Magnon, V., Dutheil, F., Tauveron, I., Mille, J., Baker, J. S., Brusseau, V., . . . Vallet, G. T. (2022). Does an increase in physiological indexes predict better cognitive performance: the PhyCog randomised cross-over protocol in type 2 diabetes. BMJ Open (Vol. 12, p. e060057). doi: http://dx.doi.org/10.1136/bmjopen-2021-060057. CC BY-NC 4.0

BMJ Open

Does an increase in physiological indexes predict better cognitive performance: the PhyCog randomised cross-over protocol in type 2 diabetes

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To cite: Magnon V, Dutheil F, Tauveron I, *et al*. Does an increase in physiological indexes predict better cognitive performance: the PhyCog randomised cross-over protocol in type 2 diabetes. *BMJ Open* 2022;**12**:e060057. doi:10.1136/bmjopen-2021-060057

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-060057).

Received 09 December 2021
Accepted 21 June 2022

Check for updates

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ABSTRACT

Introduction There has been a growing interest towards cognitive-training programmes to improve cognition and prevent cognitive impairment despite discrepant findings. Physical activity has been recognised in maintaining or improving cognitive ability. Based on a psychoneurophysiological approach, physiological indexes should partly determine neuronal dynamics and influence cognition as any effects of cognitive training. This study's primary aim was to examine if improved physiological indexes predict improved cognitive variables in the context of a clinical intervention programme for type 2 diabetes (T2D).

Method and analysis PhyCog will be a 22-week randomised controlled trial comparing cognitive performance between three arms: (1) physical activity (1 month), a 15-day wash-out, then cognitive training (1 month), (2) cognitive training (1 month), a 15-day wash-out and physical activity (1 month), and (3) an active breathing condition (psychoeducation and resonance frequency breathing for 1 month), then a 15-day wash-out, and combined physical activity and cognitive training (1 month), allowing to determine the most effective intervention to prevent cognitive impairment associated with T2D. All participants will be observed for 3 months following the intervention. The study will include a total of 81 patients with T2D.

Cognitive performance and physiological variables will be assessed at baseline (week 0—W0), during the washout (W5, 72–96 hours after week 4), at the end of the intervention (W10), and at the end of the follow-up (W22). The main variables of interest will be executive function, memory and attention. Physiological testing will involve allostatic load such as heart rate variability, microcirculation, cortisol and dehydroepiandrosterone sulfate levels. Sociodemographic and body composition will also be a consideration. Assessors will all be blinded to outcomes. To test the primary hypothesis, the relationship between improvement in physiological variables and improvement in cognitive variables (executive, memory and attention) will be collected.

Ethics and dissemination This protocol was approved by the Est III French Ethics Committee (2020-A03228-31). Results will be published in peer-reviewed journals.

Trial registration number NCT04915339.

Strengths and limitations of this study

⇒ This study will propose a unique cross-disciplinary approach with a design testing different combinations of individualised physical and cognitive training in type 2 diabetes (T2D).
⇒ The exhaustive neuropsychological test battery and physiological testing will be administrated four times in a within-subjects design in a 3-month follow-up with blinded assessors and participants.
⇒ Physical activity and cognitive exercise at home will be prescribed using a computerised application, designed to improve cognitive impairment related to T2D.
⇒ A longer follow-up period may be required to assess the adherence and whether the intervention effects will be maintained in the long term.
⇒ Although the home-based intervention is essential in this study, several parameters cannot be controlled.

INTRODUCTION

The assumption that general cognitive ability can be enhanced by practising cognitive tasks or intellectually demanding activities makes cognitive training one of the most influential topics in psychology and neuroscience. The past two decades have seen a growing interest towards designing and implementing cognitive-training programmes to improve cognitive abilities and prevent cognitive impairment associated with age[1] or chronic diseases.[2] Cognitive training is thought to produce functional and anatomical changes in the neural network underlying cognitive performance.[3] For instance, cognitively demanding training in spatial navigation increases the hippocampal volume among older adults,[4] the hippocampus being associated with memory and learning.[5] Mostly, the cognitive functions improved are the ones trained. Few studies have found improvement

