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ORIGINAL PAPER

A web-based adapted physical activity program (e-APA) versus health education program (e-HE) in patients with schizophrenia and healthy volunteers: study protocol for a randomized controlled trial (PEPSY V@ Si)

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Abstract
Patients with schizophrenia (SZ) have a high level of cardiovascular morbidity and some clinical symptoms of illness remain resistant to pharmacological approaches. A large number of studies support the effectiveness of physical activity (PA) in SZ. The aims of this trial is to assess the effects of a remote, web-based adapted PA program (e-APA) compared to a health education program (e-HE) on brain plasticity in SZ and healthy volunteers (HV) and on psychiatric, neurocognitive, circadian and physical variables. The study is an interventional, multicenter, randomized open-label trial. Forty-two SZ will be randomized to either the active group (e-APA, $N=21$) or nonactive group (e-HE, $N=21$), and 21 HV will be matched to SZ according to age, gender, and level of PA in both e-APA and e-HE groups. Interventions will consist of 32 sessions (2×60 min/week, for 16 weeks) via supervised home-based videoconferencing. Cerebral magnetic resonance imaging, psychiatric symptoms, neurocognitive and circadian rhythms assessments as well as physical tests and biological analyses will be assessed at baseline and 16 weeks after the intervention. To our knowledge, this is the first study aiming to evaluate the efficacy of APA delivered by supervised home-based videoconferencing in SZ. Moreover, using multimodal MRI, this study could clarify the pathophysiological mechanisms underlying the efficacy of APA. Finally, this innovative approach might also increase participation in long-term PA since PA-based programs are known to have low adherence and early dropout. Trial registration: ClinicalTrials.gov identifier: NCT03261817. Registered on 16 August 2017.

Keywords Schizophrenia · Adapted physical activity · Brain plasticity · MRI · Cognition · Web

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Background

Emerging evidence suggests that physical activity (PA) is relevant as an adjuvant therapy in patients with schizophrenia (SZ) to improve both physical and mental health as well as functional outcomes [1]. Indeed, studies have demonstrated that PA significantly improved positive and negative symptoms, cognitive deficits and social functioning [2–6], as well as sleep quality in this population [7–9]. PA also improves cardiovascular and respiratory capacities in SZ [10–13] by reducing weight, insulin resistance, lipidic dysregulation, type II diabetes and metabolic syndrome [14–16], leading to decreased mortality [17]. According to these studies, the clinical benefits of PA are underpinned by cerebral and biological mechanisms that could stimulate cerebral plasticity and notably increase hippocampal volume [18–20], a cerebral structure consistently described as reduced in SZ compared to the general population [21–23]. Indeed, Pajonk et al. [24] demonstrated mean hippocampal volume increases of 12% in SZ following 3 months of aerobic endurance training. However, given that these observations are not consistent in SZ [25, 26] or the general population [27], further studies are required to investigate hippocampal plasticity by assessing notably hippocampal subfields. Indeed, left cornu ammonis (CA) regions CA1-4, the subiculum (SUB), and the dentate gyrus (DG) exhibited increased volume reduction compared with other hippocampal regions in both first-episode and chronic SZ [28–30], and PA resulted in different improvements in neuroplasticity in CA4/DG during aerobic exercise in SZ [31]. Despite these obvious benefits, PA can be harmful if it is not adapted to the patient's physiological capacities because it has been reported that schizophrenia itself and antipsychotics potentially increase cardiological risks, such as clozapine-induced myocarditis and cardiomyopathy, metabolic syndrome, autonomic dysfunction, ventricular arrhythmia, sudden cardiac death, and electrocardiogram abnormalities [32, 33]. Thus, vigorous physical activity, particularly when performed by unfit individuals or individuals with compromised health, can increase the risk of cardiac maladaptations, including accelerated coronary artery calcification, exercise-induced cardiac biomarker release, myocardial fibrosis, and atrial fibrillation [34]. Finally, studies have described that chronotropic incompetence during PA (defined as the inability of the heart to increase its rate commensurate with increased activity or higher metabolic demand) is reported in approximately 60% of SZ taking regular medication, which represents an important additional risk factor in patients [35] and might explain to some extent why SZ encounter difficulties practicing and enjoying PA [36]. Therefore, PA programs should offer patient-adapted exercises and should be supervised by qualified supervisors [37]. It was partly in this context that "adapted" PA (APA) was developed in the 1970s. APA refers to an adaptation of exercises to the capabilities and needs of individuals with limiting conditions, such as disabled, health-impaired, or aged people [38].

