ABSTRACT
Introduction Recent studies on cognitive training in patients with Alzheimer’s disease (AD) showed positive long-term effects on cognition and daily living, suggesting remote computer-based programmes to increase training sessions while reducing patient’s travelling. The aim of this study is to examine short-term and long-term benefits of computer-based cognitive training at home in patients with mild to moderate AD, as a complement to the training in speech and language therapists’ (SLT) offices. The secondary purpose is to study training frequency required to obtain noticeable effects.

Methods and analyses This is a national multicentre study, conducted in SLT offices. The patients follow training in one of three conditions: once a week in SLT office only (regular condition) and once a week in SLT office plus one or three times per week at home. The trainings’ content in SLT office and at home is identical. For all three groups near and far transfer will be compared with evaluate training frequency’s effect. Our primary outcome is executive and working memory scores in experimental tasks, and the secondary is neuropsychological tests and questionnaires’ scores. Linear models’ analyses are considered for all measures with a random intercept for patients and another for per practice. The fixed effects will be: three modality groups and time, repeated measures, (T0—pretraining, T1—post-training, T2—long-term follow-up) and the interaction pairs.

Ethics and dissemination The study got ethics approval of the national ethical committee CPP Sud Méditerranée III (No 2019-A00458-49) and of the National Commission for Information Technology and Liberties (No 919217). Informed consent is obtained from each participant. Results will be disseminated in oral communications or posters in international conferences and published in scientific journals.

Trial registration number NCT04010175.

INTRODUCTION
Considering increasing occurrence of neurodegenerative disorders in the older adults, such as Alzheimer’s disease (AD), and in the absence of effective drug treatment, cognitive training appears to be a promising alternative in healthy and pathological ageing for improving cognitive functioning and quality of life. For some researchers cognitive training is also an added value to drug treatment, as it has been observed to enhance the expression of drug effects.

The efficacy of cognitive training in patients with AD is still under the debate, especially regarding the best methodological approaches to optimise the training outcomes, including training feasibility, patient commitment and motivation. The computer-based cognitive training (CBCT) seems to have several advantages as it provides wide variety of well-calibrated exercises and allows, for example, to easily adapt their difficulty to each patient. The short-term and long-term benefits of CBCT were first shown in healthy older adults, but have also been proven in patients with AD and MCI (Mild Cognitive Impairment).

Several studies have highlighted the importance of some criteria that are essential for successful training, whatever its type. Overall, studies recommend early intervention with sessions between 30 min and 1 hour and session’s frequency of several times a week.
Such a design is supposed to maintain strong commitment and motivation throughout the training, which is essential for its effectiveness. However, these recommendations face some important problems that make their application difficult. First, few people are concerned about small changes in performance, the majority will only consult when symptoms become more pronounced, which prevents the early intervention suggested by several authors. Second, involving patients in high-frequency cognitive training protocols faces several difficulties, the most important of which is frequent travel between home and speech and language therapist’s office (SLT). As the disease progresses, autonomy is compromised, and the need of a caregiver’s assistance is an additional difficulty. In addition, the change of seasons brings many health problems that interfere with training and often lead to interruptions. One way of circumventing these problems would be to offer a CBCT including some sessions at home.

Our main hypothesis is that remote cognitive training using computer-based programmes is an effective way to increase the cognitive and psychological benefits of training as an outcome of training. We also hypothesised that more frequent training (eg, several times per week) should bring greater benefits than training performed once a week.

The primary objective of this study is to examine the short-term and long-term benefits of at home CBCT as a complement to in-office CBCT in patients with mild to moderate AD. The secondary objective is to evaluate the best frequency of the at home training. To do this, we administer CBCT for 4 months under three conditions: (1) in SLT’s office once a week, (2) in SLT’s office once a week plus once at home and (3) in SLT’s office once a week plus three times at home.

METHOD
Design
This is an experimental study with minimal risks, with three parallel groups, namely the training group at the SLT’s office only (REG—regular group), the group at the SLT’s office plus one session per week at home (MFG—moderate frequency group) and the group at the SLT’s office plus three session per week at home (HFG—high frequency group). Patients will be included for 2 years, starting on 1 September 2020 and ending on 1 September 2022. For each participant, the inclusion period is approximately 8 months. During this period, participants cannot be included in other protocols that may influence their cognitive or emotional functions. Patients and their caregivers are informed of this point before signing the informed consent and the SLTs are asked to monitor them throughout the protocol. The total duration of the study is 32 months. All inclusions and testing will be carried out in SLT offices. The training will be done in SLT offices and at patients’ homes (see figure 1 for a study design). The content of the training in SLT office and at home is identical.

