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TESIS DOCTORAL

2022

THE EFFECTS OF BILINGUALISM AND MULTIDOMAIN TRAINING ON COGNITIVE PROCESSES IN OLDER ADULTS

Efectos del bilingüismo y del entrenamiento multidominio en los procesos cognitivos de las personas mayores

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PROGRAMA DE DOCTORADO EN PSICOLOGÍA DE LA SALUD

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FACULTAD DE PSICOLOGÍA
UNIVERSIDAD NACIONAL DE EDUCACIÓN A DISTANCIA

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Abstract

Aging produces cerebral changes that might affect cognitive functions as we get older. Most older adults manage to compensate for these biological changes and to maintain to a certain degree their cognitive functions until advanced age. However, others will experience cognitive decline and/or dementia. The idea that differences in brain functionality could mitigate the effects of age-related neural changes on cognition has motivated research on what lifestyle factors and activities could be related to improved cognitive functioning in later life. Moreover, research is growing to clarify whether these mitigating factors could be acquired with different interventions. One of the lifestyle factors that has been repeatedly associated with an enhancement of executive functions in older adults is life-long bilingualism. However, to date, it is not clear what specific characteristics of bilingualism lead to these effects and if these can also be developed when the second language has been acquired in adulthood. Besides life-long lifestyle factors, also currently ongoing activities such as cognitive stimulation and physical training have been related to better cognitive outcomes in older adults. In the last decade, special interest was placed in the effects of multidomain training (i.e., combined cognitive and physical training). The assumption behind this is that physical exercise initiates a cascade of neuronal responses that prime the brain for learning and neuroplasticity, augmenting thereby the cognitive enhancement produced by cognitive training.

The main objective of this dissertation was to explore lifelong and short-term factors that could be associated with the maintenance or improvement of cognitive functions in older adults. Specifically, we were interested in (1) exploring the effects of late bilingualism on executive functions in older adults, and (2) analyzing the effects of

multidomain training interventions as compared to physical and cognitive training interventions alone.

The first objective was addressed with a study described in Chapter 6. The objective of this investigation was to analyze the cognitive effects of late bilingualism as a function of variations in attentional control demands in response to specific task requirements. Twenty monolingual and 20 bilingual older adults performed a task-switching task under explicit task-cuing versus memory-based switching conditions. In the cued condition, task switches occurred in a random order and a visual cue signaled the next task to be performed. In the memory-based condition, the task alternated after every second trial in a predictable sequence without presenting any cue. Results showed that the performance of bilinguals did not vary across experimental conditions, whereas monolinguals experienced a pronounced increase in response latencies and error rates in the cued condition. These results suggest that the cognitive benefits of bilingualism do not apply to executive functions *per se* but affect specific cognitive processes that involve task-relevant context processing. Results also suggest that cognitive changes can be developed even when the second language is acquired during adulthood.

The second objective of this Doctoral Dissertation was addressed with (a) the design and implementation of a randomized controlled trial (RCT), and (b) a systematic review and three-level meta-analysis. For the first approach, we designed and implemented a clinical trial with four treatment arms: (1) Cognitive intervention + physical intervention, (2) cognitive intervention + physical control activity, (3) physical intervention + cognitive control activity, and (4) cognitive and physical control activities. The trial was registered in the registry of clinical trials (ClinicalTrials.gov) of the United

States National Library of Medicine (NLM) at the National Institutes of Health, and its rationale and design are described in detail in Chapter 7.

For the second approach, we conducted a systematic review and three-level meta-analysis on the effects of combined cognitive-physical interventions on cognitive and physical functions in healthy older adults, which is described in Chapter 8. We computed 783 effect sizes from 50 intervention studies, involving 6,164 older adults. Results showed that combined training produced a small, albeit significant, advantage over single cognitive training on executive functions. In the remaining cognitive functions (processing speed, memory, attention, language, global cognition, and composite scores) the effects of combined training did not differ from those produced by cognitive training alone. Another interesting finding was that combined training produced a significantly larger effect on balance than single physical training, confirming the contribution of cognitive functions to the postural stability of elderlies. Overall, the largest training effects were achieved on executive functions and were highest when cognitive and physical training was performed simultaneously. Furthermore, group setting was related to the highest training gains in all cognitive and physical categories, confirming the role of social interaction as an important motivational factor for optimal training effects.

Taken together, the findings of this Doctoral Dissertation contribute to the existent literature on lifelong and short-term factors that influence cognitive functioning in older adults, as well as to the knowledge on the design and preparation of a clinical trial.

Keywords: Aging, executive functions, cognitive functions, bilingualism, task-switching, randomized controlled trial (RCT), three-level meta-analysis, multidomain intervention, combined training, cognitive training, physical exercise.

Resumen

El envejecimiento natural produce cambios cerebrales que pueden afectar a los procesos cognitivos a medida que envejecemos. La mayoría de los adultos mayores logran compensar estos cambios biológicos y mantener en cierto grado sus funciones cognitivas hasta una edad avanzada, mientras que otros experimentarán deterioro cognitivo y/o demencia. La idea de que diferencias individuales en la funcionalidad cerebral podrían mitigar los efectos del envejecimiento, ha motivado en los últimos años la investigación sobre qué factores y actividades podrían estar relacionados con un mejor funcionamiento cognitivo en las personas mayores y si es posible mejorar el funcionamiento cognitivo mediante el entrenamiento.

Uno de los factores que se ha relacionado en numerosas ocasiones con un mejor rendimiento de personas mayores en tareas de funciones ejecutivas es el bilingüismo. Sin embargo, hasta ahora no existe consenso científico sobre qué características específicas del bilingüismo conducen a estos efectos y si estos se desarrollan también cuando se ha adquirido la segunda lengua en la edad adulta; es decir, al margen de periodos críticos durante el desarrollo infantil. Además de factores relacionados con el estilo de vida, también se han relacionado ciertas actividades, como la estimulación cognitiva y el entrenamiento físico, con mejoras cognitivas en adultos mayores. Especial interés ha despertado en la última década la investigación sobre los efectos que produce el entrenamiento físico y cognitivo combinado, también llamado entrenamiento multidominio. La suposición subyacente es que el ejercicio físico inicia una cascada de respuestas neuronales que preparan el cerebro para el aprendizaje y la neuroplasticidad, aumentando así el efecto producido por el entrenamiento cognitivo.

El objetivo principal de esta Tesis Doctoral fue explorar factores de estilo de vida y actividades que podrían estar asociados con el mantenimiento o la mejora de las funciones cognitivas en los mayores. Específicamente, estábamos interesados en (1) explorar los efectos del bilingüismo tardío en las funciones ejecutivas en adultos mayores y (2) analizar los efectos de intervenciones de entrenamiento multidominio en comparación con intervenciones de entrenamiento físico y cognitivo por separado, sobre las funciones cognitivas de personas mayores.

El primer objetivo se abordó mediante el estudio que se describe en el Capítulo 6. El objetivo de esta investigación fue comprobar los efectos cognitivos del bilingüismo tardío en función de variaciones en las demandas de control atencional. En el estudio 20 adultos mayores monolingües y 20 bilingües realizaron una prueba de cambio de tarea con dos condiciones experimentales: (1) En la condición señalizada, los cambios de tarea ocurrieron en orden aleatorio y una señal visual indicó la siguiente tarea a realizar; (2) en la condición basada en la memoria, la tarea alternaba después de cada segundo ensayo, sin la presentación previa de una señal. Los resultados mostraron que el rendimiento de los bilingües no cambió en función de las condiciones experimentales, mientras que los monolingües experimentaron un aumento en las latencias de respuesta y las tasas de error cuando los cambios fueron aleatorios y señalizados. Estos resultados sugieren que los beneficios cognitivos del bilingüismo no se aplican a las funciones ejecutivas *per se*, sino que afectan a procesos cognitivos específicos que implican el procesamiento del contexto relevante para la tarea. Los resultados también sugieren que se pueden desarrollar cambios cognitivos en bilingües incluso cuando el segundo idioma se ha aprendido siendo ya adulto.

El segundo objetivo de la Tesis fue analizar los efectos del entrenamiento multidominio sobre las funciones cognitivas de personas mayores. El objetivo se abordó mediante dos enfoques: (a) el diseño y la implementación de un ensayo controlado aleatorizado (RCT) y (b) una revisión sistemática y un metaanálisis de tres niveles.

Para el primer enfoque, diseñamos e implementamos un ensayo clínico con cuatro brazos de tratamiento: (1) intervención cognitiva + intervención física, (2) intervención cognitiva + control físico, (3) intervención física + control cognitivo y (4) control cognitivo + control físico. Este ensayo clínico, que fue inscrito en la base de datos de ensayos clínicos de la Biblioteca Nacional de Medicina de Estados Unidos (ClinicalTrials.gov), generó un conocimiento profundo sobre la base y el diseño de un RCT y se describe en detalle en el Capítulo 7.

Para el segundo enfoque, realizamos una revisión sistemática y un metaanálisis de tres niveles que se describe en el Capítulo 8. En este estudio analizamos los efectos del entrenamiento multidominio en comparación con los producidos por el entrenamiento cognitivo y físico por separado en las funciones cognitivas de las personas mayores. En total, computamos 783 tamaños de efecto de 50 estudios de intervención, con una muestra total de 6164 adultos mayores sanos. Los resultados mostraron que el entrenamiento combinado produce un mayor efecto en las funciones ejecutivas que el entrenamiento únicamente cognitivo. En el resto de las funciones cognitivas (velocidad de procesamiento, memoria, atención, lenguaje, cognición global y puntuaciones compuestas) los efectos del entrenamiento combinado no difieren de los del entrenamiento cognitivo por separado. Otro hallazgo interesante fue que el entrenamiento combinado produce un mayor efecto en el equilibrio que el entrenamiento físico solo, lo que confirma la contribución de las funciones cognitivas a la estabilidad postural de las

personas mayores. En general, los mayores efectos se producen cuando el entrenamiento cognitivo y físico se realiza de forma simultánea y cuando el entrenamiento se realiza en grupo. Ello sugiere que existe una interacción entre (a) los procesos fisiológicos que se activan durante el entrenamiento físico, y (b) la mejora de los procesos cognitivos que se estimulan con el entrenamiento cognitivo. También se confirma que la interacción social constituye un importante factor motivacional en el entrenamiento con personas mayores.

Palabras clave: Envejecimiento, funciones ejecutivas, funciones cognitivas, bilingüismo, cambio de tarea, ensayo controlado aleatorizado (RCT), metaanálisis de tres niveles, entrenamiento multidominio, entrenamiento combinado, entrenamiento cognitivo, ejercicio físico.

"The beginning of knowledge is the discovery of something we do not understand"

- Frank Herbert

This work is dedicated
to my two sons, Adrián and Fabio, who inspire me every day to be a better person, and
to the loving memory of my grandmother, who passed away during this journey.
She meant so much to me.

ACKNOWLEDGEMENTS

This thesis is the result of a long and sometimes complicated journey, which was also filled with joy and satisfaction. Many people have provided me with their support and contributed to the successful completion of this rewarding doctoral journey. Being a part of the UNED community and receiving so much encouragement from others, I wish to acknowledge the doctoral process's team effort.

First and foremost, I want to thank my thesis supervisor Soledad Ballesteros, for her amazing academic supervision. Her helpful guidelines and suggestions, unfailing support, and great patience helped me to resolve obstacles encountered during the preparation of this work. Soledad, it was an honor to have received your support for my doctoral studies and your vocation for science and your tireless capacity for work will always be an inspiration to me.

I would like to extend my heartfelt gratitude to José Manuel Reales, co-advisor of this dissertation. Thank you for your encouragement and support, for your valuable insights and feedback, for your crucial recommendations on methodological issues, and for the inspiring moments of brainstorming. I feel fortunate and privileged to have been working with you.

I am indebted also to my colleagues from the SAND Research Group, which has been a source of friendships as well as good advice and collaboration. I would like to thank Pilar Jiménez, for her support and constructive discussions, always positive and full of optimism. My gratitude also goes to Cristina Pérez with whom I spent endless hours at the laboratory and training sites. Cris, thank you so much for your commitment and enthusiasm, and, this must be said, for being the only person on earth who laughs about my bad jokes and responds with even worse ones. I am also grateful to Mónica Muiños and Pilar Toril for their support, suggestions, and feedback. I thank Julia Mayas for her contributions to the preparation and launching phase of the trial, as well as Antonio Prieto for his contributions to the trial design and for introducing me to EEG techniques. I would like to extend my sincere thanks to several graduate scholars who helped in the recruitment and different assessment waves in the scope of their research *practicum*. Thanks to their engagement, Vanesa, Jorge, Ana, Selena, and Diego contributed to efficient compliance with the very adjusted trial timelines. I am particularly indebted to John O'Sullivan for his unfailing support during the clinical trial, and his English language support on several manuscripts.

I also would like to express my gratitude to the Leibniz Research Centre for Working Environment and Human Factors (IfADo) in Dortmund, Germany, where I could spend a marvelous research stay under the supervision of Patrick Gajewski, in collaboration with Stephan Getzmann. These outstanding scholars encouraged me to explore new (statistical) universes, supporting me in every step with meaningful insights and feedback. I also thank Tobias Blanke for his patience when explaining programming issues to me (Stichwort: MemoSwitch Aufgabe).

Furthermore, I gratefully acknowledge the fantastic job that Manuel, Carlos, Maica, Erica, and Estefanía from the CDM FFOCHOA did in the physical training sessions of the participants. All of them showed great professionality and it was a pleasure working with this team.

My sincere appreciation also goes to all institutions that offered support for the recruitment of participants and/or facilities for our study purposes: Centros Asociados de la UNED in Madrid and Pozuelo de Alarcón, Universidad para los Mayores de la

Universidad Complutense de Madrid, Unidad de Deportes de la Junta del Distrito de Carabanchel, Centro Deportivo Municipal Francisco Fernández Ochoa, Fundación Real Madrid, Goethe-Institut Madrid, Katholische Gemeinde Deutscher Sprache, and Friedenskirche.

I also thank Lumos Labs, Inc. for providing access to the interactive "Lumosity" software, which was used by the participants with great enthusiasm and joy. My gratitude goes also to Julio Velásquez for granting us free access to his Android games for our study purposes.

I am forever grateful for the altruistic commitment of hundreds of participants to our studies. You all have my deepest gratitude and respect, and without you, nothing of this would have happened.

Furthermore, I gratefully acknowledge the funding sources that made my Ph.D. work possible. I was funded by a four-year Doctoral Fellowship from the Spanish Ministry of Economy, Industry and Competitiveness (grant # BES-2017-079760), in the scope of the project "Efectos del entrenamiento multidominio versus unidominio en el control ejecutivo y la memoria de adultos mayores" (#PSI2016-80377-R), granted to Soledad Ballesteros and José Manuel Reales. `

Last, but in no way least, I want to thank my beloved family, whose love and commitment shaped the person I am today. I am very delighted to know that my accomplishment has made my parents and family so proud. My gratitude also goes to José Luis for his unconditional support and encouragement. Thank you all.

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SYMBOL LIST

% = Percentage

A1 = Reference electrode left ear

A2 = Reference electrode right ear

AFz = Midline antero-frontal electrode

Ag = Ailver

β = Beta coefficient

Cl = Chloride

c_m = Bias correction factor in the computation of effect size

Cz = Midline central electrode

dB = Decibel

d = Cohen's d measure of effect size

df = Degree of freedom

f = Cohen´s f measure of effect size

F = Fisher's F

Fz = Midline frontal electrode

g = Hedge's g measure of effect size

Hz = Hertz

k = Number of effect sizes

n = Sample size

η_p^2 = Partial eta squared

N2 = Negative-going event-related potential at around 200 ms

O_2 = Dioxygen

p = Probability

P2 = Positive-going event-related potential at around 200 ms

P3b = Positive-going event-related potential at around 300 ms

Pz = Midline parietal electrode

S = Sample standard deviation

S^2 = Sample variance

t = Student's t

U = Mann-Whitney test statistic

V = Volume

χ^2 = Chi-squared distribution

$\bar{y}$ = Mean for variable y

z = Standardized value

LIST OF ABBREVIATIONS AND ACRONYMS

3MS = Modified Mini-Mental State examination

6MWT = 6-min Walk Test

AC = Active control

ACC = Accuracy

AD = Alzheimer's disease

AIC = Akaike Information Criterion

ANOVA = Analysis of variance

ANT = Attentional Network Task

APOE = Apolipoprotein E

ATS = American Thoracic Society

BEC-96 = Signoret's Battery of Cognitive Efficiency test

BDNF = Brain-derived neurotrophic factor

BIC = Bayesian Information Criterion

BLP = Bilingual Language Profile

BMI = Body mass index

CC = Cognitive control

CENTRAL = Central Register of Controlled Trials

CI = Cognitive intervention

CI = Confidence interval

cm = Centimeter

Cont. = Control group

cook.d = Cook's distance

cov.r = Covariance ratio

COWAT = Controlled Oral Word Association Test

CR = Cognitive reserve

CRD = Centre for Reviews and Dissemination

CEFR = Common European Framework of Reference for Languages

CSV = Comma-separated values

d. = Days

DFFITS = Difference in fit(s)
DFBETA = Difference in beta values
DLF = Daily living functioning
DMC = Data monitoring committee
EEG = Electroencephalography
e.g. = Exempli gratia (for example)
EF = Executive functions
EI = Exercise intervention
ERP = Event-related potential
ES = Effect size
et al. = Et alia (and others)
Fig. = Figure
fMRI = Functional magnetic resonance imaging
fNIRS = Functional near-infrared spectroscopy
GDS = Geriatric Depression Scale
hat = Diagonal of the hat matrix
HDD = High drive disk
HRmax = Maximum heart rate
HVLT = Hopkins Verbal Learning Test
IBM = International Business Machines Corporation
ICA = Independent component analysis
ID = Identification
IGF-1 = Insulin-like growth factor 1
IVR = Immersive virtual reality
i.e. = Id est (that is)
L1 = First acquired language
L2 = Second acquired language
LRT = Likelihood ratio test
LSI = Life Satisfaction Index
M = Mean
max. = Maximum
MCI = Mild cognitive impairment

min. = Minutes
mm = Millimeters
mo. = Month
ms = Milliseconds
MMSE = Mini Mental State Examination
MoCA = Montreal Cognitive Assessment
MSE = Mean square error
Nº = Number
N/A = Not applicable
NIH = National Institute of Health
n.s. = Nonsignificant
NTB = Neuropsychological Test Battery
PALT = Paired Associate Learning Test
PANAS = Positive and Negative Affect Schedule
PASA = Posterior-anterior shift
PC = Passive control
PET = Positron emission tomography
PI = Physical intervention
PPA = Physiological Profile Assessment
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO = International Prospective Register of Systematic Reviews
PS = Processing speed
QE = Q-test for heterogeneity of effect sizes
QE.del = Leave-one-out test statistic of the test for (residual) heterogeneity
Quadr. = Quadriceps
RAWLT = Rey Auditory Verbal Learning Test
RBANS = Repeatable Battery for the Assessment of Neuropsychological Status
RCT = Randomized controlled trial
REML = Restricted maximum likelihood
RT = Reaction time
S = Supplemental
SD = Standard deviation

SE = Standard error

SF-36 = Short form-36 questionnaire

SMD = Standardized mean difference

SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials

SPPB = Short Physical Performance Battery

SPSS = Software package for statistics by IBM

SSE = Square stepping exercise

STAC = Scaffolding Theory of Aging and Cognition

suppl. = Supplement

tau2.del = Leave-one-out amount of (residual) heterogeneity

TMS = Transcranial magnetic stimulation

TMT = Trail-Making Test

Trat. = Treatment group

TUG = Timed Up and Go Test

UNED = Universidad Nacional de Educación a Distancia

UFOV = Useful Field of View Assessment

USA = United States of America

VEGF = Vascular endothelial growth factor

vs = Versus

wks. = Weeks

WM = Working memory

WHO = World Health Organization

WMS = Wechsler Memory Scale

WMH = White matter hyperintensities

FIGURE LIST

CHAPTER 1

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Introduction

Global population aging, caused by the increase in life expectancy and decrease in fertility rates, confronts societies with new and significant challenges. It is estimated that in the European Union the old-age dependency ratio (people aged 65 and above relative to those aged 15 to 64) will increase from 29.6% in 2016 to 51.2% in 2070 (European Commission, 2018). Public health care is mainly financed by social security contributions of the working population, whereas the health care expenditure largely depends on the health status of the retired population. These changes in demographic structures encompass societies to balance public spending on pensions and health care versus the need to reduce budget deficits (Harper, 2014). Active health education, health promotion, and disease prevention, as well as small increases in pensionable age (in line with increases in healthy life expectancy), could buffer the aging effects on public pension systems (Rechel et al., 2013). However, the success of promoting health literacy and autonomous living in older people is closely related to the prevention of age-related cognitive decline, i.e., the extension of years with normal cognitive functioning. People experience with age a decline in several cognitive functions, such as reasoning, processing speed, and memory, among others. Most older adults manage to maintain to a certain degree their cognitive efficiency until advanced age, but others will develop cognitive decline and dementia. Dementia is a clinical syndrome characterized by a progressive deterioration of cognitive functioning and is the major cause of impairment in independent living among older adults (Prince et al., 2013). The World Health Organization (WHO, 2017) predicts an increase in the prevalence of dementia from 75 million in 2030 to 132 million by 2050. The most common cause of dementia is Alzheimer's disease (AD), contributing to 60 – 70% of all dementias (WHO, 2017). Even though several genetic and environmental factors have been linked with the development of AD (Yankner et al., 2008), up to half of the AD cases are potentially attributable to modifiable risk factors, such as low education, smoking, or physical inactivity (Barnes & Yaffe, 2011; Peel et al., 2005). But above all, the main risk factor for the development of AD is biological aging (Keller, 2006). Even though several pathologic brain changes overlap in normal aging and at the initial stages of AD, such as a cumulative presence of white matter hyperintensities (Gunning-Dixon & Raz, 2000; Mar et al., 2015) or progressive demyelination of fiber tracts (Bartzokis, 2004; Brickman et al., 2012), the relationship between age-related neuroanatomical changes and the pathogenesis of AD is still not clearly understood (Yankner et al., 2008).

