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ORIGINAL ARTICLE

Effect of simultaneous exercise and cognitive training on executive functions, baroreflex sensitivity, and pre-frontal cortex oxygenation in healthy older adults: a pilot study

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Abstract Aging is characterized by cognitive decline affecting daily functioning. To manage this socio-economic challenge, several non-pharmacological methods such as physical, cognitive, and combined training are proposed. Although there is an important interest in this subject, the literature is still heterogeneous. The superiority of simultaneous training compared to passive control and physical training alone seems clear but very few studies compared simultaneous training to cognitive training alone. The aim of this pilot study was to investigate the effect of simultaneous exercise and cognitive training on several cognitive domains in healthy older adults, in comparison with either training alone. Thirty-five healthy older adults were randomized into one of three experimental groups: exercise training, cognitive training, and simultaneous exercise and cognitive training. The protocol involved two 30-min sessions per week for 24 weeks. Cognitive performance in several domains, pre-frontal cortex oxygenation, and baroreflex sensitivity were assessed before and after the intervention. All groups improved executive performance, including flexibility or working memory. We found a group by time interaction for inhibition cost ($F_{(2,28)} = 6.44$; $p < 0.01$) and baroreflex sensitivity during controlled breathing ($F_{(2,25)} = 4.22$; $p = 0.01$), the magnitude of improvement of each variable being associated ($r = -0.39$; $p = 0.03$). We also found a decrease in left and right pre-frontal cortex oxygenation in all groups during the trail making test B. A simultaneous exercise and cognitive training are more efficient than either training alone to improve executive function and baroreflex sensitivity. The results of this study may have important clinical repercussions by allowing to optimize the interventions designed to maintain the physical and cognitive health of older adults.

Keywords Exercise training · Cognitive training · Simultaneous training · Motor-cognitive dual-task training · Healthy aging · Cognition

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Introduction

Aging process is associated with a normal cognitive decline, which may affect well-being, quality of life and ultimately autonomy and life expectancy [1]. Cognition covers a wide range of mental capacities

necessary to perceive, process, and interact with our environment [2]. Normal aging is associated with a decline in cognitive functions such as processing speed, memory, and executive functions [3]. In addition to some specific neuro-anatomical and functional changes in the brain [4], age-related changes in the cardiovascular system are also involved in this cognitive decline [5–8]. In fact, an alteration of cardiac autonomic control, and more specifically of baroreflex sensitivity (BRS), as well as decrease in cerebral perfusion and cerebral oxygenation, have been shown to increase the risk of cognitive impairment [9].

Cognitive functions are influenced by many physiological factors and to a large extent by cardiovascular mechanisms. During the ageing process, the development of cognitive dysfunction and dementia can be attributed to cerebral and vascular disorders [10]. In particular, many chronic diseases affect cerebral blood flow and explain an accentuated cognitive decline. It is well known that our cognitive functions are influenced by CBF as shown by numerous studies modulating CBF and affecting cognitive function [11–14]. One would expect that CBF and its regulation would be a key factor in the modification of cognitive function. Furthermore, cerebral metabolism and in particular cerebral oxygenation may be as important in influencing cognitive function, rather than changes in CBF [15, 16]. Indeed, several studies in exercise or at rest have shown that executive functions are influenced by cerebral oxygenation [17–19]. All these mechanisms are themselves under the direct influence of arterial baroreflex [15]. A direct association between the arterial baroreflex and cerebral circulation, via the autonomic nervous system, has been demonstrated in some animal models [20–22]. In human models, several studies have shown a direct association between baroreflex activity and cognitive functioning [23], and the perturbation of baroreflex activity during aging process explains the perturbation of memory functions [24]. Indeed, many brain structures involved in many cognitive functions are also responsible for the regulation of the baroreflex [25, 26] and could explain the association between cognitive functioning and baroreflex activity. For example, an original article incorporating a wide range of these physiological mechanisms [27], showed that baroreflex activity in older subjects, is associated to better aortic stiffness and white matter integrity, all this combined with better cognition in the Trail test.

The demographic transition toward an older society is not the only cause of these alterations. Life habits also play a major role, since physical inactivity and sedentary behaviors have been associated with reduced cognitive performances [28]. Yet, the level of physical activity in western countries decreased continuously over the past decades, while the duration of sedentary behaviors increased dramatically [29]. The consequence is an increase in the incidence of cognitive impairment in the near future, that is expected to double within the next 20 years [30]. In this context, one of the main challenges consists in developing efficient strategies to strengthen the "cognitive reserve" of the elderly [31]. Fortunately, interventions aimed at mitigating cognitive decline are attracting great research and societal interest. To date, two strategies have been used to prevent cognitive decline and of dementia: (i) cognitive training and (ii) exercise training [32, 33].

There is growing epidemiological evidence showing the importance of cognitive stimulation in the prevention of cognitive decline and dementia [1]. From an ecological point of view, La Rue (2010) showed a link between the frequency of activities like lecture, puzzles, knitting, or gardening and the 4-year risk of neurogenerative diseases [33]. Furthermore, several cross-sectional studies have also shown that cognitive stimulation was negatively associated with brain beta-amyloid plaque (a sign associated with Alzheimer's disease) [34] or atrophy of the brain hippocampus [35]. Lastly, recent meta-analyses and reviews have reported that cognitive training was also effective in improving cognitive function in older people [36]. On the other hand, there is an important bulk of knowledge showing a close relationship between physical activity and performance in several cognitive domains in the elderly [4, 37–40], or the risk of dementia [41]. Several mechanisms have been proposed to understand this beneficial effect of physical activity and/or exercise training, including a reduction in inflammation or the promotion of neurovascular integrity and brain plasticity through hormones and growth factors release [42–44].

Considering the positive impact of exercise training or cognitive training on the cognitive health of the elderly when they are implemented separately, we could question the interest of combining these two types of training within the same intervention. In fact, synergistic effects between both strategies

can be expected, thus inducing greater benefits than those obtained by each intervention alone [45]. For example, exercise training may improve brain plasticity by increasing cell proliferation and synaptic plasticity, while cognitive training may orientate this plasticity toward the brain areas solicited during cognitive exercises by increasing the number of neurons in pre-existing neural networks [45, 46]. This is at least what suggests a study [47] who showed in mices that exercise combined with a sequence of enriched environment yielded an approximately 30% greater increase in new neurons than either stimulus alone. On their side, Smith and colleagues [48] reported that exercise combined with cognitive training resulted in a greater cognitive improvement in mices than either stimulus alone, thus suggesting that adaptations reported by Fabel et al. [47] may have functional consequences on these animals. Results are more equivocal in humans, since recent narrative reviews [49–51], systematic reviews [52–54], and meta-analyses [55–59] have reported conflicting results. The positive benefits of combined exercise and cognitive training on cognitive performances in the elderly is unanimous. What is debated is rather the superiority of this combined training when compared with either training alone, since the difference between conditions is not systematic. One of the reasons for this heterogeneity is the diversity of protocols used to achieve this double stimulation. As underscored by Herold et al. [51], combined exercise and cognitive training can take several forms. The combination of both stimulations can be sequential (i.e., at different moments), or simultaneous (i.e., at the same time). Regarding the simultaneous combination, physical and cognitive exercises can belong to the same task, as is the case in exergaming, or be independent [51]. The very recent meta-analysis from 2021 [57] shows that the simultaneous combination is more efficient to improve cognitive performance, whenever people suffer from mild cognitive impairment or not. The simultaneous combination is also less time-consuming and probably represent a lower training load than the sequential combination [58], which potentially prevents from excessive stress, less engagement in home- or community-based activities, or other changes that could inhibit rather than promote neural plasticity and cognitive improvement [60].

To date, only one experimental study compared the cognitive benefits of simultaneous combined training with either training in healthy older people [9]. The authors reported a greater improvement in divided attention, executive control, and working memory following combined training when compared with either training [9]. These promising results need to be confirmed, and to be associated to neurophysiological measures in under to understand the mechanisms that underpin this better efficiency. Thus, the main purpose of this pilot study was to assess the impact of a simultaneous combination of exercise and cognitive training on several cognitive domains in healthy older adults, in comparison with exercise and cognitive training alone. Based on Kraft theory [45], we hypothesized that simultaneous combined training would be effective in improving executive performance, and that the magnitude of improvement would be greater than either training mode alone. Considering the role of cardiac autonomic control and cerebral oxygenation on aging-induced cognitive decline, the second purpose of this study was to assess the impact of simultaneous combined training on cerebral oxygenation and baroreflex sensitivity. We hypothesized that the improvement in executive functions was associated with the improvement of baroreflex sensitivity and / or an improvement of the brain oxygenation.

Methods

Population

Forty-seven men ($n = 16$) and women ($n = 19$) aged between 55 and 76 years old were recruited to participate in this study. Their characteristics are presented in Table 1. None of them suffered from cognitive impairment (as defined as a MSSE score inferior or equal to 24), or from cardiovascular, metabolic, neurological, and psychiatric diseases. Participants who were prescribed with a pharmacological treatment that could modify cardiovascular or neuromuscular functions were excluded. The protocol was reviewed and approved by a national ethics committee for non-interventional research (CERSTAPS # 2017–11-17) and was conducted by recognized ethical standards and national/international laws. All participants signed a written statement of informed consent.

Table 1 Characteristics of the participants

		Overall ($n=35$)	ET ($n=7$)	CT ($n=11$)	ST ($n=17$)	*p-value*
Sex	Women	19	4	5	10	-
	Men	16	3	6	7	-
Age (years)		63.9 ± 4.4	63.7 ± 5.1	63.1 ± 2.7	64.6 ± 5.0	*0.47*
Height (cm)		167.5 ± 8.8	167.3 ± 10.5	168.2 ± 10.0	167.1 ± 7.8	*0.84*
Weight (Kg)		66.9 ± 11.2	65.8 ± 11.8	68.1 ± 11.3	66.5 ± 11.5	*0.88*
Body fat (Kg)		18.2 ± 4.9	16.1 ± 2.8	17.7 ± 4.6	19.3 ± 5.6	*0.58*
Lean body mass (Kg)		48.8 ± 9.9	49.6 ± 10.4	50.2 ± 10.7	47.4 ± 9.7	*0.82*
Education level†		17.5 ± 2.8	17.2 ± 1.8	16.6 ± 2.6	18.2 ± 3.1	*0.50*
BDI		0.96 ± 1.20	0.83 ± 0.75	0.82 ± 1.25	1.13 ± 1.35	*0.70*
MOCA		27.7 ± 1.6	28.0 ± 1.4	27.3 ± 1.7	27.8 ± 1.5	*0.74*

BDI Beck's Depression Inventory, *MoCA* Montreal Cognitive Assessment, *ET* exercise training; *CT*, cognitive training; *ST*, simultaneous training; †: The level of education was calculated according to the number of years of schooling. (Kindergarten, primary, secondary, high school and university)

Study design

Participants completed two experimental sessions within a 2-week period, before and after the completion of a training program involving two 30-min sessions per week for 12 weeks. The first experimental session was dedicated to the explanation of the study, the written informed consent, and the first part of the neuropsychological assessment (MOCA, BDI, Stroop Test, TMT, Rey words test, Digit Symbol Substitution Test). During the second experimental session, participants completed the second part of the neuropsychological assessment (N-back test), as well as the BRS test and the submaximal intensity exercise test. After the baseline evaluation, participants were randomly assigned to one of three experimental groups: (1) exercise training (ET); (2) cognitive training (CT); (3) simultaneously combined exercise and cognitive training (ST).

Test and measures

Physiological assessment

Submaximal intensity exercise test. This test was performed on a stationary bicycle (Monark LC6, Monark Exercise AB, Vansbro, Sweden). Theoretical maximal heart rate was determined by the formula proposed by Gellish and colleagues [61]

$$t\mathrm{HR}_{\max} = 207 - 0.7 * \text{age} \quad (1)$$

The test began at 30 W and increased by 20 W every two minutes until the participant reached 60% of $t\mathrm{HR}_{\max}$. Participants had to pedal at 60 rotations per minute (rpm). Oxygen uptake (VO_2 $ml.kg^{-1}.min^{-1}$) was determined continuously on a 30-s basis using a portable cardiopulmonary exercise testing system (Metalyser Cortex 3B, CORTEX Biophysik GmbH, Germany). Gas analyzers were calibrated before each test using ambient air and a gas mixture of known concentrations (15% O_2 and 5% CO_2). The turbine was calibrated before each test using a 3-l syringe at several flow rates. The highest VO_2 over a 30-s period during the last stage was considered as the oxygen uptake at 60% of $t\mathrm{HR}_{\max}$ ($VO_{2peak(60\%)}$, $ml.kg^{-1}.min^{-1}$). Heart rate was measured continuously using a heart rate monitor (Polar RS800 cx, Polar Electro, Kempele, Finland).