This study obtained the authorisation of the national ethical committee CPP Sud Méditerranée III (No 2019-A00458-49, version 5 from 18 November 2019) and of the National Commission for Information Technology and Liberties (No 919217).

Patient and public involvement
Patient and public were not involved.

Participants
This study concerns people 60 years or older with a diagnosis of prodromal to moderate AD. To recruit participants, we contacted SLTs subscribers to SBT’s Happyneuron Pro digital tools through the SBT Humans Matter company network. They first answered a questionnaire to identify SLTs practicing with patients with AD. These SLT received a letter of invitation to participate in our study. Eventually, 27 SLTs from different regions of France joined the study and become clinical investigation centres. A complete list of these SLTs can be obtained from the Department of Clinical Research and Innovation of the Hospices Civils of Lyon (Direction de la Recherche Clinique, Hospice Civil de Lyon. 3, quai des Célestins, 69229 Lyon Cedex 2). Each SLT is responsible for presenting the study in his or her office to patients whose profile matches our inclusion criteria (for details on eligibility criteria see box 1). Interested patients will receive the information and consent leaflets. At the next visit, they are asked if they

Figure 1 Illustrating on the time axis the evolution of the experiment with the facts marked on a weekly basis trainings take place between the second and the 17th week for the three training groups simultaneously. D, day; HFG, high frequency group; MHG, moderate frequency group; REG, regular group; T, time of assessment; V, visit; W, week.
Box 1  Eligibility criteria

Inclusion criteria
1. Age ≥60 years.
2. Native French speaker.
3. Diagnosis of Alzheimer’s disease according to the DSM V (Diagnostic and Statistical Manual of Mental Disorders 5th Edition) criteria.
4. Mild to moderate cognitive impairment as stage of disease progression (Mini-Mental State Examination score superior to 15).
5. Unchanged psychotropic treatment in the month prior to inclusion.
6. Signed informed consent for a participation to the study (personally or by a legal representative).

Exclusion criteria
1. Uncorrected vision or hearing impairments.
2. Motor dysfunction symptoms that could prevent the tests from being carried out.
3. Not having a computer preventing cognitive training at home.
4. Receiving speech and language therapists care for more than 3 months.
5. Refusal to participate in the study.
6. Being under guardianship or curatorship.

Eligibility
The eligibility criteria are presented in box 1.

Withdrawal criteria
Each patient is free to withdraw from the study at any time without giving reasons, simply by informing one of the investigators. In case of withdrawn of consent, the data collected up to the date of withdrawal will be analysed.

Randomisation and pseudonymisation method
To avoid any unequal treatment of patients in the same SLT, we decided to randomise SLTs’ offices into different training groups, instead of randomising the patients. Thus, each office will be assigned to one of the training groups and all patients included in that SLT office will follow the same training procedure (REG, MFG or HFG). Offices will be allocated to each group in a balanced way in terms of sociodemographic considerations, depending on their geographical location. This allocation will be done by a manager from the SBT research and development department before the study beginning. If, despite randomisation, an imbalance occurs within groups due to interindividual differences such as age, gender, education and disease severity, these factors will be considered as covariates in the analysis of results.

Each patient will receive a pseudonymised number consisting of, in order, of the number of the investigating centre, the inclusion number for this centre and the patient’s initials. The SLT will keep the table of correspondence between this number and the first and last name, as well as the address and telephone number for all patients included in his/her centre.

Procedure
Our study follows a conventional protocol used to evaluate the cognitive and psychological benefits of cognitive training27 (see figure 1 and table 1 for details). Each patient will be seen 21 times (visit 1 to visit 21).

| Table 1  | The main steps of the protocol process with the timetable |
|----------|----------------------------------------------------------|
| Steps    | V0 Preinclusion  | V1 Inclusion  | V2 Assessment T0 | V3–V19 Training | V20 Assessment T1 | V21 Assessment T2 |
| Time/Actions | D-30 à D-15 | D0 | W1 | W2–W17 | W18 | W30 |
| Allocation | X | | | | | |
| Eligibility screen | X | | | | | |
| Study presentation to the patient | X | | | | | |
| Signature of the informed consent | X | | | | | |
| Assessments (Neuropsychological tests, questionnaires and experimental tasks) | X | X | X | X | X |
| Cognitive training | | | | | | |
| Group REG | | | | X | | |
| Group HFG | | | | X | | |
| Group MFG | | | | X | | |
| Collection of adverse events | X | X | X | X | X |