Despite the abovementioned benefits of PA in both physical and mental health highlighted by the literature, most SZ remain physically inactive [39–41]. Moreover, the implementation of PA-based programs is often hampered by poor adherence and early dropout in SZ (26.7%; 95% confidence interval (CI) = 19.7–35.0%) [42]. Evidence suggests that frequently encountered barriers to engage in regular PA include the following: disinterest and poor motivation [41, 43, 44]; feelings of sadness, anxiety and stress about PA in public, including social anxiety [41, 43, 44]; tiredness [43, 44]; low physical self-perception and low self-efficacy [41, 43]; lack of social support to PA and stigma [41, 43, 44]; comorbid physical health issues [41, 44]; poor access to facilities and cost [41, 43]; overweight and obesity, physical complaints, and low physical fitness [41, 43, 44]; and side effects of medication [41, 44]. Therefore, studies suggest that PA programs delivered by a qualified professional and/or supervised throughout the duration of the intervention appear to be associated with significantly reduced dropout rates [42–44]. Moreover, electronic health (e-health) technology has been developed in the general population to facilitate remote interactions and to encourage people to participate in PA over the long term [45–47]. E-interventions can be advantageous as they tend to improve access (home-based intervention without geographical limit), cost, convenience, education, care quality and effectiveness and can be delivered across an array of personal devices. However, few studies using e-technologies have been conducted in SZ [48–54]. Telepsychiatric approaches using videoconferencing technology could be an alternative tool to bypass these limitations [55]. To the best of our knowledge, no study has investigated the impact of APA programs delivered, supervised and monitored via web-based videoconferencing in SZ.

The purpose of the present study is to describe the protocol of an interventional randomized trial (PEPSY V@Si) for which the primary aim is to demonstrate in SZ that an APA program delivered via web-based videoconferencing (e-APA, active group) could improve brain plasticity as assessed by hippocampal volume.

Methods

Study design and objectives

PEPSY V@Si is designed as an interventional, multicenter, randomized open-label trial. The main objective is to demonstrate an increase in overall hippocampal volumes (right

and left) in SZ receiving a 16-week web-based e-APA program compared to SZ receiving a 16-week web-based health education (e-HE) program (Fig. 1). The secondary objective is to assess the impact of the active intervention (e-APA) compared to the non-active intervention (e-HE) on the following additional variables: (1) cerebral variables (volumetric changes in the different subregions of the hippocampus and changes in *N*-acetyl aspartate (NAA), reflecting neuronal integrity in the hippocampus and integrity of white matter in whole brain and the frontomedio-hippocampal fibers); (2) cognitive variables (i.e., working memory, episodic memory, and attentional and executive functions); (3) circadian rhythms (i.e., temperature, motor activity (actimetry) and wake-sleep cycle); (4) clinical status of participants (i.e., severity of symptoms for SZ only, quality of life, level of activity and physical abilities) and (5) biological variables (i.e., fasting glucose and lipidic dysregulation).

SZ are randomized to the active group (e-APA) or the non-active control group (e-HE). HV are matched to SZ based on age, gender, and baseline level of PA. The HV receive the same interventions as the corresponding SZ.

Ethics and regulatory considerations

Written informed consent is obtained from all participants before their inclusion. The protocol was approved by Health Authorities (ANSM;AgenceNationale de Sécurité du Médicament et des produits de santé) on 19 July 2016 (ID-RCB number 2016-A00930-51) and by the ethical committee (Comité de Protection des Personnes, CPP Nord-Ouest IV, France) on 10 January 2017 (CCP16/39) in compliance with French regulations. The trial was registered at ClinicalTrial.gov on 25 August 2017 (NCT03261817).

Recruitment and randomization

Forty-two SZ will be recruited in two centers from Caen (Principal Investigator (PI): Sonia Dollfus) and Rouen