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in other cognitive functions than the ones trained specifically, but they are on very closely related domains.[6] As such, there is little evidence of transfer to untrained cognitive abilities or generalisation to daily activities.[7] Furthermore, a recent meta-analysis has found no significant improvement in cognitive training on global cognitive functioning.[6] On the contrary, there is a consensus that motor based cognitive training[8] and more broadly physical activity benefit cognition.[9 10] Neurotrophic factors mediate the effect of physical activity on brain health and thus on cognition.[11] For instance, regular and frequent physical activity is also associated with cerebral changes such as increased hippocampal volume,[12] and enhanced white matter integrity.[10] These changes are related to memory,[13] cognitive flexibility,[14] cognitive inhibition[15] and working memory.[16] Interestingly, physical exercise, as a subset of physical activity that is a planned, structured and repetitive process that aims to maintain and improve physical fitness,[17] seems to benefit cognition in patients with type 2 diabetes (T2D) as well.[18 19] Considering the discrepancy in the findings regarding cognitive training alone, physical exercise could be an efficient way to boost the effect of cognitive training.[20 21] The interaction between physical training and cognitive training is predicted by psychoneurophysiological models suggesting that neural dynamics depends on physiological variables through epigenetic mechanisms that is, the influence of the environment on gene expression.[22 23] In this perspective, brain activity and cognition are embodied as the brain is considered as a complex adaptive system that maximise fitness via action-perception cycles.[22]

Supporting this hypothesis, several peripheral factors have been reported to improve cognitive function in healthy participants. For instance, heart rate variability (HRV, fluctuation in the time intervals between heartbeats, HRV) can influence neural activity and cognitive function.[24] HRV is associated with the activity of brain areas involved in emotional processing (eg, insula, amygdala) attention, memory and executive functioning (eg, prefrontal cortex).[25] Executive functioning can be defined as the control processes implemented when usual action plans are no longer relevant in a given context.[26] Improvements in VO2max (another relevant marker of cardiovascular health) also positively predict global cognitive functioning in older adults with T2D.[18] Beyond cardiovascular-related markers, stress biomarkers seem to influence cerebral and cognitive functioning as well.[27 28] Elevated cortisol levels prior to learning seem to boost memory,[29] while chronic elevation is associated with memory difficulties.[30] Other physiological indexes such as body composition could also predict cognition.[31 32] A high lean/fat mass ratio seems to predict better cognitive inhibition and cognitive flexibility.[33] Taken together, cognition might indeed be embodied and be determined by physiological indexes for maximising adaptation.[22 34]

T2D subjects would be a relevant population to test whether increased physiological indexes predict better cognitive functioning. First, this population presents reduced physiological indexes[35] and concomitantly cognitive impairment.[36 37] Second, physical activity[38] and cognitive training[39] are two recommended interventions for patients with T2D. In line with our hypothesis, physical activity seems to have greater effects on cognition than cognitive training among patients with T2D.[40] Indeed, a recent study found that a combination of resistance and aerobic physical training improves executive functioning in patients with T2D.[19] Furthermore, T2D is major health issue since it is one of the most frequent diseases among elderly individuals.[41 42] T2D has been consistently associated with cognitive decline, from mild cognitive impairment to dementia.[43 44] Therefore, there is a growing concern for efficient prevention strategies for T2D.[45] This study aims to test whether the robust and global cognitive effects of physical activity can be explained by physiological changes. Specifically, increased physiological indices after physical activity may predict better cognitive functioning. Furthermore, through these physiological changes, physical activity could enhance the effect of cognitive training.

Aims

The PhyCog study is a cross-disciplinary approach to cognitive functioning based on a psychoneurophysiological perspective. This approach predicts that (1) physiological indexes should partly explain cognitive functioning; (2) physical training should boost the effects of cognitive training. The main objective will be to test whether physiological changes predict changes in cognitive variables, particularly for executive functions[26] and memory.[15 46] A secondary objective will be to study the effects of several combinations of physical activity and cognitive training interventions to determine the most effective intervention to prevent, maintain or even reverse cognitive impairment associated with T2D.

Hypotheses

The experimental trial will evaluate the following hypotheses:

1. An increase in physiological variables should be associated with improved cognitive performance, especially for executive function-related measures.
2. Cognitive training after physical activity should be more efficient than the reverse order (cognitive training prior to physical activity).
3. An intervention based only on physical activity should have greater cognitive benefits than only cognitive training. If so, we will aim at assessing whether physiological changes might explain the potential superiority effects of physical activity.
4. An intervention programme combining physical activity and cognitive training should have synergetic effects on cognition (especially executive functions and memory), as previously reported.[47]
5. Promotion of physical activity and cognitive training at home using a smartphone application should be feasi-

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ble, acceptable, and a determinant of adherence and compliance.[48]

6. The cognitive effects of physical activity-based interventions (with or without cognitive training) should be maintained during the follow-up.

