	1	2	3	4	5
4. I notice changes in my breathing, such as whether it slows down or speeds up.	0	1	2	3	4	5
5. I ignore physical tension or discomfort until they become more severe.	0	1	2	3	4	5
6. I distract myself from sensations of discomfort.	0	1	2	3	4	5
7. When I feel pain or discomfort, I try to power through it.	0	1	2	3	4	5
8. I try to ignore pain	0	1	2	3	4	5
9. I push feelings of discomfort away by focusing on something	0	1	2	3	4	5
10. When I feel unpleasant body sensations, I occupy myself with something else so I don't have to feel them.	0	1	2	3	4	5
11. When I feel physical pain, I become upset.	0	1	2	3	4	5
12. I start to worry that something is wrong if I feel any discomfort.	0	1	2	3	4	5
13. I can notice an unpleasant body sensation without worrying about it.	0	1	2	3	4	5
14. I can stay calm and not worry when I have feelings of discomfort or pain.	0	1	2	3	4	5
15. When I am in discomfort or pain I can't get it out of my mind	0	1	2	3	4	5
16. I can pay attention to my breath without being distracted by things happening around me.	0	1	2	3	4	5
17. I can maintain awareness of my inner bodily sensations even when there is a lot going on around me.	0	1	2	3	4	5
18. When I am in conversation with someone, I can pay attention to my posture.	0	1	2	3	4	5

How often does each statement apply to you generally in daily life? Circle one number on each line

	Never					Always
19. I can return awareness to my body if I am distracted.	0	1	2	3	4	5
20. I can refocus my attention from thinking to sensing my body.	0	1	2	3	4	5
21. I can maintain awareness of my whole body even when a part of me is in pain or discomfort.	0	1	2	3	4	5
22. I am able to consciously focus on my body as a whole.	0	1	2	3	4	5
23. I notice how my body changes when I am angry.	0	1	2	3	4	5
24. When something is wrong in my life I can feel it in my body.	0	1	2	3	4	5
25. I notice that my body feels different after a peaceful experience.	0	1	2	3	4	5
26. I notice that my breathing becomes free and easy when I feel comfortable.	0	1	2	3	4	5
27. I notice how my body changes when I feel happy / joyful.	0	1	2	3	4	5
28. When I feel overwhelmed I can find a calm place inside.	0	1	2	3	4	5
29. When I bring awareness to my body I feel a sense of calm.	0	1	2	3	4	5
30. I can use my breath to reduce tension.	0	1	2	3	4	5
31. When I am caught up in thoughts, I can calm my mind by focusing on my body/breathing.	0	1	2	3	4	5
32. I listen for information from my body about my emotional state.	0	1	2	3	4	5
33. When I am upset, I take time to explore how my body feels.	0	1	2	3	4	5
34. I listen to my body to inform me about what to do.	0	1	2	3	4	5
35. I am at home in my body.	0	1	2	3	4	5
36. I feel my body is a safe place.	0	1	2	3	4	5
37. I trust my body sensations.	0	1	2	3	4	5

Annexe 2 : VAS subjective level of confidence

Identification number of the participant : _____

Name of the assessor : _____

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For the following question, place a slash (/) across the line in the position that best describes your response.

Do you know whether you are accurately or inaccurately assessing your heart-timing?

I have inaccurately assessed my heart-timing

I have accurately assessed my heart-timing

TEST 1	TEST 2	TEST 3	TEST 4	TEST 5	TEST 6	AVERAGE
/10	/10	/10	/10	/10	/10	/10

Annexe 3 : Instructions guidelines for the Six Minutes Walk Test

HEART online
Heart Education Assessment Rehabilitation Toolkit

Six Minute Walk Test (6MWT) instructions

Set up

Ideally the test should be conducted on a straight 30 metre track[1]. If the track needs to be adapted or shortened due to lack of space, ensure that the patient walks the same course on each re-test.

Suggested Equipment:

- 6MWT recording form
- Rate of perceived exertion - Borg scale
- Pulse oximeter with appropriate sensor
- Stop watch or timer
- Chairs (number will depend on patient's condition and risk)
- Sphygmomanometer and stethoscope, or similar method of accurately assessing BP
- Trundle wheel for measuring the 6MWT track and the distance walked
- Clip board and recording sheet
- Portable oxygen if required

Repeat measures

Two 6MWTs are often recommended for initial assessments due to a learning effect when performing the test. Recent studies have demonstrated however that a single measure is often acceptable[2,3].

Should you choose to do repeat measures in succession, this should be done each time so that measures are consistent and a duration of at least 15 minutes provided between tests to allow adequate recovery.

Administering test

1. Prior to walking say to patient:

The object of this test is to walk as FAR AS POSSIBLE for 6 minutes. You will walk back and forth along this course (demonstrate one lap) for six minutes.