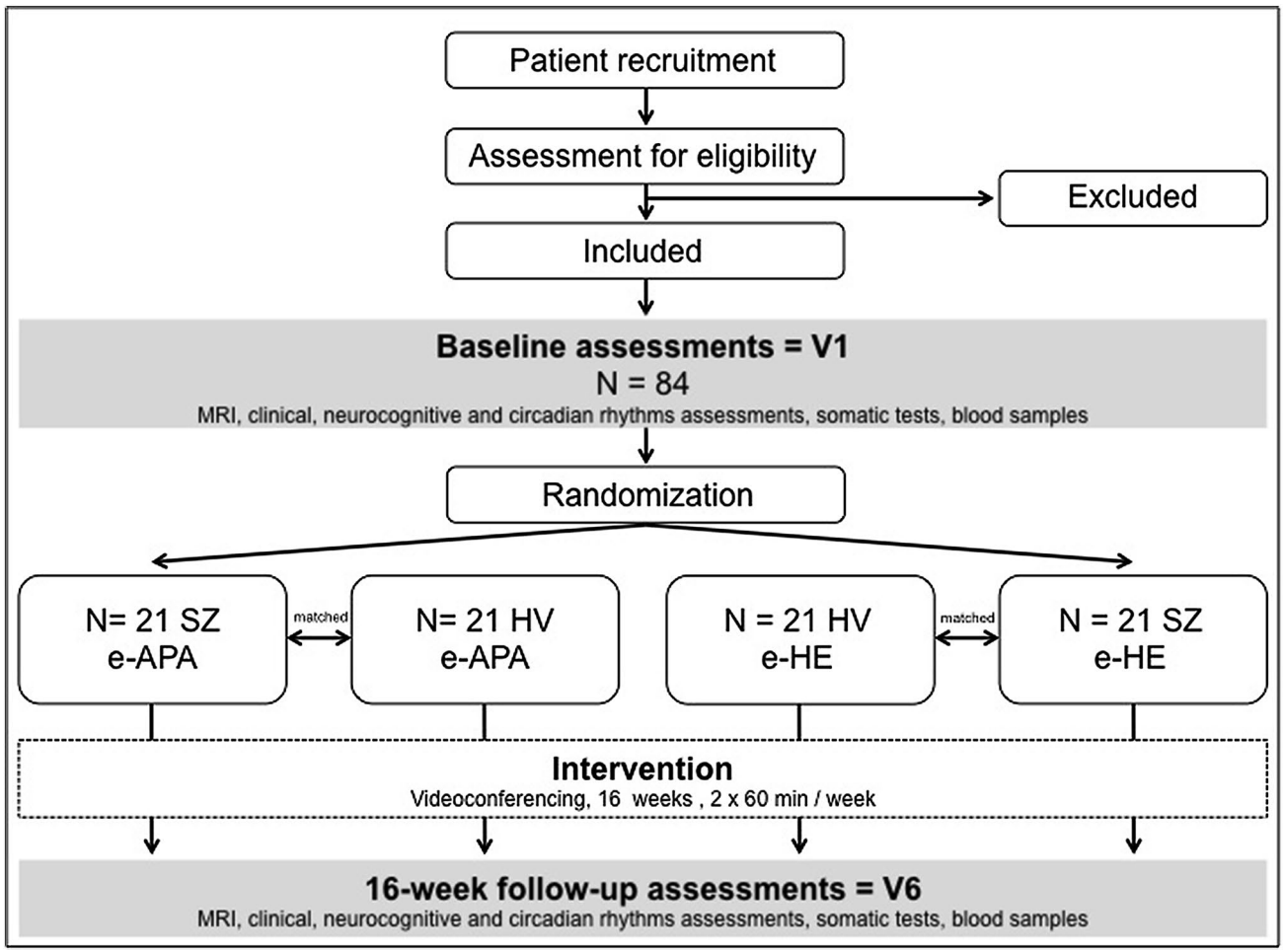

Fig. 1 Participant flow chart. *e-APA* electronic adapted physical activity program, *e-HE* electronic health education program, *HV* healthy volunteers, *MRI* magnetic resonance imaging, *SZ* patients with schizophrenia

University Hospitals (PI: Olivier Guillin) (France). SZ are diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 4th edition, text revision) criteria with the structured Mini-International Neuropsychiatric Interview (MINI, French version 5.0.0). All patients are stabilized outpatients with no change in their treatment over the past 2 months prior to their inclusion.

Forty-two HV are recruited from the general community in Caen via an announcement broadcast by press, posting or mailing.

For both groups, clinicians assess the subject's eligibility and provide to each subject and to the patient's legal representative comprehensive verbal and written information regarding the objectives and procedures of the study as well as the possible risks.

A signed informed consent is obtained from each participant and/or legal representative for SZ prior to undertaking any study-related procedure. SZ who do not wish to take part in the study will continue to undergo treatment as usual.

Inclusion and exclusion criteria are presented in Table 1 for SZ and in Table 2 for HV.

Table 1 Inclusion and exclusion criteria for patients with schizophrenia (SZ)

Inclusion criteria
Age between 18 and 60 years old
Fulfill the DSM-IV-TR criteria for schizophrenia or schizoaffective disorders
Possibility of receiving both interventions (e-APA or e-HE): having a computer, a web connection, and a webcam
No change in psychotropic drugs during the 2 months prior to inclusion
Signed and informed consent
The need to be affiliated with medical welfare
The agreement of the guardian or trustee in case of a protected major
Exclusion criteria
Age under 18 or over 60 years old
Pregnancy
Inclusion in another biomedical research protocol (during the present study)
Contraindications to MRI
Progressive neurological diseases
Physical contraindication to physical activity (moderate to severe heart failure, severe valvular disease, unstable coronary disease, acute pulmonary embolism or untreated deep venous thrombosis, uncontrolled hypertension, pulmonary arterial hypertension, or treaty)
Neuromuscular pathologies, severe sensory and/or motor neuropathy
Rheumatic and articular pathologies; rheumatologic/orthopedic problems or bone lesions at risk of fracture contraindicating physical activity
History of stroke or myocardial infarction less than 6 months prior to the selection visit

DSM-IV-TR Diagnosis and Statistical Manual of Mental Disorders, 4th edition, text revision, *e-APA* electronic adapted physical activity program, *e-HE* electronic health education program, *HE* health education program, *MRI* magnetic resonance imaging

Table 2 Inclusion and exclusion criteria for healthy volunteers (HV)