METHODS

Study design

PhyCog is a three-armed randomised controlled semi cross-over trial designed to compare the cognitive effects of separated or combined cognitive training and physical activity on psychological functioning. The three arms will test two conditions for 1 month each, separated by a 15-days wash-out. The three arms will be: (1) physical activity (1 month) and cognitive training (1 month); (2) cognitive training (1 month) and physical activity (1 month); (3) an active breathing condition (1 month) and combined physical activity plus cognitive training (1 month). The active breathing condition will be a psycho-educational intervention on cognition-protective lifestyle factors and an introduction to resonant frequency breathing (also known as cardiac coherence)[49] that will serve as an active control condition[50] in comparison with physical and cognitive training. The first month of this third arm is designed to control the effect of physical activity alone (first arm) or cognitive training alone (second arm). Cognitive performance and physiological indexes will be assessed at baseline (week 0—W0), during the washout (W5, 72–96 hours after week 4), at the end of the intervention (W10) and at the end of the follow-up (W22) (figure 1). This design enables us to test whether increased physiological indexes predict better cognitive functioning. It is expected that physiological changes occur mainly following physical activity and possibly explain its robust and global cognitive effects. This design allows us to compare different intervention combinations between physical activity and cognitive training to determine the most effective method for patients with T2D.

Procedure overview

This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT, see online supplemental information) guidelines.[51] Over a period of 18 months starting from March 2022, patients with T2D will be recruited through the university hospital of Clermont-Ferrand or diabetes association (figure 2). Physical and cognitive exercises will be offered via the Santé'UP smartphone application. A time of familiarisation with the application will be given so that participants can use it without difficulty. Patients will be randomly assigned to either one of the three arms without the experimenter knowing the outcome. Participants will have to complete a physical exercise test to ensure they are able to exercise and to determine the type, intensity and frequency of physical exercises that best suits their ability. During the testing, the information given to the participants will be sufficiently neutral to not induce any expectations concerning the study's hypotheses. Thus, the participants will be blinded to the hypotheses and the experimenter will not know which arm of the trial the participants were allocated to. The experimenter will also be blind as he won't be aware in which arms participants have been allocated to (as an independent college is in charge of the randomisation assignment). Prior to the intervention (W0, pretest), a battery of neuropsychological tests as well as several non-invasive physiological assessments will be administrated (1.5–2 hours). In addition, online questionnaires are to be completed within a week. If the questionnaires are not filled in on time, a first reminder will be sent by email before a telephone reminder if the problem persists. During a wash-out period (2 weeks) the neuropsychological and physiological testing will be administrated again 72 to 96 hour after the end of the month (W5, mid-test). After the second month, participants will complete the neuropsychological and physiological testing a third time (W10, post-test). Three months after, the neuropsychological and physiological testing will be administrated a fifth and final time (W22, follow-up).

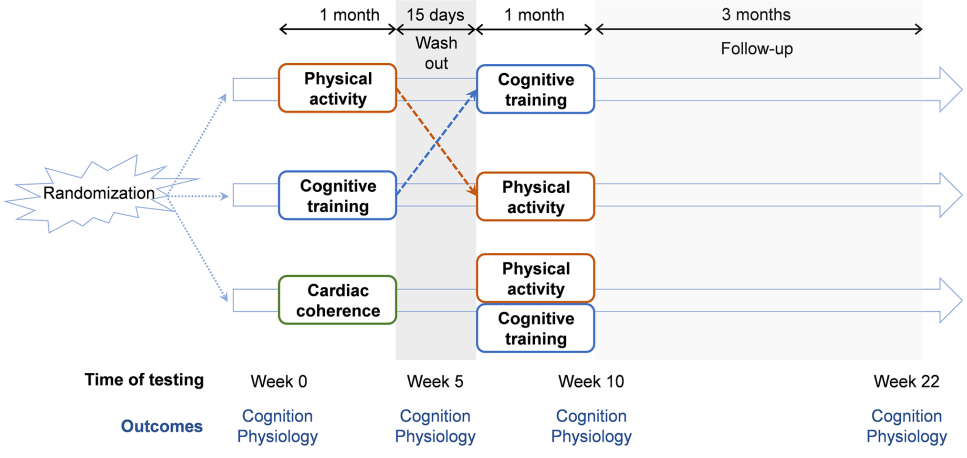

Figure 1 Study design.