Baroreflex sensitivity. Baroreflex sensitivity testing (BRS) is an established tool for assessing cardiac autonomic control and has proven to be a valuable source of information in clinical management, particularly in the assessment of prognosis in a variety of cardiac diseases [62]. In this study, baroreflex sensitivity data were obtained by a non-invasive continuous blood pressure monitor (Finapres NOVA, FMS Company, the Netherlands). Arterial blood pressure was obtained continuously and noninvasively from a finger cuff by using the system with the volume-clamp technique maintaining the diameter of the artery under an inflated finger cuff at a set point, thereby determining arterial pressure with time changes. Diodes were located in the finger cuff, on the side of the finger, to detect changes in artery diameter and changes in the inflation of the cuff to maintain the diameter at the set point. The cuff was inflated or deflated via an air bladder connected to an air hose and pump. The software, using a mathematical model, generates an aortic pulse waveform from the finger arterial pressure wave. This computation considers changes in the pulse pressure and waveform shape as the pressure pulse is transmitted down the brachial arteries to the finger arteries. The arterial blood pressure measurement obtained from a finger was validated by Guelen et al. [63].

Also, an electrocardiogram (ECG) was obtained using 3 leads. The first electrode was positioned within the frame of rib cage, right under the clavicle near shoulder, the second electrode was placed below left clavicle, at the same level of the previous electrode and the last one was positioned above the left anterior superior iliac spine. This procedure was recommended by the manufacturer. The ECG and blood pressure signals were measured continuously by a Finapres (Finapres NOVA, FMS Company, the Netherlands). The blood pressure following each R peak was recorded. Spontaneous baroreflex sequences corresponding to the activation of the baroreflex are defined as a variation in the same direction, over at least three consecutive heartbeats, of the systolic blood pressure and the RR interval. For each sequence, a linear regression was used to estimate the slope of the relationship. The average baroreflex slope of all sequences was then calculated. This method, which allows non-invasive and non-traumatic measurement of baroreflex without pharmacological stimulation, was described previously [64–66]. All this method is performed by the software. The signals were measured continuously during a first period of five minutes in a supine position (in spontaneous breathing rate), followed by 5 min in a supine position with a controlled breathing rate (12 cycles per minute), followed by five minutes in a supine position (spontaneous breathing rate) and then 5 min in a standing position (spontaneous breathing rate). The BRS (in ms/mmHg) was calculated for each period of 5 min. The algorithms used by the software to calculate BRS included parameters sur such as age, body height, body weight, and blood pressure. This short-term supine and standing resting recording during spontaneous and/or paced breathing is usually carried out for clinical pruposes [62].

Prefrontal cortex oxygenation measurement. Cerebral oxygenation and more precisely the concentration changes of [HbO_2] (Δ[HbO_2]) and [HHb] (Δ[HHb]) were recorded during the n-back test with the PortaLite fNIRS system (Artinis Medical Systems, Elst, Netherlands) and during Stroop and TMT test with the OxyMon fNIRS system (Artinis Medical Systems, Elst, Netherlands). These two systems utilize near-infrared light, which penetrates the skull and brain but is absorbed by hemoglobin (Hb) chromophores in capillary, arteriolar, and venular beds [67]. The light was transmitted with two wavelengths, 764 and 857 nm, and data were sampled with a frequency of 10 Hz. This procedure measures relative changes in [HbO_2] and [HHb] using the modified Beer-Lambert law. This law takes into account the differential pathlength factor (DPF), which is determined using the following formula: DPF ($\lambda = 807$ nm, A) = 4.99 + 0.06 7 × (age 0.814). The region of interest is the Fp1 and Fp2 of the prefrontal cortex (PFC) and were located using the 10/20 international system. Concerning the n-back task, the placement of optode was already described in previous studies [68]. The patch used in this study for Stroop and TMT task used eight optical channels, comprising four emitters and four receptors, covered the right and left DLPFC and ventrolateral PFC (VLPFC) (Brodmann areas, BAs 9/46 and 47/45/44). The distance between each emitter and receptor was 3.5 cm. The placement of this patch was already used in previous studies [69, 70]. The sensors were shielded from ambient light with a black cloth. Oxysoft version 3.0 (Artinis Medical Systems, Elst, Netherlands) was used for data collection. Initially resting PFC oxygenation was acquired in a seated position for 2 min. Because continuous-wave technology does not allow quantifying absolute concentration due to the incapacity of measuring optical path lengths, the mean of [HbO_2] and [HHb] during the total duration of each block of cognitive task, were compared to the minute preceding each block. During all the procedure, our participants were asked to always face forward during the

test, avoid making a sudden head movement, clenching their jaw, frowning, and other facial expressions. This pre-processing analysis was already used in previous studies [70]. To analyze the fNIRS results, we first performed a channel-by-channel analysis. In the absence of interaction between the channels, we averaged the channels together from the right and left hemispheres and also averaged the hemispheres together.

Neuropsychological assessment

Global cognitive test. The Montreal Cognitive Assessment test (MOCA) was used to evaluate global intellectual efficiency. Briefly, this test consists of a 30-points test divided into eight parts and fourteen subtests. It's a very complete test because it targets most cognitive functions: visuospatial skills, executives' functions, attention, working memory, short-term memory delayed recall, language. A score higher than 26 is a normal score, below this one, people have a mild cognitive impairment [71]. The dependant variable was the total score.

Executives' functions. The Trail Making Test (TMT) and the Modified Stroop Color test were used to assess executives' function and attentional abilities. Part A of TMT evaluates the information processing speed, while part B assesses cognitive flexibility or switching. In part A, the task consisted in connecting numbers (from 1 to 25) with straight lines as fast as possible. In part B, participants had to alternate between letters in alphabetical order and numbers in ascending order (1-A-2-B-3C, etc.) as fast as possible. The dependent variable was accuracy and time to complete each part.

The Computerized Modified Stroop task was used to assess executive functions. The test used in this study is based on the Modified Stroop Color Test and included three experimental conditions: naming, inhibiting, and switching. This task was already used in several articles [17, 18, 72, 73] with older. Each block lasted between 2–4 min and was interspersed with 60-s resting blocks. Overall, there were three experimental task blocks (1 naming, 1 inhibition, and 1 switching) and 2 resting blocks, for a total length between 8–14 min. In total, there were 60 Naming trials (Block 1), 60 Inhibition trials (Block 2), and 60 Switching trials (Block 3). All trials began with a fixation cross (or square for switching condition) for 1.5 s, and all visual stimuli appeared in the center of the computer screen for 2.5 s. Participants responded with two fingers (index and major finger) from each of their hands on an AZERTY keyboard. In the Naming block, participants were presented with a visual stimulus of the name of colors (RED/BLUE/GREEN/YELLOW) in French presented in the color that is congruent with the word (i.e., RED presented in red ink). Participants were asked to identify the color of the ink with a button press. In the Inhibition block, each stimulus consisted of a color word (RED/BLUE/GREEN/YELLOW) printed in the incongruent ink color (e.g., the word RED was presented in blue ink). Participants were asked to identify the color of the ink (e.g., blue). In the Switching block, in 25% of the trials, a square replaced the fixation cross. When this occurred, participants were instructed to read the word instead of identifying the color of the ink (e.g., RED). As such, within the Switching block, there were both inhibition trials in which the participant had to inhibit their reading of the word and correctly identify the color of the ink, and there were switch trials in which the participant had to switch their response mode to read the word instead of identifying the color of the ink when a square appeared before the word presented. Visual feedback on performance was presented after each trial. A practice session was completed before the acquisition run to ensure the participants understood the task. The practice consisted of a shorter version of the task. Dependent variables were reaction times (ms) and the number of errors committed (%). We also calculated two scores, inhibition score which is the result of the inhibition bloc's score minus naming blocs' performances on number or error and corresponds to pure inhibition capacities. The second, flexibility cost is equal to results of flexibility bloc's score minus inhibition blocs' performances and reflect pure flexibility capacities.

Memory. Verbal memory and learning abilities were assessed with the Rey Words test [74]. Participants had to learn fifteen words list in five tries. The total number of words recalled was recorded. Memory span was also assessed; the forward memory span evaluates the capacity of short-term memory and the backward memory span assesses working memory corresponding to the maximum information kept in mind and the ability to manipulate it. The dependant variable was the number of elements in the last trial.

Working memory. The 2-back was used to assess working memory. A series of numbers (0–9) were presented auditorily, and the participants were asked to respond to the stimuli that they hear 2 items back. The cognitive load was manipulated by using two different conditions: single- and dual-task, and not by manipulating. In the single-task condition, participants were

instructed to perform either a self-paced walk (motor task) or the 2-back task (cognitive task). In the dual-task condition, participants performed both self-paced walking and 2-back tasks simultaneously. The numbers were pseudo-randomly ordered to ensure that there were no repeats (1–1) and no sequenced series (1–2–3). The numbers were presented through wireless headphones (RS 165, Sennheiser Electronic, Wedemark, Germany). A participant might hear the series.."0 – 4 – 1 – 5….., once they hear.."1", they would have to say "0", and once they hear "5" they would have to say "4", always keeping in mind the digit heard two positions back. The experimenter noted the participant's responses and their accuracy. All participants were given instructions before each task condition (simple- or dual-task). The practice trial consisted of two trials for each task condition. Then, the experimental test consisted of 10 blocks organized as follows: single-task 2-back (2 blocks), single-task (self-selected pace) walking (1 block), dual-task 2- back (4 blocks), single-task (self-selected pace) walking (1 block), and single-task 2-back (2 blocks). Each block of single and dual-task 2-back consisted of 12 items. Each item was presented in 1.5 s, and there was a 1 s response interval (total trial time 2.5 s) before the next item was presented. Each block lasted 40 s with a 60-s rest period between blocks. The dependent variable was accuracy. This procedure was already used by two other teams [75, 76].

Psychomotor speed was assessed by the Digit Symbol Substitution Test (DSST). The participant had to associate symbols to numbers (1–9), in a table of numbers by referring to a response key. People had 120 s to draw as many symbols as possible. The dependant variable was the number of complete cells.

Training protocol

Exercise training (ET). Participants completed 30 min of stationary bicycle (Velo-Cognitif, REV'LIM, Limoges, France, Fig. 1) at 60% of their theoretical maximal heart rate ($t\text{HR}_{max}$). The corresponding power was estimated during the submaximal intensity exercise test. Heart rate was recorded continuously to adjust power output during the session. The choice of an exercise intensity of 60% of $t\text{HR}_{max}$ is based on several observations suggesting that cognitive performance was improved in optimal way at this intensity [77] and fulfills the recommendations by Lauenroth et al. [54].

Cognitive training (CT). Participants completed 30 min of cognitive games in PRESCO (HappyNeuron, Grenade Sur Garonne, France). Each session consisted of 4 different games (among 32 possible games), which were the same for all participants, but with a level of difficulty adapted to their cognitive capacities. An example of one session was presented elsewhere [70] The 32 games were used during the 12-week program in order to target all cognitive domains, with the same programming for all participants (i.e. 4 different games by sessions during 8 sessions, this sequence being repeated thrice). A detail of each session was presented in the Table 2.

Simultaneously combined exercise and cognitive training (ST). The participants performed both programmes simultaneously, with the same exercise intensities, durations and planning of the cognitive games explained above, using a specific device (Velo-Cognitif, REV'LIM, Limoges, France). This device has been previously described by Pellegrini-Laplagne et al. [70].