D, day; HFG, high frequency group; MHG, moderate frequency group; REG, regular group; T, time of assessment; V, visit; W, week.
The content of each visit is described here below. Prior to inclusion, patients likely to take part in the study will be identified in the SLT offices as part of their regular care. They will be informed by the SLT, coinvestigator, about the study. The patient will be given any explanation necessary for a good understanding of the study, as well as an information letter explaining the objectives and the course of the protocol. The SLT will also give the patient a consent form in duplicate. The patient will have 1 week to decide whether to take part in the study.

Inclusion visit: V1
If the patient agrees to take part in the study, the volunteer and the SLT (by delegation) will date and sign two copies of the consent form (one will be kept by the patient, the other will be kept by the SLT).

Assessment visit: pretraining: V2
During this visit, patients will undergo a series of experimental tasks, neuropsychological tests and questionnaires that will serve as a baseline for our primary and secondary outcomes measures of training effectiveness.

Training visits: V3–V19
Visits 3–19 will be devoted to training. These visits will be carried out at a frequency of once a week, preferably on fixed days±1 day. The patient will perform a series of short training exercises involving memory, executive functions, processing speed, visuospatial abilities for approximately 45 min using the Happyneuron Professional software (https://www.happyneuronpro.com). The number and nature of the training sessions will be identical for all participants. However, the difficulty will be adapted automatically by the software according to the patient’s state and, second, to measure the benefit of training by comparing the pretraining results (T0) with those obtained immediately after the end of the training (T1) and 3 months later (T2).

For all groups the SLT will, if possible, designate a fixed day of the week for in-office training. If the patient misses this day, it will be rescheduled, if possible, to another day of the same week. For the HFG and MFG groups which are to train at home, the SLT will schedule the day(s) for trainings at home and patients and their caregivers will receive the email on the morning of the training day. If, despite of this, patient forgets to train they will be allowed to train another day of the week. The SLT will be able to check whether or not the patient has trained on the scheduled day and, if necessary, will contact patient or his/her caregiver to reschedule the training for the next day. Patients will be also informed that they can ask the caregiver to solve for a technical problem or to call his/her SLT.

Assessment visit: post-training: V20
During this visit, the patients will complete the same assessments as during the pretraining. This will allow comparison of the effectiveness of the training in the three training conditions within and between groups.

Assessment visit: long-term follow-up: V21
During this visit, the patients will complete the same assessments as in the pretraining and post-training visits. This will allow for intragroup- and intergroup comparisons of the sustainability of the training effectiveness.

Primary measures of training benefits
In order to test the effects of the training, we will use three types of objective measures: experimental tasks, neuropsychological tests and questionnaires. Our primary outcome measures are the scores that patients with AD will obtain in executive and working memory experimental tasks. Our secondary outcome measures are the scores that patients will obtain on neuropsychological tests and questionnaires that will provide information on the overall level of improvement and, more importantly, answers on the effect of training on well-being and self-esteem. We will calculate the composite scores for our primary outcome measures. All measures will be taken at the three time points (T0—pretraining, T1—immediately after training and T2—3 months after training). The choice of these measures was made according to the cognitive functions trained and the cognitive (working memory, executive functions) and psychological (self-esteem, motivation, psychological state—depression/anxiety, assessment of quality of life) domains for which training benefits are expected. These assessments allow us to, first, determine the baseline level of the patient’s cognitive abilities and their emotional and motivational state and, second, to measure the benefit of training by comparing the pretraining results (T0) with those obtained immediately after the end of the training (T1) and 3 months later (T2).

Neuropsychological tests
Verbal fluency
The general aim of the fluency test is to assess executive functions by evaluating patient’s ability to access their lexical repertoire in relation to a given letter or a semantic category. 28

Trail Making Test A/B
Trail Making Test (TMT) consists of two parts. Part A measures processing speed—the patient must connect in ascending order the 25 numbers randomly distributed in circles on page A4. Part B measures cognitive flexibility—the patient has to perform the same task as in part A while alternating numbers and letters (ie, 1-A-2-B-3-C, etc). 29