Inclusion criteria
Age between 18 and 60 years old
Possibility of receiving both interventions (e-APA or e-HE): having a computer, a web connection, and a webcam
Signed and informed consent
The need to be affiliated with medical welfare
Exclusion criteria
Age under 18 or over 60 years old
Pregnancy
Life-long schizophrenia or schizoaffective disorder according to the DSM-IV-TR criteria
Inclusion in another biomedical research protocol (during the present study)
Contraindications to MRI
Progressive neurological diseases
Physical contraindication to physical activity (moderate to severe heart failure, severe valvular disease, unstable coronary disease, acute pulmonary embolism or untreated deep venous thrombosis, uncontrolled hypertension, pulmonary arterial hypertension, or treaty)
Neuromuscular pathologies, severe sensory and/or motor neuropathy
Rheumatic and articular pathologies; rheumatologic/orthopedic problems or bone lesions at risk of fracture contraindicating physical activity
History of stroke or myocardial infarction less than 6 months prior to the selection visit

DSM-IV-TR Diagnosis and Statistical Manual of Mental Disorders, 4th edition, text revision, *e-APA* electronic adapted physical activity program, *e-HE* electronic health education program, *MRI* magnetic resonance imaging

Randomization is established only for eligible patients and is performed at a 1:1 ratio by a central computer-assisted procedure centralized at the PEPSY V@Si data center (Ennov Clinical Software®). SZ are assigned either to the active group (e-APA) or to the non-active control group (e-HE). HV are recruited and matched to SZ based on age, gender and physical activity level according to the Ricci and Gagnon self-questionnaire [56].

Intervention/study protocol

In this study, each intervention delivered, carried out or received electronically is called an "e-intervention". Both interventional activities, e-APA and e-HE, are delivered via videoconferencing using a secure web-based platform named SAPATIC® (Santé Activités Physiques Adaptées utilisant les Technologies de l'Information et de la Communication), allowing real-time verbal and visual interactions between participants and professional trainers/researchers, reproducing face-to-face interventions. All participants' data are hosted on a HADS server (Hébergeur Agrée de Données de Santé). All participants are able to connect to the platform at home or in a connected room in ambulatory care services. Both groups spend the same amount of time with the intervention staff, and a specific time schedule is followed to ensure that each session lasts 60 min. Participants receive 2 sessions per week for 16 weeks for a total of 32 sessions.

The intervention in both groups begins with a motivational interview for increasing e-APA or e-HE participation. In the e-APA group, the motivational interview allows the professional to better understand the expectations of participants in terms of PA.

SZ assigned to the active or to the non-active control group receive their usual medications during the 16-week program.

Active group

For all participants (SZ and HV) assigned to the active group, e-APA sessions are implemented in addition to daily life activities.

The e-APA program, which was designed according to World Health Organization (WHO) and the American College of Sports Medicine (ACSM) guidelines [57], is individually supervised by qualified APA professional trainers from the Mooven company selected from a list of certified professionals chosen for the study. Physical exercises are individualized and adapted for each participant according to standardized guidelines and to his/her sporting past, treatment, preferences and fitness level (estimated by the Global Physical Activity Questionnaire—GPAQ) [58], baseline maximal exercise test and maximal strength test. Exercises are conducted at a moderate to vigorous intensity (60 to 75% of maximal heart rate based on participant's baseline maximal exercise test), which is assessed through real-time heart rate monitoring using cardiac sensors (Zephyr BioHarness® or OnRythm 500®). Exercises are performed with an intensity that allows the participant to speak with moderate breathlessness.

Three different types of exercises are proposed to participants: (1) predominantly aerobic exercises (i.e., run/walk on the spot, jumping jacks, step, or dance); (2) resistance exercises to maintain or increase arm, leg and whole-body muscle strength (i.e., series of ventral/back/side plank, burpees, wall sit, crunches, pumps, lunges, squats, or front/side raises using dumbbells or bottles of water); and (3) balance exercises combining flexibility and coordination (i.e., ventral plank, tightrope walk, heel-to-toe walk, rock the boat, banded triplanar toe taps, single-leg cross-body punches, or standing crunch with under-the-leg clap) based on WHO and ACSM guidelines. The number of repetitions and the difficulty of the exercise are gradually increased during the sessions and are modulated according to the participant's capacities at the time of the exercises. Activity difficulty is increased in duration, then frequency, and ultimately intensity only if the participant tolerates previous increases. Heart rate, perceived exertion as assessed by the Borg Rating of Perceived Exertion Scale [59], and perceived dyspnea (visual analogue scale) evaluated at each session are the three indicators that allow the professional to ensure that work is performed at the targeted intensity while respecting the participant's tolerance.