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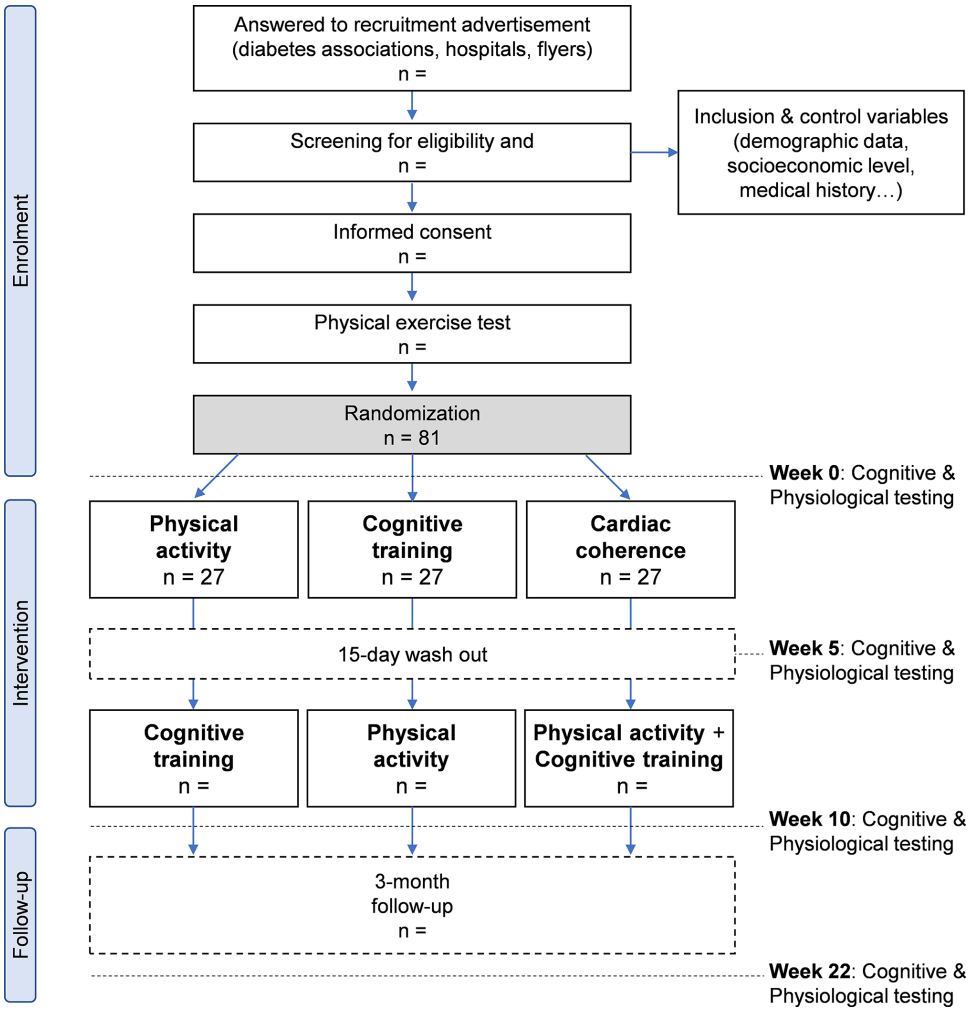

Figure 2 Flow chart of main steps for patients.

Inclusion and exclusion criteria

Patients must be between 50 and 70 years old, have normal or corrected-to-normal vision and audition. Their last measure of HbA1c from their medical record must be <9%. The absence of general cognitive decline and psycho affective condition will be assessed respectively by the Montreal Cognitive Assessment (score >25)[52 53] and by the Hospital Anxiety Depression Scale (HADS) (score <11 for each subscale).[54 55]

In order to verify the absence of memory decline, participants must have acceptable performance in the memory binding test assessing episodic.[56] The French National Adults Reading Test (fNART)[57] assessing verbal intelligence will be used as a proxy of socioeconomic status. Moreover, the Physical Activity and Sedentariness Survey[58] will be administered to control physical activity and sedentariness as they are independent risk factors.[59 60] Other exclusion criteria include prior or current severe traumatic brain injury, neurological (eg, epilepsy), neurodevelopmental (eg, autism or dyslexia) or cardiovascular disorders, psychiatric disorder (eg, schizophrenia, bipolar disorder), use of psychotropic medication and alcohol abuse.