Statistical analysis

Standard statistical methods were used for the calculation of means and standard deviations. Normal

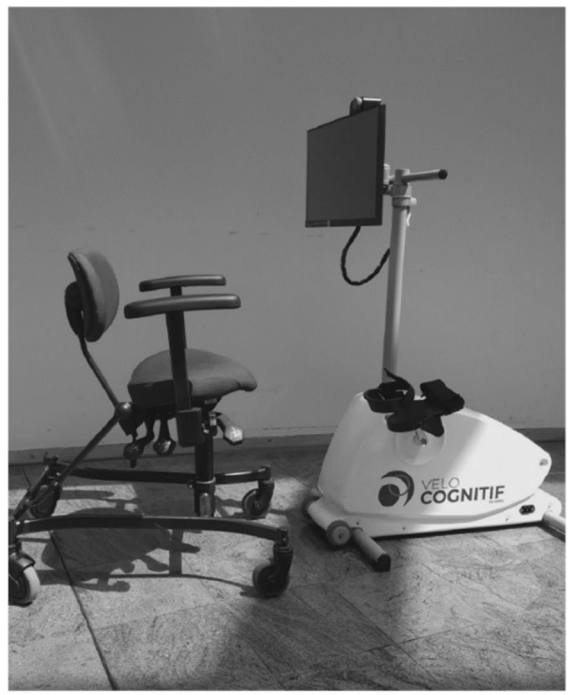

Fig. 1 Velo-cognitif® device

Table 2 Planning of cognitive training on 12 weeks (2 sessions per week)

		Game 1	Game 2	Game 3	Game 4
Session 1 / 13	Stimulated cognitive function	Language and vocabulary	Language and vocabulary	Language and vocabulary	Processing speed
	Name of the Game‡	*Mot coupés*	*Videz votre sac*	*Que d'accros dans cette histoire*	*Haute tension*
Session 2 / 14	Stimulated cognitive function	Auditory memory	Auditory memory	Verbal memory	Language and reasoning
	Name of the Game	*Vous avez un message*	*Mot, où êtes vous*	*Mémoire d'éléphant*	*Dechiffrement*
Session 3 / 15	Stimulated cognitive function	Language and reasoning	Visual-spatial skills	Visual-spatial skills	Language and vocabulary
	Name of the Game	*Menez l'enquête*	*Tours de main*	*Attention ça tourne*	*Broderies*
Session 4 / 16	Stimulated cognitive function	Mémoire visuelle	Mémoire visuelle	Mémoire visuelle	Language and reasoning
	Name of the Game	*Formes et couleurs*	*Jeux du blason*	*Images déplacées*	*écrire dans les étoiles*
Session 5 / 17	Stimulated cognitive function	Processing speed	Attention	Attention	Calcul (+attention)
	Name of the Game	*Attrapez la coccinelle*	*Attention concentrez-vous*	*Cherchez l'intrus*	*mettez de l'ordre dans ces comptes*
Session 6 / 18	Stimulated cognitive function	Visual and verbal memory	Visual and verbal memory	Visual and verbal memory	Calcul
	Name of the Game	*Le tours du monde en 80 voyages*	*On se connait*	*Garçon svp*	*Au bout du compte*
Session 7 / 19	Stimulated cognitive function	Calcul	Executive function	Executive function	Auditory memory
	Name of the Game	*A vous de compter*	*Tours de Hanoï*	*Vive l'alternance*	*chant d'oiseau*
Session 8 / 20	Stimulated cognitive function	Spatial memory	Spatial memory	Spatial memory	Executive function
	Name of the Game	*Retrouvez votre chemin*	*Objet où êtes vous*	*Mémorisez par sous ensemble*	*N back*
Session 9 / 21	Stimulated cognitive function	Language and vocabulary	Language and vocabulary	Language and vocabulary	Processing speed
	Name of the Game	*Mot coupés*	*Videz votre sac*	*Que d'accros dans cette histoire*	*Haute tension*
Session 10 / 22	Stimulated cognitive function	Auditory memory	Verbal memory	Verbal memory	Language and reasoning
	Name of the Game	*Vous avez un message*	*Mot, où êtes vous*	*Mémoire d'éléphant*	*Dechiffrement*

Table 2 (continued)

		Game 1	Game 2	Game 3	Game 4
Session 11 / 23	Stimulated cognitive function	Language and reasoning	Visual-spatial skills	Visual-spatial skills	Language and vocabulary
	Name of the Game	*Menez l'enquête*	*Tours de main*	*Attention ça tourne*	*Broderies*
Session 12 / 24	Stimulated cognitive function	Visual memory	Visual memory	Visual memory	Language and reasoning
	Name of the Game	*Formes et couleurs*	*Jeux du blason*	*Images déplacées*	*écrire dans les étoiles*

‡: *The names of the game are presented in French language since are issue from Software HappyNeuron®*

Gaussian distribution of the data was verified by the Shapiro–Wilks's test and homoscedasticity by a modified Levene Test. Repeated ANOVA measures were used to test the interaction between cognitive performances x training group (simultaneous, cognitive, or physical training). If a significant main or interaction were found, a Bonferroni post-hoc test was realized. Correlation analysis was also performed using spearman correlation. All statistical analyses were made with SPSS 17.0 and all statistical analyses with a p-value < 0,05 were considered significant. Effects sizes (ES) were also calculated with Hedges' g formula, previously described by Dupuy et al. (2015), and interpreted with Cohen's scale, where EF ≤ 0.2 (trivial), > 0.2 (small), > 0.5 (moderate), > 0.8 (large).

Results

Participants

The study included 74 healthy participants aged between 56 and 73 years old. We conducted the study between January 2019 and May 2021. The most important campaign began in January 2020 and was interrupted because of the first isolation period due to the COVID-19 pandemic. This attrition explains differences in sample sizes between experimental groups. Two participants decided to withdraw from the study, because of illness or difficulties to respect the frequency of the sessions (Fig. 2). The final sample of this study was 35 participants. There were no significant differences between groups regarding age, education level, physiological characteristics, psychological health, and cognitive status (Table 1).

Physiological assessment

We observed no effect of time on the power output at 60% of $t\mathrm{HR}_{max}$, on the $\dot{V}O_2$ at this power output and on arterial blood pressure. As shown in Table 3, we found a trend toward an interaction between groups and time [$F_{(2,25)} = 2{,}72$; $p = 0.08$] regarding the power output at 60% of $t\mathrm{HR}_{max}$, with a moderate increase in ET (ES = 0.65), a small increase in ST (ES = 0.30 and no difference in CT (ES = -0.14). We found an interaction between groups and time on the BRS measured during controlled breathing [$F_{(2,25)} = 4{,}28$; $p = 0.025$]. In this condition, BRS

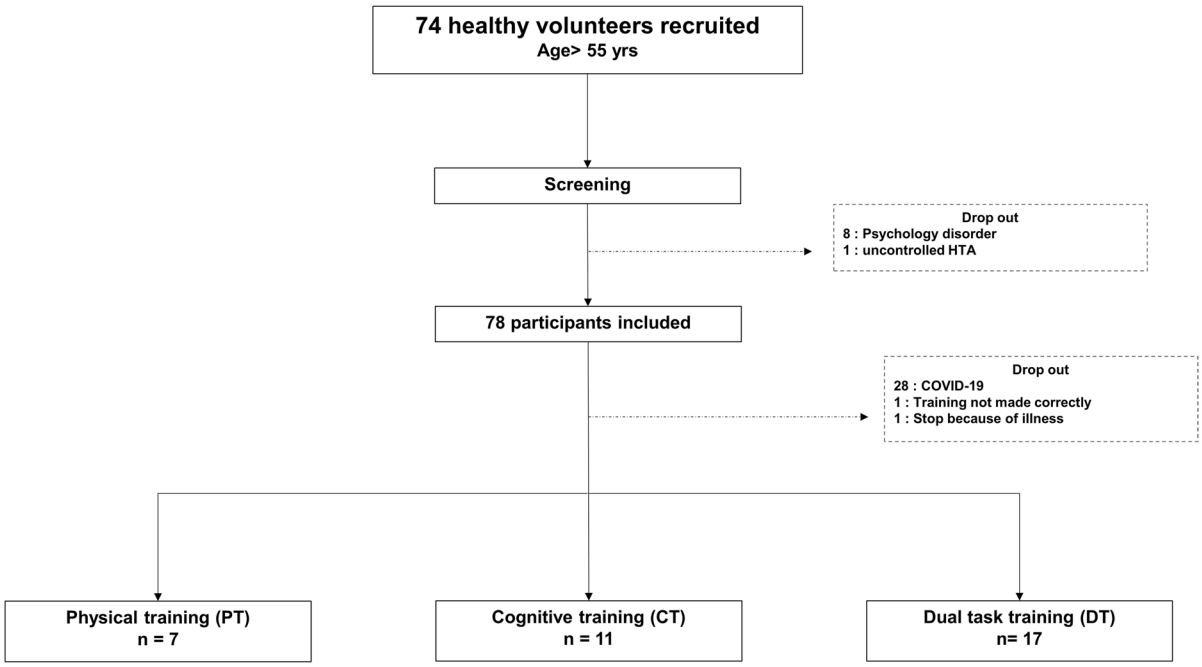

Fig. 2 Flow chart of the study

increased in ST ($p < 0.01$, ES = 0.74), while it did not change in CT (ES = -0.16) or in ET (ES = -0.40). Detailed results are presented in Fig. 3. We found no differences in the three other condition of the BRS test.

PFC oxygenation changes during the computerized modified Stroop test and the TMT are presented in Figs. 4 and 5. We found an interaction between groups and time for $\Delta[HBO_2]$ during the flexibility task [$F_{(2,28)} = 3{,}58$; $p = 0.04$]. Post hoc analysis revealed a decrease in $\Delta[HBO_2]$ for CT ($p = 0.03$, ES = -1.38), while there were no changes in ET and ST. We also found an overall decrease in $\Delta[HBO_2]$ after training during the TMT (flexibility) test, in left, right and total PFC [$F_{(1,28)} = 8{,}72$, $p < 0.001$, ES = -0,58; $F_{(1,28)} = 6{,}16$, $p = 0.01$, ES = -0,71; $F_{(1,28)} = 8{,}93$; $p < 0.005$, ES = -0,80]. As presented in Fig. 5, Δ[HHb] remained stable both during the computerized modified Stroop test and the TMT. PFC oxygenation changes during the 2-back test are presented in Fig. 6. We found a main effect of training on $\Delta[HBO_2]$ in the left PFC following in dual task condition [$F_{(1,23)} = 5{,}09$; $p = 0.03$, ES = 0,53], but not following single task condition [$F_{(1,24)} = 1{,}72$; $p = 0.20$, ES = 0,45]. In right PFC,

Table 3 Effect of training intervention on cardiovascular measures

	Overall ($n = 35$)		ET ($n = 7$)		CT ($n = 11$)		ST ($n = 17$)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
sMAP (W)	86.7 ± 28.3	94.2 ± 30.3	81.4 ± 25.4	101.4 ± 27.9	98.9 ± 30.2	93.6 ± 34.4	82.0 ± 28.1	91.3 ± 29.7
$VO_{2peak(60\%)}$ ($l.min^{-1}$)	1.28 ± 0.46	1.41 ± 0.46	1.30 ± 0.47	1.61 ± 0.42	1.37 ± 0.56	1.44 ± 0.52	1.22 ± 0.39	1.31 ± 0.43
$VO_{2peak(60\%)}$ ($ml.min^{-1}.kg^{-1}$)	18.7 ± 4.8	20.8 ± 5.3	20.4 ± 4.9	24.4 ± 4.4	20.2 ± 6.0	21.4 ± 6.2	17.0 ± 3.5	19.1 ± 4.5
SBP (mmHg)	122.2 ± 12.1	122.9 ± 12.4	118.5 ± 27.9	121.8 ± 12.1	123.8 ± 16.3	126.1 ± 14.7	123.0 ± 8.5	121.5 ± 11.4
DBP (mmHg)	76.8 ± 8.0	77.6 ± 8.0	72.9 ± 9.7	74.0 ± 7.5	79.7 ± 9.7	82.0 ± 8.6	76.6 ± 5.0	76.4 ± 7.1

sMAP sub–Maximal Aerobic Power. *VO_2 peak* peak oxygen uptake at 60% of maximal heart rate; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *ET,* exercise training; *CT*, cognitive training; *ST*, simultaneous training

