



Performance of the SmartMe&You serious video games for home telemonitoring is related to cognitive status and resting-state electroencephalographic markers in healthy and Parkinson's disease participants

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Abstract Unsupervised serious video games on the SmartMe&You home telemonitoring platform may enable the assessment of cognitive fluctuations in older individuals, with or without cognitive deficits. Here, we tested their validity in cognitively unimpaired older adults (Healthy) and patients with mild cognitive impairment and mild to moderate dementia due to Parkinson's disease (PDCD). Such validity was assessed

using Mini-Mental State Examination (MMSE) scores and resting-state eyes-closed electroencephalography (rsEEG) activity. Clinical, demographic, and rsEEG datasets were collected from 34 healthy and 68 PDCD participants. The SmartMe&You video games included 7 unsupervised cognitive tasks implemented on a commercial tablet. The rsEEG source activities in the individual delta, theta, and alpha frequency bands were estimated using the eLORETA freeware. As novel findings, we showed that game performance: (1) discriminated between healthy participants and PDCD

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patients, with overall accuracy exceeding 90%; (2) was positively associated with MMSE scores across all participants ($p < 0.00001$); and (3) was negatively associated with global rsEEG source activity in the delta and theta frequency bands ($p < 0.00001$). These findings suggest that serious videogames of the SmartMe&You home telemonitoring platform were feasible and sensitive to cognitive status across the spectrum from normal aging to Parkinson's disease-related dementia. This approach provides a scalable, low-cost, and ecologically valid tool for remote cognitive monitoring, with future potential applications in both early detection and longitudinal tracking of cognitive decline.

Keywords Resting-state electroencephalographic (EEG) rhythms · Exact low-resolution brain electromagnetic source tomography (eLORETA) · SmartMe&You serious video games · Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. It currently affects more than 10 million people worldwide, and this number is projected to increase to 25.2 million by 2050 (<https://www.parkinson.org/>).

Patients with PD are primarily characterized by motor symptoms (i.e., akinesia, tremor, postural instability, and rigidity). Still, they are frequently

characterized by cognitive deficits (PDCD), including impairments in planning, working memory, executive functions, attention, semantic verbal fluency, and visuospatial abilities [1, 26, 28]. The initial mild cognitive deficits typically progress to dementia (i.e., major cognitive impairment and substantial loss of autonomy) over the years.

An open clinical issue is the early assessment and monitoring of cognitive decline in patients with PDCD, and the need for effective, scalable tools beyond traditional paper-and-pencil neuropsychological tests. Indeed, those tests are limited in their sensitivity to early change, ecological validity, and feasibility of repeated or remote administration.

Along this line, the use of unsupervised cognitive tests implemented over computers, tablets, and smartphones has emerged as a new tool to monitor cognitive status and decline over years in patients with PD and other neurodegenerative diseases [2, 12, 15, 30, 34, 39, 40, 46, 61, 70, 71, 75, 78, 79, 81]. These digital tests offer several advantages over traditional paper-and-pencil neuropsychological batteries, including standardized administration, automated scoring, reduced practice effects through alternate forms, potential for frequent unsupervised home-based testing, and ecological validity through simulation of real-world activities [61, 70, 71, 76]. Notably, cognitive deficits in patients with PD are major predictors of quality of life and clinical outcomes [12, 13, 30, 77].

Among others, the smart cognitive tasks on computers, tablets, and smartphones have the following advantages when applied in patients with PDCD: (i) are valid and feasible for measuring working memory, executive function and visuomotor function [15, 81]; (ii) had high accuracy in the assessment of executive function and attention deteriorations [12, 81]; (iii) can be used for cognitive training with beneficial effects on cognitive functions in both hospital and home telemonitoring settings [2, 30, 46].

The tasks successfully implemented on computers, tablets, and smartphones are quite heterogeneous [30, 76] see Supplementary Material, Table S1). The "Computerized Cognitive Composite" tests include the face-name associative memory exam, the behavioral pattern separation test-object, and the Cogstate brief battery, including one card learning [34]. Furthermore, the "Brief Assessment of Cognition for Healthcare" tests probe executive function,

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processing speed, working memory, episodic memory, and semantic memory [34, 70, 71]. The “Virtual Supermarket Test Shopping Simulations” tests assess executive function, spatial navigation, memory, and attention [88]. Chinese-adapted shopping tasks in the “Virtual Supermarket Program” assess learning/memory, executive functions, language, time orientation, and complex attention [82]. The “Cognitive Assessment in Virtual Reality” tests span 13 virtual environments simulating daily activities and are grounded in 6 cognitive domains [74]. The “Parkin’Play” uses a web-based gaming system (“MyCognition AquaSnap”) to assess attention, working memory, executive function, and processing speed [52, 61, 77].

In this framework, researchers from the PDWAVES Consortium have developed simple, unsupervised serious video games, called SmartMe&You, based on neuroscientific theories of vigilance, attention, and executive functions, for use with patients with PDCD and other neurodegenerative diseases, as well as older adults. SmartMe&You video games are designed to be completed independently by the participant, without direct guidance or oversight from a clinician, researcher, technical operator, or caregiver. These video games include 7 unsupervised cognitive tasks installed on commercial tablets: two variants of a simple visual reaction-time task, three variants of Posner’s visuo-spatial anticipatory attention task, an inhibition-of-return task, and a visual Go/No-Go task. All tasks are played on the same visual grid square on the tablet screen, where the cue and go stimuli are presented during gameplay. The participant is required to provide a hand motor response as accurately and quickly as possible. Completing these 7 video games takes approximately 20 min.

Of note, SmartMe&You is explicitly grounded in neuroscientific models of vigilance regulation, attention, and executive control, with particular emphasis on their dynamic interaction during quiet wakefulness. This contrasts with many existing serious games, which are often based on broader cognitive training paradigms without a specific focus on vigilance-related mechanisms. Indeed, in terms of targeted cognitive domains, SmartMe&You tasks are designed to probe vigilance-dependent and executive components of nonverbal cognition (e.g., sustained attention, anticipatory visuospatial attention, response inhibition), rather than providing broad but less specific coverage across multiple domains. Finally,

concerning adaptivity, SmartMe&You adopts a standardized task structure optimized for repeated unsupervised administration in home settings, prioritizing reliability and comparability across sessions over highly dynamic difficulty adaptation, which is more typical of training-oriented platforms.

More specifically, the SmartMe&You serious video games were designed with a double aim: (1) to provide a comprehensive assessment of the cognitive status in older participants at risk of or with cognitive deficits over serial follow-ups, covering working memory, episodic memory, visuospatial skills, and visuomotor transformations, which are closely linked to vigilance, attention, and executive functions; and (2) to offer measures of cognitive performances that reflect the functional integrity of neurophysiological oscillatory mechanisms involved in maintaining and regulating vigilance during quiet wakefulness. Indeed, patients with PDCD suffer from sudden shifts between clear alertness and “blank stares” or unresponsiveness, often linked to dopamine levels, medication cycles (“on/off” states), and brain network disruptions from mild distraction to severe episodes resembling delirium [21]. The mentioned neurophysiological mechanisms generate ongoing electroencephalographic (rsEEG) rhythms recorded from the scalp during the resting-state, eyes-closed condition, characterized by psychomotor relaxation and mind-wandering [6, 64]. This is a typical experimental condition in clinical EEG studies of patients with PDCD [7, 9]. Compared with healthy individuals, patients with PDCD were characterized by abnormally elevated rsEEG delta and theta rhythms across widespread regions and by poor posterior rsEEG alpha rhythms [7, 9, 16, 67]. Those alterations in the rsEEG delta and alpha rhythms were associated with motor deficits, and visual hallucinations [8]. Several studies reported that rsEEG rhythms underpinning vigilance regulation were associated with global and domain-specific cognitive functions in patients with PDCD (for a review, see [73]). Global cognition, as indexed by Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores, was positively associated with widespread rsEEG alpha and beta rhythms, as well as with composite indices such as the alpha/theta ratio; on the contrary negative association between global cognition and widespread rsEEG delta and theta rhythms was previously found [5, 8, 48, 83]. Similarly, memory performance was positively related to posterior rsEEG alpha

and beta rhythms as well as alpha/delta and alpha/theta ratio, whereas increased rsEEG theta rhythms were associated with poorer memory outcomes [5, 33, 60, 85]. Visuospatial abilities were positively associated with the rsEEG alpha/theta ratio in posterior regions [25, 36, 60]. Processing speed correlated positively with rsEEG beta rhythms in parietal regions and negatively with rsEEG theta rhythms in central and temporal areas [5]. Finally, language abilities were positively correlated with rsEEG alpha and beta rhythms in parietal regions [5, 85].

In the present study, we investigated, for the first time, the validity of the unsupervised SmartMe&You serious video games, which are designed to measure cognitive functions underpinning vigilance regulation, visuospatial attention, and executive functions in a home telemonitoring setting without assistance from medical or paramedical personnel. Performance on these video games was hypothesized to be related to rsEEG rhythms during quiet wakefulness and to global cognitive status in both healthy and PDCD participants. Validity was assessed by examining associations between cortical rsEEG rhythms reflecting quiet vigilance regulation and the MMSE score, an index of global cognition.

Materials and methods

Participants and diagnostic criteria

Clinical-demographic-rsEEG datasets were collected from 34 healthy and 68 PDCD participants.

Table 1 Mean values ($\pm$ SE) of the demographic and clinical data, as well as the results of their statistical comparisons ($p < 0.05$), in the groups of healthy participants ($N = 34$) and PDCD patients ($N = 68$). Abbreviations: *M/F*, males/females; *MMSE*, Mini-Mental State Evaluation; *ADL*, activities of daily

Specifically, they were recruited and enrolled from Sapienza University of Rome (Italy), the University of Padua (Italy), the University of Salerno (Italy), IRCCS San Raffaele Roma and Cassino (Italy), IRCCS San Camillo Venice (Italy), Medipol University of Istanbul (Turkey), and Dokuz Eylül University of Izmir (Turkey) in the framework of the PREDICT-NEURODEGEN and PDWAVES (www.pdwaves.eu) projects.