Study arms

The patients will be randomly assigned to one of three arms: physical activity followed by cognitive training versus cognitive training, followed by physical activity versus cardiac coherence breathing, followed by combined physical and cognitive activity. Randomisation will be computer generated, based on an Excel file (created by an independent colleague), and will be performed using permuted blocks (size=4) according to the patients age, sex and socioeconomic status, to ensure that the arms will be balanced in terms of size and patients' characteristics. The first and second arms will be in cross-over so that the physical activity and the cognitive training programmes are counterbalanced. In partnership with E-Ajeo Santé, the start-up company behind the Santé'Up smartphone application, patients will be able to engage in adapted physical activity and cognitive exercises at home. The purpose of this application in fine is to provide cognitive and physical exercise that could benefits patients suffering from any chronic diseases. Touch screen applications are gaining popularity as they offer an ergonomic and accessible user experience.[61] This application will consider the patient symptoms and characteristics by proposing

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either muscle strengthening or endurance exercises. External parameters, such as the environment where the individual lives as well as weather forecast data, are considered to propose adapted activities. Participants will engage in physical activity around four times per weeks (based on their capacities) for 1 month with a session duration lasting from 35 to 60 min as recommended.[47 48] Physical training will consist of a combined programme of resistance (lifting weights…) and aerobic physical activity (cycling, running, walking…) to maximise its cognitive benefits.[19 47] The intensity will vary depending on the patients' abilities, but physical exercises will be at least moderate to vigorous as recommended in patients with T2D to observe its positive cerebral and cognitive effects.[62] Likewise, cognitive training will be performed on the application. Cognitive activities include learning and retaining in memory a series of visual and auditory stimuli in order to reproduce them later. For example, four rectangles of different colours light up in a specific order which must be memorised to reproduce the sequence later. The sequence increase n+1 as long as the participant's answer is correct. Then, the same activity with rectangles of different colours or shades of grey instead of colours to increase difficulty will be completed. These exercises allow work on attentional capacities and working memory (keeping the information in memory to restore it). Another cognitive training exercise will be a Go/No-Go with images of animated and unanimated objects. In the easiest level, the No-Go stimuli are very distinct from the Go stimuli and thus easily discriminated. Whereas, in the hardest level the No-Go stimuli are very similar to the Go stimuli. These exercises will be performed twice a week for a duration of 30 min.[63] The third arm consist of 1 month of resonance frequency breathing (also called Cardiac Coherence) and psychoeducation (on lifestyle factors influencing cognitive functioning such as sleep, nutrition…), followed by cognitive and physical activity combined. Resonant frequency breathing is an abdominal breathing exercise in which the duration of inspiration is equivalent to the duration of expiration[49 64] in order to re-establish a sympatho vagal balance.[65] This breathing exercise will be done via free computer applications allowing several adjustments. For example, having a visual guide during inspiration and expiration as well as having the option of an auditory guiding for people with visual difficulties. Since there are individuality differences in respiration rate,[66] the option to modify the duration of the breathing cycle is important to adapt the exercise to the patient's cardiorespiratory capacities. A training programme consisting of daily 5 min sessions (sufficient time to change HRV)[67] will be offered. The breathing condition will serve as a reference comparison for the effect of standalone physical activity and cognitive training, as active control condition are recommended over non-active ones[50] and should provide some immediate psychological benefices without impacting cognitive functions on the long term.[68] After each physical or cognitive or breathing exercising session, patients will give feedback via the application on the difficulty of the exercises so that they can be adjusted for the next session. That way, intervention adherence can also be controlled.

Sample size

The main objective will be to verify whether the improvements in physiological parameters predict the improvement of different psychological variables. This hypothesis will be tested by performing a multiple linear regression with three physiological variables (score composite of fitness level, HRV and stress biomarkers) as predictors. To conduct a power analysis, data obtained using a physical exercise intervention assessing the association between improved HRV and executive performance was used as a reference.[64] The authors reported a correlation of $r = .44, p < .05$ between cardiac functioning and the number of errors on a battery of cognitive tests. To obtain Cohen's f^2,[69] the following formula was applied $f^2 = \frac{R^2}{1-R^2}$. With $R^2 = .19$, a result of $f^2 = .24$ was obtained. On the R software,[70] power analyses was performed using the "pwr" package,[71] with three predictors, a cut-off at 0.05, and a statistical power of 0.95, revealed a total sample size of 72 participants (24 participants per group). To ensure sufficient statistical power for secondary objectives as well, a total sample size of at least 81 individuals will be targeted (27 individuals per group).