You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible.

You will be informed of the time and encouraged each minute.

Please do not talk during the test unless you have a problem or I ask you a question. You must let know if you have any chest pain or dizziness.

When six minutes is up I will ask you to STOP where you are. Do you have any questions?

2. To begin say to patient:

Start now, or whenever you are ready (start stopwatch when walking starts).

3. During the test:

Provide the following standard encouragements in even tones. Do not use other words of encouragement or body language to speed up.

- At 1 minute: *You are doing well. You have 5 minutes to go.*
- At 2nd minute: *Keep up the good work. You have 4 minutes to go.*
- At 3rd minute: *You are doing well. You are halfway done.*
- At 4th minute: *Keep up the good work. You have only 2 minutes left.*
- At 5th minute: *You are doing well. You have only 1 minute to go.*
- At 6th minute: *Please stop where you are.*

If the patient stops during the test:

Allow the patient to rest or sit in a chair if they wish, and check SpO2 and heart rate. Ask the patient why they stopped.

Keep the stopwatch running and advise: *Please resume walking whenever you feel able.*

Six Minute Walk Test (6MWT) instructions continued...

HEART online
Heart Education Assessment Rehabilitation Toolkit

4. At the end of the test:

Record the total distance walked.

Record, heart rate, blood pressure and Rating of Perceived Exertion (RPE). Record recovery time to gain additional information.

The patient should remain in a clinical area for at least 15 minutes following an uncomplicated test.

Scoring

Change in 6MWT distance can be measured in several ways. The most common include:

- Absolute change (post program distance – pre-program distance). The minimum important distance (MID) is 25 metres in patients with coronary artery disease and chronic respiratory disease[4,5].
- Percentage change may be a more relevant measure for frail patients whose baseline distance is very short eg. < 100 metres. Calculate as follows: post program distance – pre-program distance/pre-program distance x100.

Reference equations (to adjust for variables such as height, weight, age and gender predict clinical progress) are available however are no better than simply using 6MWT distance alone[6].

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Annexe 4 : Data collection sheet

Identification number of the participant : _____

Name of the assessor : _____

Test \ Time	T0	T1	T2
MAIA 2 :			
- Noticing	/5	/5	/5
- Not distracting	/5	/5	/5
- Not-worrying	/5	/5	/5
- Attention regulation	/5	/5	/5
- Emotional awareness	/5	/5	/5
- Self regulation	/5	/5	/5
- Body listening	/5	/5	/5
- Trusting	/5	/5	/5
WHO-5	/100	/100	/100
HTT	/1	/1	/1
Confidence VAS	/10	/10	/10
6MWT	m	m	m

Annexe 4 : INFORMED CONSENT

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Informed consent :

In healthy adult subjects, the effect of aerobic training at high intensity compared with low intensity will improve interoceptive sensibility: a Randomized control trial.

The informed consent is for a healthy subject included in the study after meeting all the eligibility criteria. The research department of the Guy's and St Thomas Foundation in cooperation with the Central Health Physiotherapy and the Chartered Physiotherapy clinic of London invite you to participate in this research.
Read this informed consent carefully, take your time to make your decision, iif you have any doubt, you can talk with anyone that you feel comfortable with about the research.

This informed consent will be divided in two parts:

- Information sheet : with all the informations relevant that you need to know •
  Certificate of consent : That you and the investigator have to firm to enroll on the study

INFORMATION SHEET

Purpose of the study :

The aim of the study is to determine the effect of aerobic training at a defined intensity on interoception sensibility on healthy adults. Interoception sensibility is the self-reported belief concerning one's own perception of bodily signals. The trial will improve the knowledge about physical exercise and neurological mechanisms of the body , in order to promote a healthier lifestyle.

Type of research intervention :

This research involves running and participating in different physical tests and questionnaires.

Participant selection :
We are inviting all healthy adults (between 18 and 65 years-old) living near London who have enough time to dedicate to a sporting activity. All the adults present in this trial are contacted with the database of patients from the Guy's and St Thomas hospital. Visitors to Guy's and St Thomas hospital can also be included in the study if they contact us using the flyers dropped off at the hospital reception.

Voluntary participation :

Your participation in this study is entirely voluntary, you can decide to participate or not.