Table 1 summarizes the relevant demographic (i.e., age, sex, and education) and clinical (i.e., Mini-Mental State Evaluation, MMSE; activities of daily living, ADL; and instrumental activities of daily living, IADL) information about the healthy and PDCD groups, together with the results of the statistical analyses computed to evaluate the presence or absence of statistically significant differences between these groups regarding age (*T*-test), sex (Fisher test), education (*T*-test), MMSE (Mann Whitney U test), ADL (*T*-test), and IADL (*T*-test). Statistically significant differences were found for: age ($p < 0.001$; healthy > PDCD), education ($p < 0.001$; healthy > PDCD), sex ($p < 0.01$; higher percent females in the healthy group compared to the PDCD group), MMSE ($p < 0.00001$; healthy > PDCD), ADL ($p < 0.00001$; healthy > PDCD), and IADL ($p < 0.00001$; healthy > PDCD).

Of note, the PDCD group, as expected, was older, less educated, and predominantly male, compared to the healthy control group [19, 58, 63, 66]. These differences reflect the typical demographic profile of PD in the general population, supporting that the recruitment approximates a “random” sampling of PDCD

living; *IADL*, instrumental activities of daily living; *Healthy*, cognitively unimpaired older adults; *PDCD*, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson’s disease; *SE*, standard error of the mean

Demographic and clinical data			
	Healthy	PDCD	Statistical analyses
<i>N</i>	34	68	-
Age (years)	68.7 $\pm$ 1.0 SE	73.6 $\pm$ 0.9 SE	<i>T</i> -test: $p < 0.001$
Sex (M/F)	16/18	51/17	Fisher test: $p < 0.01$
Education (years)	14.8 $\pm$ 0.7 SE	11.6 $\pm$ 0.5 SE	<i>T</i> -test: $p < 0.001$
MMSE	29.5 $\pm$ 0.1 SE	25.7 $\pm$ 0.4 SE	Mann–Whitney U test: $p < 0.00001$
ADL	6.0 $\pm$ 0.1 SE	4.9 $\pm$ 0.2 SE	<i>T</i> -test: $p < 0.00001$
IADL	7.5 $\pm$ 0.2 SE	4.5 $\pm$ 0.2 SE	<i>T</i> -test: $p < 0.00001$

patients and cognitively unimpaired older adults. Consequently, the observed differences in age, education, and sex between groups are not due to selection bias. Still, they are consistent with the underlying population characteristics, which were accounted for as covariates in subsequent analyses.

The local institutional ethical committees approved the study. All experiments were conducted with informed and overt consent obtained from each participant or caregiver, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local institutional review boards.

The following inclusion criteria were fulfilled for patients with PDCD: (i) age between 55 and 90 years; (ii) (7) education level of 5 years or higher; (iii) a gradual cognitive decline reported by either the patient or a reliable informant or observed by clinicians; and (iv) an abnormally low score in at least one of the neuropsychological tests mentioned in the following section, as defined by performances beyond 1.5 times the standard deviation (SD) from the mean value for age- and education-matched controls or equivalent scores for abnormality.

The diagnosis of PD was based on a standard clinical assessment of tremor, rigidity, and bradykinesia [31]. As measures of severity of a motor disability, the Hoehn and Yahr stage [35] and the Unified Parkinson's Disease Rating Scale-III (UPDRS III; Fahn & Elton [27] for extrapyramidal symptoms were used (Unfortunately, the data from the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale were not available). The PDCD group was formed by patients with mild to moderate dementia (PDD; $N=27$) and mild cognitive impairment (PDMCI; $N=41$) due to PD. The classification of PDD or PDMCI was based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria [4]. Specifically, PDD was defined by a prior diagnosis of Parkinson's disease, subsequent cognitive decline reported by the patient or informants or observed by clinicians, significant impairment in at least one cognitive domain documented by neuropsychological testing with performance below normative reference values, and loss of autonomy with moderate to severe impairment in instrumental activities of daily living. PDMCI was defined using the same criteria, except for the preservation of functional autonomy in

activities of daily living. For both groups, cognitive decline was not attributable to other medical or psychiatric conditions, and other major neurological or psychiatric diagnoses were excluded during clinical examination. All PD patients were under standard long-term chronic dopaminergic treatment, and all exams were performed under the ON state.

The exclusion criteria for the PDCD patients included non-PD dementia of any kind, including DLB [55, 56], drug-induced or cerebrovascular Parkinsonism, atypical Parkinsonism with absent or minimal responses to antiparkinsonian drugs, and mixed neurodegenerative diseases. Additional exclusion criteria included: (1) past or present diagnosis of epilepsy or report of seizures or epileptiform EEG activity in the past; (2) use of antiepileptics; (3) past or present dependence on opiates and alcohol; (4) an ongoing severe depressive episode, defined as a score > 20 on the 30-item Geriatric Depression Scale (GDS; [84]) or > 28 on the Beck Depression Inventory-II (BDI-II; [11]); and (5) presence of significant chronic systemic illnesses such as diabetes mellitus.

All healthy participants underwent cognitive screening as well as physical and neurological examinations to exclude subjective memory complaints, cognitive deficits, and mood disorders. Exclusion criteria for healthy seniors were (i) neurological or psychiatric diseases (previous or present), (ii) presence of a depressive episode as detected by a Geriatric Depression Scale (15-item version) score higher than 5, (iii) use of chronic psychoactive drugs, and (iv) presence of significant chronic systemic illnesses such as diabetes mellitus.

In all participants, global cognitive status and performance in various cognitive domains were assessed as follows: (i) global cognitive status was tested using the Mini-Mental State Examination (MMSE) score [29]; (ii) episodic memory was assessed by immediate and delayed recall of the Rey Auditory Verbal Learning Test [69, 80]; (iii) executive functions and attention were evaluated using the Trail Making Test (TMT) parts A and B [68]; (iv) language skills were tested using the 1-min Verbal Fluency Test for letters and categories [59]; (v) planning abilities and visuospatial functions were assessed using the immediate and delayed recall of the Rey Figure Copy [18]. Table 2 reports the following: (i) the mean values ($\pm$ SE) of the abovementioned neuropsychological

tests in the healthy and PDCD groups, (ii) the cut-off scores, and (iii) the results of the presence or absence of statistically significant differences (ANCOVA) between the healthy and PDCD groups for the neuropsychological tests used. Age, education, and sex were used as covariates. To consider the inflationary effects of repetitive univariate tests, the statistical threshold was set at $p < 0.00625$ (i.e., 7 neuropsychological tests, $p < 0.05/7 = 0.00714$) to obtain the Bonferroni correction at $p < 0.05$. Statistically significant worst scores ($p < 0.001$) in the PDCD groups compared with the healthy groups were observed across all neuropsychological tests. The findings mentioned above were not due to outliers from those individual neuropsychological scores, as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

We also assessed the number of participants with PDCD presenting: (i) cognitive deficits in memory but not in executive functions, and (ii) cognitive deficits in executive functions but not in memory. Memory was assessed using the RAVLT delayed recall and the Rey Figure delayed recall [3, 17, 23, 32, 45, 53, 87], whereas executive functions were evaluated using the TMT B–A, letter verbal fluency, and category verbal fluency [10, 17, 72, 86]. Participants

classified as having memory deficits only were those with a pathological score in at least one memory measure and no impairment in executive function tests. Conversely, participants classified as having executive function deficits only showed a pathological score in at least one executive function test and no impairment in memory measures. Ten out of 68 participants (14.7%) fell into the memory-only deficit group, while 11 out of 68 (16.2%) were classified into the executive functions-only deficit group

SmartMe&You serious video games

The serious video games for the SmartMe&You application, designed for home-based telemonitoring, were developed by researchers at Sapienza University of Rome and were administered in a hybrid setting. Specifically, the first session was conducted in a hospital environment, without direct supervision by a technical operator, clinician, or researcher. Subsequently, participants completed seven additional sessions at home, also without caregiver supervision. At this stage, the analysis presented in this manuscript is limited to data collected during the initial hospital session. Therefore, the results are not affected

Table 2 Mean values ($\pm$ SE) of the neuropsychological scores (i.e., RAVLT immediate recall, RAVLT delayed recall, TMT B–A, Verbal fluency for letters, Verbal fluency for category, Figure Rey copy immediate recall, Figure Rey copy delayed recall) in the healthy and PDCD groups. The cut-off scores and the results of the statistical comparisons are also included (ANCOVA on log 10 data; $p < 0.05$). Age, education, and sex

were used as covariates. Values at $p < 0.05$ Bonferroni corrected ($p = 0.05/7 = 0.007143$) are reported in bold. Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; TMT B–A, trail making test part B–A; *Healthy*, cognitively unimpaired older adults; *PDCD*, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease; *SE*, standard error of the mean

Neuropsychological scores				
	Cut-off of abnormality	Healthy Mean $\pm$ SE	PDCD Mean $\pm$ SE	ANCOVA
RAVLT immediate recall	< 28.53	50.4 $\pm$ 2.2 SE	28.6 $\pm$ 1.4 SE	F = 26.5, $p < 0.00001$
RAVLT delayed recall	< 4.69	10.6 $\pm$ 0.7 SE	5.0 $\pm$ 0.4 SE	F = 21.6, $p < 0.00001$
TMT B–A	≥ 187	42.1 $\pm$ 4.1 SE	133.6 $\pm$ 17 SE	F = 24.1, $p < 0.00001$
Verbal fluency for letters	< 17	40.2 $\pm$ 1.9 SE	26.8 $\pm$ 1.5 SE	F = 11.7, $p < 0.001$
Verbal fluency for categories	< 25	46.9 $\pm$ 1.6 SE	30.6 $\pm$ 1.3 SE	F = 25.6, $p < 0.00001$
Figure Rey copy immediate recall	< 20.88	34.5 $\pm$ 0.3 SE	24.7 $\pm$ 1.3 SE	F = 13.9, $p < 0.0005$
Figure Rey copy delayed recall	< 9.47	19.5 $\pm$ 1.4 SE	9.5 $\pm$ 0.9 SE	F = 33.1, $p < 0.00001$

by variability associated with home-based acquisition (e.g., environmental noise or differences in adherence).