Neuropsychological test battery (week 0, 5, 10, 22)

A trained neuropsychologist will be the main experimenter. All the tests (see table 1) are commonly used in neuropsychological practice expect for the interoceptive awareness questionnaire[72] assessing interoceptive sensibility (ie, sensation concerning the state of the internal body)[73] as well as the Client Satisfaction Questionnaire (CSQ)[74] and Psychological Outcome Profiles (PSYCHLOPS)[75] measuring patients satisfaction level of the intervention. Fist, an episodic memory test called the logical story test[76] consisting of presenting two short narrative stories with an immediate recall phase after each story and a delayed recall phase after 10 min. Then, the executive functioning is assessed by four tests. The Nback,[77] measures working memory. It consists of presenting a rapid succession of individual stimuli (letters) and the participant must indicate whether the stimulus present on the screen corresponds to the penultimate stimulus presented. The number of correct answers and reaction time are the main measures. The Trail Making Test (TMT)[78] consists of asking the participant to link letters and numbers alternatively on a sheet of paper, in alphabetic order and ascending order, respectively. The cost of the alternation is the main variable measured. The Go/No-Go[79] is a task that measures cognitive inhibition. Participants must respond only to certain stimuli (letters) called 'go' and not respond to others, the 'no-go'. Thus, on the 'no-go' trial, participants must inhibit their response. Reaction time will be the primary measure. The Stroop test[80] measures cognitive inhibition abilities by presenting

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Table 1 Neuropsychological test battery

Test	Domain assessed	References	Online
CSQ	Satisfaction of the intervention	74	No
PSYCHLOPS	Satisfaction of the intervention	75	No
Story Recall	Episodic memory	76	No
Nback	Updating of working memory	77	No
TMT	Cognitive flexibility	78	No
BORB	Visual discrimination	83	No
GoNoGo	Cognitive inhibition	79	No
IAQ	Interoception sensibility	72	No
Stroop	Cognitive inhibition	80	No
Verbal fluency	Lexical access	82	No
Cognitive Complains Survey	Meta-cognitive perception of memory functioning	84	Yes
Life Satisfaction Scale	Life satisfaction and quality of life	85	Yes
Generalised Self-efficiency Scale	Self-efficacy	86	Yes
BDI	Depression level	87	Yes
Trait STAI	Anxiety level	88	Yes
ERQ	Emotion regulation strategies	89	Yes

BDI, Beck Depression Inventory; BORB, Birmingham Object Recognition Battery; CSQ, Client Satisfaction Questionnaire; ERQ, Emotion Regulation Questionnaire; IAQ, Interoceptive Awareness Questionnaire; PSYCHLOPS, Psychological Outcome Profile; TMT, Trail Making Test.

colour names (eg, blue, red) written in an incongruent colour (eg, red written in green) generating a semantic conflict. Participants must retrieve the name of the colour with which the word is written by inhibiting the reading of the word. The rate of correct response and reaction times will be considered as well as a composite score. This composite score will be obtained through three variables: reaction for the colour words (CW) condition (naming incongruent ink colours in which colours are written), reaction time to name colours printed in black ink (W) and reaction times to name different colour patches(C). The inhibition score[81] will be computed as CW-[(C*W)/(C+W)]. Finally, the verbal fluency test[82] measures lexical access (ie, the ability to retrieve a word from memory). The participants will be asked to say as many words beginning with a specific letter or as many words as possible belonging to a semantic category during 1 min. The number of words spoken will be the primary measure. The Birmingham Object Recognition Battery (BORB)[83] which measures visuospatial perception will also be administrated. It consists of deciding whether the two lines presented have the same spatial orientation. Then, the participant must judge whether the opening of the two presented circles is in the same location.

Online testing

The participants will complete several online questionnaires at W0, W5, W10 and W22. First, a cognitive complains survey[84] evaluates the feeling or perception of cognitive impairment, particularly memory and attentional difficulties, in daily life. The life satisfaction scale[85] evaluates the level of well-being and quality of life and the generalised self-efficacy Scale[86] assesses the belief in the ability to overcome difficulties, solve problems and make choices. The Beck Depression Inventory (BDI)[87] assesses the level of depression in adults while the STAI-Trait[88] evaluates the level of long-term anxiety. Finally, the Emotion Regulation Questionnaire (ERQ)[89] measures frequently used emotional management strategies such as expressive suppression or cognitive reappraisal.

Physiological measures

Overview

To assess HRV, a chest belt monitor (Polar H10) will be used to measure accurately sinus variability of the heart rate.[90] By measuring heartbeats, the interoceptive accuracy task test will be administrated. It consists of detecting the number of heartbeats in a limited period of time. Then the number of perceived heartbeats is compared with the real number of heartbeats recorded.[91] Blood flow velocity will be measured using laser speckle contrast imaging (LSCI).[92] Biomarkers of stress include cortisol and dehydroepiandrosterone sulfate (DHEA-S) from the HPA axis.[93] The fat to lean mass ratio will be obtained using an impedance balance. Body mass index (BMI) will also be calculated at each testing time. See table 2 for a summary of the physiological variables assessed.