Nonetheless, not necessarily everything gets worse with aging. Aging is a complex and dynamic process. Some parameters that influence our future are genetically predetermined and others are a simple question of fate. However, many of the factors that mark our cognitive functions and independence in later life can be potentially chosen by us. Humans have the intrinsic capacity to adapt to changing circumstances and many older adults maintain their cognitive functioning despite underlying brain changes. Several studies compared the anatomical characteristics of normal and pathologic aging and found that almost half of the persons who met the neuropathologic Khachaturian criteria for AD were in fact dementia-free and lived a normal life (Keller, 2006; Knopman et al., 2003; Schmitt et al., 2000), suggesting that cognitive functioning in older adults is heavily modulated by how cerebral resources are used. The idea that differences in brain functionality could mitigate the effects of age-related neural changes on cognition has motivated in recent years research on what lifestyle factors and activities could be related to improved cognitive functioning in later life (Clare et al., 2017), and whether these mitigating factors could be acquired via training interventions (Ballesteros et al., 2015).

Chapter 1

Cognitive functions and age-related declines

Cognitive functions are an umbrella term that refers to different mental processes involved in perceiving, attending, learning, maintaining, and manipulating information. Results of numerous longitudinal and transversal studies indicate that normal aging is often associated with cognitive decline in several cognitive functions (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014; Salthouse, 2012), whereas others seem to remain relatively unaffected (Ballesteros et al., 2013; Ballesteros et al., 2007; Osorio et al., 2010). For example, verbal skills, implicit and procedural knowledge, and semantic memory appear to be largely spared (Goh et al., 2012; Nyberg et al., 1996; Park & Reuter-Lorenz, 2009), while there are marked age-related deficits in processing speed, episodic memory, and executive functions (Ballesteros et al., 2013; Salthouse, 1996) (**see Figure 1**).

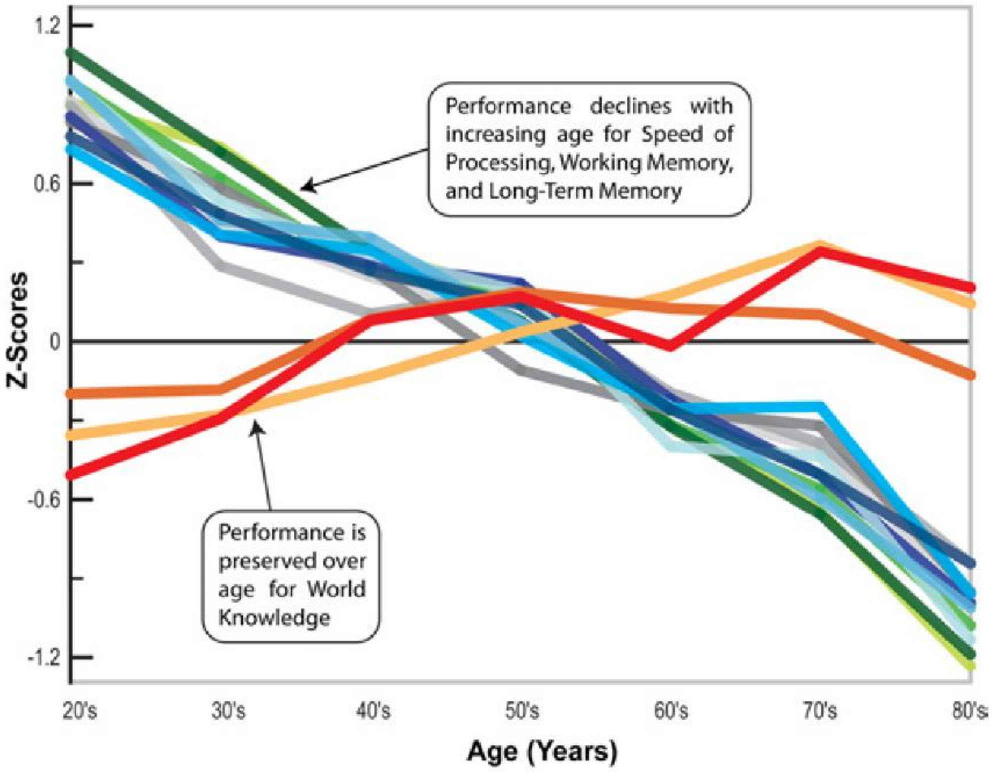

Figure 1. Cross-sectional aging data adapted from Park & Bischof (2002). Almost all measures of cognitive function show negative effects with age, except world knowledge, which even show positive age effects.

In what follows is a brief, but comprehensive description of the main functions involved in cognition, and examples of their decline with normal aging.

1. Processing speed

Human information processing, from stimuli perception to goal-directed behavior, is the result of a coordinated processing among largescale, distributed cortical networks (Mesulam, 1990; van den Heuvel & Hulshoff Pol, 2010). Perceptual speed is considered a principal marker of decline in fluid abilities (Lindenberger et al., 1993; Salthouse, 1996) in that the simultaneous or time-limited availability of information is directly related to cognitive task performance (Salthouse, 1996). With increasing age, changes in white matter lead to a progressive cortical disconnection, i.e., axonal and myelin degeneration and deformation that interfere with a rapid signal processing (Bartzokis, 2004; Bennett & Madden, 2014; O'Sullivan et al., 2001). Myelination of neuronal axons results in saltatory conduction of action potentials that markedly increases (>10-fold) signal transmission speed, and its degeneration not only reduces the transmission velocity but also increases the axonal refractory period (i.e., the recovery time before the next action potential is possible) as much as 34 times (Bartzokis, 2004). It is estimated that in old age, the total length of myelinated axons is reduced by 27–45% (Bartzokis, 2004), and thus it is not surprising that older adults often exhibit a poorer performance on cognitive tests that rely on fluid (speed-based) measures (Finkel et al., 2007; Hong et al., 2015; O'Sullivan et al., 2001). On the other hand, white matter changes do not correlate with crystalized intelligence, i.e., experiences and knowledge acquired in the past, such as verbal abilities or reading comprehension (Gunning-Dixon & Raz, 2000; Schipolowski et al., 2014). One possible explanation for the relative independence of crystallized knowledge from processing speed could be that crystallized intelligence is usually assessed with tools that do not include measures of reaction times (RT). However, also episodic memory, defined as personally experienced events in a spatio-temporal context, is generally assessed with time-independent tools, but shows a pronounced decline with increasing age. This suggests that other aspects besides cognitive slowing must be considered to explain the aging effect on cognitive performance, such as attentional control processes that modulate memory encoding and retrieval (Kramer & Madden, 2008).

2. Attention

Attention may be defined as those mechanisms that enable faster or deeper processing of some sensory inputs over others, making them available for action, memory, or thought (Egeth & Yantis, 1997; Posner, 1994). Attention accompanies cognition from the gating of information to working memory to the execution of complex behavior. Our consciousness only captures a very small part of the information that we are exposed to, and from all sensory inputs that reach our brain, only some of them get sufficiently activated to retain them in short-term memory for further processing (Lamme, 2003). But what guides the selection of some information over others? The biased competition theory proposed by Desimone and Duncan (1995) assumes that different representations compete for expression and that the role of attention is to bias this competition in favor of some competitors over others. The source of the bias can be bottom-up (e.g., driven by a stimulus) or top-down (driven by voluntary control). Visual attention is often described metaphorically as a spotlight (Posner, 1980), or a zoom lens (Eriksen & James 1986). Only stimuli within the beam of the spotlight are preferentially processed, whereas information outside the spotlight is unattended. Based on numerous neuroimaging and neurobiological results, Posner and Petersen (1990) identified three main attentional systems: (1) An executive system (sustained by frontal areas and mediated by dopaminergic neurotransmission) associated with cognitive control and action selection, (2) an orienting system (sustained by parietal and occipital areas and mediated by cholinergic neurotransmission) associated with orienting and perceptual attention, and (3) an alerting system (sustained by the brainstem and right hemisphere areas and mediated by noradrenergic neurotransmission) associated with sustained attention and vigilance. Furthermore, growing evidence shows that updating and reorientation also rely on a powerful gating mechanism subserved by frontostriatal loops (Cools et al., 2010; Shulman et al., 2009). Hence, attentional control depends on a dynamic interaction of different neural networks, that vary their influence on behavior as a function of changing situations or task demands. As we will see in the following sections, neurobiological aging causes several structural and functional brain changes and dysfunctions in neurotransmission, that affect performance in tasks that involve sustained, divided, and especially selective attention.

3. Executive functions

Executive functions (EF) are defined as cognitive processes that guide behavior in a voluntary, goal-directed manner by suppressing automatic or prepotent responses and are sustained by the previously described attentional neural networks. EF allow us to adapt to a constantly changing environment and to allocate our attentional resources efficiently within different task demands. From an overarching perspective, the capacity for effortful self-regulation is what distinguishes us from other non-human primates and underlies the unique human abilities for reasoning, problem-solving, and planning

(Diamond, 2013). The assessment of EF often is based on tests or experimental tasks that were developed to investigate attention. So, both concepts overlap to a high degree, especially regarding EF and selective and divided attention (Diamond, 2013).

Across the lifespan, the efficiency of executive control follows an inverted U-shaped curve, with its peak efficiency during young adulthood, and lowest efficiency in childhood during its development, and in older age, when aging processes lead to its progressive decline (Zelazo et al., 2004). The impairment of EF in older adults is associated with a cascade of deficits in other areas, such as reasoning, learning, and memory retrieval, and is considered one of the most important age-related dysfunctions. Based on individual differences in the performance of a series of cognitive tasks, Miyake and colleagues (Miyake et al., 2000; Friedman & Miyake, 2004) identified via confirmatory factor analyses and structural equation modeling, three main groups of separate, but moderately correlated EF: (1) updating and monitoring of working memory processes, (2) inhibition of dominant or prepotent responses, and (3) shifting between tasks or mental sets.

Working memory is defined as the component of short-term memory that involves the active maintenance and manipulation of goal-relevant information that is no longer perceptually present (Baddeley & Logie, 1999). Thus, short-term memory can be considered as passive storage with limited capacity, whereas working memory also requires additional attentional control processes for updating, manipulation, and removal of information (Engle et al., 1999; Kane et al., 2001). According to the Multiple-Component model proposed by Baddeley and Logie (1999), working memory is a system with limited capacity that stores and manipulates information. It was composed originally of three systems: the central executive, which functions as a supervisory system, and two short-term memory components: the **phonological loop** that stores verbal content, and the **visuospatial sketchpad**, that stores visuospatial content.

Some years later, Baddeley (2000) added a fourth component: the **episodic buffer**, that integrates the information from the short-term memory and long-term memory into a single episodic representation. As for the limiting storing capacity, the model posits that temporal decay is the primary mechanism of forgetting. The phonological loop was subdivided into two subcomponents, one that retains passive phonological information, and one active articulatory rehearsal process that refreshes these representations in a manner akin to subvocalization, or inner speech. This last component allows to overcome the temporal limitations and explains the gains obtained by strategic rehearsal. The capacity of simple short-term storage seems not to be affected by aging and age differences in performance arise when task difficulties increase (Bopp & Verhaeghen, 2005; Verhaeghen et al., 1997; for a meta-analysis, see Jaroslawska & Rhodes, 2019). Thus, the main source of cognitive impairment in storage and processing with advancing age seems to be an impairment of the ability to successfully manage and coordinate simultaneously different task demands (Bopp & Verhaeghen, 2007; Kramer et al., 1999; Kray & Lindenberger, 2000).

Inhibition refers to the ability to suppress otherwise automatic activation of goal-irrelevant information, i.e., the inhibition of prepotent responses (Hasher et al., 1999; Lustig et al., 2007). Conflicts in response competition arise when for example the appropriate response is relatively infrequent (e.g., withholding a response to an infrequent ‘‘no-go’’ stimulus) or when the inappropriate response is dominant and must be inhibited (e.g., the word in a Stroop task). Research has shown that the ability to efficiently inhibit interfering distractors is compromised in older adults in comparison to younger ones and that this deficit increments with increasing task difficulty (Zanesco et al., 2020). Furthermore, in older adults, inhibition is especially impaired in visual distraction, whereas in mental distraction (e.g., mind wandering) differences between younger and older adults diminish (Maillet et al., 2020). Aging also affects the ability to down-regulate no-longer-relevant information, i.e., clearing the mental workspace from task-irrelevant representations. In consequence, older adults experience more proactive interference from previous trials than younger adults (Ikier et al., 2008; May & Hasher, 1998).

Set-shifting is the ability to flexibly configure information processing in response to changing task demands. Flexibility is often assessed with task-switching paradigms in which participants must alternate between two or more different task sets (i.e., specifications of particular stimulus-response mappings), such as shifting rapidly between naming digits and naming letters (Monsell, 2003).

Older adults consistently produce higher mixing costs (i.e., the difference in performance between single-task trials and trials in which a task rule is repeated within a dual-task block) than younger adults (Kray & Lindenberger, 2000; Terry & Sliwinski, 2012), indicating that the simultaneous monitoring of two different task sets becomes more difficult with increasing age. Surprisingly, younger adults often produce higher switch costs (the difference in performance between repeating a task rule and switching to an alternate task rule) than older adults (Huff et al., 2015; Whitson et al., 2012). Younger adults are more likely to become well-tuned to a given task set, and thus, when the task set changes, inertia from the previous task set (i.e., the persistence of activation or inhibition from previous trials; Allport & Wylie 2000) slows the reconfiguration needed to respond to the switch trial. In older adults, attentional control is less tuned, and local switch costs are reduced because both task sets are still relatively active (Huff et al., 2015).

Applying neuroimaging techniques, task switching paradigms also allow to distinguish between proactive and reactive cognitive control. **Proactive control** is based on sustained activation before the appearance of the target stimuli and is related to advanced preparation for the upcoming trial (Braver, 2012). In contrast, **reactive control** is related to transient activation once the target stimulus has already appeared and refers to stimulus-driven decision making (Braver, 2012). Various studies indicate that aging is associated with a progressive shift from a proactive to a reactive cognitive control strategy, with less pronounced cue-locked activation and stronger target-locked activation (Jimura & Braver, 2010; Kopp et al., 2014). These results suggest that the ability to interpret and use contextual cues for advanced task preparation declines with age.

4. Long-term Memory

Memory can be understood as a complex psychological process involved in the codification, storage, and retrieval of information. Long-term memory is composed of several different memory systems, each one sustained by specific neural networks (Squire, 1992, 2004). Thus, we differentiate between declarative memory, which includes episodic and semantic memory, and non-declarative memory, composed of procedural memory, implicit memory, conditioning, and non-associative learning (Squire, 1992, 2004) (see **Figure 2**). Aging especially affects episodic memory, whereas other memory systems seem to remain largely spared (Squire, 1992). Results of a study conducted by Park and colleagues (2002) showed that verbal abilities and semantic memories were not affected by aging and even improved with age. Also, implicit memory has shown to

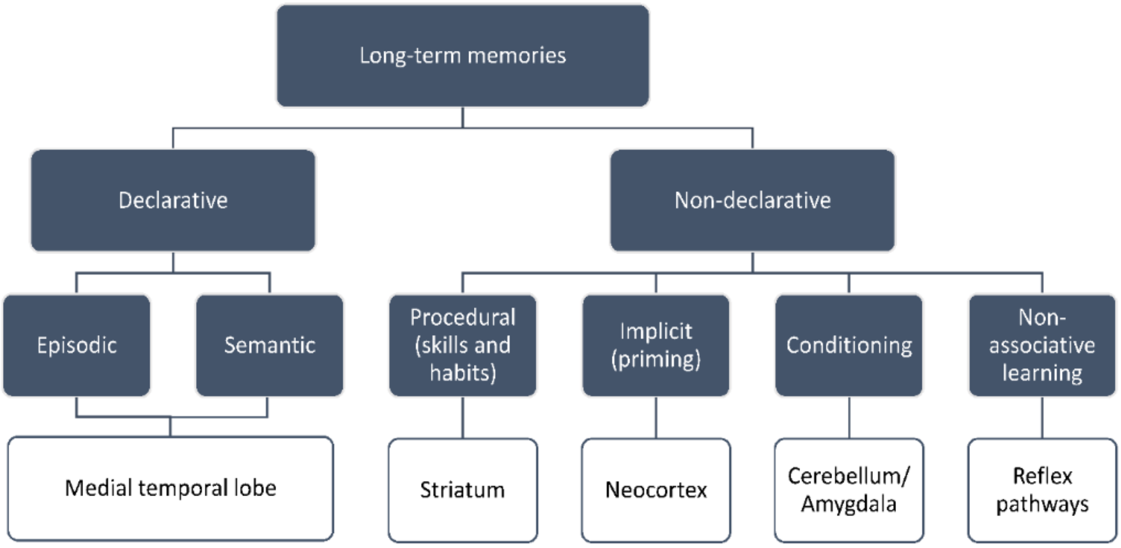

Figure 2. Taxonomy of long-term memory systems. (Squire, 2004).

remain stable across the lifespan (Ballesteros & Reales, 2004; Ballesteros et al, 2007; Ballesteros et al., 2008; Ballesteros et al., 2009; Sebastián & Ballesteros, 2012).

4.1 Declarative memory

Declarative memory refers to the conscious retrieval of information and includes episodic, semantic, and autobiographical memory. Semantic memory involves descriptive information and general decontextualized knowledge, whereas episodic memory involves information within a spatio-temporal context (Tulving, 1972, 1985). Autobiographical memory represents knowledge specific to an individual and includes both semantic information, such as a friend's name, and episodic information, such as a relative's wedding ceremony (Conway, 2001; Brewer, 1986). Squire (1987) proposed that the codification and retrieval from memory rely on specific activation patterns of functional homogeneous discrete neuronal groups. Thus, the retrieval of specific information from memory, always repeats the same activation pattern associated with this information, and complex memories integrate different neuronal assemblies in a distributed activation pattern. Declarative memory has a great capacity, and the phenomenon of forgetting is rather related to an unsuccessful retrieval due to ineffective triggering than to an actual memory loss.

Episodic memory is assessed with recognition, free-recall, and cued-recall tests. Episodic memory is most susceptible to age-related decline when assessed with free-recall tests, i.e., when participants must retrieve information on their own, without the help of external triggers (Verhaeghen & Salthouse, 1997). When episodic memory is assessed with recognition tests, age differences diminish (Osorio et al., 2009; Sebastián et al., 2011). It has been shown that instructions that focus attention on the meaning of words correlate with better performance in older adults (Logan et al., 2002). This result indicates that episodic memory retrieval is modulated by selective attention and suggests that age differences in performance sometimes reflect a failure of older adults to self-initiate the use of controlled, effortful processing strategies to support their performance (Reuter-Lorenz & Lustig, 2005).

On the other hand, **semantic memory** involves a combination of modality-specific and supramodal representations which are supported by a confluence of information throughout large regions of temporal and inferior parietal association cortices that support a variety of conceptual functions, including object recognition, social cognition, and language (Binder & Desai, 2011). Semantic memory involves highly conceptual activity that does not need to be triggered by stimuli in the immediate environment, which could explain its mayor preservation with age (Binder & Desai, 2011).

4.2 Non-declarative memory

Implicit memory is a type of long-term memory that does not underly voluntary control and its content is retrieved without consciousness. Implicit memory can be assessed with indirect measures, such as different types of priming paradigms. One often-used paradigm to measure implicit memory is repetition priming in which participants are asked to perform a speeded task involving a series of stimuli (e.g., words, textures, sounds, smells, or objects). After a short delay, the studied stimuli are presented together with new stimuli. Shorter response latencies or higher precision levels in response to the previously presented stimuli are considered the existence of priming (Ballesteros, 2017). The main difference between explicit and implicit memory tasks is that in explicit tasks, participants are asked to voluntarily retrieve specific information. In contrast, in implicit tasks the retrieval is incidental, and participants are not conscious that they manifest the influence of the previously presented material. Implicit memory has shown to resist not only age-related decline but also to remain largely intact in Alzheimer's disease patients (Ballesteros & Reales, 2004; Ballesteros et al., 2008, Fleischman, 2007). Priming effects were found for stimuli presented to different perceptual modalities, such as vision (Ballesteros et al., 2013), audition (Osorio et al., 2010; Redondo et al., 2015), touch (Ballesteros & Reales, 2004; Reales & Ballesteros, 1999), and taste (Caballero et al., 2018). Implicit memory is also more resistant to temporal decay than episodic memory and was found to remain intact for more than one month after stimuli presentation (Ballesteros et al., 2006). Despite the intuition that implicit memory might not need attentional modulation, various studies have shown that some degree of attention is necessary for information to be encoded in implicit memory (Ballesteros et al., 2006; Ballesteros et al., 2007).

Procedural memory refers to progressive skill learning, i.e., the incremental acquisition of stimulus-response associations or habits (Packard & Knowlton, 2002). This type of memory is sustained by a basal ganglia system in interaction with fronto-cortical-striatal loops (Packard & Knowlton, 2002). The interaction between basal ganglia and the medial temporal lobe memory system, i.e., the declarative memory system, is mutually exclusive and an increase in activation in one system correlates with a decrease in the other. Initial stages of learning are mainly sustained by prefrontal and medial temporal lobe structures, whereas with progressive automatization, processing shifts more and more to the caudate nucleus (Packard & Knowlton, 2002). As in the case of implicit memory, procedural memory remains mostly spared from age-related decline (Nyberg et al., 2012). However, the acquisition of new skills gets increasingly more complicated, probably due to the implication of episodic memory at the initial learning stages.

Chapter 2

Cognitive reserve, neuroplasticity, and successful aging

Cognitive functioning is a core element of the quality of life as we get older. However, cognitive functioning is sustained by a complex underlying cerebral substrate, which is exposed, like the rest of our body, to age-related changes. Our brain is constantly changing from birth throughout our lifetime, and normal, dementia-free aging is associated with several structural and functional brain changes. Neuroscientific research often aims to relate behavioral age-related cognitive decline with the underlying cerebral functioning, mostly by comparing older adults to younger ones. This allows, not only to broaden the knowledge on what changes with age but also on how the cerebral substrate might be used more efficiently despite the changes. What is it that makes some people cognitively function better than others, despite experiencing the same cerebral changes? In this Chapter, we aim to provide a comprehensive overview of the currently existing knowledge, trying to find an answer to this question.