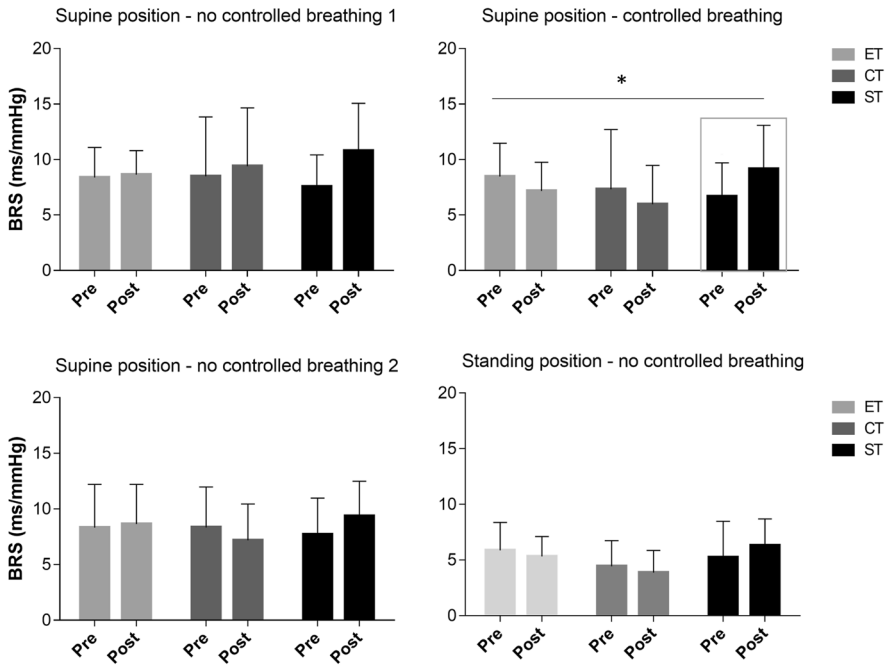

Fig. 3 Effect of simultaneous, physical and cognitive training on baroreflex sensitivity. BRS, Baroreflex sensitivity; ET, Exercise training; CT, Cognitive training; ST, Simultaneous training. * Significant interaction Time x Group, $p < 0.05$

$\Delta[HBO_2]$ remains stable in both single (ES = -0,03) and dual (ES = 0,08) conditions. Δ[HHb] is also unchanged during all 2-back test.

Cognitive assessment

As shown in Table 4, we found a main effect of time on five scores: reaction time [$F_{(1,29)} = 18,19$; $p = 0.001$; ES = -0.5] and errors' number [$F_{(1,29)} = 12,91$; $p < 0.00$; ES = -0.6] during TMT B; accuracy of flexibility [$F_{(1,29)} = 9,05$; $p = 0.005$; ES = -0.76] and of flexibility cost [$F_{(1,29)} = 8,49$; $p = 0.006$; ES = 0.71] during the computerized modified Stroop test; accuracy during the single task of the 2-back test [$F_{(1,28)} = 4,78$; p = 0.03; ES = 0.3]. Taking together, these results show that all groups improved both their flexibility scores and their working memory in the single task condition.

The ANOVA analysis also revealed an interaction between groups and time regarding the two scores of cognitive function. The first one concerns the forward span measure, that reflects episodic memory [$F_{(2,29)} = 4,22$; $p = 0.02$; ES = 0,17]. This score did not change for CT (ES = 0,25) and ST (ES = 0,17) and was reduced for ET ($p = 0.02$; ES = -1,29). We also found an interaction between groups and time for the cost of inhibition [$F_{(2,28)} = 6,44$; $p = 0.004$; ES = -0,02)]. This cost did not change for CT (ES = 0,5) and ET (ES = 0,6) groups, whereas it decreased in ST group ($p = 0.02$; ES = -0,9). Detailed results are presented in Table 4.

Association between physiological and cognitive measures

The magnitude of change in the cost of inhibition was associated to the magnitude of change in BRS during the controlled breathing condition ($r = 0,40$; $p = 0.03$). As shown in Fig. 7, this association indicates that participants who increased the more their BRS were those who displayed the greatest improvement in the cost of inhibition. No other correlations were found between physiological measures and other cognitive performances.

Discussion

The study investigated the impact of a simultaneous combination of exercise and cognitive training on several cognitive domains and some of their physiological determinants in healthy older adults, in comparison with exercise and cognitive training alone. Based on Kraft theory [45], we hypothesized that simultaneous combined training would be effective in improving executive performance, and that the magnitude of improvement would be greater than either

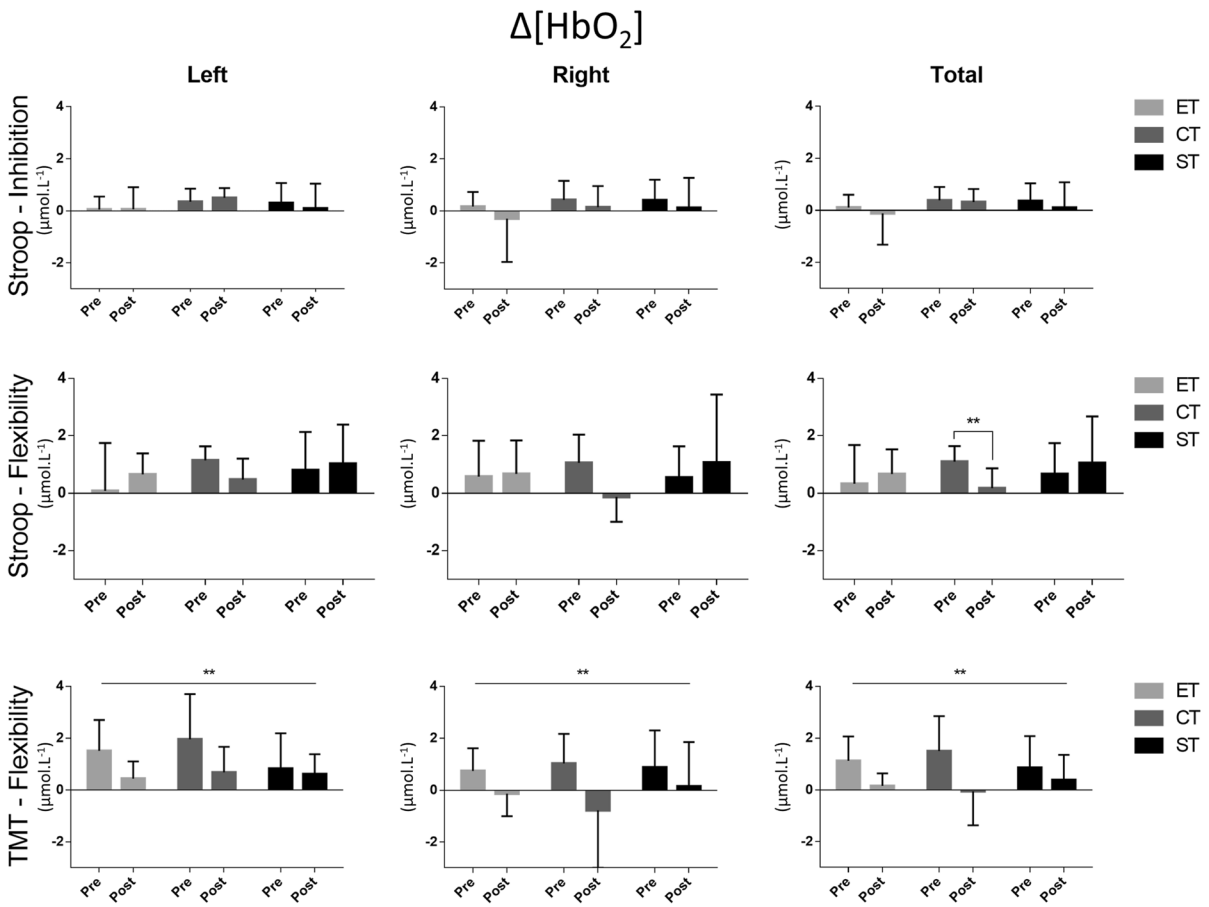

Fig. 4 Effect of simultaneous, physical and cognitive training on oxyheamoglobin during Stroop and Trail test. Δ [HbO2], Oxyhemoglobin; ET, Exercise training; CT, Cognitive training; ST, Simultaneous training. ** = $p < 0.01$

training mode alone. Considering the role of cardiac autonomic control and cerebral oxygenation on aging-induced cognitive decline, the second purpose of this study was to assess the impact of simultaneous combined training on cerebral oxygenation and baroreflex sensitivity. We hypothesized that the improvement in executive functions was associated with the improvement of baroreflex sensitivity and / or an improvement of the brain oxygenation. Our main findings were: (1) an improvement in flexibility abilities during the computerized modified Stroop test and the TMT B, as well as an improvement in working memory during the single-task of the 2-back test, whatever the group; (2) an improvement in inhibition performance and BRS during controlled breathing that was specific to ST, the magnitude of improvement of each variable being positively associated; (3), a decrease in total $\Delta[HBO_2]$ in the CT group during the flexibility block of the computerized modified Stroop test, and for all groups during TMT B, both in the left and right PFC.

Our study confirms previous observations which showed that combined exercise and cognitive training was an effective intervention to improve cognitive performance or limit cognitive impairment in older people [9, 78]. It is worth noting that CT and ET also improved executive functions like flexibility and working memory in our study. This specific effect of each mode of training implemented separately has already been reported for ET, both in young or healthy older adults [73, 79], but also for CT in older adults [80–82]. The novelty of this study was the better efficiency of ST to improve executive functions when compared with either modality alone. These results are in agreement with five other studies

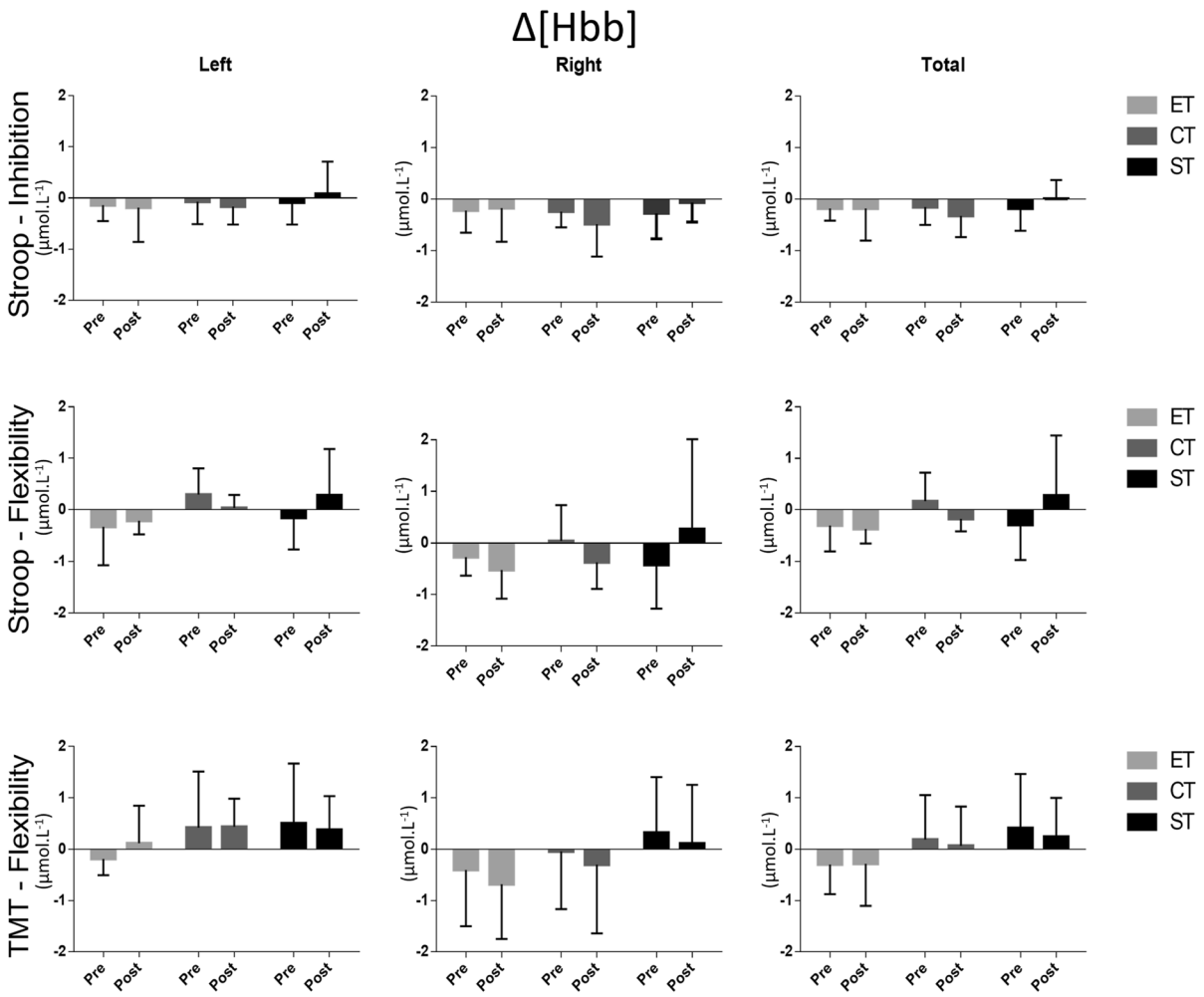

Fig. 5 Effect of simultaneous, physical and cognitive training on deoxyheamoglobin during Stroop and Trail test. Δ[HHb], deoxyhemoglobin; ET, exercise training; CT, cognitive training; ST, simultaneous training. * = $p < 0.05$; ** = $p < 0.01$