Analyses of HRV

HRV data will be recorded following methodological recommendations[94] and will be examined according to Task Force recommendations.[95] Interbeat intervals will be used to obtained HRV outcomes *via* Kubios HRV software (V.3.3.1). The presence of artefacts or occasional ectopic

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Table 2 Summary of devices used to measure physiological variables

Device	Variables	References	Characteristics
Polar H10 heart rate transmitter belt worn around the chest	HRV	90	This belt will be fully charged and wore at rest to assess heart rate
Salivate placed in the mouth of the patient for about 1 min	Cortisol, DHEA-S	98	The sample is stored at −80°C before being sent to the laboratory for analysis
Laser speckle contrast imaging	Blood flow velocity	92	By using the intrinsic tissue contrast from dynamic light scattering, it provides detailed spatiotemporal dynamics of blood flow changes in real time
The impedancemeter Inbody 770	Body composition	99	A balance to assess fat mass and muscle mass

DHEA-S, Dehydroepiandrosterone SulfateSulphate; HRV, Heart Rate Variability.

beats will be visually controlled and a filter will be applied when judged necessary. The square root of the mean squared difference of successive R-R intervals (RMSSD) and the number of adjacent N-N differing by more than 50 milliseconds, divided by the total number of N-N intervals (pNN50) will be obtained. The RMSSD and pNN50 are associated with high-frequency power (HF) reflecting parasympathetic activity. HF (0.15–0.4 Hz), represents the most efferent vagal (parasympathetic) activity to the sinus node[96] while low frequency power (LF; 0.04–0.15 Hz) is an index of both sympathetic and parasympathetic activity.[97] RMSSD, pNN50 and HF will be the vagally mediated HRV indexes primary used in the present study.

Analyses of body composition

Participants will be bare feet on the electrodes. They will enter they information controlled by the Inbody 770 (age, height…) and have their hands on the handles with electrodes as well. Then, they will get into position, they will maintain testing posture (keeping your arms straight and hold the handles away from your body at a 45° angle). Intracellular water, extracellular water, dry lean mass, body fat mass, muscle-fat analysis, BMI, body fat percentage will be obtained.

Analyses of blood flow velocity

LSCI is a technique for visualising detailed spatiotemporal dynamics of blood flow changes in real-time. Participants will maintain their hand in the LSCI for 3 min to obtain base line, by using a sphygmomanometer blow flow will be stopped for 2 min, then the sphygmomanometer will be released for 3 min. The time blow flow takes to return to baselines is the main outcome.

Analyses of stress biomarker

Biomarkers of stress include cortisol and DHEA-S from the HPA axis.[86] After a short rest so that biomarkers return to the baseline (10 min), we will perform assays using saliva samples by placing the salivate in the participant's mouth for 1 min. Then the samples will be kept in Eppendorf Tubes frozen at −80° before being sent to the laboratory of the university hospital of Clermont-Ferrand.

Statistical analyses

To test whether increases in physiological parameters predict improvements in psychological variables, the difference between W0 and W10 will be calculated for all variables (physiological variables, interoceptive scores and psychological variables). An improvement on each of these variables is expected except for visuospatial perception scores. Multiple linear regression analyses will be conducted with vagally-mediated HRV indexes (RMSSD, pNN50 and HF), stress biomarker levels (composite score between cortisol and DHEA-S levels), fitness level (composite score between BMI, lean mass/fat mass ratio and capillary blood flow velocity) as predictors. The dependent variables will be: (1) a composite score of executive functioning obtained from inhibition cost (rate of correct responses in the Go/No-Go task and rate of correct responses and reaction time for the Stroop test) alternation cost (time taken for completion of the TMT), working memory updating (rate of correct responses and Nback reaction time) and lexical access (number of words to verbal fluency tasks); (2) an episodic memory score (number of correct responses to the immediate and delayed recall of the logical stories test); (3) a score of visuospatial perception (score obtained from the detection of openings and the judgement of the orientation of lines in the BORB); (4) a score of negative mental health (composite score between the HADS and the BDI scores); (5) a care satisfaction score (derived from the CSQ and PSYCHLOPS scores); (6) the Cognitive Complaints Questionnaire score; (7) the ERQ score; (8) the Generalised Sense of Self-Efficacy Questionnaire score; (9) the Life Satisfaction Scale score. These composite scores will only be calculated if the variables correlate strongly with each other ($r \geq 0.60$). Otherwise, each variable will be studied separately. Specifically, the bottom-up stepwise method will determine which predictor explains the most variance. An analysis of variance (ANOVA) with outcomes variables changes between W0 and W5 (then between W0 and W10) and the type of intervention as between-subjects independent variables (arm 1 vs arms 2 vs arm 3) will be conducted to assess the possible superiority of physical activity over cognitive training (then the effect of

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the order of the interventions on cognitive performance). Further ANOVA will compare the episodic memory and executive functioning changes (W5 vs W10) across the three arms to determine if combined physical activity and cognitive training resulted in better memory and executive performances compared with physical activity or cognitive training alone. These analyses will also be conducted for the 3 months follow-up (W10 vs W22). One-sided analyses will be performed expect for visuospatial perception scores (bilateral testing as improvement for this outcome is not predicted).