Logical Memory
Logical Memory I and II are subtests of the Wechsler MEM IV. Each correctly recalled detail out of 25 details per story is scored 1 point, giving the maximum raw score of 50 points for two stories. Logical Memory II is a delayed condition of Logical Memory I. The test ends with recognition, in which patient must answer a series of questions about each story. 30
Mini Mental State Examination
The Mini Mental State Examination (MMSE) is a commonly used test for screening general cognitive impairment. The maximum score of the MMSE is 30 points.31

Digit Span
Two types of spans are used, forward and backward, to measure short-term and working memory, respectively. In both cases, the test ends if the participant fails to repeat two consecutive series. The maximum score is 48 points.36

Questionnaires
Geriatric Depression Scale-30 items
The Geriatric Depression Scale is 30 item self-reported scale that uses ‘yes/no’ responses. It is used to detect the symptoms of depression in older adults. Scores of 0–4 are considered normal, 5–8 indicate mild depression, 9–11 moderate depression and 12–15 severe depression.32

Questionnaire of Cognitive Complaint
This is a 10-question yes/no questionnaire covering memory, language, orientation and behaviour, allowing clinicians to distinguish a mild cognitive complaint from an at-risk one.33

Instrumental Activities of Daily Living
Eight domains of daily functioning are measured with the Instrumental Activities of Daily Living scale, with scores ranging from 0 (dependent) to 8 (independent) for women and from 0 to 5 for men.34

Pittsburgh Sleep Quality Index
It is used to measure quality and sleep cycles in older adults by assessing seven sleep domains. It is a self-reported measure giving a global score ranging from 0 (no difficulties) to 21 (severe difficulties), with scores above 5 reflecting disturbances of sleep and sleep quality.35

SF 12 (Short-Form 12)
This is a 12-question self-reported survey assessing the quality of life and more specifically the impact of health condition on daily life by exploring 8 domains. Two scores are calculated—a Mental Component Score-12 and a Physical Component Score-12.36

Motivation scale for older adults
This scale measures intrinsic motivation, self-determined and non-self-determined extrinsic motivation and amotivation in different life contexts. There are 12 motivational statements per life context. Each of these statements is rated on a scale of 1–7 points.37

Experimental tasks
Four experimental tasks were constructed to measure the near transfer of training effects on executive functions and memory, the cognitive functions targeted by the training.

Stop Signal
This task evaluates inhibition skills. The participant is asked to give a response to the presentation of a target stimulus (Go signal) and to prevent this response when the stimulus is followed or preceded by a sound signal (Stop signal). The task consists of two phases. The mean reaction time for each participant is calculated to be used in a second phase as a reference time for the presentation of the auditory signal. In total, there are 96 trials. The trials are presented randomly. The presentation of the auditory signal is adaptive. The first signal is presented after the stimulus at reference time calculated in the phase 1. Each subsequent signal is presented according to the participant’s ability to withhold the response. If the participant succeeds, the time is increased by 10 ms, if the participant fails, the time is decreased by 10 ms.38

Letter and number pairs
This task is used to assess mental flexibility. The participant sees 4 blocks of 48 letter-number pairs, that is, a total of 192 randomly presented trials. Each pair appears for 350 ms on a computer screen, either in a square located in the upper part of the screen or in a square located in the lower part of the screen. The participant is asked to judge the parity if the pair appears at the upper part of the screen, and to make consonant/vowel judgement if it appears at the lower part of the screen. Reaction time and accuracy are recorded.39

Up-dating span
This task is used to assess the updating in working memory. Series of letters appear on a computer screen, the participant is asked to memorise the last three letters presented, without knowing the length of the series. The series are presented in random order. Reaction time and accuracy are recorded.39

Operation reading letters span
This task is used to assess working memory. It consists of eight series of 2–5 letters. The letters are separated by a presentation of one, two or three operands consisting of one or two numbers. The participant is asked to memorise each series of letters while reading aloud between each letter the operations and their results. At the end of the series, the participant is asked to recall the letters in the order of their presentation.40

Computer-based cognitive training
The training will be done for each participant over a period of 4 months on the PC using the Happyneuron Pro software (https://www.scientificbraintrainingpro.fr). Patients will complete the training as described in Design section, page 5. At the beginning of each session, the SLT will ask the participant to report any event that have occurred during the week that may, in any way, disturb his/her participation in the training. These events will be reported in the electronic observation notebooks (EON). The rational for a 4-month training period is that we wish to evaluate the benefits of a relatively short period of time.
that would be less prone to drop-out and that is of sufficient duration, according to the literature, to produce benefits.\textsuperscript{41,42} We choose the training tool, Happyneuron Pro (Happyneuron Pro is a product developed by Scientific Brain Training), because it is a well-known cognitive remediation product frequently used by the SLTs in France, and in particular by the SLTs participating in our study. Research and clinical studies have shown the effectiveness of the training programmes proposed in Happyneuron Pro software to improve cognitive functions.\textsuperscript{39–48} The experimental tasks were designed and programmed on the Open Sesame free access software (V.3.2.5). This software was therefore installed on the SLT’s computers. The training sessions were programmed on Happyneuron Pro platform https://www.scientificbraintrainingpro.fr/.