Each 60-min APA session is composed of a verbal contact sequence; warm-up exercises (5–10 min); aerobic, resistance or balance exercises (40 min); a cool-down period (5–10 min); and finally a verbal feedback sequence. The warm-up and recuperation periods and verbal sequences account for at least 30% of the session duration. During the e-APA program, participants are asked to estimate their dyspnea (on a visual analogue scale) and their perception of effort and muscle pain in the pre- and post-session periods and record this information in a dedicated activity digital booklet on the SAPATIC platform. This booklet can be used to help participants recall exercises performed and difficulties encountered. Real-time videoconferencing and heart rate monitoring allows the professional to assess the participant's tolerance and difficulties in completing the targeted PA level during aerobic training, resistance exercises, and balance exercises.

Non-active control group

Participants (SZ and HV) assigned to the non-active control group receive an e-HE program, including web-delivered information on the main mental illnesses, the benefits of physical activity, healthy lifestyles (dietary balance, sleep

cycle, stress management), alcohol, drug, tobacco and cardiovascular risk factors. This program is conducted under the same conditions (duration and frequency) as the active group. Individual training of participants in the e-HE group is performed by researchers (EL, LB, MT, and SJ).

The 50-min training is followed by a 10-min quiz to assess participant involvement in the course.

Assessments

All participants (SZ and HV) are assessed for the primary endpoint at the start (baseline assessment, visit 1) and at the end of the intervention (the 16-week follow-up assessment, visit 6). Other visits are conducted between V1 and V6 to assess secondary endpoints.

The first assessment occurs at baseline (V1) prior to randomization. The final assessment occurs after completion of the 16-week intervention (V6). Other visits occur during the intervention (V2, V3, V4, and V5). The content of all assessments is outlined in Table 3.

Primary endpoint

The primary outcome is the change in left and right hippocampal volumes between V1 and V6. Neuroimaging data are acquired on a 3T scanner (InteraAchieva 3T Quasar Dual, Philips Medical System, Netherlands) at V1 and V6. A proton density-weighted T_2 image focalized on the hippocampus is acquired using anatomical MRI (aMRI).

Secondary endpoints

The secondary outcomes are recorded at 6 visits (V1–V6) (see Table 3).

Neuroimaging

Volumetric changes in the different subregions of the hippocampus are assessed from proton density-weighted T_2 images using hippocampal subfields segmentation in the left and right CA1-4, SUB, DG, miscellaneous (MISC), entorhinal cortex (ERC), Brodmann area 35 and 36 (BA 35, 36), and collateral sulcus (CS) as described elsewhere [60]. NAA in the hippocampi is assessed using magnetic resonance spectroscopy. The integrity of white matter is assessed through diffusion parameters using diffusion tensor imaging.

Neurocognitive tests

Episodic and/or working memory are assessed using the Wechsler Adult Intelligence Scale (WAIS) Memory subtest [61, 62], the Rey Auditory Verbal Learning Test (RAVLT) [63] and the Corsi test [62]. Attentional functions are assessed using the Stroop test [64] and the WAIS Coding subtest. Executive functions are assessed using the Trail Making Test (TMT) [65], the d2 test [66] and the verbal fluency test [67].

Clinical symptoms and psychoactive substance use

Psychotic and affective symptoms are assessed using the Positive and Negative Syndrome Scale (PANSS) [68], Self-evaluation of Negative Symptoms (SNS) [69], Brief Negative Syndrome Scale (BNSS) [70], and Hospital Anxiety and Depression Scale (HADS) [71]. General symptoms are appraised using the Clinical Global Impression scale (CGI) [72]. Insight of illness is evaluated using the Insight Scale (IS) [73]. The Social Adjustment Scale Self-Report (SAS-SR) [74] provides an understanding of an individual's level of satisfaction with his or her social situation.

Ryff's Psychological Well-Being Scale (PWB) [75] evaluates the participant's psychological well-being through six dimensions (autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance).

The severity of alcohol use is appraised using the Alcohol Use Disorders Identification Test (AUDIT) [76]. Participants are also asked about current or past tobacco consumption, their desire to quit tobacco and their degree of dependence according to the Fagerström test for Nicotine Dependence [77]. The use of cannabis is assessed by the Cannabis Abuse Screening Test (CAST) [78].

Biological data

Fasting blood exams are performed to measure the level of fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDLc), and low-density lipoprotein cholesterol (LDLc).

Cardiorespiratory fitness

Maximal oxygen uptake ($V0_2max$) is measured at V1 and V6 during a maximal exercise test on an electromagnetic bicycle ergometer (Ergoline er900®). The exercise test is triangular by direct measurement. Participants have to pedal as long as possible while the load is increasing by 20 watts every 2 min. Developed power, O_2 and CO_2 flow rates are recorded before the beginning of the test (resting values), at each level (relative values), until the end of the test (maximal values) and during the following 3 min of passive recovery (recovery values). Heart rate and electrocardiogram are also recorded continuously, and blood pressure is recorded at the end of each level. The ventilatory regime and gas exchange are measured cycle to cycle continuously with a