The caregivers could provide technical support to turn on the tablet for the daily session and ensure that the patient with PDCD was able to set appropriate general conditions for gaming (i.e., TV, radio, and any other device producing music or videos should be switched off to avoid interference with performance). If there are problems setting the tablet page to start the video games, the caregiver should provide support. The caregivers could recall the general rules for gaming, but they were not to suggest the response during the tasks. This is why a certain degree of digital skills was required by caregivers. Although no formal questionnaire on digital familiarity was administered, a basic level of digital literacy was an implicit inclusion criterion: all participants and caregivers were required to have routine experience with at least one touchscreen device, such as a smartphone or tablet, prior to enrolment. This ensured that no participant was entirely naïve to digital interfaces, even in the absence of a standardized assessment of technological proficiency.

As noted in a previous section, the SmartMe&You Serious Video Games implement 7 unsupervised cognitive tasks on a commercial tablet. A short video demonstrates these serious video games in action (https://www.youtube.com/watch?v=wFBm7WxX_RY).

The first two video games are simple sustained visual reaction-time tasks using a central green target (“go” stimulus) presented with randomly varying inter-trial intervals, shorter in Task 1 and longer in Task 2. Both tasks assess the ability to maintain tonic vigilance across trials and to execute rapid, coordinated visuomotor responses. The third video game presents non-spatial warning cues, consisting of brief whole-screen brightening preceding some of the go stimuli, and assesses responsivity to prompting. The next two video games (Tasks 4 and 5) implement different variants of the standard Posner task to assess visuospatial attention. In these tasks, valid spatial cues indicate the side of the grid (left or right) on which the green go stimulus is likely to appear, with different assigned probabilities; accordingly, validly cued targets are expected to elicit faster reaction times than invalidly cued ones. Another video game implements an inhibition-of-return condition, in

which a pseudo-cue serves as a non-informative spatial cue with a 50% probability of correctly predicting the side on which the go stimulus appears. Under this condition, reaction times are expected to be slower for go stimuli appearing on the same side as the pseudo-cue, corresponding to the inhibited spatial area. The final videogame is a visual go/no-go task in which green go and red no-go stimuli appear centrally, testing the ability to respond selectively to go stimuli while inhibiting impulsive responses to no-go signals.

The logical structure of visual stimuli into a grid field, in the center of the screen of the tablet, consisting of 7×7 squares, and the required hand motor responses with the index finger of the dominant hand were quite the same for all video games. Figure 1 illustrates the common response procedure underlying the SmartMe&You tasks and shows an example of the application interface used to provide visual instructions.

The application was designed to allow the user (physician) to customize parameters based on each patient’s specific characteristics. Drawing on preliminary data, parameters (e.g., the number of task repetitions, the number of stimulus appearances within each repetition, and the duration of each appearance) were optimized to ensure that the PDCD patients recruited could complete daily training with varying performance levels, reflecting their cognitive-motor status. Each task followed a standardized structure. At the start of each task, a central fixation cross appeared on the screen, and participants were instructed to maintain their gaze on it throughout the task. Simultaneously, a light blue square, referred to as the Starting BASE, appeared in a fixed position at the bottom of the screen. Participants were instructed to place the index finger of their dominant hand on this square and to keep it there until a visual target appeared.

During each trial, a square on the grid would change color, signaling a required motor response. In most tasks (Tasks 1–6), the target square turned green, indicating that the participant should quickly touch it with their dominant index finger and then immediately return the finger to the Starting BASE. The target would subsequently revert to white and reappear again after a brief interval, requiring the same sequence of actions. This cycle continued throughout the trial. At the end of each trial, both

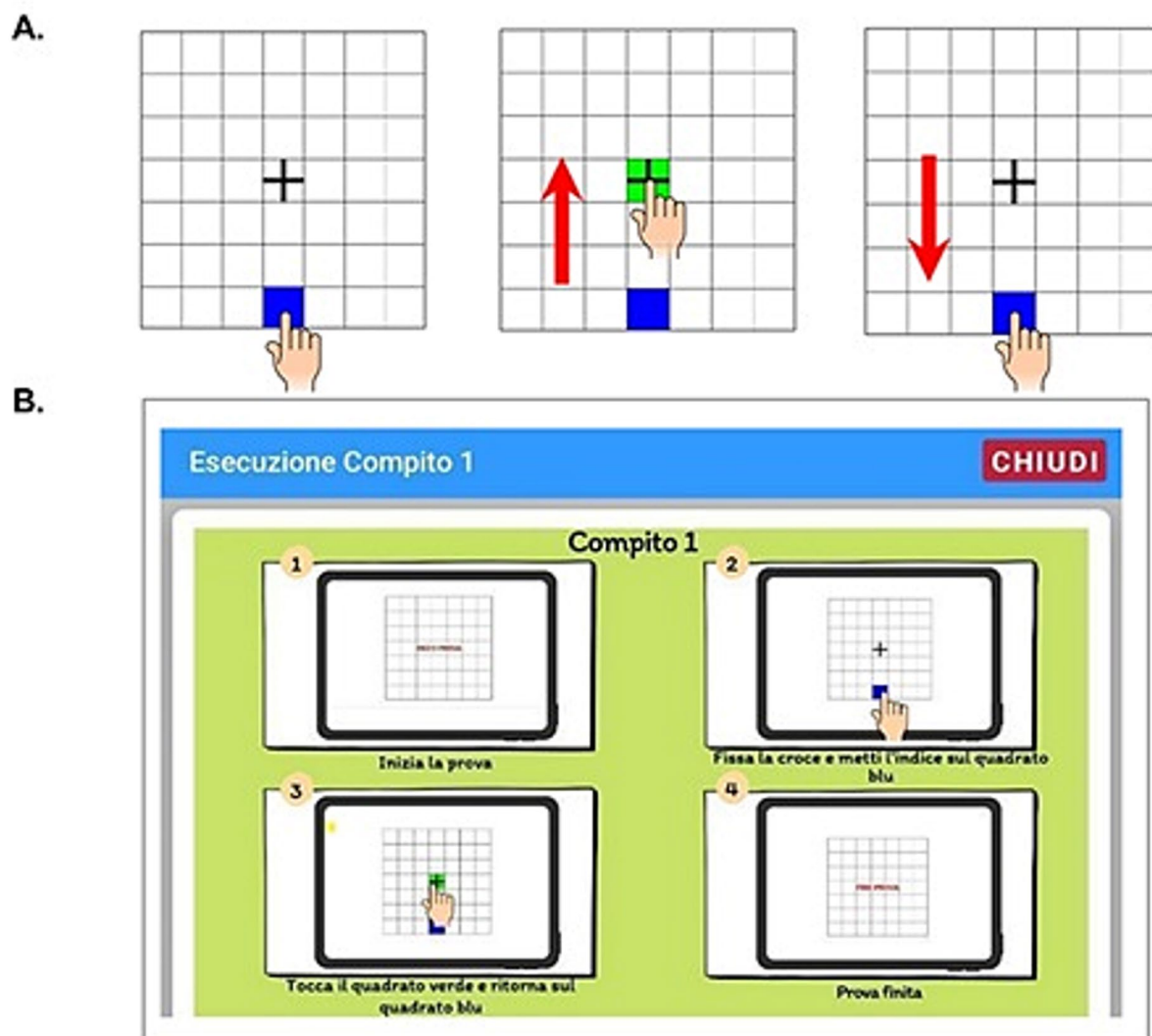


Fig. 1 Illustration of the SmartMe&You serious videogame interface and response procedure. **A** Schematic representation of the basic task layout used across the battery, showing the 7×7 visual grid, the central fixation cue, the starting blue square, and the required touch response to the green “go”

stimulus followed by return to the starting position. **B** Example of the application interface presenting the step-by-step visual instructions for Task 1 on the tablet screen. The screenshot is shown in its original Italian-language version

the target and BASE squares returned to white, and a message appeared in the center of the screen signaling the end. While Tasks 1 to 3 presented the green target at the center of the screen, Tasks 4 to 6 involved lateralized target presentations, in which the green square could appear to the left or right of the fixation cross. In Tasks 4 and 5, to assist participants, the borders of the upcoming target square were occasionally thickened before its color changed.

In contrast, task 6 increased task complexity by sometimes thickening the borders of a non-target square, thereby introducing a misleading cue intended to challenge the participant’s selective attention. Task 7 followed a modified Go–NoGo paradigm. In this condition, the central square could turn either green (Go) or red (NoGo). When green, participants were required to respond as in previous tasks—by touching the target and returning to the BASE. However,

when the square turned red, they were instructed to remain still and keep their finger on the BASE. This task specifically tested participants' response inhibition abilities (see Supplementary materials, SmartMe&You serious video games for details).

Throughout all tasks, the application automatically recorded the timing and accuracy of motor responses, as well as whether participants maintained finger contact with the Starting BASE during non-response intervals. Each task comprises a specific number of trials, depending on the experimental configuration. Visual cues at the start and end of each trial standardized transitions and ensured clarity for the participants.

This battery of tasks was designed to be intuitive, brief, and suitable for repeated use (e.g., in home telemonitoring).