For all these analyses, assumptions will be checked (multicollinearity, homoscedasticity, independence of errors, normality…) and different covariables will be controlled such as gender, age, education level and sociocultural level (approximated via the fNART).

Data management and monitoring

Study staff will be responsible for data entry and range checks for data values. All data will be stored on a secure server. Given the minimal risk nature of the study, the data will be internally monitored. The final data set will only be available to the experimenter in charge of the statistical analyses (VM). Reports on study progress and milestones will be submitted to the funder. Missing data and drop-out rates will be assessed for each individual randomised controlled trial. The final number of participants included in the final analysis will be reported as a proportion of all participants in the study. Participants with missing data will not be excluded as long as missing data do not impact hypothesis testing.

Patient and public involvement

Patients and members of the public were not involved in the development of this study protocol. However, the validation of the efficacy of an application offering cognitive training and physical activity programmes to prevent cognitive impairment in patients with T2D was a major motivation for the Santé'Up start-up and the European Regional Development Fund to finance this study.

ETHICS AND DISSEMINATION

This protocol was approved by the Est III French Ethics Committee (2020-A03228-31). Prior to inclusion, written informed consent will be required from each patient. Any adverse event will be managed by the university hospital in which the trial takes place in agreement with the ethic registration. The experimenter which will also provide transparent explanations about the trial (excluding the scientific hypotheses) and the smartphone application. They can stop their participation in the trial at any point if they request it. The researchers will take all necessary precautions to preserve confidentiality. Only the inclusion number will be registered. Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol which will have to be approved by the Est III French Ethics Committee. The results will be disseminated via peer-reviewed publications and conferences, targeting researchers, policy-makers and clinicians. The authors for publications and conferences will be the investigators of this study.

Outline

The possibility that cognition is grounded in the body gives rise to new perspectives on neuropsychological interventions in order to prevent cognitive impairment associated with ageing or chronic diseases. Assuming that physiological variables might, among other factors, determine cognitive functioning, individualised interventions (rather than 'one-size-fits-all' interventions) aiming to maximise physiological indexes might be a relevant step to take to enhance cognitive training effects.

Despite some clear methodological limitations, such as the active breathing condition in which participants are introduced to resonant breathing which is not a control condition without any sort of intervention and the length of the physical training which could have been longer to ensure the cognitive benefits of physical activity, the present study has a unique cross disciplinary approach to the prevention of T2D-related cognitive impairment. In the next step, the cognitive and physical activity training proposed by E-Ajeo Santé will be extended to other chronic diseases in which cognitive impairment is likely to occur.

As such, this study (1) will propose a theoretical explanation for the difference between the reported efficacy of cognitive training and physical activity; (2) will test different combinations of physical activity and cognitive training to determine the most efficient one; (3) will test the validity, acceptability and feasibility of a smartphone application so that patient can engage in adapted physical and cognitive exercises easily at home. While this study investigates different combinations of physical and cognitive training in order to create flexible and individualised modules that could be generalised to other chronic diseases, simultaneous cognitive and physical exercise could not be implanted. Future studies could investigate motor-cognitive training approaches (physical-cognitive training simultaneously) which have been suggested to induce greater cognitive benefits than standalone training. Such intervention could be relevant clinical leads.

Trial status

The recruitment phase begins in March 2022. The estimated end date for this study is approximately September 2023.

Acknowledgements We thank the medical staff, diabetologists, patients and their families, the local associations and Santé'Up for their participation, enthusiasm and support in the establishment of this research.

Contributors VM, GTV and FD conceptualised and designed the study, drafted the initial manuscript and incorporated the suggestions of all the consortium authors. IT, JSB and VB made relevant contributions to the recruitment and the definition of the variables of interest. JM, LS and MI made substantial contributions to the creation

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of the interventional program. All authors reviewed, contributed and approved the final manuscript as submitted.

Funding This work was supported by the European Union under the European Regional Development Fund (FEDER) in the context of a pluridisciplinary project 'Aging, Chronic Illness and Cognitive Stimulation'.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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