**Table 2.** Exercises included in cognitive training and cognitive capacity targeted by the exercise

| Game type                          | Cognitive capacity targeted by the exercise                                      |
|------------------------------------|--------------------------------------------------------------------------------|
| 1. Tower of Hanoi                  | ► Problem solving                                                               |
| 2. Put some order in these accounts| ► Vissuospatial exploration                                                      |
|                                   | ► Attention and numerical processing                                             |
| 3. Bird songs, where are you?      | ► Auditory memory                                                               |
|                                   | ► Memorising strategies                                                         |
| 4. Objects, where are you?         | ► Vissuospatial memory                                                          |
|                                   | ► Binding capacities                                                            |
| 5. Find your way back.             | ► Visual short-term memory                                                       |
|                                   | ► Working memory                                                                |
| 6. Blazon Game                     | ► Visual memory                                                                 |
|                                   | ► Attention                                                                     |
|                                   | ► Vissuospatial perception                                                      |
| 7. Waiter please                   | ► Verbal memory                                                                 |
|                                   | ► Visual memory                                                                 |
|                                   | ► Mental rotation ability                                                       |
| 8. Conduct the investigation       | ► Lexical comprehension                                                         |
|                                   | ► Categorisation skills                                                         |
| 9. It is up to you to count        | ► Working memory                                                                |
|                                   | ► Mental arithmetic                                                             |
| 10. You have got a message         | ► Verbal-auditory memory                                                        |

The training targets the following cognitive functions: working and short-term memory, executive functions, visuospatial abilities and processing speed (see table 2 for more details).

**Equipment and programming**

The SLT’s office and patient’s personal computers are the only equipment used to run our protocol. All questionnaires and neuropsychological tests (except TMT and figure from MMSE) were digitalised on Typeform. The training was provided in small groups or individually videoconferences and complemented by email exchanges and video tutorials, a digital user guide and power point presentations.

Each SLT has two personal password-protected areas, one on the Happyneuron Pro platform to manage the training and another one on the Ennov Clinical platform https://www.scientificbraintrainingpro.fr/. These personal areas are supervised by principal investigator, junior investigator of this study, and a clinical research assistant from the HCL.

The workspace on Happyneuron Pro platform is used to create the training area for each included patient and to specify the weekly frequency and the days of training sessions, depending on the training group. Once the patient’s space is created and the sessions scheduled, the patient receives a link by email on the scheduled days and he /she has to do to access the training, is to click on the link.

The study is monitored by the Clinical Research and Innovation Department of the Hospices Civils de Lyon (HCL). These personal areas are supervised by principal investigator, junior investigator of this study, and a clinical research assistant from the HCL.

The coordinating centre is composed of the three investigators (principal, senior and junior investigator) who designed the protocol and will be in charge of verification of the inclusion/exclusion criteria prior to...
the inclusion of patients in the study and of the data analyses. These investigators are not involved in data collection.

**Data management and storage**

The performance on the neuropsychological tests performed via Typeform is automatically recorded. When completed, an email containing the patients’ scores is automatically sent to the investigator and the SLT, and patients’ scores can be extracted from Typeform into Excel. Finally, the SLT enters the scores of interest into the patient’s EON.

Performances on the experimental tasks are recorded on the SLT’s office computer and the scores of interests are entered into the patient’s EON.

The training results for each session are automatically stored on a secure server hosted by a health data host. There is no transit between the servers, nor is there any storage of data on the patient’s computer. SLTs have the option of monitoring the trainings remotely: this is possible by accessing the patient’s space, which allows the SLTs to check whether the training has been carried out regularly and to monitor patients’ progress. If necessary, the SLTs can also access the results online.

All the data entered in EON are accessible during the inclusion period and after the end of the study to the clinical research assistant in charge of the follow-up of the study and to the three investigators in charge of the study and who are not involved in the data collection. Data extraction and analyses are allowed at two points of the study, mid-term, and the end of inclusion period. The final trial dataset that will be used for statistical analyses will be available to the three investigators in charge of this study.