Throughout all tasks, the application automatically records the timing and accuracy of motor responses, as well as whether participants continued finger contact with the starting blue square during non-response intervals. Each task comprises a specific number of trials, depending on the experimental configuration. Visual cues at the start and end of each trial standardized transitions and ensured clarity for the participants. Performance data are transmitted in real time to the web-based SmartMe&You-TELE-MAIA platform hosted on the GARR cloud infrastructure (<https://smartme.cloud.garr.it/>), where they are stored, displayed, and accessed for analysis by the research team.

For each SmartMe&You serious video game, performance was indexed by percent accuracy and reaction time (ms). In the present study, we considered the global SmartMe&You serious video games' percent accuracy and reaction time, calculated as the average across the 7 video games.

rsEEG recording

The rsEEG recordings were obtained using local, routine professional digital EEG systems licensed for clinical use. All rsEEG recordings were performed in the morning to minimize potential variations due to circadian rhythms. Standard instructions for the resting-state condition emphasized remaining awake and psychophysically relaxed, allowing mind wandering, and following the experimenter's requests to keep the eyes closed during the rsEEG recording (5 min). The experiments monitored the participants' behavioral state during the rsEEG recordings and annotated any deviations and alarms that occurred.

In line with previous studies from our group, ensuring methodological continuity and enhancing replicability, a common electrode montage of 19 scalp exploring electrodes, placed according to the 10–20 system (i.e., O1, O2, P3, Pz, P4, T3, T5, T4, T6, C3, Cz, C4, F7, F3, Fz, F4, F8, Fp1, and Fp2), characterized the EEG data recordings in all clinical units and was used for the data analysis. The reference electrode was typically placed between Fz and Cz of the 10–20 system, and the ground electrode was in the posterior midline. To minimize the influence of differences in reference electrode placement, all EEG data were re-referenced to the common average for data analysis.

Electrooculographic (EOG) activity, recorded using a standard bipolar montage, was also monitored to control eye movements and blinking. As a minimum standard in all clinical units, electrophysiological data were filtered using a bandpass of 0.3–70 Hz and a sampling rate of 256 Hz.

Preliminary rsEEG data analysis

The rsEEG data were centrally analyzed by experts at the Sapienza University of Rome unit, who were blinded to participants' diagnoses. The recorded rsEEG data were exported as a European data format (.edf) or EEGLAB set (.set) files and then processed offline using the EEGLAB toolbox [22] version eeglab14_1_2b) running in the MATLAB software (Mathworks, Natick, MA, USA; version: R2014b).

During preprocessing, the rsEEG data were divided into epochs of 2 s (i.e., 5 min = 150 rsEEG epochs of 2 s) and subjected to offline analysis. A three-step procedure was employed to detect and remove the following items: (i) recording channels (electrodes) showing prolonged artifactual rsEEG activity due to bad electric contacts or other reasons; (ii) rsEEG epochs with artifacts at recording channels characterized by generally good signals; and (iii) intrinsic components of the rsEEG epochs with artifacts.

The first step involved a visual analysis of the recorded rsEEG activity by two independent experimenters chosen from a panel of four experts (i.e., M.D.B., R.L., M.C., and G.N.). Their task was to identify electrodes affected by irremediable artifacts. Typically, no more than three electrodes were removed from each participant. In cases where the

clinical units used a digital EEG system with more than 19 electrodes, the removed electrodes were replaced with the nearest electrodes not among the 19 selected electrodes. These additional electrodes, along with the artifact-free selected electrodes, were then used to interpolate artifact-free rsEEG data at all scalp sites corresponding to the removed electrodes. This process, facilitated by the EEGLAB toolbox [22] version eeglab14_1_2b), ensured that all participants had artifact-free EEG data at the 19 selected electrode sites.

The second step involved a visual analysis of the recorded rsEEG activity by the experimenters above (i.e., M.D.B., R.L., M.C., and G.N.) to identify artifactual rsEEG epochs. These epochs were contaminated by muscular, ocular, and head movements, or by non-physiological artifacts, and were subsequently removed from the database. Notably, muscle tension artifacts were identified by careful observation of the effects of various frequency-bandpass filters and by inspection of EEG power-density spectra. These artifacts manifested as unusually high and stable values of EEG power density in the 30–70 Hz frequency range, in contrast to the typical decline observed in EEG power density from 25 Hz onward.

The third step involved applying independent component analysis (ICA) in EEGLAB to remove components representing residual artifacts. These artifacts included (i) blinking and eye movements, (ii) involuntary head movements, (iii) neck and shoulder muscle tensions, and (iv) electrocardiographic pulse activity [20, 38]. For each rsEEG dataset, fewer than 3 ICA components were removed from the original solutions, which were based on 19 ICA components. Subsequently, the rsEEG datasets were reconstructed with the remaining artifact-free ICA components. To ensure the integrity of the data, the putative artifact-free rsEEG epochs underwent visual double-checking by the independent experimenters (i.e., M.D.B., R.L., M.C., and G.N.). This step confirmed or finalized the inclusion or exclusion of each rsEEG epoch.

For harmonization purposes, the artifact-free EEG data for the common 19 electrodes were digitally frequency-band-passed at 0.1–45 Hz. They were also down-sampled, when appropriate, to ensure that the sampling rate of all artifact-free rsEEG datasets was 256 Hz. Furthermore, the EEG data were re-referenced to the common average reference.

Following these procedures, the artifact-free epochs exhibited a similar proportion (greater than 75%) of the total amount of rsEEG activity recorded across all participant groups (i.e., healthy and PDCD).

Spectral analysis of the rsEEG epochs

Standard digital Fast Fourier Transform (FFT)-based analysis, employing the Welch technique with a Hanning window and no phase shift, was used to compute the power density of artifact-free rsEEG epochs recorded at all 19 scalp electrodes, with a frequency resolution of 0.5 Hz.

The rsEEG frequency bands of interest were individually identified based on specific frequency landmarks, namely the transition frequency (TF) and the individual alpha frequency (IAF). In the (eyes-closed) rsEEG power density spectrum, the TF was defined as the minimum rsEEG power density between 3 and 8 Hz. In comparison, the IAF peak was defined as the maximum power density peak between 6 and 14 Hz [42–44]. The TF and IAF were computed for each participant involved in the study. Based on TF and IAF, individual delta, theta, and alpha bands were estimated as follows: delta from TF –4 Hz to TF –2 Hz, theta from TF –2 Hz to TF, low alpha (alpha 1 and alpha 2) from TF to IAF, and high-frequency alpha (or alpha 3) from IAF to IAF + 2 Hz. Specifically, the individual alpha 1 and alpha 2 bands were computed as follows: alpha 1 from TF to the frequency midpoint of the TF-IAF range and alpha 2 from that midpoint to the IAF peak. The other bands were defined using standard fixed-frequency ranges employed in the reference rsEEG studies of our Consortium [6–8]: beta 1 from 14 to 20 Hz, beta 2 from 20 to 30 Hz, and gamma from 30 to 40 Hz.

Estimation of rsEEG source activation

We used the official freeware tool, exact LORETA (eLORETA), to linearly estimate the cortical source activity underlying scalp-recorded rsEEG rhythms [62]. The current implementation of the eLORETA freeware employs a head volume-conductor model comprising the scalp, skull, and cerebral cortex. In the scalp compartment, the exploring electrodes can be virtually positioned to provide EEG data as input to source estimation [62]. The cortical model is based on a realistic cerebral shape derived from the Montreal

Neurological Institute (MNI152) template, typically used in neuroimaging studies. The EEG inverse problem is solved via weighted L2-norm minimization through an iterative process to ensure convergence. It iteratively finds weights that compensate for deeper sources, reducing the blurriness and improving accuracy from rsEEG data collected from 19 scalp electrodes.

For estimating EEG cortical source activities (i.e., the eLORETA solutions), the current input comprised EEG spectral power density computed at 19 scalp electrodes. This estimation is performed within the electrical cortical source space, which comprises 6,239 voxels at 5 mm resolution and is restricted to the cortical grey matter of the head volume-conductor model. Within each voxel, an equivalent current dipole is located to represent the mean ionic currents generated by the local populations of cortical pyramidal neurons. The eLORETA package provides the Talairach coordinates, the lobe, and the Brodmann area (BA) for each voxel of the cortical model. The resulting solutions estimate the associated “neural” current density values at any cortical voxel within the head volume conductor model for each frequency bin.

The eLORETA solutions from the rsEEG data were normalized by the following procedure. We averaged the eLORETA solutions across (i) all frequency bins from 0.5 to 45 Hz and (ii) 6,239 voxels of the cortical model to obtain the eLORETA “mean” solution. Afterward, we computed the ratio between any original eLORETA solution at a given frequency-bin/voxel and the eLORETA mean solution. As a result, any original eLORETA solution at a given frequency-bin/voxel changed to a normalized eLORETA solution.

Consistent with the low spatial resolution of the current EEG methodological approach (i.e., 19 scalp electrodes), we performed a global analysis of the eLORETA solutions. For this purpose, we collapsed the 6,239 eLORETA solutions. For the present eLORETA cortical source estimation, a frequency resolution of 0.5 Hz was used.

Main statistical analyses

Six main statistical analyses were conducted using the commercial software STATISTICA 10 (StatSoft Inc., www.statsoft.com) or the freeware tool jamovi 2.3 (www.jamovi.org). In the ANCOVAs, age,

education, and sex were used as covariates. Furthermore, the sphericity assumption was assessed using Mauchly’s test, and the Greenhouse–Geisser correction was applied when appropriate.

Statistical analysis #1: Group differences in SmartMe&You serious video games performance (working hypothesis 1)

Aim: To test that the performance of the global SmartMe&You serious video games may be worse in the PDCD group than in the healthy group.

Analysis: Two rank-transformed ANCOVAs were performed ($p < 0.05$, Bonferroni-corrected), with percent accuracy and reaction time from the SmartMe&You serious video games as dependent variables. The Rank transformation ANCOVAs included the factor group (healthy and PDCD).