1. Age-related neurobiological changes

Normal aging comes along with brain changes, such as reductions in gray matter and white matter volume, blood flow reductions, and neurochemical alterations, that affect cognitive performance (Salat et al., 2004). The whole-brain atrophy rate is -0.45% per year in adulthood (Fotenos et al., 2005), with larger reductions in prefrontal and parietal areas than in posterior brain areas (Raz et al., 2005; Resnick et al., 2003). To date, the relationship between grey and white matter thinning is not clearly understood. However, the results of several studies suggest that the volumetric changes in grey matter are rather associated with changes in the dendritic architecture, than with neuronal loss per se (Freeman et al., 2008; Taubert et al., 2020). According to Raz and Daugherty (2018), the progressive decline in brain functions in normal aging is originated from a continuous reduction of energy resources that are necessary for the normal functioning of cellular metabolic processes. Shifts in the homeostasis of important ions lead to increased oxidative stress, reducing progressively neurotransmission and promoting age-related tissue degeneration (Raz & Daugherty, 2018). As mentioned earlier, one of the most vulnerable processes to oxidative damage is neuronal myelinization (Bartzokis, 2004). Myelination of association pathways that connect frontal and parietal areas continues until the end of the fifth or beginning of the sixth decade of life (Bartzokis, 2004). However, with increasing age, cells cannot produce the same myelin thickness per axon as earlier, making thus late-to-myelinate tracts more susceptible to myelin breakdown than early-myelinating neurons in the primary motor and visual areas (Bartzokis, 2004; Bender et al., 2016; Raz & Daugherty, 2018). These later developing white matter tracts are more vulnerable to age-related decline and are part of neural networks that underly the processing of higher cognitive functions (Zhu et al., 2015).

The structural age-related changes mentioned above come along with different functional brain changes. A progressive dysregulation in cognitive-related neurotransmission interferes increasingly with the efficiency of information processing. Aging research has dedicated special attention to the dopaminergic system, as a core element in the processing of higher cognitive functions. Frontal depletion of dopaminergic receptors has been hypothesized to cause frontal neural “noise” (Bäckman et al., 2006; Li, Lindenberger, & Sikström., 2001), leading to less distinct neural representations. Computational modeling of dopamine depletion has been shown to explain the age-related decline in performance in working memory tasks (Li, Lindenberger, & Sikström, 2001). A progressive loss of neural specialization also affects the processing of faces versus places (Park et al., 2004; Voss et al. 2008), categories that are normally processed in very defined and differentiated areas, whereas in older adults the differentiation diminishes. Further functional changes are found in form of a dysregulation of the default mode network. The default network consists of bilateral and symmetrical cortical areas in parietal, prefrontal, and temporal brain areas (Raichle, 2015). Active processing in working memory implies decreases in the activation of the default mode network, allowing the inhibition of task-irrelevant interferences (Keller et al., 2015). Older adults produce less task-induced deactivation in comparison to younger adults, especially with increasing task demands (Brown, 2015; Park et al., 2010; Sambataro et al., 2010). In synthesis, neurobiological aging interferes with efficient information processing, which depends on a rapid interaction of task-relevant activations and deactivations of distributed neural networks. However, as will be mentioned in the next Chapter, the effect of cerebral aging on cognition varies greatly across individuals. While some individuals experience a sharp decline, others barely experiment cognitive changes.

2. Cognitive reserve

As described in the previous Chapters, age-related structural and functional brain changes profoundly affect cognitive functioning in later life and progress in some cases to cognitive decline and dementias. However, several studies have shown that a considerable proportion of individuals who presented postmortem brain changes that were compatible with Alzheimer´s Disease (AD) pathology, were dementia-free in life (Katzman et al., 1988; Knopman et al., 2003), a finding that gave rise to the concept of “reserve”. According to Stern and colleagues’ recently published whitepaper on this topic

(2020, p. 2), “reserve is a heuristic to help explain individual differences in cognition, function, or clinical status relative to aging and brain disease.”.

Two different, but not mutually excluding, propositions have been made to explain the interindividual variability of disease expression. The model of **brain reserve** refers to a higher resistance to neurologic damage based on morphological aspects, such as the brain size or the number of synapses (Katzman et al., 1988; Satz, 1993). The **cognitive reserve** model refers to the resilience or plasticity of cognitive networks to efficiently operate despite age- or disease-related brain changes (Stern, 2009). Both models propose a potential mechanism for coping with brain damage. However, the proposition of brain reserve (also referred to as the passive model) presents several problems in explaining individual differences in disease expression. Intracranial volume and head circumference are generally achieved by puberty (Pfefferbaum et al., 1994) but dementia risk appears to be highly modifiable by lifestyle factors and health behavior, even in older age. Furthermore, passive models assume that brain damage is accumulative, without differentiating between types of damage nor accounting for functional differences in coping with them (Stern, 2009). Finally, the brain reserve model assumes that clinical disease expression sets on, once a threshold of the amount of damage that can be sustained, is reached. This is the point that probably most defines the model of cognitive reserve: Given two individuals with the same brain reserve, a person with low cognitive reserve would begin to express clinical features once the neuropathologic burden reaches the tolerable threshold for coping with the damage. In contrast, a person with high cognitive reserve could maintain cognitive efficiency by recruiting alternative brain networks (Stern, 2009). Cognitive reserve (CR) can be influenced by innate individual differences and lifetime exposures. However, the amount of cognitive reserve is not fixed or unchangeable. Likewise, CR may already be present before the onset of brain changes or emerge in form of compensatory processes in response to brain insults to maintain cognitive function (Stern et al., 2018).

Preexisting CR is developed by lifelong exposures to socio-behavioral factors that have been related in numerous epidemiologic studies to reduced risk of developing dementia, such as cognitive ability, education, occupation, physical exercise, leisure activities, social engagement, and bilingualism (Bialystok et al., 2007; Clare et al., 2017; Ferreira et al., 2015; Meng & D'Arcy, 2012; Valenzuela & Sachdev, 2006; Xu et al., 2015). The positive influence of cognitively demanding leisure activity on CR is dose-dependent (Fratiglioni et al., 2000; Fabrigoule et al., 1995), raising the question of how much exposure is needed to create a time-resistant mechanism that counteracts age-related decline.

3. Neuroplasticity and successful aging

Whereas CR is generally estimated from life-long activities that have shown to correlate with more efficient cognitive functioning in later life, the *Scaffolding Theory of Aging and Cognition* (STAC; Park & Reuter-Lorenz, 2009) explains individual differences in cognitive functions, based on age-related neurobiological changes and neuroplasticity. That is, the brain's capacity to reorganize itself in response to internal and/or external influences. Both are similar in that they postulate the existence of latent neural resources that allow individuals to maintain their cognitive performance in the face of pathology or age-related burden. However, the STAC theory provides a theoretical framework for understanding how experiences, fitness, and training positively influence cognition even on a short-term basis. This theory understands structural and functional age-related brain changes as neural challenges which are susceptible to be modulated by stimulating activities, improving thereby cognitive functions (Park & Reuter-Lorenz, 2009; for a review see Ballesteros et al., 2018).

A central concept in this theory is "compensation", which could be defined as functional changes in response to age-related or pathological interferences to maintain normal cognitive functioning. Compensatory mechanisms are fostered by experiences and new learning, enhanced cardiovascular health, and mentally challenging activities, making these activities core elements in the cognitive maintenance of older adults (see **Figure 3** for a graphic description of the factors that influence neurocognitive aging). Compensatory mechanisms provide an alternative neural substrate for processes that cannot be longer sustained by the originally responsible structures. This assumption is

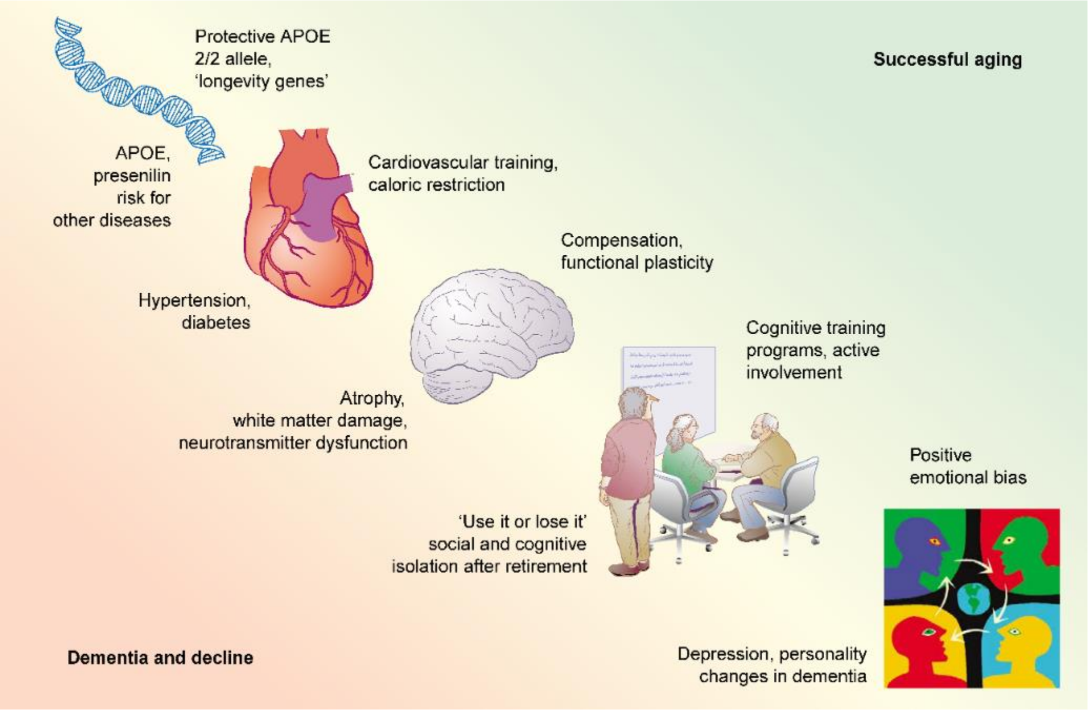

Figure 3. Factors influencing neurocognitive aging. The figure illustrates several factors influencing whether aging will be successful or lead to impairment. APOE = apoliprotein E. (Reuter-Lorenz & Lustig, 2005).

based on the results of numerous neuroimaging studies that found differences in the neural activation patterns between young and older adults when performing cognitive tasks. For example, when performing cognitively demanding tasks, older adults exhibit a shift in neural activation from posterior to anterior brain areas and a reduction in brain asymmetry whereas younger adults show a more distributed activation pattern (Cabeza et al., 2008).

When overactivation correlates with poorer performance it is understood as a neural correlate of cognitive decline. However, when overactivation correlates with improved performance, functional changes are understood as successful compensation (Cabeza et al., 2002; Gutchess et al., 2005; Morcom et al., 2007; Reuter-Lorenz & Park, 2014). For example, Osorio and colleagues (2010) assessed implicit memory with a word-stem completion task in younger and older adults. Even though both groups produced similar behavioral priming effects, older adults' performance was sustained by additional frontal activity in compensation for lower activity at posterior sites (Osorio et al., 2010). In conclusion, the STAC theory provides a comprehensive framework that explains the interdependent effects of detrimental and protective factors on the cognitive and psychological outcomes in senescence.

Chapter 3

Bilingualism

"If experience can shape brain structure and cognitive ability, then bilingualism is a prime candidate for such effects. Language use is the most intense, sustained, and integrative experience in which humans engage." (Bialystok, 2017).

Bilingualism refers to the coexistence of more than one language system within an individual, as contrasted to monolingualism. There are many ways to become bilingual, such as growing up with a heritage language at home (a minority language that contrasts with a more dominant social language), receiving formal education in a second language, temporarily residing in another country, living in a country where the official language is different from the community language, and so on. Each of these circumstances is associated with a different set of social, cognitive, and personal factors, making the bilingual experience deeply heterogeneous and potentially altering its consequences on cognition (Bialystok et al., 2009).

1. Language acquisition

Language acquisition is different for children and adults in that they use different mechanisms for second language (L2) learning. Whereas children learn languages implicitly, i.e., without awareness, adults apply to some extent analytical abilities for L2 acquisition (DeKeyser, 2003). These maturational differences in language acquisition motivated the formulation of the critical period hypothesis, which proposes the existence of some cut-off point in a person's life beyond which it becomes impossible to achieve nativelike proficiency in another language (Birdsong, 1999). Different explanations have been proposed for the developmental constraints in language acquisition, such as a loss of neural plasticity in the learner's brain, a loss of access to Universal Grammar[1], and a

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[1] Universal Grammar is proposed as part of an innate biologically supplied language faculty as an explanation of how it is that learners come to know properties of grammar that go far beyond the linguistic input (e.g., Chomsky, 1965, 2007).

"maladaptive gain" in processing resources as a learner matures. However, increasingly counterevidence suggests that there may not be such a critical period (Birdsong, 2006, Hyltenstam & Abrahamsson, 2003, Bongaerts, 1999; Flege et al., 1999), and that "the attested straight-line age function in L2A over the lifespan is the product of different causal mechanisms along the way; that is, the result of developmental factors up to the end of maturation, and non-developmental factors thereafter" (Birdsong, 1999, p. 12). The shift during childhood from implicit to explicit learning underlies two of the main age-related distinctions in L2 learning: children learn better, and adults learn faster (Marinova-Todd et al., 2000). Children do better in terms of ultimate attainment because many elements of language are hard to learn explicitly; adults learn faster because their capacities for explicit learning let them take shortcuts (DeKeyser, 2003). Nonetheless, even though L2 acquisition after childhood requires effortful processing, native-like proficiency might still be attained in late second language acquisition (Birdsong, 2006). Recent approaches understand second-language acquisition as complex skill acquisition, such as learning to play the piano or developing mathematical abilities (Segalowitz & Hulstijn, 2005). With increasing skill level, the language processing shifts progressively from declarative to procedural knowledge, reducing attentional demands and incrementing efficiency. Such a transition from non-automatic to automatic performance seems to be a part of nearly all skill acquisition.

In language learning, increased performance efficiency can be seen as contributing to fluency, that is, the ability to use language rapidly, smoothly, and accurately (Segalowitz & Hulstijn, 2005).

2. Bilingual language processing and language control

Numerous studies have found a bilingual advantage in executive functions, (for a review, see Adesope et al., 2010; Bialystok, 2017). For example, Costa et al. (2008) analyzed the performance of a large sample of monolingual and bilingual young adults on the ANT task. Bilinguals were overall faster, took more advantage of the alerting cues, and displayed less interference from incongruent stimuli than monolinguals. Similar results showing an advantage for bilinguals have been reported using the flanker task (Pelham & Abrams, 2014; Verreyt et al., 2016), and the Stroop task (Bialystok et al., 2008; Coderre & Van Heuven, 2014.).

Surprisingly, in verbal fluency and lexical decision tasks monolinguals normally perform better than bilinguals (Gollan et al., 2005; Sadat et al., 2012; Ransdell & Fischler, 1987). The reason for this can be found in how dual-language management is processed. In a bilingual brain, both languages share the same neural substrate, and both linguistic codes are simultaneously active. In fluent bilinguals, one concept will activate two signifiers, and to name the concept in one language, it has to be inhibited in the other language, producing a constant competition in selection (Kroll et al., 2014). This means that bilinguals are exposed to greater cognitive demands than monolinguals, even when language production appears to be equivalent (Bialystok, 2017). Conflict in joint activation is resolved via domain-general attentional control mechanisms (Bialystok et al., 2009), leading to a progressive overlap of language control and domain-general neural networks (Abutalebi & Green, 2007; De Baene et al., 2015; Hervais-Adelman et al., 2011; Luk et al., 2012). However, the demands of language selection and control largely depend on the interactional context of language use, with higher cognitive demands in a dual-language context than when only one language is spoken at a time (Green & Abutalebi, 2013). Thus, the degree to which bilingualism shapes the brain and improves executive functions is related to the time of exposure to a dual-language context (Hartanto & Yang, 2016; Hartanto & Yang, 2020; Pliatsikas et al., 2016).

Short intensive second language (L2) learning has been linked to neuroplastic changes (Schlegel et al., 2012; Stein et al., 2012), an improvement of executive functions (Bak et al., 2016), and neural enhancement in the processing of executive tasks (Sullivan et al., 2014; for a review see Li, Legault, & Litcofsky, 2014). However, results are mixed, and other studies did not find a significant effect of L2-learning on cognition in older adults (Berggren et al., 2020; for a review see Ramos et al., 2017), suggesting that cognitive benefits of L2-learning do not only depend on the level of competence achieved but also on the amount of L2 immersion and balance in the usage of the two languages. This could explain the moderate effects of L2 learning in older adults (Berggren et al., 2020) and strengthens the assumption that the cognitive benefits of bilingualism for later life cognition depend on the long-term fostering of a neural reserve.

3. Bilingualism and cognitive reserve

Within the several activities that have been linked to fostering CR, bilingualism has received increasing attention during the last years. Results from numerous studies suggest that being bilingual or multilingual exerts protective effects, enabling bilinguals to tolerate more neuropathological burdens than monolinguals (Perani et al., 2017; Schweizer et al, 2012). Several studies have shown that, on average, bilinguals are diagnosed with Alzheimer's disease 5-6 years later than monolinguals (Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015). Language use involves not only the processing of verbal communication, but also the conceptualization and interpretation of the ongoing experience, and is sustained by extensive brain activity, engaging frontal, temporal, and parietal lobes, as well as some posterior regions (Friederici, 2011). The necessity for an overall extensive neural processing could explain the findings of more preserved white matter integrity in aging bilinguals, and several studies reported stronger functional connectivity in neural networks that underly executive processing (Grady et al., 2015; Luk et al., 2011). Furthermore, better performance in executive tasks in elder bilinguals is related to increased GM in regions that show atrophy in monolinguals, suggesting that life-long bilingualism fosters the development of a neural reserve which, in turn, protects bilinguals before the onset of age-related cognitive decline (Abutalebi et al., 2015). The precise reasons for the neuroprotective effects of bilingualism are still unknown, but several hypotheses are receiving increasing support. Thus, it has been suggested that increased activity within front-parietal and frontostriatal networks associated with the bilingual experience may protect against age-related declines in cellular and synaptic functions within these EC circuits (Gold, 2015). **Figure 4** shows a schematic representation of potential bilingual CR mechanisms. Increased neuronal activity within EC circuits and corresponding increases in the delivery of oxygen and glucose may result in a synergistic cascade of beneficial effects in the bilingual brain. This potential mechanism could promote the strengthening of dynamic neuronal-glial interactions, promoting myelination and angiogenesis (Gold, 2015).

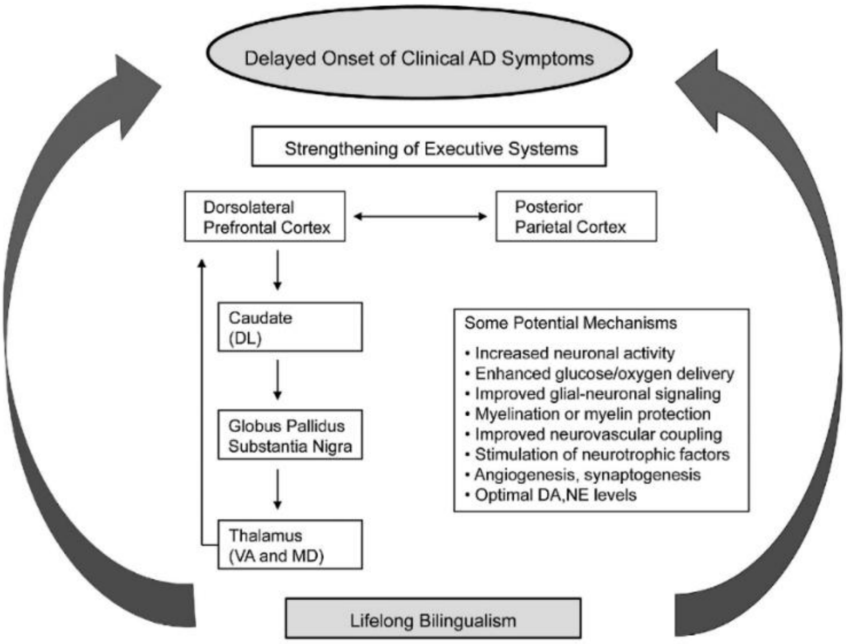

Figure 4. A schematic representation of potential bilingual CR mechanisms. DA, dopamine; NE, norepinephrine. (Gold, 2015).

Chapter 4

The effects of training interventions on healthy aging

Neuroimaging studies give a valuable insight into neuroplasticity in relation to cognitive performance. However, as occurs in any correlational analysis, they do not enable the establishment of causality, but set the stage for experiments (e.g., fMRI with varying task demands), and for longitudinal studies (e.g., measurements of a given variable in a sample at different time points). When a longitudinal study involves the evaluation of a therapeutic intervention, it is called an intervention study. In what follows, we describe the most promising training interventions designed to improve cognition in older adults, which are (1) cognitive training interventions, (2) physical exercise interventions, and (3) combined physical-cognitive interventions, also called multidomain interventions.

1. Cognitive training interventions

In the last decade, an increasing number of studies investigated the effects of cognitive training on cognition in older adults. The assumption behind cognitive training is that one's general cognitive ability can be enhanced by practicing cognitive tasks or intellectually demanding activities. For example, Gajewski and Falkenstein (2012) conducted an intervention study with 140 healthy older adults to investigate the differential effects of physical versus cognitive training on task switching and its neural correlates, compared to active and passive controls. Their results indicated that cognitive training produced significantly larger improvements of response selection and error detection compared to the other groups. The form of delivering the training as well as the measured functions vary greatly between the studies. Whereas some studies choose tailor-made training protocols (e.g., McAvinue et al., 2013; Richmond et al., 2011; Wang et al., 2011), many other studies rely on computerized brain-training platforms for cognitive training (Boot et al., 2013; Mahncke et al., 2006; Mayas et al., 2014). Video games, or digital brain-training platforms, have the advantage that besides the cognitive training component, users might be more entertained, thus increasing their engagement with the training. A meta-analysis conducted by Toril and colleagues (2014) on the training effects of video games in 439 healthy adults compared to 439 controls, found that cognitive training with video games produces significant improvements in processing speed, attention, memory, and global cognition.

Despite the promising effects of cognitive training on cognition, results on transfer and maintenance effects are not consistently observed. Within transfer effects, we can distinguish between near transfer, when the training in a specific task generalizes to other tasks within the same cognitive domain, and far transfer effects when training effects generalize to untrained other domains and domain-general functions. A recent systematic review (Butler et al., 2018) suggests that cognitive training produces durable improvements in the trained function, but that the training effects do not generalize to other untrained functions. However, the authors found great heterogeneity in interventions in terms of outcome measures, training, transfer, and durability. The training effects might be influenced by differences in study designs and vary across cognitive domains that are trained and assessed. Also, differences in the training protocols influence the effectiveness of the intervention and for example, unsupervised at-home training is less effective than group-based training sessions (Lampit et al., 2014, Rieker et al., 2022).