**Statistical considerations**

**Estimation of samples size**

The sample size per training group was estimated on the basis of previous protocols and literature reviews which show that the number of patients included in the protocols varies between 15 and 150 per group. Taking into account the data of previous studies and expected size effect, we decided to include 55 patients per group. Indeed, the size of each group was estimated to be 45, assuming a small effect of the intervention (Cohen’s d=0.40), with a repeated measures factor Time of assessment (pretraining, immediate post-training, long term post-training) and an independent measures factor Group (MFG, HFG, REG) to reach a power of 0.8 with an alpha at 0.05. We estimated a 10% drop-out of participants. Thus, we estimated the inclusion of 50 patients per group. In addition, to consider the cluster randomisation, we estimated that we need to increase our sample by 10%, bringing the number of patients per group to 55. This number is compatible with our capacity to recruit patients.

**Statistical methods description**

Linear models are considered for all behavioural measures collected with one random intercept per patient and one per practice. The analysis will concern independent measures factor Group with three modalities (MFG, HFG, REG) and repeated measures factor Time with three modalities (T0—pretraining, T1—post-training, T2—long term monitoring) and the interaction between these two factors. The significance level is set at 0.05. In our longitudinal analysis, we risk floor, ceiling and curvilinear effects since we have stopped the inclusion at an MMSE score higher than 15. For this reason, we plan to adjust the initial values first, and to avoid the biases linked to the adjustment, we will refer to the causal directed acyclic graph. We will then apply methods that take into account the floor and curvilinear effects, by adjusting the mean value of the observations, and then through a linear mixed model in a structural model we will study the evolution on the time axis and the common effects of the covariables.

The interim analyses are also planned, using the same models as described above, at three time points: 1—after inclusion of 15 patients in each group, 2—after inclusion of 30 patients in each group and 3—after inclusion of 40 patients in each group. We decide to perform interim analyses to see if trends would emerge on smaller samples than those estimated by the power analysis to be necessary to obtain a training effect. These analyses are not intended to alter the protocol or planned inclusions.

Statistical analyses will be carried out using STATISTICA software.

**Risks and benefits**

There are no particular risks for patients to participate in this study. The only disadvantages could be computer-related fatigue, especially for patients included in the HFG.

The major personal benefit for patients would be an improvement in their cognitive and emotional state or a slowing of the progression of cognitive impairment. The secondary benefit could be the improvement of their quality of life.

There is also a collective benefit since if the results of this study confirm our hypothesis, we could give recommendations concerning at home training.

**Ethics and dissemination**

The study is conducted with the approval of the national ethics committee (CPP—Comité de Protection des Personnes, Sud Méditerranée III, No 2019) and of the National Commission for Information Technology and Liberties (No 919217). Any modification to the study design must be addressed to the clinical research assistant and if necessary, a request for modification must be addressed to the national ethical committee that issued the authorisation for the study. The results of the study will be disseminated in the form of oral or posters presentations at international scientific conferences.

Dimachki S, et al. BMJ Open 2022;12:e050993. doi:10.1136/bmjopen-2021-050993
and seminars for health professionals (eg, Alzheimer’s Association International Conference, Union Nationale pour le Développement de la Recherche et de l’Evaluation en Orthophonie) and published in a relevant scientific journal (eg, Journal of Alzheimer’s Disease). The presentations are allowed after the first statistical analyses planned at the midpoint of inclusion.

**Significance**

Overall, this study will contribute to the knowledge of the effects of cognitive training on cognition in patients with AD in the prodromal to moderate stages. The comparison of results obtained for neuropsychological tests, questionnaires and experimental tasks by REG patients with those obtained by MFG patients will inform about the effects of cognitive training at home carried out in addition to training in SLT office. This will provide clear indications about the usefulness of this type of cognitive training programme for patients with AD. The comparison of the results obtained by MFG patients with those obtained by HFG patients will provide indications as to the best frequency of training sessions needed.

Beyond the benefits of cognitive training on patients with AD cognition, and the importance of trying to determine the best frequency for optimal effects, other issues, which are independent of the cognitive training programme, may impact on its success if not carefully considered. AD has an important impact on autonomy, emotional balance and motivation, which are often linked to self-esteem. Thus, it seems important, when designing cognitive training protocols for patients with AD to take into account psychological, environmental and autonomy factors for a more optimal cognitive training plan, which aims at the well-being of the individual as a whole.