Table 3 Assessments during the PEPSY V@Si trial

VISITS		V1		V2	V3	V4	V5	V6	V7
TIME POINT (days)	D-15	D-14 to D0	D-7	D0	D30 ± 4 d	D56 ± 4 d	D90 ± 4 d	D120 ± 8 d	D127 ± 2 d
ENROLLMENT									
MINI diagnosis	x								
Eligibility screen	x								
Pregnancy test	x								
Informed consent	x								
Sociodemographic data	x								
Ricci and Gagnon self-questionnaire	x								
Randomization			x						
INTERVENTION									
e-APA				x →	→	→	→	→	
e-HE				x →	→	→	→	→	
ASSESSMENTS									
Concomitant treatments	x	x	x	x		x	x	x	x
Adverse events collection	x	x	x	x		x	x	x	
Physical examinations (blood pressure, heart rate, weight, BMI, waist circumference)	x					x		x	
Blood analyses (fasting glucose, triglycerides, total cholesterol, HDLc, LDLc)	x							x	
Neurocognitive tests (TMT, Stroop test, WAIS Coding subtest, WAIS Memory subtest, RAVLT, d2 test, verbal fluency, Corsi test)	x							x	
Clinical self-evaluations (HADS, SAS-SR, Ryff, Diener, ISP-25, MFI-20, BREQ-2, AUDIT, CAST, Fagerström, Pichot, Epworth)	x					x		x	
Clinical heteroevaluations for SZ only (PANSS, CGI)	x				x	x	x	x	x
Clinical evaluations for SZ only (BNSS, SNS, IS)	x					x		x	
Circadian typology questionnaire	x							x	
GPAQ	x							x	
24-h body temperature			x^1	x^2				x^1	x^2
Actimetry			x^3	x^4				x^3	x^4
Sleep schedule			x^3	x^4				x^3	x^4
MRI		x						x	
Exercise test and electrocardiogram		x						x	
Body composition assessment (bioelectrical impedance analysis)		x						x	
Muscle strength assessment (handgrip)	x							x	

x^1: capsule ingestion, delivery of the temperature monitor; x^2: capsule fecal elimination, return of the temperature monitor; x^3: delivery of actimetry sensor and sleep schedule; x^4: return of the actimetry sensor and sleep schedule after one-week recording

BMI body mass index, *BNSS* Brief Negative Syndrome Scale; *BREQ-2* Behavioral Regulation Exercise Questionnaire; *CGI* Clinical Global Inventory, *D* day, *e-APA* electronic adapted physical activity program, *e-HE* electronic health education program, *GPAQ* Global Physical Activity Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *HE* health education program, *IS* Insight Scale, *MFI-20* Multidimensional Fatigue Inventory, *MINI* Mini-International Neuropsychiatric Interview, *PANSS* Positive And Negative Syndrome Scale, *RAVLT* Rey Auditory Verbal Learning Test, *SNS* Self-Assessment of Negative Symptoms, *TMT* Trail-Making Test, *WAIS* Wechsler Adult Intelligence Scale, *SAS-SR* Social Adjustment Scale-Self Report, *SZ* patient with schizophrenia

pneumotachograph. Parameters, such as ventilation, oxygen consumption and respiratory quotient, are recorded.

Body composition and muscle strength

Body composition assessment is performed using the BIA101® impedance analyzer, which measures body impedance using four electrodes (two on the right wrist and two on the right ankle).

Evaluation of maximal muscle strength is recorded with a hand dynamometer (model TK-200®). The force developed in isometry by the upper limbs (the gripping force of the hand) is analyzed. Three successive measurements are collected in a standardized position for each arm, consisting of an orthostatic position with their arm at the side and the instrument held in the extension of the forearm.

Motor activity and circadian rhythms

Actimetry recording is performed continuously for 7 days at baseline (V1) and after the 16-week intervention (V6) using a lightweight, autonomous and waterproof actimeter (e-tact actimeter®, BodyCap, France). The following parameters are analyzed using ACTISOMM® software [79]: duration of total night rest period; duration of the total period of daytime activity; average night activity; average daytime activity; magnitude, mesor and acrophase of circadian rhythms of motor activity; and night inactivity index (%) (corresponding to the number of minutes where the amount of movement is zero, divided by the number of minutes of the night). Coupled with the sleep schedule, the data allow us to analyze the sleep/wake cycle.

In addition, circadian rhythmicity dysregulation has been reported in SZ and manifests as alterations in the sleep–wake cycle, core body temperature cycle and rhythmic hormonal profiles (i.e., cortisol and melatonin) [80, 81]. It has been described that PA could positively impact sleep cycles in the general population [82, 83] and in SZ [8, 9]. However, it is still difficult to understand exactly how PA impacts sleep and vice versa. Sleep and PA could influence each other through complex and reciprocal interactions involving multiple physiological and psychological pathways, i.e., thermoregulation [83]. Thus, core body temperature is recorded via the gastrointestinal tract using the e-Celsius® performance telemetry system (BodyCap, France) before and after the intervention program. The temperature is recorded from ingestion until fecal elimination of the capsule. This device consists of a portable monitor that allows the continuous collection and recording of internal temperature data. This electronic capsule, which is packaged in a biocompatible PVC (polycarbonate) envelope, includes a temperature sensor that measures the gastrointestinal temperature every 30 s. The temperature data are then transmitted by telemetry to the monitor, which records them in real time.