Clinical implication: Significant group differences would support the use of SmartMe&You serious video games as a tool to detect cognitive decline in PDCD patients at the group level.

Statistical analysis #2: Classification accuracy of SmartMe&You serious video games performance (working hypothesis 2)

Aim: To test that the performance of the global SmartMe&You serious video games (i.e., percent accuracy and reaction time) may enable good classification between healthy and PDCD individuals.

Analysis: The following indexes measured the performance of the above binary classification: (i) sensitivity: the rate of positives who were correctly classified as positives (i.e., “true positive rate” in the signal detection theory); (ii) specificity: the rate of negatives (control) who were correctly classified as negatives (i.e., “true negative rate” in the signal detection theory); (iii) accuracy: the mean of the sensitivity and specificity (the number of subjects in the groups was the same); (iv) area under the receiver operating characteristic (AUROC) curve; and (v) confidence interval of AUROC. The AUROC curve served as the primary reference index.

Clinical Implication: High classification accuracy would indicate that SmartMe&You’s serious video games could serve as a practical, non-invasive screening tool for cognitive impairment.

Statistical analysis #3: Group differences in global rsEEG markers (control hypothesis 1)

Aim: To test that the global rsEEG source activities may differ between the healthy and PDCD groups.

Analysis: An ANCOVA was performed, with global rsEEG source activities (i.e., log10-transformed global normalized eLORETA solutions) as the dependent variable ($p < 0.05$). The ANCOVA included the factors Group (healthy and PDCD) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma). Post-hoc comparisons were conducted using the Duncan test ($p < 0.05$, Bonferroni corrected). Confirmation of that hypothesis required two criteria: (i) a statistically significant ANOVA interaction involving the Group factor ($p < 0.05$) and (ii) a post-hoc Duncan test revealing statistically significant ($p < 0.05$ Bonferroni corrected) differences in the global rsEEG source activities between the two groups (Healthy $\neq$ PDCD).

Clinical Implication: Identifying specific rsEEG differences may clarify neurobiological correlates of cognitive decline in PDCD.

Statistical analysis #4: Classification accuracy of global rsEEG markers (control hypothesis 2)

Aim: To test that the global rsEEG source activities may enable good classification between healthy and PDCD individuals.

Analysis: The following indices measured the performance of the above binary classification: sensitivity, specificity, accuracy, AUROC curve, and confidence interval of AUROC. The AUROC curve served as the primary reference index.

Clinical Implication: High classification accuracy would indicate that rsEEG markers serve as a practical, noninvasive screening tool for cognitive impairment.

Statistical analysis #5: Association between SmartMe&You serious video games performance and global cognitive status (working hypothesis 3)

Aim: To test that the performance of the SmartMe&You serious video games may be associated with the MMSE score, as a measure of

global cognitive status, in healthy and PDCD participants as a whole group.

Analysis: Two general linear models (GMLs; $p < 0.05$ Bonferroni corrected) were implemented. The global percent accuracy and reaction time of the Serious Video Games in the SmartMe&You study were used as predictors. The MMSE score was used as the dependent variable.

Clinical Implication: A positive association would indicate that SmartMe&You's serious video game performance reflects global cognitive abilities and could serve as a remote cognitive assessment tool.

Statistical analysis #6: Association between global rsEEG markers and SmartMe&You serious video games performance (working hypothesis 4)

Aim: To test that the global rsEEG source activities may be associated with the global performance of the SmartMe&You serious video games in healthy and PDCD participants as a whole group.

Analysis: Several GMLs ($p < 0.05$, Bonferroni corrected) were implemented. The global rsEEG source activities (log10-transformed) that showed statistically significant differences between the healthy and PDCD groups were used as predictors. The percent accuracy and reaction time of the global SmartMe&You serious video games were used as dependent variables.

Clinical Implication: A positive association would indicate that neurophysiological abnormalities may directly impair neural processes required for successful performance on the SmartMe&You video games

The potential impact of outliers on the statistical results was evaluated using the iterative (leave-one-out) Grubbs' test to detect outliers. The null hypothesis of non-outlier status was tested at the threshold $p > 0.001$ to exclude individual values with a high probability of being outliers.

Aim: To test that the performance of the SmartMe&You serious video games may be associated with the MMSE score, as a measure of global cognitive status, in healthy and PDCD participants as a whole group.

Analysis: Two general linear models (GMLs; $p < 0.05$ Bonferroni corrected) were implemented. The global percent accuracy and reaction time of

the Serious Video Games in the SmartMe&You study were used as predictors. The MMSE score was used as the dependent variable.

Clinical Implication: A positive association would indicate that SmartMe&You's serious video game performance reflects global cognitive abilities and could serve as a remote cognitive assessment tool.

Results

Group differences in SmartMe&You serious video games performance (working hypothesis 1)

All healthy individuals and the vast majority of enrolled PDCD patients (90%) accepted the procedure well and were able to play the SmartMe&You serious video games unsupervised. Unsupervised use of the SmartMe&You platform appears feasible in participants with an MMSE score > 15 and relatively preserved functional autonomy, defined as ADL and IADL scores ≥ 2 .

Table 3 reports the mean values ($\pm$ SE) for percent accuracy and reaction time for the global SmartMe&You serious video games across the healthy and PDCD groups. The results of the statistical comparisons among the healthy and PDCD groups are also presented (rank-transformed ANCOVA). Age, education, and sex were used as covariates. To consider the inflationary effects of repetitive univariate tests, the statistical threshold was set at $p < 0.025$ (i.e., 2 performance indexes, $p < 0.05/2 = 0.025$) to obtain the Bonferroni correction at $p < 0.05$. Statistically significant differences were found for: (i) the global percent accuracy ($F = 48.6$, $p < 0.00001$), with lower percent accuracy in the PDCD group than in the healthy group; and (ii) the global

reaction time ($F = 17.1$, $p < 0.0001$), with slower reaction time in the PDCD group than in the healthy group.

The findings above were not attributable to outliers in the accuracy and reaction time values of the individual SmartMe&You video games, as shown by a Grubbs test with an arbitrary threshold of $p > 0.001$ (see Figure S1 of the Supplementary Materials, SmartMe&You serious video game performance in healthy and PDCD groups, for details).

Classification accuracy of SmartMe&You serious video games performance (working hypothesis 2)

The global SmartMe&You serious video game's percent accuracy and reaction time served as discriminant input variables for computing the AUROC curves. These AUROC curves were used to index classification accuracy in distinguishing healthy vs. PDCD individuals. The results of this analysis are reported in Table 4. The contrast between healthy and PDCD individuals showed an AUROC of 0.920 for global percent accuracy and an AUROC of 0.767 for global reaction time (see Figure S2 of the Supplementary Materials, SmartMe&You serious video game performance in healthy and PDCD groups, for details).

Group differences in global rsEEG markers (control hypothesis 1)

The mean TF was 6.1 Hz (± 0.2 SE) in the healthy group and 4.8 Hz (± 0.2 SE) in the PDCD group. Furthermore, the mean IAF was 9.6 Hz (± 0.1 SE) in the healthy group and 7.5 Hz (± 0.2 SE) in the PDCD

Table 3 Mean values ($\pm$ SE) of the global performance (i.e., percent accuracy and reaction time) on the serious video games of the SmartMe&You home telemonitoring platform in the healthy and PDCD groups. The performance values were calculated as the average of the accuracy and reaction time across the seven serious video games. The results of the statistical comparisons (Rank transformation ANCOVA; $p < 0.05$,

Bonferroni corrected) are also included. Age, education, and sex were used as covariates in the statistical models. Abbreviations: Healthy, cognitively unimpaired older adults; PDCD, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease; SE, standard error of the mean

Global SmartMe&You serious video games performance

Global SmartMe&You performance	Healthy	PDCD	Rank transformation ANCOVA
Accuracy (%)	92.0 $\pm$ 1.2 SE	62.3 $\pm$ 2.8 SE	$F = 48.6$, $p < 0.00001$
Reaction time (ms)	295 $\pm$ 12 SE	396 $\pm$ 14 SE	$F = 17.1$, $p < 0.0001$

Table 4 Results of the classification between healthy vs PDCD individuals based on the global performance (i.e., percent accuracy and reaction time) on the serious video games of the SmartMe&You home telemonitoring platform. Abbreviations:

AUROC, Area Under the Receiver Operating Characteristic curve; Healthy, cognitively unimpaired older adults; PDCD, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

Classification of healthy vs PDCD individuals based on the global SmartMe&You serious video games performance

Groups	Global SmartMe&You performance	Specificity (%)	Sensitivity (%)	Accuracy (%)	AUROC
Healthy vs PDCD	Accuracy	79.4	89.7	86.3	0.920
	Reaction time	44.1	86.6	72.5	0.767

group. Two ANCOVAs were conducted to assess whether there were statistically significant differences between the two groups in TF and IAF. Age, education, and sex were used as covariates. To consider the inflationary effects of repetitive univariate tests, the statistical threshold was set at $p < 0.025$ (i.e., 2 frequency landmarks, $p < 0.05/2 = 0.025$) to obtain the Bonferroni correction at $p < 0.05$. Statistically significant differences were found for: (i) the TF ($p < 0.00001$), with slower TF in the PDCD group than in the healthy group; and (ii) the IAF ($p < 0.00001$), with slower IAF in the PDCD group than in the healthy group.

Figure 2 shows the mean values ($\pm$ SE; log 10 transformed) of the global rsEEG source activities (i.e., global normalized eLORETA current densities) relative to a statistically significant ANCOVA interaction effect ($F = 8.5$ $p < 0.00001$) between the factors group (healthy and PDCD) and band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma). Age, education, and sex were used as covariates.

The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 8 frequency bands, $p < 0.05/8 = 0.00625$) showed that the discriminant pattern healthy < PDCD was fitted by the global rsEEG delta, theta and alpha 1 source activities ($p < 0.00001$).