In an interventional study, Ballesteros and colleagues (2014) investigated the effects of commercially available non-action computer games on several cognitive functions in older adults. Forty participants were either assigned to 20 training sessions of cognitive training or to an active control group who participated in discussion meetings. After the intervention and at the 3-month follow-up only the intervention group showed, besides the expected improvements in the games, cognitive enhancement in untrained tasks that assessed choice reaction time, attentional control, and immediate and delayed visual memory. Nonetheless, training effects disappeared after several months, and the authors suggest that periodic boosting sessions would be necessary to maintain the benefits. But was it the specificity of the computer games, that are specifically designed to improve cognitive functions, that explained the training effects, or would any computer game produce similar effects?

Ballesteros et al. (2017) conducted another randomized controlled trial using the same cognitive training platform as an intervention. In this case, they compared the training effects with those produced by virtual simulation strategy games as an active control condition. Results indicated that both interventions produced similar improvements in spatial working memory and that the sham activity even produced larger effects on selective attention. However, the control games involved an open-world life simulation in which the player had to create and maintain a virtual life and control several virtual characters and their relationships. This made it impossible to determine which cognitive functions were involved and incidentally trained during this process, bringing up the critical question of how to control for training effects of sham interventions.

2. Physical exercise interventions

In a large-scale prospective cohort study with 416 175 participants who were followed over eight years, Wen and colleagues (2011) found that 15 minutes a day or 90 minutes a week of moderate physical activity increased life expectancy up to three years and that the relation to health outcome was dose-responsive in that those who were most active had a reduced risk of all-cause mortality. Besides the evident positive effects on physical health outcomes, physical exercise has also shown to improve cognitive functions (for reviews see Muiños & Ballesteros, 2018; Northey, 2018). For example, Voelcker-Rehage et al. (2011) found in a 12-month intervention study that three days of cardiovascular or coordination training per week not only improved executive functions and processing speed but also correlated with a reduction of prefrontal overactivation. Another study (Liu-Ambrose and colleagues, 2010, 2012) found that a twelve-month resistance training produced significantly more improvements in executive functions than toning and balance training. Interestingly, the intervention did not detain the course of brain volume reduction, suggesting that cognitive improvements were more related to functional than structural training-induced brain changes. However, it seems that also neurogenesis and synaptic modulation remain functional in advanced age. Neurogenesis refers to the proliferation, survival, and differentiation of neural precursor cells into mature neurons or glia that are integrated into the rest of the brain structure (Kempermann et al., 1998).

Animal studies have shown neurogenesis in the hippocampus following environmental enrichment (e.g., promoting social interaction, cognitive stimulation, and physical exercise) (Bonaccorsi et al., 2013; Hirase & Shinohara, 2014). Interestingly, results suggested that physical exercise and cognitive stimulation induce neuroplastic changes by different mechanisms at the cellular level. Physical exercise promotes the proliferation of precursor cells, whereas environmental enrichment and learning processes predominantly promote the survival of newborn cells (Kempermann et al., 2010; Kronenberg et al., 2006). Numerous studies have confirmed that similar processes also occur in the corresponding regions of the human brain (Erickson et al., 2009; Erickson et al., 2011; Niemann et al., 2014), even though the number of new neurons declines with age.

Furthermore, physical exercise has been related to higher levels of circulating brain-derived neurotrophic factor (BDNF). BDNF is a growth factor involved in neurogenesis, synaptogenesis, and dendritic branching, and its actions constitute one of the key mechanisms of exercise-induced brain plasticity and cognitive enhancement (Håkansson et al., 2017; Ruscheweyh et al., 2011). The increase of BDNF is highest after a single bout of exercise and potentiated by a preceding period of regular exercise (Szuhany et al., 2015). Nonetheless, this effect is only temporary, and BDNF levels return to their serum baseline levels within 30 minutes after exercise cessation (Walsh, 2016). The transient BDNF response to exercise is hypothesized to initiate a cascade of neuronal responses that prime the brain for learning and neuroplasticity (Rasmussen et al., 2009), representing thus a potential mechanism for maximizing cognitive improvements via multidomain training interventions (Walsh & Tschakovsky, 2018). In a recent intervention study, Nilsson and colleagues (2020) investigated the strength of association between cognitive gains and BDNF serum levels as a function of whether physical training preceded or followed the cognitive training. In line with the BDNF mechanisms described above, their results indicated that cognitive gains correlated with BDNF levels only when exercise was performed before cognitive training.

3. Multidomain interventions

In recent years promising approaches were made investigating the effects of combined physical and cognitive training, also denominated as multidomain training.

A crucial question is whether multidomain interventions, as opposed to single cognitive training or single physical training, might produce a synergistic effect on cognition, i.e., a combined effect greater than either one produced by its components separately. For example, Barnes and colleagues (2013) investigated the training effects of multidomain training (intensive computerized brain training + aerobic exercise) and each of its training components alone combined with cognitive and physical control activities (educational DVDs and stretching and toning) on several cognitive domains. Results showed that, in comparison to the active control group, multidomain training and cognitive training alone produced similar training effects on divided attention, but only the multidomain group showed a significant improvement in selective attention. Furthermore, only the multidomain group showed an effect on verbal fluency and none of the groups improved in memory functions. By contrast, applying a similar four-arm design, Shatil (2013) not only did not find an advantage in combining cognitive training and physical exercise, but cognitive training alone produced even higher effect sizes than in combination with physical exercise. However, in Shatil's study, participants were slightly older than in Barnes' study and nearly 60% could not deal with intensive aerobic training. Thus, the physical exercise component varied in both studies. Whereas in one study, one exercise session lasted 45 minutes involving 15 minutes of low to moderate aerobic exercise, in the other study, a session lasted 60 minutes and included 30 minutes of intense exercise at 60-75% of maximum heart rate. As seen, as in single-domain interventions, also in multidomain interventions the variability in experimental designs influence the training outcomes. In some studies, physical training and cognitive training were delivered on separate days (e.g., Fabre et al., 2002; Ng et al., 2018). In other studies, the training was sequentially implemented within the same session (e.g., McEwen et al., 2018; Linde & Alfermann, 2014) while in other studies, like in those using exergames, both trainings were performed simultaneously (e.g., Falbo et al., 2016; Schättin et al., 2016). Furthermore, the type of cognitive training and physical exercise varies from study to study, as well as the intervention duration. Also, other activities such as Tai Chi and dance have shown promising effects on cognition in older adults (for reviews, see Muiños & Ballesteros, 2020; Muiños & Ballesteros, 2021). Even though these activities miss a clearly definable cognitive component, they still involve physical, cognitive, and social aspects. Dance interventions have shown to improve several cognitive functions, such as executive functions (e.g., Rehfeld et al., 2017; Douka et al., 2019), verbal fluency (Kim et al., 2011), and short-term memory (Porat et al., 2016; Kosmat & Vranic, 2017). Furthermore, dance not only exercises the body and mind but also fosters social interaction, which could lead to higher motivation and engagement.

4. Methodological issues

The ultimate objective of cognitive, physical, or combined intervention studies is to determine the most effective and efficient ways to improve and/or maintain cognitive functions in older adults, contributing therewith to health promotion and disease prevention. Different rationale and designs of training interventions are necessary to investigate distinct factors involved in the training effects. However, to produce usable information that can be replicated and generalized to the population, it is imperative to separate the training effects from other factors that could influence the measured functions. Therefore, the study design is of great importance when analyzing the therapeutic effect of any intervention.

The three most common study designs are uncontrolled trials (without a control group), non-randomized or quasi-experimental trials (with a control group, but the treatment allocation is nonrandom), and randomized controlled trials (RCTs) in which participants are randomly allocated to either placebo (or sham) treatment or one or more experimental groups). RCTs are considered the gold standard of clinical research for presenting an unbiased and valid assessment of the study outcomes. Clinical trials are planned, designed, executed, and analyzed following strict guidelines to minimize potential biases and confounding factors that might modulate the treatment effect. Bias is defined as a systematic error that deviates data from the truth caused by partial judgment or personal preference and can occur at any stage of a clinical trial (Chow & Liu, 2004). Biases are inevitable, and it is crucial to identify any potential bias and implement procedures such as randomization or blinding to minimize or eliminate the bias. Randomization in treatment allocation ensures that those baseline differences that could be related to the treatment effects are, as far as possible, equally distributed between the groups (Chow & Liu, 2004).

Confounding effects are factors such as race and gender that cannot be separated by the design under study, and if not properly controlled, they can interfere with the treatment effect that the trial is designed to demonstrate. Blinding is defined as a procedure in which various groups of individuals involved with the trial are withheld from the knowledge of treatments and allocation. This technique aims to control bias caused by subjective judgments due to the knowledge of the identity of the treatments. However, even randomized trials can yield biased results if they lack methodological rigor or inadequate reporting: By contrast, nonrandomized trials might control for confounding factors with a high-quality study design (Concato et al., 2000). Therefore, to guarantee the quality and integrity of a clinical investigation, it is important to elaborate a well-designed study protocol detailing how the trial is to be carried out and how the data are to be collected and analyzed.

Another strong method for analyzing treatment effects are meta-analyses. Meta-analyses summarize effect sizes on similar topics by statistical techniques and examine the impact of moderators on the effect sizes. Systematic reviews and meta-analyses offer an opportunity to test treatment effects in very large samples while controlling for confounding factors such as study quality or sample characteristics. A difficulty in meta-analyses is that a study might include more than one outcome measure, which produces an interdependency of effect sizes. Traditional univariate approaches often apply the samplewise procedure which consists in averaging the dependent effect sizes within studies into a single effect size by calculating a weighted average (Cheung, 2019). However, this method underestimates the degree of heterogeneity or the variance of the population and might lead to lower statistical power due to information loss (Cheung, 2019).

A relatively novel approach for dealing with the dependency of effect sizes without losing informative differences between effect sizes consists in applying a three-level structure to a meta-analytic model (Assink & Wibbelink, 2016). This approach considers three different variance components and allows effect sizes to vary between participants (sampling variance), outcomes (within-sample variance), and studies (between-study variance). This allows for analyzing training effects on different cognitive functions within the same study (i.e., within-study heterogeneity), as well as their reliability across different studies (i.e., between-study heterogeneity).

Chapter 5

Objectives of the Dissertation

This Doctoral Dissertation had two main objectives, both embedded in the research on the prevention of age-related cognitive decline.

The **first objective** was to investigate the influence of a **life-long proxy of cognitive reserve** on the cognitive functions of older adults. For this purpose, we chose bilingualism, as dual-language management has been related on numerous occasions with a cognitive advantage in elderly individuals. Furthermore, we wanted to dissociate these effects from early-childhood bilingualism which develops during critical periods before the completion of brain maturation. For this goal, we conducted an experiment with monolingual and bilingual older adults. The sample was composed of older bilinguals who had acquired their L2 after the age of 18 but had been exposed for various decades to a dual-language environment.

We argue that the primary modulating factors of bilingualism on cognition are rather related to a balanced use of the two languages and the time of exposure and proficiency than to the age of acquisition. Therefore, if there were to be found differences between monolinguals and post-adolescent bilinguals (i.e., bilinguals that had acquired their second language after puberty), it would provide evidence that the cognitive benefits of bilingualism also could be developed at later stages in life and potentially accessible to anyone, independently of socio-demographic characteristics determined by birth. Furthermore, we were interested in comparing attentional task-switching abilities, as attentional set-shifting and language switching share common networks for their processing and involve similar domain-general control mechanisms. We hypothesized that bilinguals would be more trained in flexibly adjusting their attention to changing environmental demands. Thus, we predicted that bilinguals would show an advantage over monolinguals when task switches were unpredictable and in response to external cues. On the other hand, given the detrimental effects of cognitive aging on working memory, we expected to find higher mixing costs in the memory-based switching condition, and that mixing costs would be higher for monolinguals. This objective is addressed in the article on bilingualism and task switching in older adults (Rieker et al., 2020), presented in Chapter 6.

The **second objective** of this Dissertation was to investigate the **potential scaffolding effects of multidomain interventions** in comparison to physical and cognitive training alone on different cognitive functions in older adults. This objective was addressed with the design (Ballesteros, et al., 2020) and implementation of a randomized controlled trial (RCT) and with a systematic review and three-level meta-analysis (Rieker et al., 2022), which will be described below.

RCT design and implementation

The objective of the RCT was to investigate the differential effects of multidomain versus single-domain training on executive control and memory in older adults. To this end, we designed a clinical trial with four treatment arms: (1) Cognitive intervention + physical intervention, (2) cognitive intervention + physical control activity, (3) physical intervention + cognitive control activity, and (4) cognitive and physical control activities. Our goal was to keep in the four arms all parameters concerning the intervention (training length, site, modality, etc.) as equal as possible, controlling thereby for any potential expectation and motivation bias that might occur. Also, if any activity might produce, directly or indirectly an effect on cognition, we decided that the most appropriate sham activities would be those whose effects could be controlled for. So, the effects of physical and cognitive interventions should be as differentiated as possible from those produced by their respective control activities. Furthermore, the sample should be representative of the general population. To that end, participants would be recruited from different neighborhoods, representing different socioeconomic backgrounds. A detailed description of the trial protocol was published and is shown in Chapter 7.

The implementation of this trial was originally the main objective of the present thesis. From January 2019 to March 2020, we recruited 267 participants, of which, 157 underwent pretest assessment. Of these, 132 participants were randomly assigned to one of the four training combinations. On March 14, 2020, the Spanish government declared the state of alarm due to the pandemic outbreak of Covid-19. The University and all its laboratories had to shut down and all the activities, including this RCT, were suspended. By the moment the trial was suspended, 86 participants had finished the training, and 46 participants were about to start the training phase, but only 43 participants had undergone the posttest assessment. This means that, even though a large part of the trial had been accomplished, it was missing the most important part, which was to finalize the training of all the participants, conduct the post-test, analyze the data, and write down the results. As our research involved high-risk individuals because of their age and the sanitary situation did not improve in the following year, we were not able to restart nor repeat the trial.

A systematic review and three-level meta-analysis

The goal of this study was to provide the current state of the art of multidomain interventions in older adults and to obtain empirical evidence on the differential training effects of multidomain versus single-domain interventions by applying mathematical methods. We addressed this objective by conducting a systematic review and a multivariate three-level meta-analysis comparing the training effects of multidomain interventions with those achieved by single-cognitive and single-physical interventions.

This work was predominantly exploratory about the outcome variables. So, we included a broad array of those cognitive functions that have shown to be most sensitive to cognitive aging (see Chapter 1). Furthermore, we included three main categories of physical outcome measures.

The rationale for doing so was twofold: on one hand, we wanted to compare the effects of single-physical exercise versus multidomain training on cognition (see Chapter 4 for the beneficial effects of exercise on cognition). On the other hand, we wanted to ensure that the effect sizes achieved by multidomain training would not differ as a function of improvements in physical conditions, i.e., that multidomain interventions received the same dose of physical exercise as single-physical training interventions. A novelty of this study was to control for the intensity of the aerobic training and the type of cognitive training. As far as we know, this is the first meta-analysis that computes the effect sizes only from groups that received an equivalent physical training type and dosage. Also, as we wanted to include as much primary data as possible, we did not put restrictions on study types (e.g., using only RCTs) and controlled for the influence of design differences by adding the study quality as a moderator. As most intervention studies assess more than one cognitive function and measure them with more than one tool, we rejected the classical meta-analytic approach of pooling the effect sizes of each study into one. Our aim was to obtain an effect size estimate for each cognitive function, with a minimum loss of information. Therefore, we calculated the effect sizes and variances from each dependent variable and modeled three different sources of variance (sample variance, within-study variance, and between-study variance), which allowed us to control for the non-independence among ES.

Our working hypothesis in this study was that multidomain training would produce overall higher effect sizes than cognitive or physical training alone. This recently published work is described in detail in Chapter 8.

Chapter 6

The effect of bilingualism on cue-based *vs*. memory-based task switching in older adults

The Effect of Bilingualism on Cue-Based vs. Memory-Based Task Switching in Older Adults

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Rieker, J. A., Reales, J. M., & Ballesteros, S. (2020). The Effect of Bilingualism on Cue-Based vs. Memory-Based Task Switching in Older Adults. *Frontiers in Human Neuroscience, 14*, Article 610548. https://doi.org/10.3389/fnhum.2020.610548

Abstract

Findings suggest a positive impact of bilingualism on cognition, including the later onset of dementia. However, it is not clear to what extent these effects are influenced by variations in attentional control demands in response to specific task requirements. In this study, 20 bilingual and 20 monolingual older adults performed a task-switching task under explicit task-cuing versus memory-based switching conditions. In the cued condition, task switches occurred in random order and a visual cue signaled the next task to be performed. In the memory-based condition, the task alternated after every second trial in a predictable sequence without presenting a cue. The performance of bilinguals did not vary across experimental conditions, whereas monolinguals experienced a pronounced increase in response latencies and error rates in the cued condition. Both groups produced similar switch costs (difference in performance on switch trials as opposed to repeating trials within the mixed-task block) and mixing costs (difference in performance on repeat trials of a mixed-task block as opposed to trials of a single-task block), but bilinguals produced them with lower response latencies. The cognitive benefits of bilingualism seem not to apply to executive functions per se but to affect specific cognitive processes that involve task-relevant context processing. The present results suggest that lifelong bilingualism could promote in older adults a flexible adjustment to environmental cues, but only with increased task demands. However, due to the small sample size, the results should be interpreted with caution.

Keywords: aging, bilingualism, cued task switching, memory-based task switching, executive function

1. Introduction

Modern societies are characterized by population aging due to increased life expectancy and falling birth rates, with older adults making up a growing proportion of the population (Gavrilov & Heuveline, 2003). This demographic aging implies exponential growth in the number of people who will experience age-related declines in cognition, and in the incidence and prevalence of dementia, and entails an important economic impact on caregivers and public health systems (World Health Organization, 2012; Hurd et al., 2013). However, not all people respond similarly to a neuropathological burden. While cerebral changes result in significant cognitive declines in some older adults, others can compensate for these changes and maintain their normal cognitive functioning up to advanced age (Riley et al., 2002). This phenomenon is referred to as cognitive reserve (Barulli & Stern, 2013).

Cognitive reserve is defined as the interindividual variability in how tasks are processed, allowing some people to cope better than others with brain pathology and age-related brain changes (Stern, 2009). Several activities and other environmental factors have been identified as fostering cognitive reserve, such as higher educational and occupational achievements (Bennett et al., 2003), or engaging in cognitively stimulating leisure activities (Ferreira et al., 2015; Ballesteros et al., 2018). It has been suggested that bilingualism contributes to this reserve as well, as it has been shown that, on average, bilinguals are diagnosed with Alzheimer's Disease approximately 4 years later than monolinguals (Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015), although some large prospective studies could not replicate this effect (for a recent review see Van den Noort et al., 2019). The benefits of the cognitive reserve can also be observed in healthy aging. Normal aging is associated with neurobiological changes that produce progressive declines in different cognitive domains (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014), and most older adults manage to compensate for these cerebral changes by recruiting additional brain areas, or by overrecruiting frontal areas (Cabeza et al., 2008; Osorio et al., 2010). It appears that healthy older bilinguals perform non-verbal executive tasks without having to over-activate frontal areas (Gold et al., 2013; Ansaldo et al., 2015; for a recent review see Zhang et al., 2020) suggesting that the simultaneous management of two languages might lead to better maintenance of cerebral functionality in advanced age.

Bilinguals constantly need to monitor and control two different language codes that share the same neural substrate (Crinion et al., 2006), and one language is produced by inhibiting the other (Runnqvist et al., 2012). This increased demand for cognitive control seems to lead on some occasions to superior performance in tasks that involve executive functions (EF; see Adesope et al., 2010; Bialystok et al., 2012). Studies with children (Carlson & Meltzoff, 2008; Kapa & Colombo, 2013; for a review see Barac et al., 2014) and older adults (Bialystok et al., 2004; Salvatierra & Rosselli, 2010; Goral et al., 2015) have reported a bilingual advantage in executive control. With younger adults, results are more mixed (for reviews of results in young adults vs. results with children and older adults, see Bialystok, 2017; Antoniou, 2019), and bilingual brain mechanisms might compensate for lower-level executive functioning, for example, in childhood when executive functions are still developing (Casey et al., 2000), or in late adulthood when age-related decline appears (Zelazo et al., 2004). Several studies have shown that the bilingual advantage increases with task difficulty (Bialystok, 2006; Costa et al., 2009; Hernández et al., 2013; Qu et al., 2015). However, other studies have failed to find evidence for a cognitive benefit of bilingualism (Paap & Greenberg, 2013; Antón et al., 2016; Scaltritti et al., 2017). Different factors have been proposed as contributing to the inconsistencies found in the literature, such as task impurities when assessing EF (Hartanto & Yang, 2020), as well as differences in study designs, assessment tasks, and insufficient assessment of other variables known to modulate cognition such as physical exercise and cognitive stimulation (Calvo et al., 2016). Recent meta-analyses (Lehtonen et al., 2018; Donnelly et al., 2019) conclude that the average effect size for a bilingual advantage is small and that it disappears when controlling for publication bias (Paap et al., 2020). However, growing evidence suggests that attentional advantages might be related to long-term dual-language management (Stocco et al., 2014). The amount of the second language (L2) immersion (time spent in the country where L2 is spoken) and the frequency of language switching are important modulating factors of the effects of bilingualism on cognition (Prior & Gollan, 2011; Pliatsikas et al., 2016; Pot et al., 2018).

Most of the studies that have investigated EF in bilinguals have focused on inhibitory control (Bialystok et al., 2004; Costa et al., 2009) and task switching (Costa et al., 2008; Prior & Gollan, 2011; for a review see Bialystok, 2017). The assumption that inhibition is part of the mechanism for bilingual effects on cognition is based on the inhibitory control model (Green, 1998). According to this model, a supervisory attention system is guided by top-down cues, leading to the inhibition of the non-target language so that language processing can adapt to the contextual requirements. Extensions of this model (Green & Abutalebi, 2013) include the differential influences of cognitive control processes as a function of the type of interactional context for language use and distinguish between three different contexts: (1) single-language; (2) dual-language; and (3) dense code-switching. In a single-language context, bilinguals use only one language in the same situation. In dual-language and code-switching contexts, bilinguals switch between the two languages in the same situation, but in the case of code-switching, languages are freely mixed in single utterances. Hartanto & Yang (2020) found that bilinguals with greater exposure to a dual-language context displayed significantly better task-switching abilities, replicating their findings of a previous study (Hartanto & Yang, 2016). They also found that dense code-switching was related to better inhibitory control and goal maintenance (Hartanto & Yang, 2020), a result that contrasts with a nonsignificant result regarding the relationship between dense code-switching and inhibitory control in another recent study (Kałamała et al., 2020). It seems that within dual-language contexts, situations that require constant goal reconfiguration and top-down control in response to outside constraints are more likely to translate into a cognitive advantage than free and unrestrained language switches (Blanco-Elorrieta & Pylkkänen, 2018).