reporting a greater executive functions enhancement after a combined exercise and cognitive training when compared with exercise training alone [9, 83–86]. Among these studies, only two of them were interested in aging and confirmed this result in healthy older adults [9, 78]. The protocol used by Raichlens et al. [9] was very close to the protocol used in the present study, since it consisted in three 30-min sessions per week for twelve weeks, using multi-domain cognitive games and moderate intensity continuous exercises. They reported a greater improvement following ST in a serial subtraction test during a dual-task condition (walking), thus suggesting a greater impact on divided attention, executive control, and working memory [9]. In the same way, Theill and colleagues [78] reported a greater improvement in a test involving visual memory and learning after ST when compared with either training modality alone. Similarly to the present study and the one of Raichlen et al. [9] they proposed two 40-min sessions per week during ten weeks of simultaneous working memory training and moderate intensity brisk walk training. So, according to our findings, they observed dual task training superiority on cognitive training alone after a combined training of independents cognitive and physical tasks. They confirmed observations made with the first experimental condition, thus suggesting that this greater improvement in executive performance could be reached with different modalities of ST.

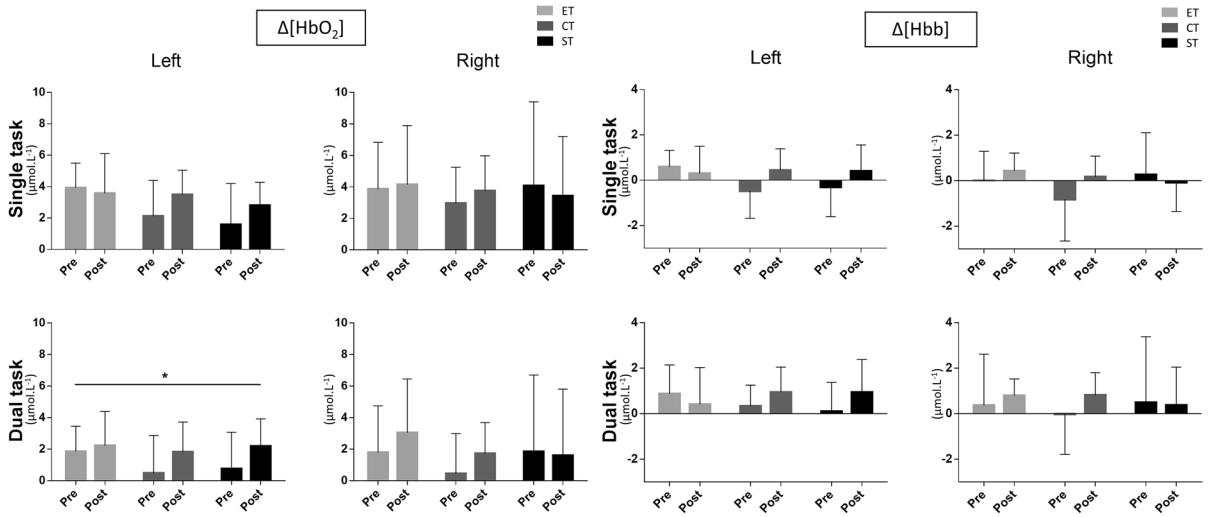

Fig. 6 Effect of simultaneous, physical and cognitive training on cerebral oxygenation during 2-Back test in single and dual-task condition. For one group, first column corresponds to pre-test and second column to post-test. Δ[HbO2], oxyhemoglobin; Δ[HHb], deoxyhemoglobin; ET, exercise training; CT, cognitive training; ST, simultaneous training; $*=p<0.05$

The specific effect of ST on inhibition is in accordance with the conclusions of the recent meta-analysis of Dhir et al. [87]. Indeed, the authors reported that a program combining moderate intensity continuous exercises and multi-domains cognitive tasks improved inhibitory control, particularly when proposed to healthy older adults experiencing the normal age-related cognitive decline [87]. This result may have important clinical implications since the ability to exert an inhibitory control over behavioral urges or unhelpful thoughts plays a key role in mental health and wellbeing [88]. Similarly, it is important to keep in mind that inhibition plays a key role in executive functions. According to Miyake [89], executive functions are numerous, but they are interrelated and share some underlying commonalities. In this context, inhibitory control is a key component of an efficient executive control. In fact, several studies suggested that the alteration in inhibitory processes could play a major role in the age-related decline in several cognitive domains [90]. Also, as mentioned by Boucard et al. [91], inhibition performance appears to be particularly sensitive to daily physical and cognitive activity, because of its elementary and ubiquitous properties in the construction of executive functions. This hypothesis has been validated in interventional study by Albinet et al. who observed in elderly people, after a 5-month swimming training programme, a specific improvement of the inhibition process among other tested executive functions. Our results abound in the sense of this hypothesis, since inhibition was the single executive function that was sensitive to simultaneous training.

To the best of our knowledge, this is the first study that assessed BRS changes after CT, ET or ST in healthy older adults. We observed an improvement in BRS during controlled breathing that was specific to ST; the magnitude of this improvement was positively associated to the gains in inhibition. The fact that this observation was limited to controlled breathing is probably due to the fact that breathing frequency influences significantly cardiac autonomic control [92] and its reproductibility [93–95]. Therefore, controlling breathing frequencey reduces physiological noise, improves the signal-to-noise ratio and in fine increases statistical power, which is of great importance in our study if we consider the relatively small sample size. Furthermore, although we don't have any comparison, this result is not surprising considering the positive impact of exercise training on BRS [96]. Indeed, in their narrative review [96], La Rovere et al. [96] indicated that exercise training limited the effect of aging on BRS, as well as its consequences on blood pressure and its underlying determinants. In addition, a recent study reported that a cognitive training, involving tasks that target processing speed

Table 4 Effect of training intervention on cognitive measures

		Total ($n=35$)		ET ($n=7$)		CT ($n=11$)		ST ($n=17$)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
BDI		0.96 ± 1.2	0.84 ± 0.97	0.83 ± 0.75	0.83 ± 0.40	0.81 ± 1.2	0.45 ± 0.93	1.1 ± 1.3	1.1 ± 1.1
Forward span		6.3 ± 1.2[b]	6.3 ± 1.2[b]	6.4 ± 0.78	5.3 ± 0.75*	5.8 ± 1.1	6.1 ± 0.94	6.5 ± 1.3	6.8 ± 1.3
Backward span		4.9 ± 1.2	5.2 ± 1.3	4.6 ± 0.97	4.7 ± 1.1	4.6 ± 1.2	4.7 ± 1.2	5.2 ± 1.3	5.6 ± 1.3
DDST		53.5 ± 9.2	55.6 ± 9.0	53.0 ± 7.7	53.0 ± 7.6	54.9 ± 7.2	56.9 ± 6.9	52.7 ± 11.3	55.9 ± 10.8
Rey's Words	Immediate recall	57.0 ± 7.4	57.3 ± 6.2	58.7 ± 6.7	57.7 ± 4.8	56.4 ± 4.9	56.3 ± 6.3	56.7 ± 9.0	57.8 ± 6.9
TMT A	Errors (n)	0.08 ± 0.28	0.02 ± 0.16	0.14 ± 0.37	0.14 ± 0.37	0	0	0.11 ± 0.33	0
	RT (ms)	35.8 ± 8.1	34.2 ± 9.9	32.8 ± 7.4	33.3 ± 10.6	38.6 ± 9.2	35.2 ± 10.7	35.2 ± 7.5	34.1 ± 9.7
TMT B	Errors (n)	0.60 ± 0.81	0.20 ± 0.53[a]	1.14 ± 1.06	0.28 ± 0.75	0.81 ± 0.75	0.18 ± 0.60	0.23 ± 0.56	0.17 ± 0.39
	RT (ms)	81.1 ± 25.6	69.2 ± 20.0[a]	89.6 ± 27.6	69.6 ± 28.1	85.0 ± 29.3	67.0 ± 13.9	75.2 ± 22.2	70.3 ± 20.6
STROOP	Naming *(Errors. n)*	0.91 ± 1.7	0.51 ± 0.65	0.71 ± 0.95	0.42 ± 0.53	1.1 ± 1.1	0.27 ± 0.46	0.88 ± 2.3	0.70 ± 0.77
	Naming *(RT. ms)*	808.7 ± 106.1	788.6 ± 127.7	774.5 ± 57.3	725.8 ± 135.4	754.3 ± 98.8	734.5 ± 118.6	857.9 ± 107.2	849.5 ± 106.3
	Inhibition *(Errors. n)*	1.1 ± 1.7	0.60 ± 0.94	0.28 ± 0.48	0.71 ± 0.95	1.0 ± 1.4	0.90 ± 1.2	1.5 ± 2.1	0.35 ± 0.70
	Inhibition *(RT. ms)*	974.1 ± 128.1	955.8 ± 127.5	908.7 ± 105.2	891.5 ± 147.9	933.5 ± 114.8	939.6 ± 144.3	1029.0 ± 127.5	992.8 ± 99.4
	Inhibition cost *(Errors. n)*	0.38 ± 1.7	0.08 ± 1.3[b]	-0.42 ± 0.78	-0.28 ± 1.4	-0.09 ± 1.5	0.63 ± 1.3	1.06 ± 1.8	-0.43 ± 1.1*
	Inhibition cost *(RT. ms)*	166.3 ± 108.1	167.2 ± 109.4	134.2 ± 102.8	165.7 ± 131.6	179.2 ± 70.1	205.1 ± 111.8	171.1 ± 131.1	143.3 ± 97.6
	Flexibility *(Errors. n)*	12.4 ± 7.9	8.0 ± 5.5[a]	14.8 ± 7.5	12.6 ± 6.5	12.7 ± 8.5	8.1 ± 5.8	11.2 ± 7.9	6.1 ± 3.7
	Flexibility *(RT. ms)*	1351.8 ± 157.8	1320.9 ± 13.3	1244.4 ± 107.3	1272.8 ± 195.3	1372.1 ± 130.7	1291.0 ± 207.1	1382.8 ± 177.7	1360.1 ± 164.4
	Flexibility cost *(Errors. n)*	11.3 ± 7.5	7.4 ± 5.3[a]	14.6 ± 7.6	11.8 ± 6.0	11.7 ± 7.8	7.2 ± 5.9	9.7 ± 7.3	5.7 ± 3.4
	Flexibility cost *(RT. ms)*	543.1 ± 194.1	532.2 ± 196.0	469.9 ± 116.7	547.0 ± 201.2	614.7 ± 179.3	556.4 ± 209.9	524.9 ± 219.7	510.6 ± 194.6
N-BACK	Single task *(Accuracy)*	32.8 ± 8.9	35.1 ± 5.9[a]	34.7 ± 9.2	35.1 ± 7.5	29.7 ± 11.0	35.1 ± 5.3	33.9 ± 7.4	35.1 ± 5.9
	Dual Task *(Accuracy)*	30.9 ± 7.8	32.0 ± 7.2	30.8 ± 8.3	30.4 ± 8.2	29.5 ± 10.1	31.7 ± 8.5	31.8 ± 6.3	32.9 ± 6.2
	Single task *(walk. m)*	42.2 ± 7.6	41.6 ± 8.2	42.9 ± 7.2	45.0 ± 6.6	42.5 ± 8.5	39.6 ± 7.0	41.6 ± 7.7	41.6 ± 9.3
	Dual Task *(walk. m)*	40.6 ± 8.1	40.1 ± 8.3	42.6 ± 7.2	43.0 ± 6.7	40.4 ± 8.8	38.3 ± 7.3	39.8 ± 8.4	40.0 ± 9.5