The findings above were attributable to outliers in the individual global and regional rsEEG source activities, as indicated by a Grubbs' test with an arbitrary threshold of $p > 0.001$.

Classification accuracy of global rsEEG markers (control hypothesis 2)

The global rsEEG source activities showing statistically significant ($p < 0.05$ Bonferroni corrected) differences between the healthy and PDCD groups (i.e., global delta, global theta, global alpha 1 eLORETA

current densities; log 10 transformed) served as discriminant input variables for the computation of the AUROC curves. These AUROC curves were used to index classification accuracy in distinguishing healthy vs. PDCD individuals. The results of this analysis are reported in Table 5. The contrast between healthy and PDCD individuals showed an AUROC value higher than 0.8 (i.e., good classification) with the global delta (AUROC = 0.868), global theta (AUROC = 0.841), global alpha 1 (AUROC = 0.820) source activities.

Association between SmartMe&You serious video games performance and global cognitive status (working hypothesis 3)

GLMs assessed the association between performance on the global SmartMe&You serious video games (i.e., percent accuracy and reaction time) and MMSE scores, as measures of global cognitive status, in healthy and PDCD participants as a whole group. A conservative statistical threshold at $p < 0.025$ (i.e., Bonferroni correction at $p < 0.05$ for 2 global SmartMe&You serious video games performance indexes, $p < 0.05/2 = 0.025$) was set to consider the inflationary effects of repetitive univariate tests. The results of this analysis are reported in Table 6. There was a statistically significant positive association between the percent accuracy of the global SmartMe&You serious video games and the MMSE score ($\beta = 0.662$, $t = 7.1$, $p = 0.00001$). Furthermore, there was a statistically significant negative association between the reaction time in the global SmartMe&You serious video games and the MMSE score ($\beta = -0.283$, $t = -3.2$, $p = 0.0001$). Figure 3 shows scatterplots illustrating a strong relationship between performance on the global SmartMe&You serious video games (i.e., percent accuracy and reaction time) and MMSE score.

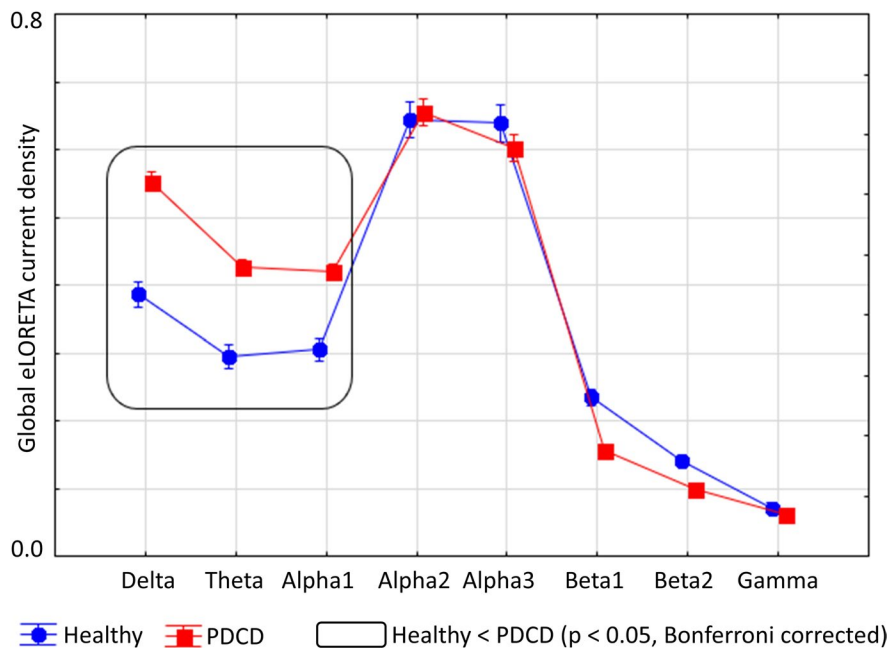


Fig. 2 Mean values ($\pm$ SE; log 10 transformed) of the global rsEEG source activities relative to a statistical ANCOVA interaction effect ($F=8.5$, $p<0.00001$) between the factors Group (healthy and PDCD) and Band (delta, theta, alpha1, alpha2, alpha3, beta1, beta2, and gamma). Age, education, and sex were used as covariates. The rectangles indicate the frequency bands in which the rsEEG source activities statistically presented a significant pattern, as indicated by the following com-

parison: Healthy < PDCD (i.e., $p<0.05$, Bonferroni corrected). Abbreviations: ROI=region of interest; rsEEG=resting state electroencephalographic; eLORETA=exact Low-Resolution Brain Electromagnetic Source Tomography; Healthy=cognitively unimpaired older adults; PDCD=patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

Table 5 Results of the classification between healthy vs PDCD individuals based on the global rsEEG source activities (i.e., global delta, global theta, global alpha 1 eLORETA current densities; log 10 transformed). Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; rsEEG, resting state electroencephalographic;

eLORETA, exact Low-Resolution Brain Electromagnetic Source Tomography; Healthy, cognitively unimpaired older adults; PDCD, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

Classification of healthy vs PDCD individuals based on rsEEG markers

Groups	rsEEG markers	Specificity (%)	Sensitivity (%)	Accuracy (%)	AUROC	CI (95%)
Healthy vs PDCD	Global delta	76.5	88.2	84.3	0.868	0.79–0.94
	Global theta	55.9	86.8	76.5	0.841	0.76–0.92
	Global alpha1	58.8	83.8	75.5	0.820	0.73–0.90

Association between global rsEEG markers and SmartMe&You serious video games performance (working hypothesis 4)

GLMs assessed the association between the global rsEEG markers and performance on the global SmartMe&You serious video games (i.e., percent

accuracy and reaction time) in the healthy and PDCD participants as a whole group. The global rsEEG markers were those that showed statistically significant differences between the healthy and PDCD groups (i.e., global delta, global theta, and global alpha 1 source activities; log10-transformed). A conservative statistical threshold at $p<0.00833$ (i.e., Bonferroni correction at p

Table 6 Results of general linear models (GLMs) assessing the association between the global performance (i.e., percent accuracy and reaction time) on the serious video games of the SmartMe&You home telemonitoring platform (predictors) and the MMSE score (dependent variable), as a measure of the global cognitive status, in the healthy and PDCD participants as a whole group ($p < 0.05$). Age, education, and sex

General linear models (GLMs) assessing the association between the global SmartMe&You video game performance and the MMSE score

Predictor: global SmartMe&You performance	Dependent variable: global cognitive status	β standardized	t	p
Accuracy	MMSE score	0.662	7.1	0.00001
Reaction time	MMSE score	-0.283	-3.2	0.0001

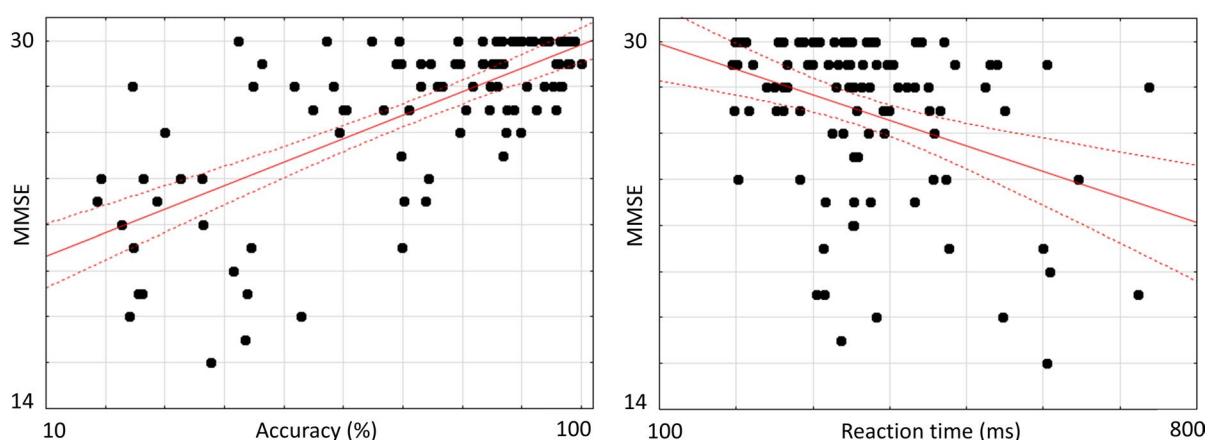


Fig. 3 Scatterplots illustrating the association between the global performance (i.e., percent accuracy and reaction time) on the serious video games of the SmartMe&You home telemonitoring platform and the MMSE score, as a measure of the global cognitive status, in the healthy and PDCD participants

< 0.05 for 3 rsEEG markers X 2 global SmartMe&You serious video games performance indexes, $p < 0.05/6 = 0.00833$) was set to consider the inflationary effects of repetitive univariate tests. The results of this analysis are reported in Table 7. There were statistically significant negative associations between the global SmartMe&You serious video games percent accuracy and the global delta ($\beta = -0.329$, $t = -3.91$, $p = 0.0001$), theta ($\beta = -0.311$, $t = -3.75$, $p = 0.0003$), and alpha 1 ($\beta = -0.254$, $t = -3.11$, $p = 0.002$) rsEEG source activities. Furthermore, there were statistically significant positive associations between the global SmartMe&You serious video games reaction time and the global delta ($\beta = 0.420$, $t = 4.06$, $p = 0.0001$), theta

were used as covariates. Standardized β , t , and p values are reported for each GLM. Values at $p < 0.05$ Bonferroni corrected ($p = 0.05/2 = 0.025$) are reported in bold. Abbreviations: MMSE, Mini-Mental State Evaluation; Healthy, cognitively unimpaired older adults; PDCD, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

as a whole group. Abbreviations: MMSE=Mini-Mental State Evaluation; Healthy=cognitively unimpaired older adults; PDCD=patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

($\beta = 0.332$, $t = 3.22$, $p = 0.002$) rsEEG source activities. Figures 4 and 5 present scatterplots illustrating a strong relationship between the performance on the global SmartMe&You serious video games and global rsEEG source activities.