On the other hand, the interest in the relationship between bilingualism and task-switching stems from behavioral data that show similar dynamics when shifting between dominant and less dominant templates (Meuter & Allport, 1999; Runnqvist et al., 2012). Further support for the commonalities between attentional set-shifting and dual-language management comes from neuroimaging evidence that shows an overlap in brain networks involved in language selection and nonverbal task switching (Meuter & Allport, 1999; Abutalebi & Green, 2007; Luk et al., 2011; Runnqvist et al., 2012; Baene et al., 2015; Coderre et al., 2016).

Cognitive processing of mental set-shifting might also vary as a function of task requirements. The conditional routing model (Stocco et al., 2010, 2014) proposes that bilingualism improves the ability to flexibly reallocate attention in complex and non-habitual task requirements, whereas the management of more direct stimulus-response mappings is not influenced by bilingual language processing. An example could be the reorientation in response to unpredictable external cues vs. reorientation in response to rule changes that occur in a sequenced order. In both cases, working memory (WM) plays an important role. WM allows for simultaneously maintaining and processing information to guide goal-directed behavior (Baddeley & Hitch, 1994). In memory-based, as well as in cued task switches, task sets need to be monitored and retrieved from memory and assembled with the correct stimulus-response mapping. However, the activation process is different for memory-based and randomly cued task switches. In memory-based set-shifting, the activation is triggered endogenously by a goal-directed monitorization in WM. When cued task switches occur randomly, the demand for a set shift is unpredictable and cannot be controlled by internal monitoring. In this case, the task-set activation is stimulus-driven; that is, triggered by a task-relevant cue (Corbetta et al., 2008).

Task-switching paradigms typically consist of blocks of switch and repeat trials and blocks of non-switch trials where only single-task sets are performed. The difference in performance between switch and repeat trials is called ‘‘switch cost’’ and reflects task-set reconfiguration processes associated with changing task sets across trials (Monsell, 2003). The difference in performance between repeat trials in the switch block and trials in the single-task block is called ‘‘mixing cost.’’ This difference is thought to reflect the active maintenance of multiple task configurations in working memory and is more sensitive to age-related cognitive changes (Kray & Lindenberger, 2000).

Task-switching paradigms comprise different variants of switch tasks. In the cued-switching version, shifts are generally random, and a cue signals the task to be performed next. In alternating-run versions, shifts occur in a predictable sequence after every N-trial, with or without the appearance of a cue. If no cue accompanies the sequence, then set-shifting is ‘‘memory-based,’’ as switches are triggered endogenously by working memory. To our knowledge, to date, only four studies have investigated task-switching abilities in older adults and three of them found significant group differences. Gold et al. (2013) analyzed performance in memory-based switching with predictable task sequences and found that bilinguals showed lower switch costs than their monolingual counterparts, with overall better levels of behavioral performance. Using a cued task-switching paradigm, Houtzager et al. (2017) found that switch and mixing costs were lower in the bilingual group. de Bruin et al. (2015) compared active and nonactive older bilinguals and monolinguals. They found a significant difference in raw switch costs between active bilinguals and monolinguals, which disappeared when controlling for baseline performance. Soveri et al. (2011) also used a cued task-switching paradigm, but their within-group design did not include a monolingual control group. Although the participants were slightly younger than in the other two studies, a positive relation was found between lower mixing costs and frequent language switching.

The present study had two main goals. The first was to investigate the influence of explicitly cued vs. memory-based switching conditions on the set-shifting abilities of bilingual and monolingual older adults. Specifically, we were interested to find out whether bilingualism would influence mental flexibility *per se*, or if differences between monolinguals and bilinguals would be more prominent when task switches were externally triggered (aleatory rule changes in response to a cued) in comparison to task switches that were endogenously triggered (memory-based sequential changes).

Therefore, our experimental design included two conditions requiring different types of attentional control: first, a memory-based switching condition based on the alternating-runs paradigm in which the task alternates every N-trial; second, a cued switching condition based on an explicit task-cueing paradigm with randomly alternating tasks, each preceded by an instructive cue (Monsell et al., 2003). Memory-based task switching is predictable and controlled endogenously by working memory processes (Monchi et al., 2001), whereas cued task-switching requires a context-dependent reorientation of attention (Monchi et al., 2001; Baene et al., 2015). Given the similarity of explicitly cued task switching and context-related dual-language management, we expected bilinguals to produce lower switch costs than monolinguals when task-set reconfiguration had to be adjusted in response to unpredictable external cues, whereas there would be no difference between groups when set-shifting was memory-based and triggered endogenously.

The second goal of our study was to investigate whether bilingualism influences age-related decline in WM. A large body of research has provided evidence of a positive relationship between cognitive aging and mixing costs (i.e., the difference between repeat trials of a mixed task block and non-switch trials of a single-task block; Kray & Lindenberger, 2000; Reimers & Maylor, 2005; Wasylyshyn et al., 2011; Huff et al., 2015). Mixing costs reflect the active maintenance of multiple task configurations in working memory and could be expected to increase when task switches are memory-based. However, the aging effect on mixing costs seems to increase with increasing task complexity (Kray, 2006; Terry & Sliwinski, 2012). Task complexity increases when rule changes are unpredictable and dependent on external cues, as the reconfiguration process additionally requires the correct interpretation and implementation of the informative cue (Tornay & Milán, 2001). For this reason, we expected to find larger mixing costs in the cued-switching condition than in the memory-based condition and that mixing costs would be larger in monolingual older adults than in bilingual older adults.

1. Materials and methods

2.1 Participants

Forty-two older adults were recruited through flyers and media postings, informative talks at strategic locations, and snowball sampling (referrals from participants). The inclusion criteria were a score of 26 or above on the Mini-Mental State Examination (MMSE; Folstein et al., 1975), a score of below 5 on the Yesavage Geriatric Depression Scale (Yesavage et al., 1983; Spanish adaptation by Martínez de la Iglesia et al., 2002), no current history of psychiatric or neurological pathology, and for the monolingual participants, no mastery of a foreign language above the A1 level of the Common European Framework of Reference for Languages (CEFR). One bilingual participant did not meet the inclusion criteria (score above 5 on the depression scale) and was excluded from further analysis. Data of one monolingual participant was not recorded due to technical problems. Thus, the final sample was composed of 20 monolingual native Spanish older adults (eight males, Mage = 72.65, SD = 6.38, range = 60–83 years) and 20 German-Spanish bilingual older adults (four males, Mage = 72.25, SD = 9.12, range = 60–95 years). **Table 1** summarizes the demographics and screening test scores for monolinguals and bilinguals. T-tests showed no significant differences between the two groups (all ps > 0.05) for all these measures. Growing evidence suggests that the amount of the second language (L2) immersion (time spent in the country where L2 is spoken) and the frequency of language switching are important modulating factors of the effects of bilingualism on cognition (Prior & Gollan, 2011; Pliatsikas et al., 2016; Pot et al., 2018; Hartanto & Yang, 2020). Our bilingual sample was composed of highly balanced, late bilinguals who had been exposed to their L2-environment for more than 40 years on average. Fourteen bilinguals reported German as their first language (L1) and

Table 1. Mean values of socio-demographic background variables for monolinguals and bilinguals.

	Monolinguals (***n*** **= 20)**	**Bilinguals** (***n*** **= 20)**	***t(df)***	***p***
Men/women	8/12	4/16	$t_{(38)} = -1.378$	0.176
Age	72.25 (6.38)	72.65 (9.12)	$t_{(38)} = -0.161$	0.873
Education[1]	4.55 (2.06)	4.65 (1.42)	$t_{(38)} = -0.178$	0.859
MMSE[2]	28.85 (1.04)	29.3 (.8)	$t_{(38)} = -1.533$	0.134
Depression[3]	1.2 (1.2)	.7 (.92)	$t_{(38)} = -1.480$	0.147

[1]Level of educational attainment was defined as follows: 1 = Primary education, 2 = Lower secondary education, 3 = Post-secondary non-tertiary education, 4 = Upper secondary education, 5 = Short-cycle tertiary education, 6 = Bachelor's or equivalent, 7 = Doctoral or equivalent. [2]Mini-Mental State Examination (Folstein et al., 1975). [3]Short Form of the Geriatric Depression Scale (GDS) (Yesavage et al., 1983). SDs are shown in parentheses.

Spanish as their second language (L2), and six reported Spanish as their L1 and German as their L2. All participants were right-handed, had normal or corrected-to-normal vision and none reported color blindness. Bilingualism was assessed with the validated Bilingual Language Profile questionnaire (BLP; Birdsong et al., 2012; see Appendix A for detailed information on the BLP). It has four components with a mean Cronbach's alpha of 0.787 (Gertken et al., 2014): language history (e.g., ''At what age did you start learning the following languages?'' ''How many years have you spent in a country/region where the following languages are spoken?''), language use (e.g., ''In an average week, what percentage of the time do you use the following languages with friends?'' ''When you count, how often do you count in the following languages?''), language proficiency (e.g., ''How well do you speak Spanish?'' ''How well do you read Spanish?'') and language attitudes (e.g., ‘‘I feel like myself when I speak Spanish’’, ‘‘I identify with a Spanish-speaking culture’’). For each component, two scores are computed (one for each language) and the difference between the two scores indicates the relative dominance of each language in that specific area. The scores for each component vary as follows: −120 to +120 for language history, −50 to +50 for usage, −24 to +24 for proficiency, and −24 to +24 for attitudes. The score of each component is multiplied by a weighting factor so that each component receives equal weighting (54.5) in the global language score. The difference between the total scores of the two languages constitutes the language dominance index, which ranges from −218 to +218. In the present study, we subtracted the German score from the Spanish score. A positive score indicated dominance in Spanish, and a negative score indicated dominance in German. A score of zero represents balanced bilingualism. The linguistic background information for bilinguals is shown in **Table 2**. No statistically significant differences were found between monolinguals and bilinguals regarding the demographic background information.

Table 2. Mean values of linguistic background variables[1] for bilinguals.

Spanish use (% week)	40 (21.82)
German use (% week)	60 (21.95)
Age of acquisition	19.9 (7.41)
BLP global score	-28.66 (61.93)
Language history	-12.3 (23.22)
Language use	-11.35 (23.93)
Language proficiency	-.67 (9.49)
Language attitudes	-5.09 (15.77)

[1]Bilingual Language Profile (BLP) (Birdsong et al., 2012). Negative values indicate dominance in German. SDs are shown in parentheses.

All participants gave their written informed consent. The study protocol was approved by the Institutional Review Board of the Universidad Nacional de Educación a Distancia (UNED) and the study was conducted following the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 Assessing task switching

The experimental task was adapted from Rubin & Meiran (2005) and contained three conditions: (1) in the single-task condition only one task had to be performed at a time; (2) in the cued-switching condition two tasks alternated in random order and a cue signaled the task to be performed next; and (3) in the memory-based switching condition two tasks alternated after every second trial without the appearance of a cue. It involved two bivalent target stimuli with two possible shapes (circle or square, both 60 × 60 mm) and in one of two possible colors (yellow or blue), presented in the center of the screen on a black background. In the cued-switching condition, a visual cue signaled the next task to be performed: a white splotch (18.8 mm) indicated that participants would have to identify the color of the target stimulus, and the white outline of a star (18.8 mm) that they would have to identify its shape. Although the cue was irrelevant in single-task blocks, it was presented in both single-task and cued-switching blocks to minimize differences between the conditions. In the memory-based switching condition, to help participants keep track of the correct trial sequence in the event of an error, two cues appeared on the screen (the same pictorial cues as in the cued-switching block), one indicating the correct condition of the just-completed trial, and one signaling the following trial condition. For a schematic representation of the task-switching paradigm, see **Figure 1**. Each experimental run comprised eight blocks of trials. The first two blocks (23 trials each) were single-task blocks, one for shape and one for color. The third block

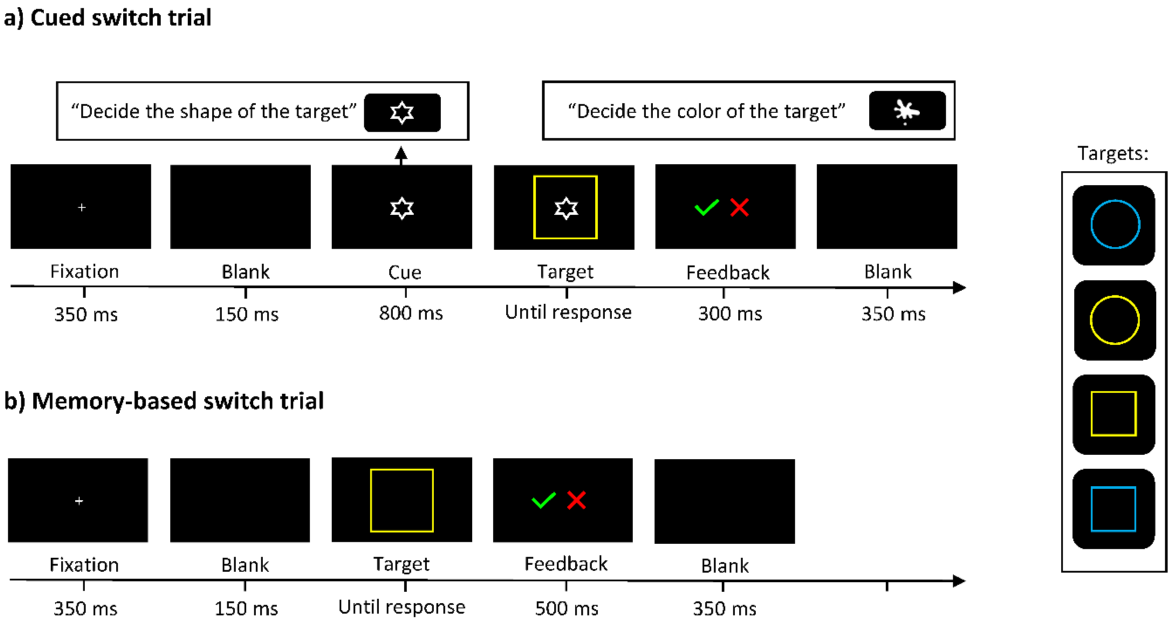

Figure 1. A schematic representation of the task-switching paradigm. In Cued switch trials **(A):** An instructional cue indicated the next task to be performed. In Memory-based switch trials **(B)**: The task changed after every second trial without the appearance of a cue; that is, participants had to identify the shape of two consecutive stimuli and the colour of the next two stimuli, and so forth. In single-task trials (not figured), participants only had to identify the colour or the shape of the target.

previous trial blocks but in reverse order, starting with the memory-based switching block, followed by the cued-switching block, and ending with the single-task blocks. Altogether, the experiment contained 46 switch trials and 46 repeat trials in the cued condition, 46 switch trials and 46 repeat trials in the memory condition, and 92 non-switch trials (46 for color and 46 for shape) in the single-task condition, yielding a total of 276 trials per run.

2.3 Procedure

Participants were tested individually in a single session. The experimental session lasted about 90 min. Stimuli were displayed on a laptop computer with a 15.6-inch monitor and a refresh rate of 60 Hz. Experimental scripts were designed, and data collection was managed with E-Prime 2.0 (Psychology Software Tools Inc., Pittsburg, PA, USA) experimental software. Participants were comfortably seated approximately 60 cm from the monitor. Non-switch trials and cued switch trials started with the presentation of the fixation point in the center of the screen for 350 ms, followed by a 150 ms blank screen. Then the instructional task cue appeared, and after 800 ms the target stimulus surrounded the cue and both stimuli remained on the screen until a response was given, or for a maximum of 10 s. Auditory feedback was presented for 300 ms (an incorrect response was followed by a low-frequency beep and a correct response by a high-frequency beep). The trial ended with a 350 ms blank screen. Memory-based switch trials also started with a 350 ms fixation point, followed by a 150 ms blank screen. Then the target stimulus appeared in the middle of the screen and remained until an answer was given or for 10 s. The auditory feedback was presented for 500 ms, and in the event of an incorrect response, two informative cues appeared on the screen simultaneously with the tone, indicating the correct response for the present task and the one that would follow. The trial ended with a 150 ms blank screen. At the beginning of each experimental block, written instructions for the upcoming task were displayed on the screen and remained until the space key was pressed. The response mapping was as follows: the blue response was assigned to the left index finger and the yellow response to the left middle finger. Similarly, the square response was assigned to the right index finger and the circle response to the right middle finger. The response keys for the color task were labeled with the appropriate colors and the response keys for the shape task were labeled with the appropriate shape. Before beginning the actual task, participants performed 16 practice trials of each condition. Data from these practice trials were not included in the analyses.

2.4 Data analysis

RTs in colour versus shape judgments in single-task blocks did not differ significantly across participants ($t_{39} = -.072, p = .943$), so we collapsed the data across the two conditions. For all reaction time (RT) analyses, only correct trials were included. Trials with response latencies below 200 ms and above 3000 ms were excluded from the analysis. The RT-trimming procedure eliminated 2.28% and 2.93% of non-switch trials, 10.11% and 7.01% of repeat trials, and 12.55% and 8.26% of switch trials for monolinguals and bilinguals, respectively. In total, 7.19% of the trials were eliminated and were not included in the analysis. After data trimming, all distributions of response latencies showed acceptable levels of normality, homoscedasticity, and independence. There were no negative associations between error rates and reaction times (RT) in any experimental condition, thus ruling out the possibility of a speed-accuracy trade-off. Error rates were analysed using Mann-Whitney U tests. A significance level of $p < .05$ was adopted for all contrasts. Significance levels of multiple comparisons were Bonferroni-corrected to their number of comparisons. All the statistical analyses were conducted with SPSS v. 20.0 statistical software.

2. Results

Table 3 presents a summary of the response latencies, error rates, and composite switch and mixing costs per experimental and linguistic condition, and **Figure 2** shows the response latencies by task version and trial type for monolinguals and bilinguals.

3.1 Switch costs as a function of task version

Shifting attention to a new task requires more cognitive resources than the repetition of the same task. Switch costs are defined as the difference in performance on

Table 3. Mean reaction time (RT) in milliseconds and error rates in switch, repetition, and non-switch trials, and switch and mixing costs by experimental condition for monolinguals (*n* = 20) and bilinguals (*n* = 20).

Trial type	**Task block**	**Monolinguals**	**Bilinguals**
		Response latencies in ms	
Switch	Cued	1475 (330)	1288 (305)
	Memory	1353 (322)	1321 (328)
	Cued-Memory	123 (153)	-33 (158)
Repeat	Cued	1327 (291)	1158 (299)
	Memory	1066 (234)	1018 (250)
	Cued-Memory	260 (220)	140 (155)
Non-switch	Single task	921 (181)	787 (239)
		Error rates in %	
Switch	Cued	8.35 (5.5)	5.55 (4)
	Memory	6.25 (4)	4.05 (3)
Repeat	Cued	7.3 (5.5)	2.6 (2)
	Memory	5.05 (2)	3.5 (2)
Non-switch	Single task	1.15 (0)	1.45 (1)
		Switch and mixing costs	
Switch costs	Cued	148 (189)	130 (119)
	Memory	286 (179)	303 (155)
Mixing costs	Cued	406 (181)	371 (187)
	Memory	145 (173)	231 (151)

SDs for RTs, and Medians for error rates are shown in parentheses.

switch trials as opposed to repeat trials, within the mixed-task blocks. In our study, mixed-task blocks were either memory-based (task switches occurred after every second trial without the appearance of a cue) or cue-based (task switches occurred in random order and were triggered by a pictorial cue). To analyze the effect of both types of task settings

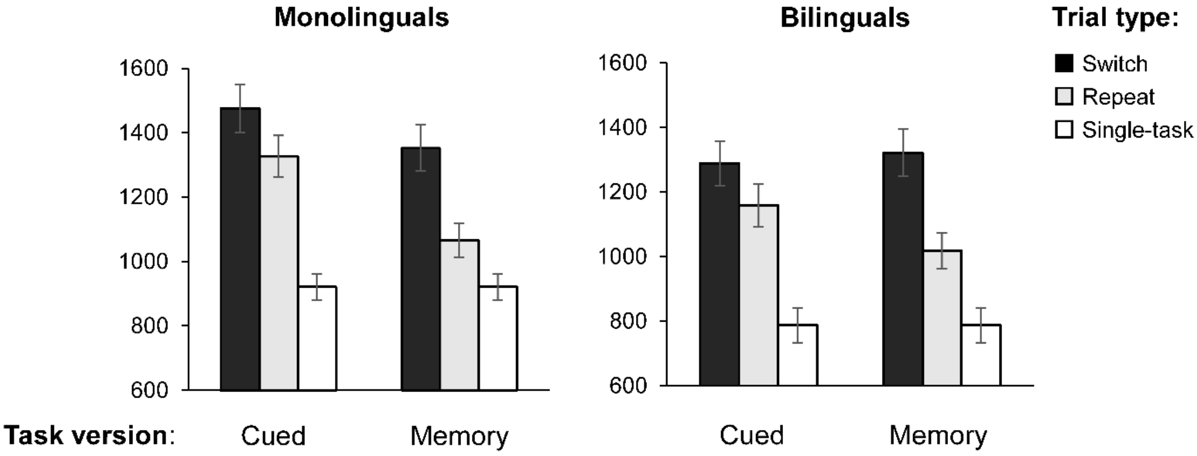

Figure 2. Mean RTs on switch, repeat, and non-switch trials by task version (cued, memory-based, and single task) for monolinguals and bilinguals. Error bars: +/- 1 *SE*.