BDI Beck's Depression Inventory; *DSST* Digit Symbol Substitution Test; *TMT* Trail Making Test; *RT* Reaction Time; *n*: number; m: meter. **a**: main effect of time ($p<0.05$). **b**: interaction Time by Group; * different from pré ($p<0.05$), *ET*, exercise training; *CT*, cognitive training; *ST*, simultaneous training

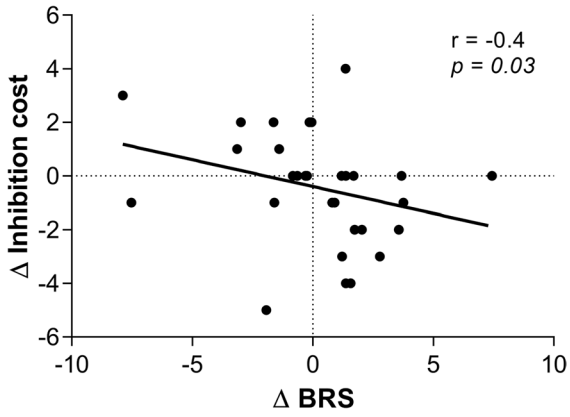

Fig. 7 Correlation between baroreflex sensitivity and inhibition performance changes after training. BRS, baroreflex sensitivity

and attention, improved these cognitive domains as well as cardiac autonomic control (as measured by heart rate variability) in older adults suffering from amnesia and mild cognitive impairment [97]. Surprisingly, we found no changes in BRS following CT and ET. A possible explanation may be the training dose [98]. In fact, the protocol by Lin et al. [97] consisted in four 1-h sessions per week for 6 weeks, which represented a 4-time higher dose than in our study. The issue of a possible dose–response relationship should be explored more specifically.

As previously mentioned, we observed a positive association between BRS and inhibition changes after ST, participants who improved the most BRS being those who improved the most the cost of inhibition. This result is in agreement with the predictions of the neuro-visceral integration model by Thayer and Lane [99], which suggests that resting cardiac autonomic control relates to PFC activity and predicts executive performance. In fact, these authors suggest the existence of a common reciprocal inhibitory cortical-subcortical neural circuit that serves as a structural link between psychological processes such as emotion and cognition, and health-related physiological processes, and that this circuit can be indexed with cardiac autonomic control [99]. Several studies have already shown that resting BRS was associated to better cognitive performance [100, 101], and that exercise training induced improvement in executive performance was mediated by a higher cardiac autonomic control [102, 103]. As mentioned earlier, Albinet et al. (2016) observed a specific improvement in inhibition after 5 months of swimming training in elderly people. This improvement seemed to be explained and mediated by an improvement in the cardiac parasympathetic control, as measured by heart rate variability. Our results are in accordance with these observations since cardiac autonomic control is a key component of BRS.

As for BRS, this is the first study that assessed PFC oxygenation changes after CT, ET or ST in healthy older adults. Our main result was a decrease in $\Delta[HBO_2]$ in all groups during TMT B, both in the left and right PFC, together with an improvement in performance during this test. This result is in accordance with a recent study which reported that older subjects displayed a lower cerebral oxygenation ($\Delta[HBO_2]$) during a Stroop task after aerobic training [104]. It should be kept in mind that the functional activity of the brain is related to the blood supply [105] and that neuronal activation requires an increase in cerebral blood flow and metabolism [106]. This mechanism has been illustrated by Mehagnoul-Schipper et al. [107] who reported simultaneous increases in cerebral blood volume and cerebral oxygenation during cognitive activation in older adults. It also appears that the magnitude of this adaptation is proportional to the complexity of the cognitive task [108]. Our results, and more specifically the decrease in $\Delta[HBO_2]$ after the interventions, therefore suggest that one of the benefits of CT, ET and ST is to decrease the level of cortical activation required for a specific cognitive task. This is in accordance with observations made by Voelcker-Rehage et al. [109], who reported that 12 months of aerobic and coordination training resulted in a decreased task-related activation in the PFC during a Flanker task (a measure of cognitive inhibition). Interestingly, we observed similar results in CT. This adaptation was expected, since it has been shown that cognitive training improved brain plasticity, which plays an important role in neuronal activity [110]. Nevertheless, this hypothesis of lower cortical activation after a training programme, demonstrating some form of neuronal economy, needs to be confirmed.

Many physiological mechanisms at the molecular level can explain the cognitive improvements observed in the elderly people after a physical training. A number of molecules that are considered as growth factors are released during exercise, thus promoting cerebral plasticity. For example, it is well

established that molecules such as BDNF, IGF or VEGF will induce synaptogenesis, neurogenesis or angiogenesis [111–114]. All these molecular factors potentially induce structural changes in the cerebral vasculature, and contribute to an increase of the volumes of the grey nuclei, the hippocampus, and the grey and white matters. More specifically to simultaneous training, Eduard Kraft (2012) makes the following synergetic hypothesis: 1) physical activity facilitates synaptic plasticity and neurogenesis via neurotrophic factors such as BDNF or IGF-1; 2) cognitive stimulation would guide synaptic plasticity in the brain areas activated by the cognitive task, through the selection of the most active synapses 3) The combination of the two would make it possible to include new neurons and create new synapses (thanks to increased neurogenesis and synaptogenesis) in brain networks selected by cognitive activity. In other words, physical stimulation would catalyze the effect of cognitive stimulation and therefore the restructuring of the neural network. These mechanisms are probably involved in the structural changes in the neural circuits that control both baroreflex regulation and the cognitive processes involved in inhibition. Future neuroimaging studies may allow us to validate these hypotheses.

Though this study had several strengths, it was not without limitations, and the interpretation of our results requires some caution. One of the main limitations is the small sample size, which limits statistical power and in fine the generalization of our results. As mentioned in Fig. 2, many participants were unable to complete this study due to lockdown of the COVID. The size of this study, which involved people aged 55 and over, does not allow us to distinguish a possible specific effect in middle-aged people (55–65 years) and in the older adults (> 65 years). The same comment applies to the men and women involved in this study. Future studies with a larger sample size would allow us to address these limitations. Nevertheless, the calculation of effect size by Hedge's g allows us to appreciate our results from a clinical point of view. Although the size of this study may be considered a limitation, it must be kept in mind that this is the first study to compare simultaneous cognitive and physical training to physical and cognitive training alone on cognitive function in healthy older adults. This is also the first study in healthy older people to propose physiological mechanisms that allow a better understanding of cognitive outcomes. Finally, it is not excluded that the superiority of ST training when compared with ET and CT training, is dependent on the dose of training. However, in the context of two training sessions per week, DT training may improve some cognitive functions and cardiovascular indices, but not CT or ET. It would be interesting to see whether this superiority of training is still observed when the intensity and/or frequency of training is increased in future comprehensive studies.

Conclusion

The aim of this study was to investigate the effect of a simultaneous combination of exercise and cognitive training on several cognitive domains and some of their physiological determinants in healthy older adults, in comparison with exercise and cognitive training alone. Considering the role of cardiac autonomic control and cerebral oxygenation on aging-induced cognitive decline, a second purpose of this study was to assess the impact of simultaneous combined training on cerebral oxygenation and baroreflex sensitivity. Our main findings were (1) an improvement in flexibility abilities during the computerized modified Stroop test and the TMT B, as well as an improvement in working memory during the single-task of the 2-back test, whatever the group; (2) an improvement in inhibition performance and BRS during controlled breathing that was specific to ST, the magnitude of improvement of each variable being positively associated; (3), a decrease in total HBO_2 in the CT group during the flexibility block of the computerized modified Stroop test, and for all groups during TMT B, both in the left and right PFC. This study brings additional evidence that simultaneous exercise and cognitive training is more efficient in improving executive performance than either training modality alone. It also provides new information regarding the mechanisms that subtend this effect and underscores the interest of the neurovisceral integrative model by Thayer and Lane (2000) to provide a theoretical framework. Future studies should investigate the impact of simultaneous cognitive and physical training on larger cohorts with more intense sessions (longer or more session per week).

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Declarations

Conflict of interest The authors declare no competing interests.

References

1. Wilson RS, et al. The Influence of Cognitive Decline on Well-Being in Old Age. Psychol Aging. 2013;28(2):304–13. https://doi.org/10.1037/a0031l96.
2. Borson S. Cognition, aging, and disabilities: Conceptual issues. Phys Med Rehabil Clin N Am. 2010;21(2):375–82. https://doi.org/10.1016/j.pmr.2010.01.001.
3. Fjell AM, Walhovd KB. "Structural Brain Changes in Aging: Courses, Causes and Cognitive Consequences", 2010. Rev Neurosci. 2010;21(3):187–221. https://doi.org/10.1515/revneuro.2010.21.3.187.
4. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychol Sci. 2003;14(2):125–30. https://doi.org/10.1111/1467-9280.t01-1-01430.
5. Monahan KD. NEW INVESTIGATOR AWARD OF THE NEURAL CONTROL AND AUTONOMIC REGULATION SECTION Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol. 2007;293:3–12. https://doi.org/10.1152/ajpregu.00031.2007.-Arterial.
6. Zeki Al Hazzouri A, Haan MN, Deng Y, Neuhaus J, Yaffe K. Reduced heart rate variability is associated with worse cognitive performance in elderly Mexican Americans. Hypertension. 2014;63(1):181–7. https://doi.org/10.1161/HYPERTENSIONAHA.113.01888.
7. P. Nicolini *et al.*, "Autonomic dysfunction in mild cognitive impairment: Evidence from power spectral analysis of heart rate variability in a cross-sectional case-control study," *PLoS ONE*, 2014; 9(5), https://doi.org/10.1371/journal.pone.0096656.
8. Schapkin SA, Freude G. Cardiovascular Costs of Working Memory Performance: Effects of Age and Performance Feedback. Ind Health. 2013;51(4):386–97. https://doi.org/10.2486/indhealth.2012-0203.
9. D. A. Raichlen *et al.*, "Effects of simultaneous cognitive and aerobic exercise training on dual-task walking performance in healthy older adults: Results from a pilot randomized controlled trial," *BMC Geriatrics*, 2020; 20(1), https://doi.org/10.1186/s12877-020-1484-5.
10. Sahathevan R, Brodtmann A, Donnan GA. Dementia, stroke, and vascular risk factors; a review. Int J Stroke. 2012;7:61–73.
11. de Aquino LV, Antunes HK, dos Santos RV, Lira FS, Tufik S, de Mello MT. High altitude exposure impairs sleep patterns, mood, and cognitive functions. Psychophysiology. 2012;49:1298–306.
12. LiuK SunG, LiB JiangQ, YangX LiM, LiL QianS, ZhaoL ZZ, von Deneen KM, Liu Y. The impact of passive hyperthermia on human attention networks: an fMRI study. Behav Brain Res. 2013;243:220–30.
13. SunG YangX, JiangQ LiuK, LiB LiL, ZhaoL LiM. Hyperthermia impairs the executive function using the Attention Network Test. Int J Hyperthermia. 2012;28:621–6.
14. Virues-Ortega J, Buela-Casal G, Garrido E, Alcazar B. Neuropsychological functioning associated with high-altitude exposure. Neuropsychol Rev. 2004;14:197–224.
15. Ogoh S, Tarumi T. Cerebral blood flow regulation and cognitive function: a role of arterial baroreflex function. J Physiol Sci. 2019;69(6):813–23. https://doi.org/10.1007/s12576-019-00704-6.
16. Ogoh S. Relationship between cognitive function and regulation of cerebral blood flow. J Physiol Sci. 2017;67(3):345–51. https://doi.org/10.1007/s12576-017-0525-0 (Epub 2017 Feb 3 PMID: 28155036).
17. Goenarjo R *et al.*, "Cerebral oxygenation reserve: The relationship between physical activity level and the cognitive load during a stroop task in healthy young males," *International Journal of Environmental Research and Public Health*, 2020; 17(4), https://doi.org/10.3390/ijerph17041406.
18. Dupuy O *et al.*, "Higher levels of cardiovascular fitness are associated with better executive function and prefrontal oxygenation in younger and older women," *Frontiers in Human Neuroscience*, 2015; 9(FEB), https://doi.org/10.3389/fnhum.2015.00066.
19. Mekari S, Fraser S, Bosquet L, Bonnéry C, Labelle V, Pouliot P, Lesage F, Bherer L. The relationship between exercise intensity, cerebral oxygenation and cognitive performance in young adults. Eur J Appl Physiol. 2015;115(10):2189–97. https://doi.org/10.1007/s00421-015-3199-4.
20. Nakai M. An increase in cerebral blood flow elicited by electrical stimulation of the solitary nucleus in rats with cervi- cal cordotomy and vagotomy. Jpn J Physiol. 1985;35(1):57–70.
21. Nakai M, Iadecola C, Reis DJ. Global cerebral vasodilation by stimulation of rat fastigial cerebellar nucleus. Am J Physiol. 1982;243(2):H226–35.
22. Iadecola C, Nakai M, Mraovitch S, Ruggiero DA, Tucker LW, Reis DJ. Global increase in cerebral metabolism and blood flow produced by focal electrical stimulation of dorsal medullary reticular formation in rat. Brain Res. 1983;272(1):101–14.
23. Saint Martin M, Sforza E, Thomas-Anterion C, Barthelemy JC, Roche F, Grp PS. Baroreflex Sensitivity, Vascular Risk Factors, and Cognitive Function in a Healthy Elderly Population: The PROOF Cohort. J Am Geriatr Soc. 2013;61:2096–102. https://doi.org/10.1111/jgs.12548.
24. Saint Martin M, Roche F, Thomas-Anterion C, Barthelemy JC, Sforza E, Cerebrovasc PRC. Eight-Year Parallel Change in Baroreflex Sensitivity and Memory Function in a Sample of Healthy Older Adults. J AM