Sample size calculations

The number of participants to be included takes into account the risk of participants being lost to follow-up. Based on preliminary and comparable studies (12-week PA program in SZ), one could estimate that 20% of participants would discontinue the protocol prematurely [84].

Given the literature regarding the impact of PA on hippocampal volume in SZ [24], a difference of 6% between mean volume changes (as a percentage of total brain volume) between groups with and without PA for a standard deviation of hippocampal volume(s) of 8% is quite conceivable and clinically relevant based on Pajonk's study [24]. The standard deviation (Sv) of the change in hippocampal volume(s) is estimated at 5% ($\sqrt{2(s)^2-(1-r)}$) based on a correlation coefficient ($r \geq 0.8$) between baseline assessments (V1) and at the end of PA program.

For an alpha risk of 5% and a power of 80%, the number of subjects required was calculated using version 3.1.9.2 of the G * Power software and was equal to 10 [85]. Given the small number of participants and the possibility that the distribution of changes in relative hippocampal volumes is not normal, a Mann–Whitney test can be used. In this case, a correction must be made using the ARE (asymptotic relative efficiency) of the Mann–Whitney test in relation to the Student's test based the following ratio: $10/0.864 \approx 15$, i.e., the number of participants to be included per group. It is customary to consider a 20% increase in those lost to follow-up, so the number of participants would be 18 per group. Our inclusion capacity is higher, and to ensure that tests for the secondary objectives will be performed, 84 participants are included (21 for each of the 4 groups).

Statistical analysis

To meet the main objective, Student's *t*-test will be used to determine whether the averages of two samples are significantly different (SZ_e-APA vs. SZ_e-HE). In the first step to analyze primary and secondary outcomes, analyses of covariance (ANCOVAs) will be computed between the four groups of participant (SZ_e-APA vs. SZ_e-HE vs. HV_e-APA vs. HV_e-HE). Primary or secondary outcomes will be considered as the dependent variable, and the group will serve as the independent variable. In the second step, gender and age will be included as covariates in the analyses. Post hoc analyses will be conducted when a significant main effect is observed using a Tukey's HSD test to correct for multiple comparisons. We will also conduct intragroup Pearson correlation analyses in the SZ groups to evaluate the relationships among neuroimaging, physiological data with clinical, neurocognitive data

and medication. The same correlations will be tested in the HV group with the exception of medication. The correlations will be considered statistically significant after adjustment for multiple comparisons. All statistical analyses will be performed with JMP v12.0 Software (SAS Institute, Inc., Cary, NC) or IBM®-SPSS® 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Statistical analyses with a significance level at $P < 0.05$ will be associated with effect size calculations [86–88].

Study outings before the start or the beginning of interventions (e-APA or e-HE) before the 10th session are systematically replaced. Study outings after the 10th session are not replaced. Any participant who prematurely leaves the program after the 10th session and before the end of the study benefits for all the examinations planned at the end of the study. Causes of nonobservances are analyzed and listed. Rates and reasons for prematurely leaving the study are analyzed in relation to their impact on the obtained results. In cases of premature study departure, data are collected in the CRF at the time of the event and are taken into account in the analysis of the primary outcome (hippocampal volumes) if the number of planned sessions exceeds 75% (24 sessions or more). Analyses will be conducted for the intention to treat and will concern all of the variables. Participants are considered non-compliant if absent from 4 consecutive sessions.

Data management and monitoring

Data are initially collected and anonymously registered using paper forms (case report form, CRF), which are then be securely stored and extracted into protected electronic files (e-CRF) in Ennov Clinical Software®.

The medical procedures used in this trial comply with the most recent recommendations of the Declaration of Helsinki and French Public Health Law 2004-806 of 9 August 2004 on participant protection and safety in accordance with good clinical practice. A data manager mandated by the promotor (CHU de Caen, Avenue de la Côte de Nacre, CS30001, Caen, France) ensures monitoring of this trial to guarantee that accurate, full, and reliable data are collected.

Safety and emergency procedures

All adverse events (AEs) reported by participants or observed by clinicians and APA professionals are recorded. All serious AEs are reported to the ANSM.

Discussion

Through this study, we will aim to demonstrate the benefits of a remote, web-based APA video conferencing program (e-APA) in patients with schizophrenia. This type of APA program has never been investigated in SZ. The trial consists of an interventional randomized controlled study designed to examine whether a 16-week APA program delivered via web-based videoconferencing (e-APA) improves cerebral, clinical, neurocognitive, biological and physiological variables in SZ compared to those in a non-active controlled group (e-HE) that also receives web-based videoconferencing. We hypothesize that the e-APA program may benefit hippocampal plasticity and schizophrenia-related symptoms.