**Competing interests**  Franck Tarpin-Bernard and Bernard Croisile are cofounders and shareholders of SBT Humans Matter.

**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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**REFERENCES**

1. Cespón J, Minnucci C, Pelliciacci MC. Interventional programmes to improve cognition during healthy and pathological ageing: cortical modulations and evidence for brain plasticity. *Ageing Res Rev* 2018;43:81–98.

2. Günter V, Schäfer P, Holzner BJ, et al. Long-term improvements in cognitive performance through computer-assisted cognitive training: a pilot study in a residential home for older people. *Aging Ment Health* 2003;7:200–6.

3. Joubert C, Chainay H. Aging brain: the effect of combined cognitive and physical training on cognition as compared to cognitive and physical training alone - a systematic review. *Clin Interv Aging* 2018;13:1267–201.

4. Chandler MJ, Locke DE, Crook JE, et al. Comparative effectiveness of behavioral interventions on quality of life for older adults with mild cognitive impairment: a randomized clinical trial. *JAMA Netw Open* 2019;2:e193016.

5. Carretti B, Borella E, Zavaglini M, et al. Impact of metacognition and motivation on the efficacy of strategic memory training in older adults: analysis of specific, transfer and maintenance effects. *Arch Gerontol Geriatr* 2011;52:192–7.

6. Requena C, Maestu F, Campo P, et al. Effects of cholinergic drugs and cognitive training on dementia: 2-year follow-up. *Dement Geriatr Cogn Disord* 2006;22:339–45.

7. Kallio E-L, Öhman H, Hietanen M, et al. Effects of cognitive training on cognition and quality of life of older persons with dementia. *J Am Geriatr Soc* 2018;66:664–70.

8. Gates NJ, Sachdev PS. Is Cognitive Training an Effective Treatment for Preclinical and Early Alzheimer’s Disease? *JAD* 2014;42:S551–9.

9. Canu E, Sarasso E, Filippi M. Effects of pharmacological and nonpharmacological treatments on brain functional magnetic resonance imaging in Alzheimer’s disease and mild cognitive impairment: a critical review. *Alzheimer Res Ther* 2018;10.

10. Galante E, Venturini G, Fiaccadori C. Computer-based cognitive intervention for dementia: preliminary results of a randomized clinical trial. *G Ital Med Lav Ergon* 2007;29:R26–32.

11. Joubert C, Chainay H. Effects of cognitive and aerobic training on working memory and executive function in aging, a Pseudo-Randomized trial: pilot study. *J Ageing Res Healthc* 2019;2:46–76.

12. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med* 2014;11:e1001756.

13. Klimova B. Computer-based cognitive training in aging. *Front Aging Neurosci* 2016;8:313.

14. Klimova B, Maresova P. Computer-based training programs for older people with mild cognitive impairment and/or dementia. *Front Hum Neurosci* 2017;11:269.

15. Choi J, Twaremley EW. Cognitive rehabilitation therapies for Alzheimer’s disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychol Rev* 2013;23:48–62.

16. Cavalo M, Angilletta C. Long lasting neuropsychological effects of a computerized cognitive training trial in patients affected by early stage Alzheimer’s disease: are they stable over time? *J Appl Gerontol* 2019;38:1035–44.

17. García-Casal JA, Loizeau A, Csipke E, et al. Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis. *Aging Ment Health* 2017;21:454–67.
21 Hwang HR, Choi SH, Yoon DH, et al. The effect of cognitive training in patients with mild cognitive impairment and early Alzheimer's disease: a preliminary study. *J Clin Neurol* 2012;8:190.

22 Belleville S, Boller B. Comprendre le stade compensatoire de la maladie d’Alzheimer et agir pour promouvoir la cognition et la plasticité cérébrale. [Understanding the compensatory stage of Alzheimer’s disease and acting to promote cognition and cerebral plasticity. *Canadian Journal of Experimental Psychology/Revue Canadienne de Psychologie Expérimentale* 2016;70:288–94.

23 Förster S, Buschert VC, Teipel SJ, et al. Effects of a 6-month cognitive intervention on brain metabolism in patients with amnestic MCI and mild Alzheimer’s disease. *J Alzheimers Dis* 2011;26:337–48.

24 Mendoza Laiz N, Del Valle Diaz S, Rioja Collado N, et al. Potential benefits of a cognitive training program in mild cognitive impairment (MCI). *Restor Neurol Neurosci* 2018;36:207–13.

25 Clare L, Woods RT, et al. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer’s disease: A review. *Neuropsychol Rehabil* 2004;14:385–401.