Procedure and protocol :

As we want to know the effect of aerobic training at high versus low intensity on interoception sensibility on healthy adults, we will compare 2 training groups. The first group will have to run for 30 minutes at a high intensity. The intensity will be defined in function of your cardiovascular capacity, you will need to run at more than 70% of your resting Heart beat. The second group will have to run for 30 minutes at a low intensity, the intensity will also be set in function of your cardiovascular capacity. If you are in this group, you will need to run with a Heartbeat between 50% and 70% of your resting heart rate. Both groups will be allocated in a physiotherapy center having a treadmill near the hospital of Guy's and St Thomas. During the first sessions the physiotherapists will indicate to you how to recover well and improve your running technique if needed. We will ask you to monitor by yourself (with the help of the heartbeat detector of the treadmill) your heartbeat. We will ask you to come to the office center 3 times per week, with at least 1 day of rest between two consecutive sessions. The schedule will be set according to your and the physiotherapist's availability.
We will assess your physical capacity, your ability to detect your own heartbeat and estimate it, your interoceptive sensibility and your well-being. The measurement will be held at the Guy's and St Thomas before the beginning of the sessions, at the mid-term of the study and after the last sessions of running.

Duration :

The intervention will begin at the first assessment before the first running session and will last 8 weeks for a total of 24 running sessions.

Confidentiality :

All the personal data during the study will be kept under secure and confidential conditions. You will be identified with an identification number, neither the assessors and the data analyst will know your name and surname. Your data will be saved on the datacenter of the hospital Guy's and St Thomas securised with a password that only the medical staff and the investigators will have access to.
No name or personal data apart from the results of the assessments will be published.

Right to refuse or withdraw :

Your participation being entirely voluntary, your choice will not influence the quality of care provided to you, whether in physiotherapy centers or in Guy's and St Thomas hospital. You can leave the study at any time without any specific justification. We will consider your withdrawal in the event that you miss more than 2 training sessions out of the 24.

Risk and side effect :

The main risks and side effects will be due to the sudden increase of training load. You may experience muscle aches during the day or days following the session. You may also feel pain related to the running technique, especially due to muscle tension. The Physiotherapists in

charge of your sessions will be at your disposal and will do their best to reduce or avoid the risk of pain. It will be essential to notify your physiotherapist if you experience discomfort or pain, especially muscle or joint. Depending on your shoes, you may have blisters or chafing in the ankle. After training, the side effects of running will be muscle fatigue, fatigue and a feeling of dehydration if you haven't drunk enough. You will be provided with drinking water as well as glasses to hydrate yourself during the sessions however you should do your best to avoid possible malnutrition or dehydration, the physiotherapists will not be able to give you food.

In the case of a pain preventing the practice of the running sessions, a day of rest or one less session may be considered, this decision should be studied with your referent physiotherapist but it can only be taken by you.

Benefit

This clinical trial will improve your physical condition and more particularly your aerobic condition. Aerobic exercise has many benefits such as weight management, improving blood quality, improving cardiovascular health, increasing your quality of sleep, improving your mental health and strengthening your immune health. In addition, you will have access to a massage every week to relax the important muscles during the running activity.Thanks to this study, the research department of Guy's and St Thomas hospital will improve its recognition in England, which will make it possible to obtain more funding affecting directly the quality of care provided. Your participation will also help to better understand, manage and finance the health system in England, with health promotion being a major focus, identifying new effects of aerobic exercise on the body will help encourage people to be more active.

Who to contact

For any questions related to the trial design, administration, privacy of data and anything related with the assessment of outcomes, the researcher responsible for the study will be available by phone or at the following address: Westminster Bridge Rd, London SE1 7EH, United Kingdom The clinical research unit at St Thomas' is located on the 4th floor of North Wing.
The physiotherapists of the Central Health Physiotherapy and the Chartered Physiotherapy clinic will be available at any time by phone to answer your doubt about the intervention procedure, the training session or the recovery process after a running session. The protocol as well as the clinical trial has been reviewed and approved by the ethics committee of the hospital guy's and St Thomas in order to be sure that the participants are carried out of any negative consequences related to the study.

CERTIFICATE OF CONSENT

Statement by the participant :

I have carefully read all the information sheets. I have understood the nature of the procedure and the risk and benefit of the intervention. I asked questions and understood the answers given to me in order to make my decision. I voluntarily consent to be part of this research.

- I agree to voluntary participate to this study :

YES	NO

- I authorize the researcher to use my data to publish them :

YES	NO

Name and Surname of the Participant : _____
Date : ___/___/_____
Signature of the Participant :

Contact to call in case of injury :

Name and Surname : _____
Email address : _____
Phone Numbers : _____

Statement by the researcher :

I have accurately read out the information sheet to the potential participant, and do the best of my ability to make sure that the participant understands that the following points will be done :

1. Running sessions at more than 70% of HRR or between 50 and 70% of HRR for 30 minutes during 8 weeks 3 times a week.
2. Three assessments of the aerobic capacity and 3 self-reported questionnaires

I confirm that the participant was given an opportunity and complete time to ask questions about the study, and all questions asked by the participant will receive a correct answer with the best of my ability. I confirm that the individual has not been forced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Name of the Researcher taking the consent :_____
Date : ___/___/_____
Signature of Researcher taking the consent :