on switch costs, we conducted a 2 (Group: monolinguals and bilinguals) x 2 (Task type: cued vs. memory-based) x 2 (Trial type: switch vs. repeat) mixed ANOVA on TR as dependent variable, with Group as between-subjects factor and Task and Trial type as within-subjects factors. The main effect of Task type was significant ($F_{(1,38)} = 26.996$, $\text{MSE} = 22250.218$, $p < .001, \eta_{\text{p}}^2 = .415, 1 - \beta = .999$). Also, response latencies were larger on switch than on repeat trials ($F_{(1,38)} = 101.077$, $\text{MSE} = 18637.808, p < .001, \eta_{\text{p}}^2 = .727, 1 - \beta = 1$), confirming that both task versions elicited switch costs for shifting attention. As indicated by a significant Task x Trial type interaction $\left(F_{(1,38)} = 30.334,\ \text{MSE} = 7045.376,\ p < .001,\ \eta_{\text{p}}^2 = .444, 1 - \beta = 1\right)$, response latencies increased from the memory-based to the cued version. This was especially the case in repeat trials, leading to smaller switch costs in the cued condition. We found a significant Group x Task interaction $\left(F_{(1,38)} = 8.569,\ \text{MSE} = 22250.218,\ p =\right.$

.006, $\eta_{\mathrm{p}}^{2} = .184, 1-\beta = .814$), suggesting that monolinguals and bilinguals adjusted in a different way to cued vs. memory-based task blocks. The magnitude of switch costs in both tasks was similar for monolinguals and bilinguals, as indicated by a non-significant main effect of Group (p = .219), and a non-significant three-way interaction Group × Trial × Task type (p = .383). To further investigate the significant Group x Task interaction, we performed Bonferroni corrected pairwise comparisons on the Group x Trial x Task interaction. Results revealed that, whereas monolinguals´ RTs were significantly larger on cued switch trials when compared to memory-based switch trials (mean difference = 123 ms, p = .001), the performance of bilinguals did not differ on switch trials of both task versions (mean difference = -33 ms, p = .35). See **Figure 3**. On repeat trials both groups showed a similar pattern, with higher RTs in the cued than in the

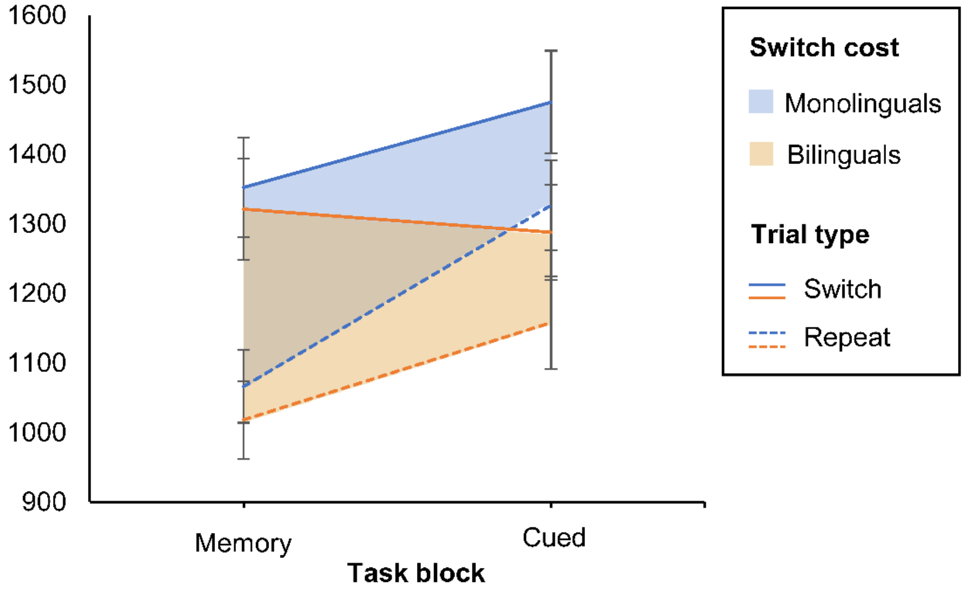

Figure 3. Switch costs by task version for monolinguals and bilinguals. The continuous lines indicate switch trials, and the discontinuous lines indicate repeat trials. The shadowed areas represent switch costs (i.e., the difference between both trial types). Error bars: +/- 1 *SE*.

memory-based condition (mean difference = 260 ms, $p < .01$ and 140 ms, $p < .01$ for monolinguals and bilinguals, respectively).

An analysis of the error rates confirmed that the task repetition was more demanding for monolinguals than for bilinguals in a setting of unpredictable cued task switches. Monolinguals committed significantly more errors than bilinguals on cued repeat trials [monolinguals: 7.3%, bilinguals: 2.6% $(U = 109.5,\ z = -2.145,\ p = .012)$]. Performance of the two groups did not differ in accuracy in the remaining factor levels, and error rates were overall lower in the memory-based condition (repeat trials: $4.28\%, p = .665$; switch trials: $5.1\%, p = .455$) than in the cue-based condition (switch trials: 6.95%, p = .494).

In sum, these results suggest that, when rule changes were triggered by external cues, bilinguals switched more efficiently between task sets across trials than monolinguals. These findings are congruent with the previously discussed literature in that bilinguals may allocate their cognitive resources in a more parsimonious way when task demands increase.

3.2 Mixing costs as a function of task version

The repetition of a task rule in a context of set shifting is always more effortful than performing the same task in a single-task context due to more complex task-set monitoring requirements (Monsell, 2003). This is what is indexed as “mixing costs” (i.e., the difference between repeat trials of a mixed task block and non-switch trials of a single-task block). To analyse the effect of single-task trials vs. repeat trials of both task versions, we conducted a 2 (Group: monolinguals and bilinguals) x 3 (Task type: single-task vs. memory-repeat trials vs. cued repeat trials) mixed ANOVA, with Group as between-subjects factor and Trial type as within-subjects factor. The main effect of Trial type was significant ($F_{(1,38)} = 94.618,\ \mathrm{MSE} = 16.082,\ p < .001,\ \eta_{\mathrm{p}}^{2} = .711, 1 - \beta = 1$), indicating that the repetition of a trial in a mixed task block was overall more demanding than performing one task at a time. Neither the main effect of Group ($p = .116$), nor the Trial type x Group interaction resulted statistically significant ($p = .094$), suggesting that both groups produced similar mixing costs in both conditions. Bonferroni corrected pairwise comparison showed a trend for bilinguals being faster on single-task trials $\left(F_{(1,38)} = 3.982, p < .052,\ \eta_{\mathrm{p}}^{2} = .095, 1 - \beta = .494\right)$ and on cued repeat trials $\left(F_{(1,38)} = 3.271, p < .078,\ \eta_{\mathrm{p}}^{2} = .079, 1 - \beta = .422\right)$ whereas, as mentioned earlier, the performance on memory-based repeat trials was similar for both groups ($p < .534$).

To compare the magnitude of mixing costs as a function of task version, we ran an additional ANOVA, with Group as between-subjects factor and Mixing cost (memory-based vs. cued) as within-subjects factors. The main factor of Mixing cost was significant $\left(F_{(1,38)} = 44.353, \mathrm{MSE} = 18066.958, p < .001, \eta_{\mathrm{p}}^{2} = .539, 1 - \beta = 1\right)$, confirming that Mixing costs were overall higher in the cued condition (406 ms and 371 ms) than in the memory-based condition (145 ms and 231 ms, for monolinguals and bilinguals, respectively). A marginally significant Group × Mixing cost interaction $\left(F_{(1,38)} = 4.028, \mathrm{MSE} = 18066.958, p = .052, \eta_{\mathrm{p}}^{2} = .096, 1 - \beta = .498\right)$ suggested that monolinguals experienced a larger increase in composite mixing costs from the cued to the memory-based task version (261 ms increase for monolinguals and 140 ms increase for bilinguals). Altogether, it seemed that both groups experienced an increase in the magnitude of mixing costs when task switches were unpredictable and externally cued, and that this increase was slightly larger for monolinguals.

3. Discussion

The results of the present study suggest that bilinguals shift their attention more efficiently than monolinguals when the task requirements mimic context-related dual-language management (i.e., aleatory and externally triggered task switches). The difference in response latencies between cued and memory-based switch trials was significantly larger in monolinguals than in bilinguals. The performance of bilinguals did not differ across task versions, whereas monolinguals experienced a pronounced increase in response latencies when set-shifting was unpredictable and triggered by an external cue. Task performance also differed in terms of accuracy, as monolinguals had a significantly higher error rate than bilinguals on cued repeat trials, suggesting that it was overall more effortful for them to shift attention under unpredictable task switching conditions than it was for bilinguals. However, the magnitude of composite switch and mixing costs was similar for monolinguals and bilinguals, suggesting that composite scores might not sufficiently capture fine-grained differences in performance.

To compare task-switching abilities under different cognitive demands, in the present study we adapted a task-switching paradigm that contained both memory-based and cued task-switching blocks. This procedure served to tax slightly different underlying control mechanisms. The memory-based task-switching paradigm involves predictable sequences of rule changes and requires primarily the monitoring of information in working memory. By contrast, cued task-switching, like language-switching, additionally requires context-dependent attentional reorientation and increased cognitive control demands. Thus, we predicted that a bilingual advantage would only be found when set shifting was triggered externally. The results of this pilot study confirmed only partially this hypothesis. Monolinguals and bilinguals did not differ significantly in response latencies within each task version, but significant group differences were found in the dynamics between the two versions. The two groups performed almost identically in the memory-based switch task; hence this variable could be taken as baseline performance. Contrary to monolinguals, whose performance decreased, bilinguals maintained the same performance in the cued condition. Bilinguals had lower response latencies on cued switch trials and lower error rates on cued repeat trials, suggesting a bilingual advantage in the flexible adjustment to task-relevant context processing. These results are congruent with the existing literature regarding the similarity between cued task switching and linguistic code switching (Christoffels et al., 2007; Prior & Gollan, 2011). Bilinguals might be more trained in efficiently interpreting contextual requirements to flexibly adjust their behaviour. Previous research has shown that explicit cueing in a set of random-switching facilitates the task-set reconfiguration when enough time is given to prepare for the next trial (Tornay & Milán, 2001). Our experimental design included a cue-target interval of 800 ms, thus providing enough time for task preparation. Differences in efficient preparatory task-set activation are related primarily to individual differences in cognitive control, whereas age-related changes mainly appear to affect target response selection and task performance in general (Adrover-Roig & Barceló, 2010). In this line, our results suggest that cognitive aging affects the working-memory processes of monolinguals and bilinguals similarly, but that bilinguals might use contextual cues more efficiently and start the task-set reconfiguration earlier than monolinguals.

Our results also suggest that a long period of second-language immersion might parallel the cognitive benefits produced by an early age of acquisition. In our study, late bilinguals had been immersed in their second-language environment for more than 40 years on average and were highly balanced. However, dual-language exposure alone does not seem enough to modulate cognitive control. The balance in language use has been widely discussed as a core factor to explain the bilingual advantage (Hartanto & Yang, 2020; Verreyt et al., 2016; Yang et al., 2016). Even in balanced bilinguals, only high-frequency language switchers showed an advantage over monolinguals in tasks that measure cognitive flexibility (Barbu et al., 2020).

Long-time balanced dual-language immersion might lead to changes related to a more efficient reorientation to stimuli-driven task demands. As mentioned earlier, memory-based task switching requires more implication of WM sustained by an interaction of frontoparietal areas that are very sensitive to aging. Previous research has shown that, contrary to the so-called age-related posterior-anterior shift (PASA; Cabeza et al., 2008), this shift is reversed in some bilinguals to more subcortical/posterior regions during the performance of executive function tasks (Grundy et al., 2017; Rodríguez-Pujadas et al. 2013). Context-dependent reorientation (as in cued task-switching) relies on an interaction of fronto-striatal loops with special implication of the basal ganglia (Van Schouwenburg et al., 2010; Shulman et al., 2009). Several authors have proposed that at the initial stages of bilingualism, language control is mostly managed by prefrontal areas (Stocco et al., 2014; Ullman, 2001). Then, as dual-language management becomes more automatic, its neural processing shifts partly to subcortical areas (Lieberman, 2000; Tettamanti et al., 2005) as occurs in procedural knowledge (Packard & Knowlton, 2002). Bilinguals show expanded morphology in basal ganglia (Burgaleta et al., 2016). Damage to this brain area produces pathologic code switching (Abutalebi & Green, 2008; Lieberman, 2000) in a similar way as it affects task switching abilities in early Parkinson disease patients (Packard & Knowlton, 2002). Neuroimaging findings suggest that age-related changes in prefrontal areas affect bilinguals to a similar degree as monolinguals.

However, bilinguals instead of overrecruiting those areas rely more on subcortical areas developed by life-long dual language management. Our behavioral results fit with the current knowledge on bilingual neural processing and suggest that in older adults, processes that rely heavily on WM are affected in a similar way in monolinguals and bilinguals, but that bilingualism might improve processes that require a flexible reorientation to environmental cues.

Bilingualism is just one of the many components that might contribute to cognitive reserve. Numerous other factors and life-style habits can counteract its hypothetical benefits. Also, findings are heavily influenced by study design, and while retrospective studies tend to a protective effect of bilingualism on cognition, prospective studies often fail to find differences between monolinguals and bilinguals (Paap et al., 2016; Watson et al., 2016). The best alternative to investigate the effect of bilingualism on aging is to conduct powered randomized controlled trials that enable adequate control of baseline characteristics, psychological assessment, and experimental manipulations. To date, there are no results from such studies, but several promising study protocols, especially on the effect of foreign language learning in older adults, have recently been registered, and we can thus hope to obtain more insight into these important research questions in the near future.

4. Limitation and future directions

A limitation of the present study is the small sample size. Possible differences between monolinguals and bilinguals, especially in composite switch and mixing costs, could be missed due to low statistical power. Small samples also increase the risk of type I errors, and the statistically significant interaction effect found in switch trials across conditions would need replication. However, the present study provides an innovative approach, contributing to the ongoing debate on the reliability of a bilingual advantage and prepares the ground for a larger-scale investigation, focusing not only on bilingual balance and language use, but also on specific task characteristics.

Chapter 7

Effects of multidomain versus single-domain training on executive control and memory in older adults: study protocol for a randomized controlled trial

Effects of multidomain versus single-domain training on executive control and memory in older adults: study protocol for a randomized controlled trial

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Ballesteros, S., Rieker, J.A., Reales, J.M., Mayas, J., Jiménez, M.P., Prieto, A., Toril, P. (2020). Effects of multidomain versus single-domain training on executive control and memory in older adults: study protocol for a randomized controlled trial. *Trials*, 21, Article 404. https://doi.org/10.1186/s13063-020-04293-3

Abstract

Background: Previous research suggests that both cognitive training and physical exercise help to maintain brain health and cognitive functions that decline with age. Some studies indicate that combined interventions may produce larger effects than each intervention alone. The aim of this study is to investigate the effects of combined cognitive and physical training compared to cognitive training and physical training alone on executive control and memory functions in healthy older adults.

Objectives: The main objectives of this four-arm randomized controlled trial (RCT) are: to investigate the synergetic effects of a simultaneous, group-based multidomain training program that combines cognitive video-game training with physical exercise, in comparison to those produced by cognitive training combined with physical control activity, physical training combined with cognitive control activity, or a combination of both control activities; to investigate whether event-related potential latencies of the P2 component are shorter and N2 and P3b components assessed in a memory-based task-switching task are enhanced after training; and to find out whether possible enhancements persist after a 3-month period without training.

Methods: In this randomized, single-blind, controlled trial, 144 participants will be randomly assigned to one of the four combinations of cognitive training and physical exercise. The cognitive component will be either video-game training (cognitive intervention, CI) or video games not specifically designed to train cognition (cognitive control, CC). The physical exercise component will either emphasize endurance, strength, and music–movement coordination (exercise intervention, EI) or stretching, toning, and relaxation (exercise control, EC).

Discussion: This RCT will investigate the short and long-term effects of multidomain training, compared to cognitive training and physical training alone, on executive control and memory functions in healthy older adults, in comparison with the performance of an active control group.

Trial registration: ClinicalTrials.gov, NCT03823183. Registered on 21 January 2019.

1. Background

Age-related cognitive decline negatively affects the performance of daily living activities and the quality of life of many older adults. Neurocognitive frailty is the principal threat to successful aging (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) as cognitive performance is central to daily life (Salthouse, 2012). Cross-sectional studies have reported declines in a series of cognitive abilities (Bopp & Verhaeghen, 2005; Park, et al., 2002; Reimers & Maylor, 2005; Rönnlund et al., 2005), although these declines are less pronounced in longitudinal studies (Rönnlund et al., 2005). Aging is associated with a progressive decline in a wide range of cognitive abilities, such as set shifting (Reimers & Maylor, 2005), working memory (Park, et al., 2002; Rönnlund et al., 2005), and episodic memory (Bopp & Verhaeghen, 2005; Nilsson, 2003; Rönnlund et al., 2005). Yet other cognitive functions which rely on previous experiences, such as vocabulary and general knowledge (Bialystok & Craik, 2006; Park et al., 2002; Verhaeghen, 2003), procedural knowledge (Mireles & Charness, 2002), and implicit memory (Fleischman & Gabrieli, 1998; Mitchell & Bruss, 2003; Ballesteros & Reales, 2004; Sebastián & Ballesteros, 2012), are mainly preserved, not only in healthy older adults but also in those with mild cognitive impairment (Ballesteros et al., 2004), people with Alzheimer disease (Ballesteros & Reales, 2004; Ballesteros et al., 2008), and older adults with type 2 diabetes mellitus (Redondo et al., 2015).

Cerebral aging is associated with gray and white matter reduction in several areas of the brain, including the lateral prefrontal cortex, the cerebellum, and the medial temporal lobe system including the hippocampus. In contrast, minimal decreases occur in the entorhinal and occipital cortices (Raz et al., 2005). The prefrontal cortex organizes the incoming information and interacts with the hippocampus while performing working memory tasks (Baddeley 2003; Dennis et al., 2008). Cognitive-control functions refer to the ability to adapt behavior in order to process only relevant over competing irrelevant information to attain certain goals. Neuroanatomical changes occurring in the lateral prefrontal cortex and the medial temporal lobe–hippocampus complex are associated with declines in executive functions, working memory, and episodic memory. The failure of these basic cognitive functions predicts upcoming difficulties with the performance of daily-living activities and compromises independent living (Owsley et al., 2002). However, even in advanced age, the human brain preserves a certain degree of plasticity and functional reorganization, which allows people to adapt to age-related cerebral changes in order to maintain successful task performance (Ballesteros et al., 2013; Osorio et al., 2010; Sebastián et al., 2011). Neuroplasticity in older adults is contingent on individual behavior (Brehmer et al., 2014; Li, Brehmer, Shing et al., 2006; Lövdén et al., 2010; Pascual-Leone et al. 2005; Styliadis et al., 2015) and is susceptible to be modified by interventions designed to delay or prevent age-related cognitive decline (Ball et al., 2002). Brain plasticity and its role in neural adaptations to age-related cerebral changes are also influenced by comorbidities, environmental factors, personality traits (psychosocial variables), and genetic and epigenetic factors (Ballesteros et al., 2015). A recent Frontiers Research Topic monograph focused on research conducted in the field of cognitive and brain plasticity induced by physical activity, cognitive training (computerized interventions, learning therapy, video games), and combined intervention approaches, as well as other forms of brain stimulation that target brain activity, such as electroencephalography and neurofeedback (Ballesteros et al., 2018). During the last two decades, researchers have conducted a variety of intervention studies directed to promote behavioral flexibility and to enhance several cognitive processes that decline with age.

Indeed, evidence for the benefits of cognitive training, video games, and physical exercise is growing rapidly, as well as research directed at gaining a better understanding of the underlying mechanisms and their translation to clinical practice (Raz & Lindenberger, 2013; Stanmore et al., 2017; Zhu et al., 2016).

Cognitive training is an intervention that allows structured training in a series of tasks relevant to different cognitive functions, such as executive functions, speed of processing, episodic memory, cognitive control, or attention. Among cognitive psychologists and neuroscientists, there is increasing interest in exploring whether cognitive training with specially designed computerized training programs and video games of different kinds enhances cognition. Video games are electronic games that require interaction with a computer or other electronic devices with a user interface that provides visual and auditory feedback. Computerized cognitive programs and video games are currently receiving great attention in exploring the possibility of transfer to untrained tasks (Anguera et al., 2013; Ballesteros et al., 2017; Ballesteros et al., 2014; Basak et al., 2008; Mozolic et al., 2011; Toril et al., 2016). Many intervention studies based on cognitive training support the idea that training in older adults improves some aspects of cognition but not others. In recent years, several meta-analyses (Lampit et al., 2014; Powers et al., 2013; Toril et al., 104; Vazquez et al., 2018; Wang et al., 2016) have examined the effectiveness of computer-based interventions in healthy older adults. These meta-analytic studies have shown low to moderate training effects in older adults in several cognitive processes that decline with age, such as processing speed, attention, and memory. However, others (Sala et al., 2018) have reported that playing video games had little consequences on cognition. Due to different study designs (e.g., the inclusion of active or passive control groups (Barnes et al., 2013; Linde & Alfermann, 2014) and types of training (e.g., video games of different kinds, computerized cognitive programs (Barcelos et al., 2015; Desjardins-Crepeau et al., 2016; McDaniel et al., 2014; Ngandu et al., 2015), results have been heterogeneous, making it difficult to reach solid conclusions (Lauenroth et al., 2016).

In addition, other types of training such as physical activity of different kinds are also explored to improve the physical and cognitive status. The term "physical activity" includes many activities related to voluntary body movements (Ballesteros et al., 2015). A large body of evidence supports the beneficial effects of physical activity on executive functions and memory (Colcombe & Kramer, 2003; Bamidis et al., 2014; Hötting & Röder, 2013; Niemann et al., 2014; Smith et al., 2010; Voelcker-Rehage & Niemann, 2013). Although early physical activity intervention studies, which mainly centered on cardiovascular training, showed that cardiovascular activity produced increases in hippocampal volume in older adults while improving spatial memory performance (Erickson et al., 2009; Erickson et al., 2011), other types of physical exercise, such as motor fitness and coordination training, also resulted in increased hippocampal volume in healthy older adults (Niemann et al., 2014). Complex physical activities such as dancing (Kattenstroth et al., 2010; Kattenstroth et al., 2013; Zilidou et al., 2018) or the practice of martial arts (Krampe et al., 2014; Muiños & Ballesteros, 2014; Muiños & Ballesteros, 2015, Pons van Dijk et al, 2013; Wayne et al., 2014) have also shown beneficial effects on cognition in older adults.