Considered as an adjunctive treatment in curative and supportive interventions, APA is an original and promising nonpharmaceutical strategy that may help to better manage symptoms and health concerns in SZ [41, 89]. APA is cost effective, feasible and efficient method used to address various symptomatic features and provide cardiovascular prevention of vulnerable and sedentary populations such as SZ. Patients with severe mental illness, such as SZ, often exhibit poor adherence to treatment and PA recommendations, limiting their recovery, functional outcomes and improvements in general health [42, 82]. The use of e-technologies may bypass many barriers to PA practice in this population and enhance the engagement and participation of patients in PA programs in clinical practice [90–92].

There are several originalities in this study. First, regarding the methodology of the randomized controlled trial, we used a non-active control group (e-HE) to explore whether the active intervention could improve brain plasticity, symptoms and physical concerns compared with non-active intervention. Exploring the brain with multimodal MRI could allow us to best identify how APA impacts the brain by assessing structural (gray and white matter), functional and anatomical connectivity as well as the metabolic and arterial flow of the brain. Moreover, comparing SZ and HV will allow us to determine whether the expected benefits on brain plasticity and other variables occur in both groups or whether the effects of PA in SZ are attenuated. This notion is in line with previous studies, but the effects have not been completely elucidated to date [27, 93]. Second, both interventions are delivered by qualified professionals in real time using interactive videoconferencing, reproducing face-to-face interventions and allowing participants and professionals to see each other with the aim to reinforce the participants' motivation. Videoconferencing allows participants to see themselves through the screen and instantaneously correct the movements if they are poorly executed. Finally, it allows the professional to interact and reassure the patient to decrease the level of anxiety. The self-image causes a reappropriation of one's body to a body that is capable of doing (self-confidence). The use of e-technologies and videoconferencing may also facilitate participation in PA over the long term. Moreover, it will enable participants to approach the intervention at their own pace and to overcome barriers towards regular PA without geographical limits. Third, the

e-APA intervention will consist of adapted exercises that will simultaneously allow the participant to control commitment to practice and provide constant metabolic expenditure measures (cardiac monitoring) to foster participant motivation and adapt the program to the specific needs of each participant while standardizing the program. Fourth, many variables that have never been simultaneously explored before in SZ, such as multimodal imaging data along with clinical, cognitive, biological, physiological and circadian rhythms assessments, are investigated in this study. Finally, findings from this study will add to the growing scientific literature on the impact of PA in SZ. Furthermore, the study results may have clinical implications for the improvement of the multimodal management of SZ and other severe mental illnesses.

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Authors' contributions MT: participation in HE program conception and dispensation, subject recruitment, participant assessments, MRI assessments, data analysis, and manuscript drafting and revision. EL: HE program conception and dispensation, subject recruitment, MRI assessments, imaging pre- and postprocessing, data analysis, neurocognitive assessments, and manuscript revision. SJ: HE program conception and dispensation and neurocognitive assessments. PL: methods on the evaluation of APA. LB: APA video conferencing and SAPATIC platform management, participation in HE and APA program conception, and manuscript revision. AH: study conception and design, APA program conception, and SAPATIC platform conception and management. ER: exercise test dispensation. RM: methodological conception and manuscript revision. PAC: e-Celcius and Zephyr BioHarness® management. GQ: study conception and design, circadian data analysis, and manuscript revision. SD: study conception and design, principal investigator, patient recruitment, participant assessments, MRI assessments, data analysis, and manuscript revision. All authors have read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest MT participated in educational conferences for the following industrial laboratories: Otsuka, Lundbeck, and Janssen. SD has been an expert and consultant or participated in educational conferences for the following industrial laboratories or companies: Gedeon Richter, Lundbeck Otsuka, Roche, Takeda, Fabre, Janssen, ONO Pharma and Verasci. She also has a license agreement on SNS with MedAvante-ProPhase. EL, SJ, PL, ER, RM and GQ have no competing conflicts. AH is the manager of the V@Si company, and LB is employed by V@Si. PA is employed by Bodycap Company.

Ethical approval The protocol was submitted to the French Health Authority, namely, the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM), for formal approval to conduct the study conduct and to ensure that the study meets the local regulations of a properly constituted Ethics Committee. The project was approved by Health Authorities (ANSM) on 19 July 2016 (ID-RCB number 2016-A00930-51) and by the local ethical committee (Comité de Protection des Personnes, CPP Nord-Ouest IV, France) on 10 January 2017 in compliance with French regulations. The trial was registered at ClinicalTrial.gov on 25 August 2017 (NCT03261817). Initial information about the study is given to eligible participants by the regular staff during a routine appointment or by coworkers. Further detailed written and oral information about the trial are then provided by the project coworker. Voluntary participation is assured, and participants can withdraw at any time and receive standard treatment regardless of whether they choose to participate. Each participant provides written informed consent before any intervention is started.

Trial status The current PEPSYV@SI protocol version is 5 dated 6 March 2018. The first participant was recruited in September 2017, and the study is currently enrolling participants. The study is expected to be completed in December 2021.

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