GERIATR SOC. 2015;63:270–5. https://doi.org/10.1111/jgs.13252.
25. Ding K, Tarumi T, Wang C, Vernino S, Zhang R, Zhu DC. Central autonomic network functional connectivity: correlation with baroreflex function and cardiovascular variability in older adults. Brain Struct Funct. 2020;225:1575–85. https://doi.org/10.1007/s00429-020-02075-w.
26. Kimmerly DS. A review of human neuroimaging investigations involved with central autonomic regulation of baroreflex-mediated cardiovascular control. AUTONOMIC NEUROSCIENCE-BASIC & CLINICAL. 2017;207:10–21. https://doi.org/10.1016/j.autneu.2017.05.008.
27. Tarumi T, de Jong DLK, Zhu DC, Tseng BY, Liu J, Hill C, Riley J, Womack KB, Kerwin DR, Lu H, et al. Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. Neuroimage. 2015;110:162–70. https://doi.org/10.1016/j.neuroimage.2015.01.041.
28. Ku PW, te Liu Y, Lo MK, Chen LJ, Stubbs B. Higher levels of objectively measured sedentary behavior is associated with worse cognitive ability: Two-year follow-up study in community-dwelling older adults. Exp Gerontol. Dec. 2017;99:110–4. https://doi.org/10.1016/j.exger.2017.09.014.
29. Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: Emerging evidence for a new health risk. Mayo Clinic Proceedings. 2010;85(12):1138–41. https://doi.org/10.4065/mcp.2010.0444 (Elsevier Ltd).
30. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimer's and Dementia. 2013;9(1):63-75.e2. https://doi.org/10.1016/j.jalz.2012.11.007 (Elsevier Inc.).
31. Colzato LS. Editorial. Journal of Cognitive Enhancement. 2017;1(1):1–2. https://doi.org/10.1007/s41465-016-0001-4.
32. Barnes DE, et al. The mental activity and exercise (MAX) trial: A randomized controlled trial to enhance cognitive function in older adults. JAMA Intern Med. 2013;173(9):797–804. https://doi.org/10.1001/jamainternmed.2013.189.
33. la Rue A. Healthy Brain Aging: Role of Cognitive Reserve, Cognitive Stimulation, and Cognitive Exercises. Clin Geriatr Med. 2010;26(1):99–111. https://doi.org/10.1016/j.cger.2009.11.003.
34. Landau SM, et al. Association of lifetime cognitive engagement and low β-amyloid deposition. Arch Neurol. 2012;69(5):623–9. https://doi.org/10.1001/archneurol.2011.2748.
35. Valenzuela MJ, Sachdev P, Wen W, Chen X, and Brodaty H, "Lifespan mental activity predicts diminished rate of hippocampal atrophy," *PLoS ONE*, 2008: 3(7), https://doi.org/10.1371/journal.pone.0002598.
36. Reijnders J, van Heugten C, van Boxtel M. Cognitive interventions in healthy older adults and people with mild cognitive impairment: A systematic review. Ageing Res Rev. 2013;12(1):263–75. https://doi.org/10.1016/j.arr.2012.07.003.
37. Sanders LMJ, Hortobágyi T, la Bastide-van Gemert S, van der Zee, EA and van Heuvelen MJG, "Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis," *PLoS ONE*, 2019; 14(1), Public Library of Science, https://doi.org/10.1371/journal.pone.0210036.
38. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-Analysis. British Journal of Sports Medicine. 2018;52(3):154–60. https://doi.org/10.1136/bjsports-2016-096587 (BMJ Publishing Group).
39. Chen FT, Etnier JL, Chan KH, Chiu PK, Hung TM, Chang YK. Effects of Exercise Training Interventions on Executive Function in Older Adults: A Systematic Review and Meta-Analysis. Sports Medicine. 2020;50(8):1451–67. https://doi.org/10.1007/s40279-020-01292-x (Springer).
40. Ludyga S, Gerber M, Brand S, Holsboer-Trachsler E, Pühse U. Acute effects of moderate aerobic exercise on specific aspects of executive function in different age and fitness groups: A meta-analysis. Psychophysiology. 2016;53(11):1611–26. https://doi.org/10.1111/psyp.12736.
41. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology. 2012;78(17):1323–9. https://doi.org/10.1212/WNL.0b013e3182535d35.
42. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends in Neurosciences. 2007;30(9):464–72. https://doi.org/10.1016/j.tins.2007.06.011 (Elsevier Ltd).
43. Stillman CM, Esteban-Cornejo I, Brown B, Bender CM, Erickson KI. Effects of Exercise on Brain and Cognition Across Age Groups and Health States. Trends in Neurosciences. 2020;43(7):533–43. https://doi.org/10.1016/j.tins.2020.04.010 (Elsevier Ltd).
44. Stillman CM, Erickson KI. Physical activity as a model for health neuroscience. Ann N Y Acad Sci. 2018. https://doi.org/10.1111/nyas.13669.
45. Kraft E. Cognitive function, physical activity, and aging: Possible biological links and implications for multimodal interventions. Aging Neuropsychol Cogn. 2012;19(1–2):248–63. https://doi.org/10.1080/13825585.2011.645010.
46. Bamidis PD, et al. A review of physical and cognitive interventions in aging. Neuroscience and Biobehavioral Reviews. 2014;44:206–20. https://doi.org/10.1016/j.neubiorev.2014.03.019 (Elsevier Ltd).
47. Fabel K, Wolf SA, Ehninger D, Babu H, Leal-Galicia P, and Kempermann G, "Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice," *Frontiers in Neuroscience*, 2009; 3(NOV), https://doi.org/10.3389/neuro.22.002.2009.
48. Smith AM, Spiegler KM, Sauce B, Wass CD, Sturzoiu T, Matzel LD. Voluntary aerobic exercise increases the cognitive enhancing effects of working memory training. Behav Brain Res. 2013;256:626–35. https://doi.org/10.1016/j.bbr.2013.09.012.
49. Tait JL, Duckham RL, Milte CM, Main LC, and Daly RM, "Influence of sequential vs. simultaneous dual-task exercise training on cognitive function in older adults," *Frontiers in Aging Neuroscience*, 2017; 9(NOV).

Frontiers Media S.A., https://doi.org/10.3389/fnagi.2017.00368.
50. Fissler P, Küster O, Schlee W, Kolassa IT. Novelty interventions to enhance broad cognitive abilities and prevent dementia: Synergistic approaches for the facilitation of positive plastic change. Progress in Brain Research. 2013;207:403–34. https://doi.org/10.1016/B978-0-444-63327-9.00017-5 (Elsevier B.V.).
51. Herold F, Hamacher D, Schega L, and Müller NG, "Thinking while moving or moving while thinking - concepts of motor-cognitive training for cognitive performance enhancement," *Frontiers in Aging Neuroscience*, 2018; 10(AUG). https://doi.org/10.3389/fnagi.2018.00228.
52. Law LLF, Barnett F, Yau MK, Gray MA. Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A systematic review. Ageing Research Reviews. 2014;15(1):61–75. https://doi.org/10.1016/j.arr.2014.02.008 (Elsevier Ireland Ltd).
53. Joubert C and 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," *Clinical Interventions in Aging*, 2018; 13. Dove Medical Press Ltd., pp. 1267–1301, https://doi.org/10.2147/CIA.S165399.
54. Lauenroth A, Ioannidis AE, and Teichmann B, "Influence of combined physical and cognitive training on cognition: A systematic review," *BMC Geriatrics*, 2016; 16(1). BioMed Central Ltd., https://doi.org/10.1186/s12877-016-0315-1.
55. Zhu X, Yin S, Lang M, He R, Li J. The more the better? A meta-analysis on effects of combined cognitive and physical intervention on cognition in healthy older adults. Ageing Research Reviews. 2016;31:67–79. https://doi.org/10.1016/j.arr.2016.07.003 (Elsevier Ireland Ltd).
56. Gheysen F *et al.*, "Physical activity to improve cognition in older adults: Can physical activity programs enriched with cognitive challenges enhance the effects? A systematic review and meta-analysis," *International Journal of Behavioral Nutrition and Physical Activity*, 2018; 15(1). BioMed Central Ltd., https://doi.org/10.1186/s12966-018-0697-x.
57. Gavelin HM *et al.*, "Combined physical and cognitive training for older adults with and without cognitive impairment: A systematic review and network meta-analysis of randomized controlled trials," *Ageing Research Reviews*, 2021; 66. Elsevier Ireland Ltd, https://doi.org/10.1016/j.arr.2020.101232.
58. Guo W, Zang M, Klich S, Kawczyński A, Smoter M, Wang B. Effect of combined physical and cognitive interventions on executive functions in older adults: A meta-analysis of outcomes. Int J Environ Res Public Health. 2020;17(17):1–19. https://doi.org/10.3390/ijerph17176166.
59. Wollesen B, Wildbredt A, van Schooten KS, Lim ML, and Delbaere K, "The effects of cognitive-motor training interventions on executive functions in older people: A systematic review and meta-analysis," *European Review of Aging and Physical Activity*, 2020; 17(1). BioMed Central Ltd, https://doi.org/10.1186/s11556-020-00240-y.
60. Fiatarone Singh MA, et al. The Study of Mental and Resistance Training (SMART) Study-Resistance Training and/or Cognitive Training in Mild Cognitive Impairment: A Randomized, Double-Blind, Double-Sham Controlled Trial. J Am Medical Dir Assoc. 2014;15(12):873–80. https://doi.org/10.1016/j.jamda.2014.09.010.
61. Gellish RL, Goslin BR, Olson RE, McDonald A, Russi GD, Moudgil VK. Longitudinal modeling of the relationship between age and maximal heart rate. Med Sci Sports Exerc. 2007;39(5):822–9. https://doi.org/10.1097/mss.0b013e31803349c6.
62. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. Ann Noninvasive Electrocardiol. 2008;13(2):191–207. https://doi.org/10.1111/j.1542-474X.2008.00219.x.PMID:18426445;PMCID:PMC6931942.
63. Guelen I, Westerhof BE, van der Sar GL, van Montfrans GA, Kiemeneij F, Wesseling KH. Bos WJW Validation of brachial artery pressure reconstruction from finger arterial pressure. Journal of Hypertension. 2008;26(7):1321–7. https://doi.org/10.1097/HJH.0b013e3282fe1d28.
64. Bertinieri G, Di Rienzo M. Caval- lazzi A, Ferrari AU, Pedotti A, Mancia G : A new approach to analysis of the arterial baroreflex. J Hypertens. 1985;3:S79–81.
65. Yamamoto Y, Hughson RL. Coarse- graining spectral analysis : new method for studying heart rate varia- bility. J Appl Physiol. 1991;71(3):1143–50.
66. Westerhof BE, Gisolf J, Stok WJ, Wesseling KH, Karemaker JM. Time-domain cross-correlation baroreflex sensitivity: performance on the EUROBAVAR data set. J Hypertens. 2004;22(7):1371–80. https://doi.org/10.1097/01.hjh.0000125439.28861.ed.
67. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage. 2012;63(2):921–35. https://doi.org/10.1016/j.neuroimage.2012.03.049.
68. Goenarjo R, Dupuy O, Fraser S, Perrochon A, Berryman N, Bosquet L. Cardiorespiratory fitness, blood pressure, and cerebral oxygenation during a dual-task in healthy young males. Behav Brain Res. 2020;17(380):112422. https://doi.org/10.1016/j.bbr.2019.112422.
69. Agbangla NF, Audiffren M, Pylouster J, Albinet CT. Working Memory, Cognitive Load andCardiorespiratory Fitness: Testing the CRUNCHModel with Near-Infrared Spectroscopy. Brain Sci. 2019;9(2):38. https://doi.org/10.3390/brainsci9020038.PMID:30744137;PMCID:PMC6406418.
70. Pellegrini-Laplagne M, Dupuy O, Sosner P, Bosquet L. Acute Effect of a Simultaneous Exercise and Cognitive Task on Executive Functions and Prefrontal Cortex Oxygenation in Healthy Older Adults. Brain Sci. 2022;12(4):455. https://doi.org/10.3390/brainsci12040455.PMID:35447987;PMCID:PMC9027217.
71. Nasreddine ZS, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J m Geriatr Soc. 2005;53(4):695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
72. Goenarjo R, Dupuy O, Fraser S, Berryman N, Perrochon A, Bosquet L. Cardiorespiratory fitness and prefrontal cortex oxygenation during Stroop task in older males.