Several studies suggest that social engagement plays a key role in the maintenance of cognitive functioning and psychological well-being in older adults (Ballesteros et al., 2015; Ballesteros et al., 2014, Peter et al., 2013) (for a recent review, see Dause & Kirby, 2019). In the present multidomain intervention, social engagement is not considered a source of variance, as it is not a factor manipulated in the intervention, but rather a design feature included to enhance cognitive and physical functioning. So, cognitive and physical training, as well as their control activities, will be performed in a social environment. In this way, the four groups will be trained in the same social conditions; that is, in small groups and in the presence of a trainer.

2. Objectives and hypotheses

The main objective of this randomized controlled trial (RCT) is to investigate the synergetic effects of a group-based multidomain training program that combines cognitive video-game training with physical exercise, in comparison to those produced by cognitive training combined with physical control activity, physical training combined with cognitive control activity, or a combination of both control activities, on behavioral and electrophysiological measures of executive control (set-shifting, response inhibition, and information updating and monitoring) and memory functions (immediate and delayed visual and verbal memory). These cognitive functions, which are often compromised in later years, are essential for everyday activities. The second objective is to investigate whether event-related potential (ERP) latencies of the P2 component are shorter and N2 and P3b components assessed in a memory-based task-switching task are enhanced after training. Electrophysiology provides a very useful online measure to identify the contribution of different processing stages of executive functioning. ERPs can help us to understand the specific executive control impairments occurring with age, as well as the possible effects of the different types of intervention investigated in this RCT. To this end, the task-switching paradigm is a valid task that helps to identify the cognitive processes that most decline with aging (Gajewski et al., 2018). However, electrophysiological studies conducted to evaluate training-related effects in older adults using this task are scarce (Gajewski et al., 2017). Finally, we are interested in finding out whether possible enhancements persist after a 3-month period without training.

We expect to find greater behavioral improvements in executive control and memory functions after training, larger maintenance effects, and shorter ERP latencies of the P2 component and enhanced N2 and P3b components in the multidomain training condition in comparison to both single-domain conditions. We also expect the multidomain group and both single-domain groups to outperform the active control group at the 3-month follow-up period.

In this RCT, we will use questionnaire data to verify that the groups do not differ in their levels of intrinsic motivation and engagement. At the end of the assessment session, participants will report their expectations regarding their performance in the assessment tasks using a 5-point Likert scale. Moreover, at the 1st, 8th, and 16th training sessions, the participants will respond to questions about motivation and engagement for each of the training video games. These factors will be examined by comparing the intervention arms to the active control condition. The engagement and motivation data will be used in secondary analyses as covariates to rule out these factors as sources of variation in the primary outcome variables.

3. Methods

The design is a four-arm, parallel RCT designed to investigate the effectiveness of combined cognitive and physical training versus cognitive and physical training alone but combined with a control activity, in comparison to an active control group, to promote cognitive and neurofunctional improvements in older adults. **Figure 1** shows the

Consolidated Standards of Reporting Trials flow diagram corresponding to the present study.

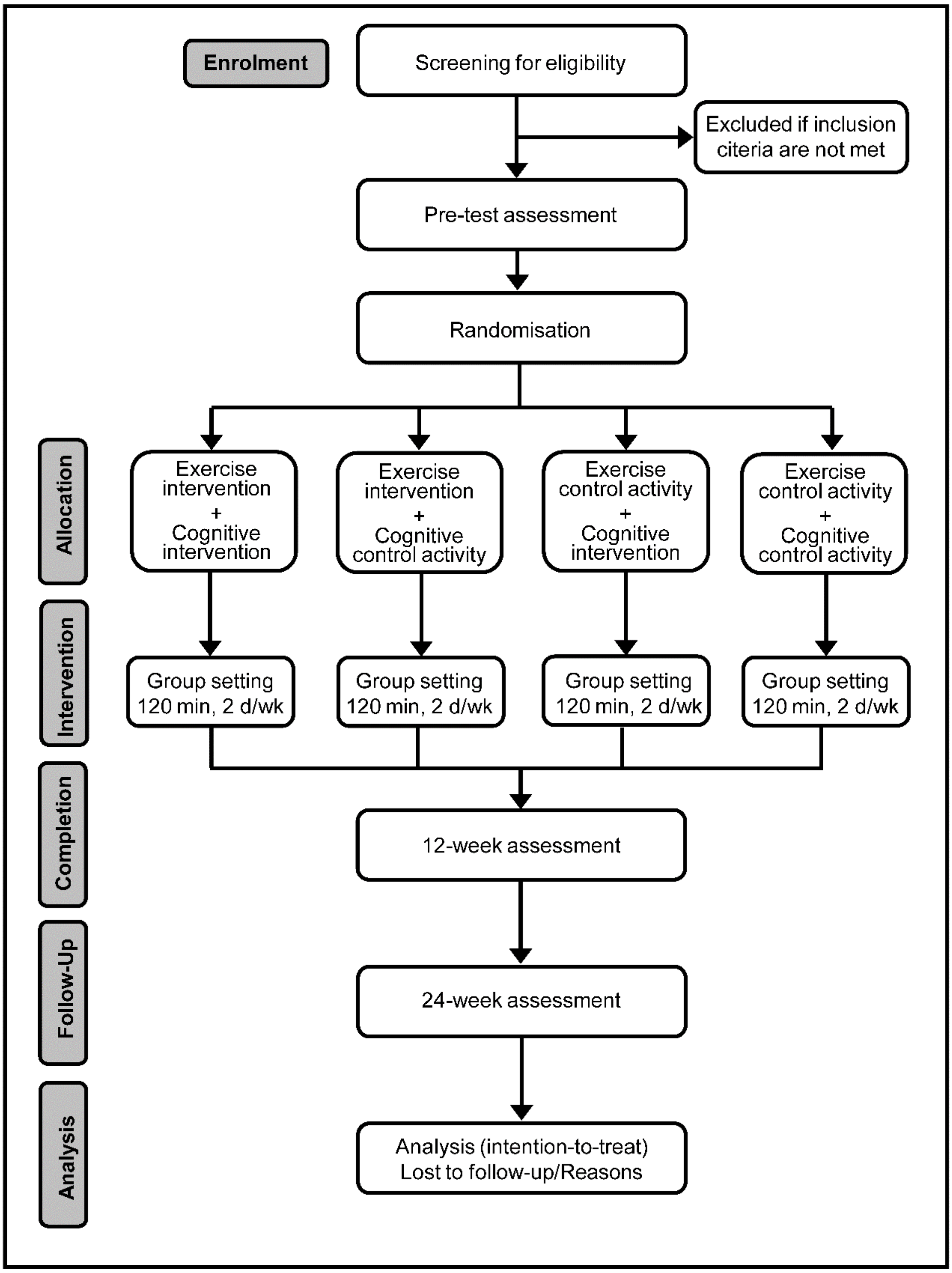

Figure 1. Flow chart of the study protocol. d/wk days per week.

3.1 Study design

Participants will complete one of the four combinations of cognitive training with video games and physical exercise. The cognitive component will be either a brain-training video-game program selected from Lumosity (cognitive intervention, CI) or video games not specifically designed to train particular cognitive functions such as attention, memory, or executive control (cognitive control, CC). The physical exercise component will be either a senior-friendly adaption of BODYATTACK™ (https://www.lesmills.com/), a combination of dance, aerobic, strength, and muscular resistance (exercise intervention, EI), or its control condition comprising stretching, toning, and relaxation (exercise control, EC). The duration of sessions for all groups will be the same, and all participants will perform physical exercise and video-gaming activities in a social environment (in small groups formed by 10–12 participants) and in the presence of the trainer.

To summarize, the study will have a 4 × 3 mixed factorial design with four intervention conditions—multidomain (CI + EI), unidomain cognitive intervention (CI + EC), unidomain physical intervention (EI + CC), and active control (CC + EC)—assessed at three different time points (pretest, posttest, 3-month follow-up), with "Type of training" as between-subject factors and "Time" as the within-subject factor. The dependent variables will be behavioral and/or electrophysiological measures of executive functions (inhibition, shifting, working memory), memory functions (short-term and long-term visual and word memory), and emotional well-being, quality of life, and motivation.

3.2 Trial setting

This study will be conducted in Madrid (Spain) at the UNED Psychology building. The screening, pretest, post-test, and follow-up assessments will be conducted in our laboratories at the Psychology building. The training sessions of the four groups will be conducted in three waves in spaces specifically equipped and prepared for this purpose at our university site as well as at a city council facility.

3.3 Participants

Participants will be male and female, healthy, and independently living volunteers aged between 60 and 80 years. Those who complete the baseline assessments and meet the inclusion criteria (see later) will be randomly assigned to one of the four intervention conditions. The timing of group allocation will take place between 1 and 8 weeks after baseline.

Participants may discontinue their intervention for personal or medical reasons. To minimize dropouts and improve adherence to the intervention, four face-to-face adherence reminder sessions will take place during the training program emphasizing the importance of training compliance. Furthermore, to increase participant retention and to reduce loss to follow-up, all participants will receive a personalized report of their performance and training progress at the end of the study. Participants will receive a small refund in compensation for their traveling expenses.

Even though this trial is low risk, participants might harm themselves during the practice of physical exercise. To minimize the risk of injuries, each participant will be carefully monitored during the training sessions. The interventions will be designed in collaboration with the exercise instructors, after a detailed analysis and taking into account each participant's possible medical issues. Spontaneously reported adverse events or other unintended effects will be registered and analyzed, and if necessary, the protocol will be modified to eliminate the causing element. We have signed an insurance policy in case any participant suffers harm during the physical training.

3.4 Inclusion and exclusion criteria

Participants will have normal or corrected to normal vision and hearing, and will be free of neurological or musculoskeletal conditions, psychiatric conditions, or traumatic brain damage. They will not practice intense sports or other forms of physical exercise and will not play video games of any sort for more than 1 h per week. To determine eligibility, participants will be screened individually. Exclusion criteria will be a score of below 26 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), a score of 6 or more on the Yesavage Geriatric Depression Scale (Yesavage et al., 1982) (Spanish adaptation by Martínez et al., 2002), less than 20/60 vision with or without correction based on self-report, inability to complete the training activities, inability to communicate in Spanish, current plans to move to another city, and significant heart or lung disease.

3.5 Sample size

We conducted an a priori power analysis using G*Power 3.1 (Faul et al., 2009) to calculate the appropriate sample size. Using an α value of 0.05, power of 0.80, and a medium effect size ($f = 0.38$) for video-game training (Toril et al., 2014) and physical training (Falck et al., 2019), and four groups within the F-test family, a total sample size of 124 is required. Considering a drop-out rate of 12%, a total of 144 participants would be sufficient to detect significant main effects. According to this calculation, the adequate number of participants in each group (multidomain training, video-game training, physical activity training, and active control) is 36. According to this, we will set a sample size of 36 participants per arm, which is adequate for the experimental design. According to Montgomery et al. (2003), with this number of participants, the design would be underpowered to detect an interaction effect, as it would need a fourfold increase in sample size. However, given that lower interaction effects would not be clinically relevant, we decided to maintain our initial sample size estimation.

In the elaboration of this protocol, we have followed the SPIRIT 2013 explanation and elaboration guidance for reporting protocols of clinical trials (Chan et al., 2013).

3.6 Recruitment

Participants will be recruited through organized information sessions about the project at senior programs at universities and through radio advertisements.

3.7 Randomization and blinding

After the baseline assessments, participants will be randomly allocated to one of the four training protocols in a stratified process using the online tool Random Lists (move this to the other linehttps://www.randomlists. com/). JMR will generate the random sequence and will assign participants to interventions. At first, participants who came in couples will be randomly allocated as a unit to one of the four groups, and afterward the same procedure will be performed with the individual participants. This procedure aims to minimize dropouts due to separating couples in different groups. Participants and exercise instructors will be blinded to treatment allocation (single-blind). Data analysis will not be blinded, as it will be performed by the investigators who actively collaborate in the study. We do not envision any reason why participants should be unblinded, either during the trial or at the end of the study.

3.8 Interventions

Participants will complete 16 training sessions of sequentially combined physical and cognitive training, or the corresponding control activities. Participants will be trained in small groups on 2 days per week for 2 h. The first 60 min of each session will be dedicated to the exercise intervention (EI) or the exercise control activity (EC), followed by 60 min of cognitive training with video games (CI) or the cognitive control activity (CC). Both CI and CC will be conducted on tablets (Brigmton BTPC 1018OC). EI and EC will be led by physical exercise instructors and accompanied by a music soundtrack.

3.8.1 Cognitive intervention

In each session, participants in the CI group will play 10 video games selected from the commercial Lumosity computerized training program (http://lumosity.com/). Lumosity provides a series of games targeting the improvement of several cognitive functions. **Table 1** presents a short description of the games and their trained domains. These functions are sensitive to age-related cognitive decline and closely related to the ability to perform activities of daily living, such as driving. The participant will play the games in a predetermined sequence, for approximately 5–10 min for each game. Each participant in the CI group will have a Lumosity user account assigned. These games are adaptive meaning that as performance improves, the difficulty increases, progressively adjusting to the participant's performance level.

3.8.2 Physical intervention

The exercise intervention will consist of BODYATTACK™, which is a registered trademark of moderate to high-intensity training that combines aerobic exercises with strength and balance exercises. During the exercise protocol, participants will train at 65–80% of their maximum heart rate. The training sessions are predetermined by the distributer and comprise standardized movements, exercises, and music soundtracks (see **Table 2**). Exercises include large plyometric movements and more controlled movements, and train equally upper and lower body muscles with dynamic movement coordination. The sequence of exercises is as follows: 10-min warm-up, 35-min main phase (with active recovery between intervals), and 10-min cool-down.

Table 1. Short description of the video games for the cognitive intervention.

Game name	Trained function	Description
Train of Thought	Divided attention	The player directs trains to their matching station.
Assist Ants	Divided attention	The player prevents collisions by placing obstacles in their paths.
Trouble Brewing	Divided attention	The player simultaneously serves orders to different customers.
Playing Koi	Divided attention	The player keeps track of which fish has already been fed, in a square of randomly appearing fishes.
Memory Serves	Working memory and divided attention	The player matches different pieces of luggage to their corresponding owners.
Disillusion	Flexibility	The game consists of matching tiles with different shapes, colors, or symbols.
Ebb and Flow	Flexibility	Players swipe to the direction in which the leaves are moving or pointing to.
MasterPiece	Spatial reasoning	The player reorientates a shape so that it fills a hollow section.
Speed Pack	Visualization	The player has to fit the last item into an already filled suitcase.
Highway Hazards	Information processing	Player dodges obstacles in a race through a virtual desert.

Table 2. Description of the exercise intervention.

Activity	Trained function	Description
Adaptation of "Bodyattack"	Cardiovascular fitness	Aerobic exercises
	Endurance	Strength movements
	Coordination	Movements to music soundtrack
	Balance	Stabilization exercises
	Flexibility	Stretching

3.8.3 Cognitive control activity

The cognitive control component will exclusively involve language-specific processes and crystalized knowledge (see **Table 3**). These domains are preserved with age, and even though an implication of executive functioning cannot be ruled out, this is clearly not the main active component. The cognitive control games are available within the gaming service Google Play Games, which mimics cognitive training platforms. This will create the impression of receiving an intervention, thereby reducing expectation biases. Participants will play 10–15 min each game in a predetermined sequence.

3.8.4 Physical control activity

The physical control activity will consist of BODYBALANCE™ (https://www.lesmills.com/), which is a music-guided exercise that combines Tai Chi, Yoga, and Pilates exercises. The sequence of exercises of each session is as follows: 10-min warm-up with Tai Chi exercises; 35-min main phase with Yoga and Pilates exercises with a focus on breathing, stretching, balance, and strengthening of abdominal muscles; and 10-min cool-down with meditation and relaxation. The physical activity intervention and the physical control activity are briefly described in **Table 4**.

Table 3. Short description of the video games for the cognitive control condition.

Game name	Trained function	Description
Hangman	Lexical access	The player guesses a word by suggesting letters within a certain number of guesses.
Grammar	Lexical access	The player chooses the correct spelling of a word within three possibilities
Definitions	Semantics and lexical access	The player chooses the correct word according to a given definition.
Word search	Lexical access	The player chooses the correct word according to a given definition
Crossword	Semantics and lexical access	The player constructs words by solving clues
Synonyms and antonyms	Semantics and lexical access	The player produces a word with a similar or opposite meaning to a given word
Trivia Quiz	Crystalized knowledge	The player answers questions of general knowledge.

Table 4. Description of the activities of the exercise control condition.

Game name	Trained function	Description
Adaption of "Pilates"	Flexibility	Stretching
	Relaxation	Respiratory exercises

3.9 General procedure

After baseline, participants who meet the inclusion criteria will be randomly assigned to one of the four groups. The active control group was introduced in the design to control for placebo effects (Boot et al., 2013). The main question is whether the multidomain group will outperform the single-domain groups at posttest, and whether these groups will outperform the active control group in a series of cognitive-control and memory tasks (see below). We focused on these cognitive domains because they deteriorate with age and are critical for independent living.

All methodological designs of primary and secondary outcomes are constructed using the rules of counterbalance and stimulus rotation. Response keys will be counterbalanced across conditions. The computerized tasks have been programmed with E-Prime 2.0 (Psychological Software Tools Inc.). Continuous EEG activity will be recorded in our laboratories with thin electrodes from 40 scalp sites using NuAmps amplifiers while participants perform the task-switching task.

3.10 Outcome measures

Each group will be assessed at three time points. Possible improvement will be assessed at posttest (12 weeks) and follow-up (24 weeks) using baseline (week 0) outcomes as a reference point. A schematic diagram of the time schedule of data collection for all outcome measures is shown in **Figure 2** (see also Appendix B: SPIRIT checklist).

To report the primary and secondary outcomes, we will follow the outcome definition proposed by Saldanha et al. (2014) and Zarin et al. (2017) that includes the domain, the specific measurement, the specific metric, the method of aggregation, and the time points that will be used for analysis.

3.11 Primary outcomes: training effects on cognitive functions

3.11.1 Set-shifting

Memory-based task switching Executive functions will be assessed with a memory-based task-switching paradigm. In this task (Gajewski et al., 2017; Gajewski et al., 2010), digits from 1 to 9 (excluding number 5) are presented in white on a black

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT**	$-t_1$	0	*Baseline*	*12 weeks (post-test)*	*24 weeks (follow-up)*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
CI + EI			●———	———	———●
CI + EC			●———	———	———●
CC + EI			●———	———	———●
CC + EC			●———	———	———●
ASSESSMENTS:					
Primary outcomes:					
ERP + Memory based task switching			X	X	X
n-Back task			X	X	X
Stroop task			X	X	X
TMT A+ B			X	X	X
WMS-III Faces immediate + delayed			X	X	X
WMS-III Word-Pair immediate + delayed			X	X	X
Secondary outcomes:			X	X	X
PANAS			X	X	X
LSI			X	X	X
SPPB			X	X	X
6MWT			X	X	X

Fig. 2 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) diagram illustrating the schedule of enrolment, post allocation, and close-out for all assessments. CC: cognitive control, CI: cognitive intervention, EC: exercise control, EI: exercise intervention, ERP: event-related potential, LSI: Life Satisfaction Index, 6MWT: 6-Minute Walk Test, PANAS: Positive and Negative Affect Schedule, SPPB: Short Physical Performance Battery, TMT: Trail Making Test, WMS-III: Wechsler Memory Scale – Third Edition.

background on the computer screen. A cue indicating the relevant task is presented simultaneously with the digit below the fixation point. The cue "NUM" indicates a numerical task (smaller or greater than 5), "PAR" the parity task (odd vs. even), and "TAM" (a diminutive for Spanish "tamaño" (size) font) the fontsize task (small vs. large). Each stimulus is presented in small (7 mm × 10 mm) and large (12 mm × 18 mm) size. Participants will perform three single and two mixed blocks. In the single blocks, they must process digits according to the one-task rule (i.e., numerical, parity, or font

size task only). In the memory-based mixed blocks, participants must switch between different tasks within the block. In the cue block they are instructed to switch the rule after every three trials in the following order "NUM–NUM–NUM–PAR–PAR–PAR–TAM–TAM–TAM", while a cue is presented in every trial simultaneously with the digit. In the memory block, participants are instructed to switch the rule after every three trials in the same order, while "XXX" instead of a cue is presented; that is, participants have to keep track of the trial sequence in their working memory. When three consecutive errors are made, or no response is given, cues are presented on three consecutive trials to help participants to find the track. Single blocks consist of 35 trials each, and two mixed blocks consisting of switch and no-switch trials: a cued block (90 trials) and a memory block (90 trials). The mixed blocks are equal with respect to the stimulus type, response type, and frequency of task switch (33.3%). The stimulus–response mapping of the three tasks is overlapping; that is, responses according to "smaller than 5", "even", and "small size" are assigned to the left key and "larger than 5", "odd", and "large size" to the right key. The assignment will be counterbalanced across participants. The outcomes of interest are mean reaction times (RTs) between groups corresponding to correct trials at pretest, posttest, and follow-up time points. The specific metric will be the change from baseline.

3.11.2 Processing speed and flexibility

Trail Making Test (TMT) The TMT is a neuropsychological test of visual attention and task switching. The test comprises two parts (A and B). Each part consists of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1–25, and the participant draws lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1–13) and letters (A–L); the task consists of connecting the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1–A–2–B–3–C, etc.). The total times in seconds for Parts A and B represent the TMT-A and TMT-B direct scores. Scores of TMT-A account for perceptual speed, whereas the B–A difference score is an indicator of task-switching abilities. The outcomes of interest are the mean time scores of the difference score, TMT-B minus TMT-A, to assess task switching between groups at pretest, posttest, and follow-up time points. The specific metric will be the change from baseline.

3.11.3 Working memory

The *N*-back task is a continuous performance task to assess maintenance and updating of information in working memory. This task has been used with older adults (Basak et al., 2008; Dahlin et al., 2008; Redondo et al., 2016). Participants are presented with a sequence of stimuli (consonant letters) and indicate whether the last stimulus matches the one presented "n" trials back by pressing one of two keys (one for "yes" or another for "no"). We used a three level *N*-back task. In the 0-back condition, the letter X is the target. We include the 0-back condition as an index of perceptual-motor speed to control for the role of speed of processing in working memory performance. In the 1-back condition, participants must remember the stimulus presented just before the current stimulus; in the 2-back level, they have to remember the stimulus presented two positions before. Each participant first performs a practice block of 17 trials at each level, followed by the experimental trials. Each level contains three blocks of 27 trials (81 trials per level), yielding a total of 243 trials. Each block of 27 trials consists of 17 "nontargets" ("no" response) and 10 "targets" ("yes" response). The outcomes of interest are the mean accuracy between groups as assessed by Hits–False alarms. The specific metric will be the change from baseline (pretest) to posttest and follow-up.