Control analyses

We performed six additional control analyses to understand the core results better.

The first additional analysis revealed the same abovementioned results on SmartMe&You video game performance and rsEEG markers in demographic-matched subgroups (i.e., groups with the same mean

Table 7 Results of general linear models (GLMs) assessing the association between the global rsEEG source activities (i.e., global delta, global theta, global alpha 1 eLORETA current densities; predictors) and the global performance (i.e., percent accuracy and reaction time) on the serious video games of the SmartMe&You home telemonitoring platform (dependent variables) in the healthy and PDCD participants as a whole group. Age, education, and sex were used as covari-

ates. Standardized β , t , and p values at $p < 0.05$ are reported. Values at $p < 0.05$ Bonferroni corrected ($p = 0.05/6 = 0.00833$) are reported in bold. Abbreviations: *rsEEG*, resting state electroencephalographic; *eLORETA*, exact Low-Resolution Brain Electromagnetic Source Tomography; *Healthy*, cognitively unimpaired older adults; *PDCD*, patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

General linear models (GLMs) assessing the association between rsEEG markers and global SmartMe&You serious video game performance

Predictor: rsEEG markers	Dependent variable: global SmartMe&You performance	β standardized	t	p
Global delta	Accuracy	-0.329	-3.91	0.0001
Global delta	Reaction time	0.420	4.06	0.0001
Global theta	Accuracy	-0.311	-3.75	0.0003
Global theta	Reaction time	0.332	3.22	0.002
Global alpha1	Accuracy	-0.254	-3.11	0.002
Global alpha1	Reaction time	0.219	2.12	0.03

values for age, gender, and sex ratio) of 25 healthy and 28 PDCD participants, unveiling that the main findings were not due to group imbalance and statistically significant differences in age, education, and sex between healthy and PDCD groups.

The second additional analysis revealed that regional rsEEG markers differed between the healthy and PDCD groups and enabled good classification between healthy and PDCD individuals. Furthermore, it revealed that regional rsEEG markers were associated with the global performance of the SmartMe&You serious video games in healthy and PDCD participants as a whole group.

The third additional analysis revealed a strong correlation between global SmartMe&You video game performance and performance in episodic memory, language, and planning/visuospatial abilities across healthy and PDCD participants.

The fourth additional analysis revealed that PDCD patients performed markedly worse on the seven SmartMe&You serious video games than the healthy group. Compared with healthy participants, patients with PDCD showed lower accuracy and slower reaction times in the seven SmartMe&You Serious video games. Furthermore, good accuracy in classifying healthy participants versus PDCD patients was observed, based on the percent accuracies across the seven SmartMe&You video games.

The fifth additional analysis showed that the results observed for SmartMe&You video games in the

hospital environment were also replicated in the first session conducted at home, thereby demonstrating that SmartMe&You video games are suitable for unsupervised use by PDCD participants in a home setting.

Finally, the sixth additional analysis revealed a strong association between age and overall SmartMe&You video game percent accuracy across healthy and PDCD participants.

The detailed results were reported in the Supplementary Materials.

Discussion

Performance on the SmartMe&You video games and cognitive status in PDCD patients

A novel finding from this study was that all healthy individuals and the vast majority of enrolled PDCD patients (90%) accepted the procedure well and were able to play the SmartMe&You serious video games unsupervised. The only exceptions were some of the PDCD patients with moderate dementia and caregivers with insufficient digital skills. Furthermore, PDCD patients performed markedly worse on the SmartMe&You serious video games than the healthy group, as expected. Compared with healthy participants, patients with PDCD showed lower accuracy and slower reaction times in the seven SmartMe&You Serious video games. When considering performance across

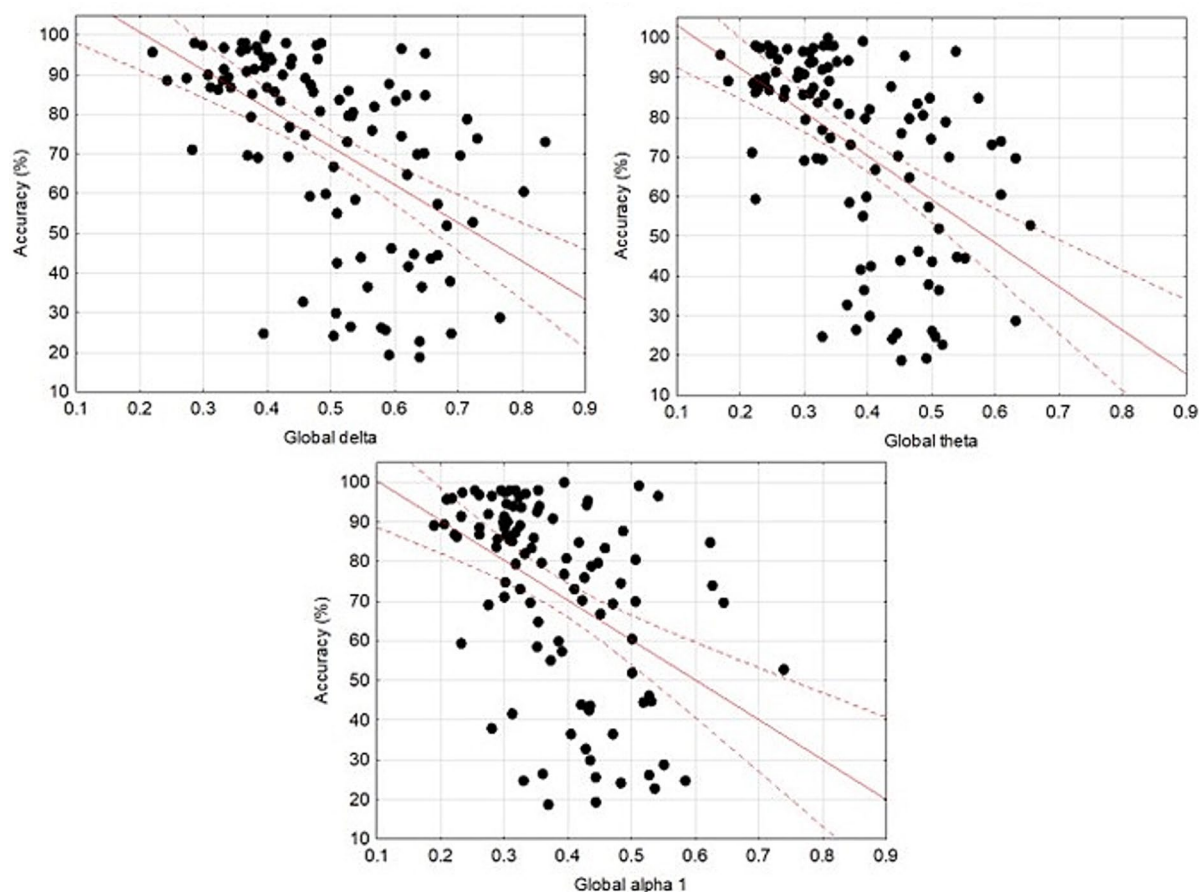


Fig. 4 Scatterplots showing the association between the global rsEEG source activities in slow frequency bands (i.e., global delta, global theta, and global alpha 1 eLORETA current densities; log 10 transformed) and the global percent accuracy on the serious video games of the SmartMe&You home telemonitoring platform in the healthy and PDCD participants as

a whole group. Abbreviations: rsEEG=resting state electroencephalographic; eLORETA=exact Low-Resolution Brain Electromagnetic Source Tomography; Healthy=cognitively unimpaired older adults; PDCD=patients with mild cognitive impairment and mild-moderate dementia due to Parkinson's disease

a single SmartMe&You task (i.e., visual non-spatial reaction-time task, visuospatial attention task, visual non-spatial attention task, short-term visuospatial episodic memory task, short-term visual non-spatial episodic memory task, modified Posner's task, modified Go-NoGo task), these differences were confirmed. These differences appeared particularly pronounced ($p < 0.000005$) in visuospatial attention, visual non-spatial attention, short-term visual non-spatial episodic memory task, and modified Go-NoGo tasks requiring visuo-spatial and non-spatial abilities and the ability to refrain from impulsive motor responses.

Another novel finding was high accuracy (i.e., AUROC > 0.9) in classifying healthy participants

versus PDCD patients, based on the global SmartMe&You video game's percent accuracy. When considering a single SmartMe&You task, this good classification accuracy was confirmed. Furthermore, the performance (i.e., percent accuracy and reaction time) on the global SmartMe&You serious video games was associated with the MMSE score (a measure of global cognitive status) in healthy and PDCD participants as a whole group. The higher the performance (i.e., the lower accuracy and slower reaction time) of the SmartMe&You video games, the higher the neuropsychological test scores. These results are in agreement with previous evidence that computerized cognitive tasks are an effective means

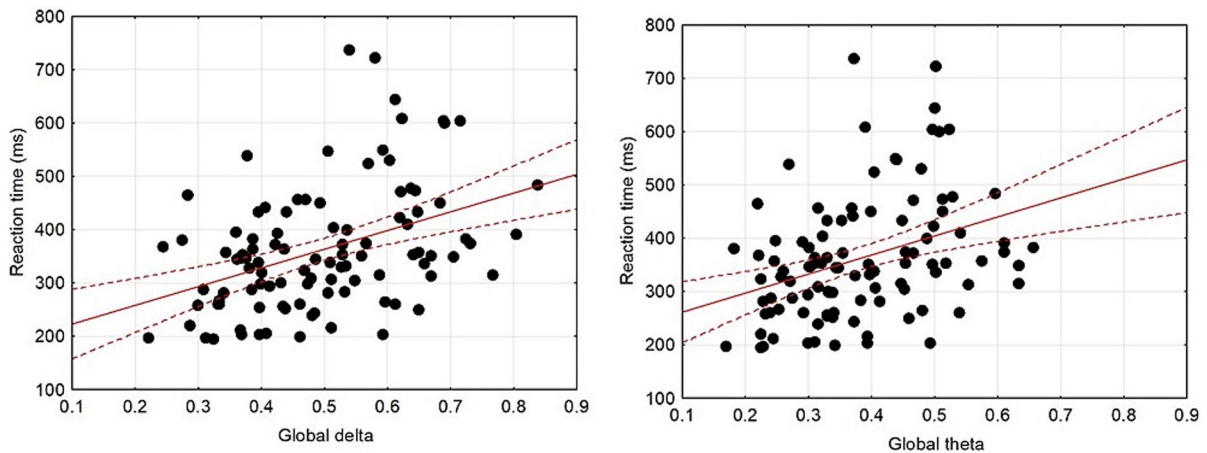


Fig. 5 Scatterplots showing the association between the global rsEEG source activities in slow frequency bands (i.e., global delta and global theta eLORETA current densities eLORETA current densities; log 10 transformed) and the global reaction time on the serious video games of the SmartMe&You home

to assess cognitive decline in patients with MCI and dementia [12, 15, 34, 39, 61, 70, 71, 81].