Physiol Behav. 2021;242: 113621. https://doi.org/10.1016/j.physbeh.2021.113621.
73. Mekari S *et al.*, "Effect of high intensity interval training compared to continuous training on cognitive performance in young healthy adults: A pilot study," *Brain Sciences*, 2020; 10(2), https://doi.org/10.3390/brainsci10020081.
74. Rey A, "L'examen clinique en psychologie," Presses Universitaires de France, 1958.
75. Goenarjo R, Dupuy O, Fraser S, Perrochon A, Berryman N, Bosquet L, "Cardiorespiratory fitness, blood pressure, and cerebral oxygenation during a dual-task in healthy young males," *Behavioural Brain Research*, 2020; 380, https://doi.org/10.1016/j.bbr.2019.112422.
76. Fraser SA, Dupuy O, Pouliot P, Lesage F, and Bherer L, "Comparable cerebral oxygenation patterns in younger and older adults during dual-task walking with increasing load," *Frontiers in Aging Neuroscience*, 2016;8(OCT), https://doi.org/10.3389/fnagi.2016.00240.
77. Lambourne K, Tomporowski P. The effect of exercise-induced arousal on cognitive task performance: A meta-regression analysis. Brain Research. 2010;1341:12–24. https://doi.org/10.1016/j.brainres.2010.03.091.
78. Theill N, Schumacher V, Adelsberger R, Martin M, and Jäncke L, "Effects of simultaneously performed cognitive and physical training in older adults," *BMC Neuroscience*, 2013; 14, https://doi.org/10.1186/1471-2202-14-103.
79. Predovan D, Fraser SA, Renaud M, and Bherer L, "The effect of three months of aerobic training on stroop performance in older adults," *Journal of Aging Research*, 2012; 2012, https://doi.org/10.1155/2012/269815.
80. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, and Tennstedt SL. The ACTIVE cognitive training trial and health-related quality of life: Protection that lasts for 5 years downloaded from. J Gerontol A Biol Sci Med Sci. 2006;61(12):1324–9. https://doi.org/10.1093/gerona/61.12.1324.
81. Basak C, Qin S, O'Connell MA. Differential effects of cognitive training modules in healthy aging and mild cognitive impairment: A comprehensive meta-analysis of randomized controlled trials. Psychol Aging. 2020;35(2):220–49. https://doi.org/10.1037/pag0000442.
82. Corbett A, et al. The Effect of an Online Cognitive Training Package in Healthy Older Adults: An Online Randomized Controlled Trial. J Am Med Dir Assoc. 2015;16(11):990–7. https://doi.org/10.1016/j.jamda.2015.06.014.
83. Yokoyama H *et al.*, "The effect of cognitive-motor dual-task training on cognitive function and plasma amyloid β peptide 42/40 ratio in healthy elderly persons: A randomized controlled trial," *BMC Geriatrics*, 2015;15(1), https://doi.org/10.1186/s12877-015-0058-4.
84. León J, Ureña A, Bolaños MJ, Bilbao A, Oña A. A combination of physical and cognitive exercise improves reaction time in persons 61–84 years old. J Aging Phys Act. 2015;23(1):72–7. https://doi.org/10.1123/JAPA.2012-0313.
85. Hiyamizu M, Morioka S, Shomoto K, Shimada T. Effects of dual task balance training on dual task performance in elderly people: A randomized controlled trial. Clin Rehabil. 2012;26(1):58–67. https://doi.org/10.1177/0269215510394222.
86. Falbo S, Condello G, Capranica L, Forte R, and Pesce C, "Effects of Physical-Cognitive Dual Task Training on Executive Function and Gait Performance in Older Adults: A Randomized Controlled Trial," *BioMed Res Int*, 2016; 2016, https://doi.org/10.1155/2016/5812092.
87. Dhir S, Teo WP, Chamberlain SR, Tyler K, Yücel M, Segrave RA. The Effects of Combined Physical and Cognitive Training on Inhibitory Control: A Systematic Review and Meta-Analysis. Neurosci Biobehav Rev. 2021;128:735–48. https://doi.org/10.1016/j.neubiorev.2021.07.008 (Elsevier).
88. Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog Neurobiol. 2013;108:44–79. https://doi.org/10.1016/j.pneurobio.2013.06.005.
89. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The Unity and Diversity of Executive Functions and Their Contributions to Complex 'Frontal Lobe' Tasks: A Latent Variable Analysis. Cogn Psychol. 2000;41(1):49–100. https://doi.org/10.1006/cogp.1999.0734.
90. Hasher L, Zacks RT. Working memory, comprehension, and aging: A review and a new view. In: Bower GH, editor. The psychology of learning and motivation, vol. 22. San Diego, CA: Academic Press; 1988. p. 193–225.
91. Boucard GK, Albinet CT, Bouquet CA, Clarys D, Audiffren M, Bugaiska A. Impact of physical activity on executive functions in aging: A selective effect on inhibition among old adults. J Sport Exerc Psychol. 2012;34(6):808–27. https://doi.org/10.1123/jsep.34.6.808.
92. Li C, Chang Q, Zhang J, Chai W. Effects of slow breathing rate on heart rate variability and arterial baroreflex sensitivity in essential hypertension. Medicine (Baltimore). 2018;97(18): e0639. https://doi.org/10.1097/MD.0000000000010639.PMID:29718876;PMCID:PMC6392805.
93. Driscoll D, Dicicco G. The effects of metronome breathing on the variability of autonomic activity measurements. J Manipulative Physiol Ther. 2000;23(9):610–4. https://doi.org/10.1067/mmt.2000.110944.
94. Melo HM, Martins TC, Nascimento LM, Hoeller AA, Walz R, Takase E. Ultra-short heart rate variability recording reliability: The effect of controlled paced breathing. Ann Noninvasive Electrocardiol. 2018;23(5):12565. https://doi.org/10.1111/anec.12565.
95. Gisselman AS, D'Amico M, Smoliga JM. Optimizing Intersession Reliability of Heart Rate Variability-The Effects of Artifact Correction and Breathing Type. J Strength Cond Res. 2020;34(11):3199–207. https://doi.org/10.1519/JSC.0000000000002258.
96. la Rovere MT, Pinna GD. Beneficial effects of physical activity on baroreflex control in the elderly. Annals of Noninvasive Electrocardiology. 2014;19(4):303–10. https://doi.org/10.1111/anec.12170 (Blackwell Publishing Inc.).
97. Lin Fv *et al.*, "Processing speed and attention training modifies autonomic flexibility: A mechanistic intervention study," *NeuroImage*, 2020; 213, https://doi.org/10.1016/j.neuroimage.2020.116730.

98. Bamidis PD *et al.*, "Gains in cognition through combined cognitive and physical training: The role of training dosage and severity of neurocognitive disorder," *Frontiers in Aging Neuroscience*, 2015; 7, https://doi.org/10.3389/fnagi.2015.00152.
99. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61(3):201–16. https://doi.org/10.1016/s0165-0327(00)00338-4.
100. Tarumi T, et al. Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. Neuroimage. 2015;110:162–70. https://doi.org/10.1016/j.neuroimage.2015.01.041.
101. saint Martin M, Sforza E, Thomas-Anterion C, Barthélémy JC, Roche F. Baroreflex sensitivity, vascular risk factors, and cognitive function in a healthy elderly population: The PROOF cohort. J Am Geriatr Soc. 2013;61(12):2096–102. https://doi.org/10.1111/jgs.12548.
102. Abou-Dest A, Albinet CT, Boucard G, and Audiffren M, "Swimming as a positive moderator of cognitive aging: A cross-sectional study with a multitask approach," *Journal of Aging Research*, 2012; 2012, https://doi.org/10.1155/2012/273185.
103. Albinet CT, Boucard G, Bouquet CA, Audiffren M. Increased heart rate variability and executive performance after aerobic training in the elderly. Eur J Appl Physiol. 2010;109(4):617–24. https://doi.org/10.1007/s00421-010-1393-y.
104. Coetsee C, Terblanche E. Cerebral oxygenation during cortical activation: the differential influence of three exercise training modalities. A randomized controlled trial. Eur J Appl Physiol. 2017;117(8):1617–27. https://doi.org/10.1007/s00421-017-3651-8.
105. Voelcker-Rehage C, Niemann C. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci Biobehav Rev. 2013;37(9):2268–95. https://doi.org/10.1016/j.neubiorev.2013.01.028.
106. Davenport MH, et al. Cerebrovascular Reserve: The Link Between Fitness and Cognitive Function? Exerc Sport Sci Rev. 2012;40(3):153–8. https://doi.org/10.1097/JES.0b013e3182553430.
107. Mehagnoul-Schipper DJ, et al. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. Hum Brain Mapp. 2002;16(1):14–23. https://doi.org/10.1002/hbm.10026.
108. Agbangla NF, Audiffren M, Pylouster J, Albinet CT, "Working memory, cognitive load and cardiorespiratory fitness: Testing the CRUNCH model with near-infrared spectroscopy," *Brain Sciences*, 2019; 9(2), https://doi.org/10.3390/brainsci9020038.
109. Voelcker-Rehage C, Godde B, and Staudinger UM, "Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults," *Frontiers in Human Neuroscience*, no. MARCH, 2011, https://doi.org/10.3389/fnhum.2011.00026.
110. Chapman SB, et al. Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. Cereb Cortex. 2015;25(2):396–405. https://doi.org/10.1093/cercor/bht234.
111. Stimpson NJ, Davison G, Javadi A-H. Joggin' the Noggin: Towards a Physiological Understanding of Exercise-Induced Cognitive Benefits. Neurosci Biobehav Rev. 2018;88:177–86. https://doi.org/10.1016/j.neubiorev.2018.03.018.
112. Dupuy O, Goenarjo R, Fraser SA, Bherer L, Bosquet L. Master Athletes and cognitive performance: what are the potential explanatory neurophysiological mechanisms? Mov Sport Sci. 2019;104:55–67. https://doi.org/10.1051/sm/2019023.
113. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 2002;25:295–301. https://doi.org/10.1016/s0166-2236(02)02143-4.
114. Ploughman M. Exercise is brain food: The effects of physical activity on cognitive function. Dev Neurorehabil. 2008;11:236–40. https://doi.org/10.1080/17518420801997007.