26 Realdon O, Rossetto F, Nalin M, et al. Technology-enhanced multi-domain at home continuum of care program with respect to usual care for people with cognitive impairment: the Ability-TelereHABITation study protocol for a randomized controlled trial. *BMC Psychiatry* 2015;15:282.

27 Cruz VT, Pais J, Bento V, et al. A rehabilitation tool designed for intensive web-based cognitive training: description and usability study. *JMIR Res Protoc* 2013;2:e59.

28 Croisile B, Beaumont C, Hadjedj T. La Batterie Neuropsychologique Courte (BANCO) : étalonnage chez 347 sujets normaux de 50 92 ans. *La Revue De Gériatrie* 2011;36:645–54.

29 R.M R. Validity of the TRAIL making test as an indicator of organic brain damage 1958;8:271–6.

30 Erdodi LA, Abeare CA, Lichtenstein JD, et al. Wechsler adult intelligence Scale-Fourth edition (WAIS-IV) processing speed scores as measures of noncredible responding: the third generation of embedded performance validity indicators. *Psychol Assess* 2017;29:148–57.

31 Kaidar P, Huguet-Diener L, Poirenaud J. French standardization of the mini mental state (MMS), greco’s version. *Revue de neuropsychologie* 2003;13:209–36.

32 Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17:37–49.

33 Thomas-Anterion C, Ribas C, Honore-Masson S. Le Questionnaire de Pointe Cognitive (QPC) : Un outil de recherche de plainte suspecte d’évoquer une Maladie d’Alzheimer ? L’année de Motivation pour les Personnes Âées (EMPA). *Int J Psychol* 1991;26:219–40.

34 Amieva H, Lafont S, Auriaocme S, et al. Inhibitory breakdown and dementia of the Alzheimer type: a general phenomenon? *J Clin Exp Neuropsychol* 2002;24:909–16.

35 Vianin P, Urben S, Magistretti P, et al. Increased activation in Broca’s area after cognitive remediation in schizophrenia. *Psychiatry Res* 2014;221:204–9.

36 Friedman NP, Miyake A, Young SE, et al. Individual differences in executive functions are almost entirely genetic in origin. *J Exp Psychol Gen* 2004;133:83–100.

37 Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer’s disease. *Int Psychogeriatr* 2010;22:346–72.

38 Choi J, Twnsley EW. Cognitive rehabilitation therapies for Alzheimer’s disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychol Rev* 2013;23:48–62.

39 Vianin P, Urben S, Magistretti P, et al. Increased activation in Broca’s area after cognitive remediation in schizophrenia. *Psychiatry Res* 2014;221:204–9.

40 Barrouillet P, Bernardin S, Campos V. Time constraints and resource sharing in adults’ working memory spans. *J Exp Psychol Gen* 2004;133:83–100.

41 Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer’s disease. *Int Psychogeriatr* 2010;22:346–72.

42 Choi J, Twnsley EW. Cognitive rehabilitation therapies for Alzheimer’s disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychol Rev* 2013;23:48–62.

43 Vianin P, Urben S, Magistretti P, et al. Increased activation in Broca’s area after cognitive remediation in schizophrenia. *Psychiatry Res* 2014;221:204–9.

44 Remly C, Rigard C, Peyroux E, et al. «Cognitus & Moi»: a computer-based cognitive remediation program for children with intellectual disability. *Front Psychiatry* 2016;7:10.

45 Bowie CR, Gupta M, Holhausen K, et al. Cognitive remediation for treatment-resistant depression: effects on cognition and functioning and the role of online homework. *J Neuropsych Dis* 2013;201:680–5.

46 Bobillier Chaumon M-E, Michel C, Tarpin Bernard F, et al. Can ICT improve the quality of life of elderly adults living in residential home care units? From actual impacts to hidden artefacts. *Behav Int Technol* 2014;33:574–90.

47 Joubert C, Chainay H. Effects of cognitive and aerobic training on working memory and executive function in aging, a Pseudo-Randomized trial: pilot study. *J Aging Res Healthcare* 2019;2:46–70.

48 Franck N. Clinique de la schizophrénie. *EMC - Psychiatrie* 2010;1:16–18.

49 Sherman DS, Mauser J, Nuno M, et al. The efficacy of cognitive intervention in mild cognitive impairment (MCI): a meta-analysis of outcomes on neuropsychological measures. *Neuropsychol Rev* 2017;27:440–84.