Overall, these new findings suggest that SmartMe&You's video games can be used to detect cognitive deficits in patients with MCI and in most patients with mild-to-moderate dementia due to PD. As such, these video games have the potential to serve as a reliable, unsupervised digital home telemonitoring cognitive battery for periodic assessment of cognitive status in patients with PDCD, supporting monitoring at planned follow-ups every 6–12 months throughout the disease course. Additionally, they may be used to assess the effects of pharmacological and non-pharmacological (e.g., non-invasive brain stimulation) interventions on cognitive functions in clinical practice and trials (e.g., even in phase 4), particularly in vigilance, spatial attention, and executive functions. These effects may be partly explained by key structural features of the SmartMe&You serious games, such as adaptive difficulty levels that dynamically match task demands to individual performance, multimodal stimulation (e.g., combined visual and motor engagement) that enhances cognitive load and ecological validity, and reinforcement mechanisms that promote sustained engagement and learning. Together, these characteristics may preferentially target and modulate specific neurocognitive processes. This potential opens up

telemonitoring platform in the healthy and PDCD participants as a whole group. Abbreviations: rsEEG=resting state electroencephalographic; eLORETA=exact Low-Resolution Brain Electromagnetic Source Tomography; Healthy=cognitively unimpaired

exciting possibilities for future research and clinical applications in patients with neurodegenerative diseases.

Performance on the SmartMe&You video games and rsEEG rhythms in PDCD patients

An interesting and novel finding was the association between performance (i.e., percent accuracy and reaction time) on the SmartMe&You serious video games and slowed rsEEG rhythms in patients with PDCD. The more widespread rsEEG delta and theta rhythms, the lower performance on those video games (i.e., lower accuracy and slower reaction time). These results suggest that in patients with PDCD, abnormal neurophysiological synchronization of brain oscillations at delta, theta, and alpha frequencies, reflecting dysfunction in cortical arousal and vigilance regulation, is associated with poor performance on the SmartMe&You serious video games, as hypothesized. The neurophysiological mechanisms explaining the relationship between poor cognitive performance on the SmartMe&You video games and the slowing of rsEEG rhythms cannot be derived from the present finding. Rather, it can be speculated that these mechanisms may be related to “thalamocortical dysrhythmia” and abnormal functioning of subcortical neuromodulatory systems.

According to the theory of “thalamocortical dysrhythmia” [37, 50, 51], older individuals with PD and other neurological disorders who exhibit cognitive and motor deficits are expected to show aberrant rsEEG delta and theta rhythms widespread over the scalp, associated with a reduction in amplitude of posterior rsEEG alpha rhythms. This effect on rsEEG rhythms would be due to a “slowing” of cortical pyramidal neuron activity to frequencies below 7 Hz. It would arise from an abnormally prominent “bursting mode” of thalamocortical and corticothalamic circuit neurons, triggered by reduced excitatory input to thalamic relay cells [37, 50, 51]. However, given the limited spatial resolution of the present EEG montage, these interpretations should be considered indirect and hypothesis-generating rather than direct evidence of specific underlying thalamocortical mechanisms. Such a “bursting mode” in thalamocortical and corticothalamic neurons may also interfere with the transition from quiet vigilance to focused visuospatial attention and effective executive functions during performance on the SmartMe&You video games.

The “thalamocortical dysrhythmia” in PDCD patients may also be linked to dysfunction in excitatory input to thalamocortical and corticothalamic neurons from subcortical activating systems, including cholinergic, noradrenergic, dopaminergic, and histaminergic pathways [14, 24, 65].

Overall, the present results in patients with PDCD suggest that the observed slowing of rsEEG rhythms during quiet wakefulness, characterized by increased rsEEG delta and theta rhythms and decreased rsEEG alpha rhythms, may reflect an underlying “thalamocortical dysrhythmia” driven by dysfunction in subcortical neuromodulatory systems. These neurophysiological abnormalities may directly impair neural processes required for successful performance on the SmartMe&You video games, which demand sustained attention, visuospatial processing, and executive control.

Methodological remarks

A first limitation of the study is the low spatial resolution of the current EEG techniques. EEG data were recorded from 19 scalp electrodes (10–20 International System). Fine-grained spatial analyses typically require electrode densities of at least 32–48 electrodes [49, 54]. We adapted the EEG

methodological approach to the limited electrode montage available (i.e., 19 scalp electrodes) for the EEG source estimation. We used an EEG source estimation technique intrinsically designed to map distributed source activity, namely eLORETA [62]. Furthermore, EEG source estimation focused on global source activity (i.e., the 6,239 eLORETA solutions were collapsed). Moreover, in Supplementary Materials, EEG source estimation on five broad cortical regions suitable for investigating low spatial-frequency components of ongoing EEG rhythms, which can be adequately sampled with the 10–20 system. These components were extensively studied to identify “microstates” in ongoing EEG activity [41, 47, 57]. These “microstates” are quasi-stable topographic voltage patterns characterized by two large centroids of positive and negative potential that shift across the scalp. They are generated by widely distributed cortical networks, as revealed by resting-state functional MRI, and can be investigated using a 10–20 montage system [41, 57]. Based on these considerations and data, the International Federation of Clinical Neurophysiology has endorsed the use of EEG source estimation from rsEEG data obtained with this montage in exploratory studies on neurological and psychiatric patient databases [7].

A second limitation of the study is that baseline levels of digital literacy and prior experience with tablet devices were not formally assessed here. As familiarity with touch-based interfaces may influence task performance, this represents a potential limitation. Participants with greater prior exposure to digital technologies may have been advantaged, which could have affected potentially affecting the results. Future research should consider including a standardized measure of digital literacy or collecting information on prior device use to better control for this variable.

Conclusions

The SmartMe&You unsupervised video games have been designed to measure cognitive functions underpinning vigilance regulation, visuospatial attention, and executive functions in patients with PDCD and other neurodegenerative diseases. In the present study, we tested the SmartMe&You video games in patients with PDCD compared with control participants.

The results showed that almost all patients with PDCD accepted and used the SmartMe&You video games at home unsupervised by medical and paramedical personnel. These results also showed an association between poor performance on those video games and MMSE score, a measure of global cognition. Furthermore, this poor performance was associated with slowed rsEEG rhythms in patients with PDCD. This slowing was manifested as widespread, abundant rsEEG rhythms at delta and theta frequencies, as well as reduced posterior rsEEG alpha rhythms. It has been speculated that the effects may be due to pathological mechanisms of thalamocortical dysrhythmia that may interfere with vigilance regulation, visuospatial attention, and executive functions required for good performance on the SmartMe&You video games.

Notably, the abovementioned results observed for SmartMe&You video games in the hospital environment were also replicated in the first session conducted at home, thereby demonstrating that SmartMe&You video games are suitable for unsupervised use by PDCD participants in a home setting.

Overall, the SmartMe&You serious video games may represent a useful, practical, free, “green”, and unsupervised digital tool for assessing cognitive status in patients with PDCD. While the potential application in telemonitoring frameworks is promising, the present cross-sectional design does not allow conclusions regarding trajectories of cognitive decline. Therefore, any role in tertiary prevention must be considered a prospective application requiring validation through future longitudinal studies. In this context, tertiary prevention encompasses all strategies aimed at slowing disease progression following diagnosis. These include not only pharmacological interventions and non-invasive brain stimulation protocols, but also — and perhaps more fundamentally—lifestyle modifications targeting established modifiable risk factors: reducing intake of animal fats and refined sugars, limiting alcohol consumption, increasing physical activity, fostering socio-affective engagement, and improving sleep quality and duration. The SmartMe&You serious video games could contribute to this framework as a monitoring tool embedded within intervention studies designed to evaluate the impact of such strategies on cognitive trajectories, rather than as an intervention in itself.

Future research should aim to validate these digital biomarkers in larger, more diverse cohorts, assess their sensitivity to longitudinal cognitive change, and integrate them with other digital and biological indicators to enhance precision in dementia risk profiling and monitoring.

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Author contribution RL and CDP contributed to conceptualization, methodology, data curation, investigation, formal analysis, validation, writing of the original draft, supervision, and project administration. CB, FS, PB, and AA contributed to conceptualization, funding acquisition, resources, methodology, writing of the original draft, supervision, and project administration. FG contributed to conceptualization, resources, methodology, writing of the original draft, and supervision. AC, CC, EF, and MDB contributed to participant recruitment, data acquisition, data curation, resources, supervision, and

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Data Availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Consent to participate and publication Informed consent was obtained from all participants.

Competing interests The authors declare no competing interests.

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