3.11.4 Inhibitory control

The Stroop interference effect reflects the extra time needed to resolve the conflict generated by an automatically processed irrelevant dimension. The Stroop task assesses response inhibition. We use the computerized Color–Word version of the Stroop task (Ballesteros et al., 2017) with two different conditions: in the congruent condition, color name words match with the ink color; while in the incongruent condition, color names are printed in an incompatible ink color. In both conditions, participants are instructed to name the color of the ink as soon as possible. Longer response latencies and higher error rates on incongruent trials (when the color of the letters conflicts with the word) compared to congruent trials (when color and word match) constitute the Stroop effect. The Stroop effect correlates negatively with the efficiency of inhibitory control. The Stroop task contains 18 practice trials and two experimental blocks of 126 trials each, with a proportion of incongruent trials of 66%. Responses are assigned to the keys "v", "b" and "n", and the stimulus–response mapping is counterbalanced across participants. The dependent variable is the mean RT corresponding to the congruent and incongruent correct trials of the groups at pretest, posttest, and follow-up. The specific metric will be the change from pretest in the computerized version of the Stroop task to assess response inhibition.

3.11.5 Immediate and differed visual and verbal memory

Wechsler Memory Scale—Third Edition (WMS–III; Wechsler, 1997) Faces. The WMS-III Faces subtest uses a recognition paradigm to assess immediate and delayed visual memory. In Faces I, participants are presented with 24 target faces at a speed of 2 s per picture. Then, they are shown 48 faces (24 targets and 24 distractors) and are asked to identify the target faces by responding either "yes" or "no" to each face. Participants are prompted to keep the target faces in mind. In Faces II, participants are shown 48 faces (24 targets and 24 distractors) after a 30-min delay and are asked to identify the target faces. The hits–false alarms mean between groups at pretest, posttest, and follow-up assessments will be the outcome of interest. The specific metric will be the change from pretest to posttest and follow-up.

Wechsler Memory Scale—Third Edition (WMS–III; Wechsler, 1997) Word-Pair List. The WMS-III Word-Pair subtest assesses immediate and delayed verbal memory. In this test, four trials of eight unrelated word pairs are presented at a rate of 3 s per pair. In the immediate recall condition, after the presentation of the four lists, the first word of each pair is read to the participant, who has to provide the associated word of the pair. After a delay of approximately 25–35 min, the same procedure is repeated, and the participant provides the second word of each pair. Finally, a recognition task is administered where 24 word pairs are presented and the participant is asked to identify the pair as either "new" or "old". The hits–false alarms mean between groups at pretest, post-test, and follow-up assessments will be the outcome of interest. The specific metric will be the change from pretest to posttest and follow-up.

3.11.6 Electrophysiological measures

Electroencephalograph acquisition. While performing the experimental memory-based switching task, continuous electroencephalograph (EEG) activity will be recorded using a NuAmps amplifier (Neuroscan Inc.) inside a soundproof, electromagnetically shielded room. We will use a 34-channel elasticized Quik-Cap with Ag/AgCl sintered electrodes (Sinha et al., 2016). To control ocular artifacts, vertical and horizontal electrooculograms will be recorded in two bipolar channels. Eye blinks and vertical eye movements will be monitored via electrodes located below and on the supraorbital ridge of the left eye. Horizontal artifacts will be monitored via electrodes on the outer canthus of each eye. Linked mastoids (A1, A2) will be used as a reference, and participants will be grounded to the AFz electrode. All data will be digitized using a NuAmps amplifier in continuous recording mode. The sampling rate will be 1000 Hz, and all channels will be online bandpass filtered (0.1–140 Hz) and notch filtered (50 Hz) to eliminate power line artifacts. Continuous data will be filtered offline using a digital Butterworth filter (0.1–40 Hz; 12 dB per octave roll-off), an infinite impulse response filter that achieves a given filtering characteristic. After filtering, data will be separated into baseline-corrected and nonoverlapping epochs time-locked to the target onset. Epochs containing high amplitude/ frequency and muscle, or other irregular artifacts will be removed by visual inspection. Only artifact-free epochs from correct trials will be selected for averaging. The existence of blinks and other ocular movements will not be a criterion for epoch rejection. This kind of artifact will be eliminated using Independent Component Analysis (ICA) (Anemüller et al., 2003; Jung et al., 2001; Jung et al., 1997; Lee et al., 1999; Makeig et al., 1997; Onton et al., 2005). After submitting EEG data to ICA decomposition, artifactual components will be removed by inspection of their activity, scalp topography, and spectral power. The length of the epoch in the target-locked ERP will be 1100 ms, and 600 ms in the response-locked ERP. We focus on P2, N2, and P2b. Analyses will be centered on the posttarget and postresponse ERPs at the midline electrodes located at the frontal, central, and parietal lobes (Fz, Cz, and Pz) where the components of interest are usually maximum. P2 is a positive ERP component associated with the retrieval of stimulus–response sets that will be measured between 150 and 300 ms. N2 will be measured at the most negative pick between 150 and 400 ms after target onset. P3b will be measured in the time window of 300–600 ms after target onset. This wave is associated with context updating and working memory (see Gajewski et al., 2017; Gajewski et al., 2018).

3.12 Secondary outcomes

3.12.1 Assessment of emotional and affective well-being

The Positive and Negative Affect Schedule (PANAS, Watson et al., 1988). The PANAS is a self-report questionnaire designed to assess the affective state. It consists of two 10-item scales to measure both positive and negative affect. Positive affect reflects the point to which a person feels enthusiastic, active, and alert, with energy and rewarding participation. Negative affect represents a general dimension of subjective distress and unpleasant participation that includes a variety of aversive states, such as disgust, anger, guilt, fear, and nervousness. Participants in the PANAS respond to a 20-item test using a 5-point scale that ranges from very slightly or not at all (1) to extremely (5). We use the Spanish version (Sandín et al., 1999) which provides good consistency and reliability indexes, and also confirms the original two factors of the questionnaire. The reliability (Cronbach's α) and validity, both convergent and discriminant, have also been corroborated in the elderly Spanish population (Nolla et al. 2014). The outcomes of interest are the mean score per group of positive and negative affect assessed with the PANAS questionnaire at three time points: pretest, post-test, and follow-up. The specific metric will be the change from baseline.

The Life Satisfaction Index (LSI) The LSI (Neugarten et al., 1961) is a 20-item self-report questionnaire to measure psychological well-being in older adults. The instrument consists of five subscales, including zest for life (four items), resolution and fortitude (five items), congruence between desired and achieved goals (three items), positive self-concepts (three items), and mood tone. Respondents express their agreement or disagreement with the statements based on a 3-point Likert scale (agree = 2 points; disagree = 1 point; and “don’t know” = 0 points). The higher the overall score, the higher the individual’s life satisfaction.

The outcome of interest is the mean score per group of the individual’s life satisfaction assessed with the LSI questionnaire at three time points: pretest, posttest, and follow-up. The specific metric will be the change from baseline.

3.12.2 Assessment of physical condition

The Short Physical Performance Battery (SPPB) The SPPB (Guralnik et al., 1994) measures functional status and physical performance. First described in 1994, it is a composite measure assessing walking speed, standing balance, and sit-to-stand performance. The SPPB is calculated from three components: the ability to stand for up to 10 s with feet positioned in three ways (together side by side, semi-tandem, and tandem); time to complete a 3-m or 4-m walk; and time to rise from a chair five times.

Lower-extremity physical performance is assessed in the study with a composite measure of walking speed, standing balance, and sit-to-stand performance. The outcome will be the performance mean in the battery of the groups at three time points: pretest, posttest, and follow-up. The specific metric will be the mean change from pretest to the other time points.

The 6-Minute Walk Test (6MWT) The 6MWT (Harada et al., 1999) is commonly used to assess exercise capacity. The participant walks for 6 min as fast as possible. The primary outcome is the distance completed. The test is administered in accordance with the protocol endorsed by the ATS (2002). The test is performed on a straight 30-m corridor and all participants receive standardized scripted instructions and scripted phrases of encouragement each minute during the test. Besides the distance, monitored parameters are changes in oxygen saturation (SpO2), and pretest and posttest dyspnea and fatigue using the Borg scale (Borg, 1982).

Functional capacity is assessed in the study with the 6MWT. The outcome measure will be the mean absolute value in the test obtained by the groups at three time points: pretest, posttest, and follow-up. The specific metric will be the mean change from pretest to the other time points of the study.

3.13 Statistical analysis

All data from participants with complete baseline assessment and who attended at least one training session will enter into a primary intention-to-treat analysis. For the secondary per-protocol analysis, only the data of participants with a complete cognitive assessment and an attendance rate ≥ 70% will be considered.

Executive functions (set-shifting, maintenance, inhibitory control) and memory functions (short-term, visual, and verbal immediate and delayed memory) will be assessed at pretest, posttest, and follow-up. The statistical analysis corresponding to the behavioral results will be carried out with the SPSS statistical package for Windows (SPSS 25.0; IBM Corporation). Results will be considered significant at $p < 0.05$, with Bonferroni-corrected post hoc tests performed as appropriate. We will explore the missing data to ascertain their pattern and will apply an adequate technique of multiple imputation. Repeated ANOVA measures will be conducted with four groups (multidomain training, cognitive training, exercise training, active control) at three time points (pretest, posttest, follow-up) to test the primary hypothesis (i.e., differences in efficacy between interventions compared to the active control condition). Repeated ANOVA measures will also be performed to determine the effect of the interventions on secondary outcomes. To evaluate the effect size of the combined multimodal group versus each individual intervention group and the control arm, we will use multimodal regression with an interaction term. Electrophysiological data will be analyzed with Neuroscan Curry software (version 8.0.2), the EEGLAB toolbox (Delorme & Makeig, 2004), and the ERPLAB plugin for EEGLAB (Lopez-Calderon & Luck, 2014).

3.14 Data monitoring committee and data management

Personal information about participants obtained during the individual interviews as well as performance data and all study-related information will be coded in a database and stored securely at the study site to maintain participants' confidentiality. A coded identification (ID) number to maintain participant confidentiality will identify all data collection and administrative forms. The electronic data will be stored securely on a university computer and a hard disk drive (HDD) that are password protected. Paper copies, as well as HDDs, will be securely stored in a locked cabinet at the study site. All forms, lists, appointment records, consent forms, and any other listings that link participant ID numbers to other identification information will be stored in a separate, locked file in a limited access area. Only the members of the researcher team directly involved in data collection, maintenance, and management will have access to the data set. The data monitoring committee (DMC) will be composed of JAR and JMR, who will regularly check on the correctness of data collection and encoding and its correspondence with the entrances in the laboratory diary. The DMC will be responsible for securing the data on a weekly basis on the devices mentioned earlier. The data will be stored securely in our laboratory for 5 years. We have not planned to conduct subgroups of interim analyses.

3.15 Steering committee

The steering committee will meet at least on a quarterly basis to monitor the trial processes, independently of the funding organization. The committee will check compliance with the assessment and training protocols and the timelines and will oversee and manage the trial. Its members, who form an active part of the research group, are SB and JMR. They will verify trial processes, such as participant enrollment, informed consent, eligibility, allocation of participants to groups, and adherence to trial interventions.

3.16 Dissemination plans

After completion of the trial, the results will be presented at international and national conferences and will be published in appropriate scientific journals. We will also deliver the results to the participants.

1. Discussion

We investigate the potential for cognitive training and physical exercise to prevent or minimize the negative effects occurring with aging. This clinical trial examines the efficacy of a combined intervention on moderate cognitive decline as well as affective well-being and physical condition in healthy older adults. This multimodal intervention study will contribute to the increasing body of literature investigating ways to promote brain plasticity and maintain healthy and active aging.

To summarize, cognitive decline and physical decline have negative effects on older adults and impact negatively on society due to the increasing number of older adults that will suffer cognitive decline and neurodegenerative diseases in the next decades. Finding effective ways to prevent the negative impact of declining cognition would have a key effect on the current limited social and health care resources.

5. Trial status

This clinical trial was registered at the National Institute of Health (NIH) with the Clinicaltrials.gov identifier NCT03823183 (https://register.clinicaltrials.gov/ Clinical-Trials.gov) on 21 January 2019. The protocol version number is number 1 (January 2019). Recruitment started in February 2019 and is expected to be completed in February 2020. Once the trial is completed, results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial is active and ongoing. We expect to have the final results by the middle of 2021.

Chapter 8

The effects of combined cognitive-physical interventions on cognitive functioning in healthy older adults: A systematic review and multi-level meta-analysis

The effects of combined cognitive-physical interventions on cognitive functioning in healthy older adults: A systematic review and multi-level meta-analysis

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Rieker, J. A., Reales, J. M., Muiños, M., & Ballesteros, S. (2022). The effects of combined cognitive-physical interventions on cognitive functioning in healthy older adults: A systematic review and multilevel meta-analysis. *Frontiers in Human Neuroscience*, 16. https://doi.org/10.3389/fnhum.2022.838968

Abstract

Research has shown that both physical exercise and cognitive training help to maintain cognition in older adults. The question is whether combined training might produce additive effects when the group comparisons are equated in terms of exercise intensity and modality. We conducted a systematic electronic search in MEDLINE, PsycInfo, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify relevant studies published up to February 2021. Seven hundred and eighty-three effect sizes were obtained from 50 published intervention studies, involving 6,164 healthy older adults, and submitted to a three-level meta-analysis. Results showed that combined training produced a small advantage in comparison to single cognitive training on executive functions, whereas both types of training achieved similar effects on attention, memory, language, processing speed, and global cognition. Combined training achieved higher training gains in balance than single physical training, indicating a transfer from cognitive training to balance. Performing cognitive and physical exercise simultaneously, and interactive training (e.g., exergames, square stepping) produced the largest gains in executive functions, speed, and global cognition, as well as the largest improvements in physical functions. Aerobic training was associated with higher effects on attention and fitness, whereas non-aerobic training produced larger effects on global cognition and balance. For all cognitive and physical outcomes, training resulted more advantageous when performed in a social context, even though individual training obtained similar results in balance as group training.

Keywords*:* aging, cognitive training, three-level meta-analysis, multidomain training, combined training, physical exercise

1. Introduction

Highly developed nations are experiencing large increases in the proportion of elderly citizens, due mostly to reduced birth rates and the increased longevity of their inhabitants (Reuter-Lorenz & Park, 2014). Demographic estimations predict that the proportion of the population above 60 will reach 35% by 2050 (Eurostat, 2016). Furthermore, the old-age dependency ratio (people aged 65 and above relative to those aged 15 to 64) will increase from 29.6% in 2016 to 51.2% in 2070 (European Commission, 2018). As aging affects several key cognitive functions negatively, such as processing speed, working memory, long-term episodic memory, and executive control functions (Baltes & Lindenberger, 1997; Park et al., 2002; Rönnlund et al., 2007), there is considerable interest in finding effective ways to improve and/or maintain these cognitive functions that are central for performing daily living activities.

Several longitudinal and cross-sectional studies conducted during the last two decades have shown that cognitive training interventions (e.g., Ball et al., 2002; Willis et al., 2006; Basak et al., 2008; Anguera et al., 2013; Ballesteros et al., 2014; Toril et al., 2016; Ballesteros, et al., 2017), regular physical activity (e.g., Colcombe & Kramer, 2003; Guiney & Machado, 2012; Muiños & Ballesteros, 2018; Prakash et al., 2015; Voelcker-Rehage & Niemann, 2013), and exposure to novelty (Park et al., 2014) can promote and/or maintain cognitive functioning in late adulthood.

A large body of research shows the positive link between physical activity and cognition. For a detailed description of the brain mechanisms associated with physical activity and its effects on cognition, see Kraft (2012) and Ballesteros et al. (2015). These reviews support the view that the combination of physical activity and cognitive training may generate synergistic effects, resulting in larger benefits than each intervention alone.

1.1 Physical training

Physical activity can be defined as any bodily movement produced by skeletal muscles that require energy expenditure. Both moderate- and vigorous-intensity physical activity improve health (World Health Organization, 2019). A large body of research also corroborates the benefits of physical activity on brain structures and functions (Bherer et al., 2013; Erickson et al., 2011; Liu-Ambrose et al., 2012; Ruscheweyh et al., 2011; Voelcker-Rehage et al., 2010), and as a protection against age-related cognitive decline in executive functions and memory (Bamidis et al., 2014; Colcombe & Kramer, 2003; Hötting & Röder, 2013; Voelcker-Rehage & Niemann, 2013). Aerobic exercise has been specially related to improvements in cognition (e.g., Colcombe & Kramer, 2003; Hindin & Zelinsky, 2012), but coordination training (Voelcker-Rehage et al., 2011), resistance training, Tai Chi (Muiños & Ballesteros, 2015; Pons van Dijk et al., 2013), and dance (Esmail et al., 2019; Kattenstroth et al., 2013; Zilidou et al., 2018; for reviews see Muiños & Ballesteros, 2020; Muiños & Ballesteros, 2021; Netz, 2019) produce positive effects on brain and cognition in older adults.

1.2 Cognitive training

Cognitive training refers to a structured intervention that includes tasks designed to improve or maintain the cognitive functions that decline most with age. In the last years, several meta-analyses (Chiu et al., 2017; Gavelin, et al., 2020; Kelly et al., 2014; Lampit et al., 2014; Powers et al., 2013; Tetlow & Edwards, 2017; Toril et al., 2014; Vazquez et al., 2018; Wang, 2016) examined the effects of cognitive-based training in older adults. Overall, their results indicated that video games and other cognitive-based training programs lead to small to moderate improvements in several aspects of cognition.

A systematic overview of systematic reviews (Gavelin et al., 2020) on 46 reviews found a small mean effect of cognitive training in healthy and cognitively impaired older adults. Furthermore, larger effect estimates were related to higher review quality, and the authors concluded that cognitive training seems to improve cognition, but that the scarcity of high-quality evidence and heterogeneity in reported findings do not allow to estimate the clinical value of the effects.

However, other reviews (Gates et al., 2019; Lintern & Boot, 2019) were less optimistic about the effects of cognitive training. If effective, it seems that the transfer effects to untrained cognitive functions are either weak (Simons et al., 2016; Souders et al., 2017) or null when controlling for placebo effects and publication bias (Sala et al., 2018). Furthermore, several of the mentioned meta-analyses on cognitive training included also studies in which the participants also performed physical exercise (e.g., Maillot et al., 2012; Barnes et al., 2013; Legault et al., 2011; Shatil et al., 2013), confounding the effect of pure cognitive training with a potentially additive effect of cognitive training combined with physical activity.

1.3 Combined physical and cognitive training

The concurrent or simultaneous performance of physical exercise and cognitively challenging activities is known as combined, multidomain, or dual-task training. Research on dual-task performance has a long tradition of investigating how increased attentional demands affect either cognitive or physical performance due to prioritization in resource allocation to one or the other domain. Thus, these paradigms assume that our information processing system is limited and that conflicts in resource allocation are solved via interference control (McIsaac et al., 2015). On the other hand, neuroscientific approaches do not assume that one activity is necessarily executed on behalf of the other, but that combining physical and cognitive training might result in a mutual enhancement of both activities (Hötting & Röder, 2013).

Animal studies have shown that physical exercise and cognitive stimulation contribute differentially to neuroplasticity in the mice brain, and whereas physical exercise promotes neurogenesis, cognitive stimulation promotes the differentiation of these new cells (Kempermann et al., 2010; Kronenberg et al., 2006, van Praag et al., 1999). In humans, numerous studies have shown the beneficial effect of physical training on cognitive and functional brain plasticity in older adults, especially in hippocampal areas (Erickson et al., 2009; Erickson et al., 2011; Niemann et al., 2014), suggesting similar mechanisms of neurogenesis as in animal models. Regular exercise has also been related to higher brain-derived neurotrophic factor (BDNF), which is involved in neurogenesis, synaptogenesis, and dendritic branching (Håkansson et al., 2017; Ruscheweyh et al., 2011), resulting in increased learning-related plasticity (Cassilhas et al., 2016; Hötting and Röder, 2013). The release of BDNF serum is higher when physical exercise precedes cognitive training than vice versa (Nilsson et al., 2020), suggesting that physical exercise may have a facilitating effect on cognitive training interventions.

A crucial question is whether combined physical and cognitive interventions, as opposed to single cognitive training or single physical training, produce synergistic effects on cognition, i.e., a combined effect that is greater than the effect produced by its components separately (Ballesteros et al., 2015; Bamidis et al., 2014; Hötting & Röder, 2013; Kraft, 2012; Lustig et al., 2009). A systematic review (Laurenroth et al., 2016) analyzed 20 intervention studies on cognitive and physical combined training. The authors concluded that simultaneous or successive physical exercise and cognitive training were more effective than physical or cognitive exercise interventions alone. However, the results should be treated with caution due to the methodological heterogeneity of the original studies. Another review (Law et al., 2014) included 8 randomized controlled studies (RCT), but only 3 involved cognitively healthy older adults. Despite the small number of studies, the results indicated that participants' cognition in the combined cognitive and physical training condition was better than that of controls.

1.4 Meta-analytic evidence on combined interventions

Several meta-analyses were conducted on the effects of combined interventions on the cognitive functions of older adults. The meta-analysis conducted by Zhu et al. (2016) included 20 interventional controlled trials (n = 2,667 healthy older adults). The results showed that combined interventions were superior to controls with a small effect size (0.29 random-effects model, p = 0.001) and physical exercise alone (overall effect size 0.22, p < 0.01), but not to cognitive training.

The meta-analysis of Guo et al. (2020) included 21 RCTs conducted with healthy participants and adults with mild cognitive impairment (MCI) (n = 1,665). Combined interventions and cognitive training alone produced larger effects in executive functions compared to controls (Standardized Mean Difference; *SMD* = 0.26, p < .01). Differences were found between the effects produced by combined training and cognitive training alone (*SMD* = 0.13, p > .05) or physical training alone (*SMD* = 0.13, p > .05).

A network meta-analytic study (Bruderer-Hofstetter et al., 2018) included 11 combined or multi-component RCTs conducted with healthy older adults (n = 670). According to their results, multi-component interventions were more effective than physical exercise and cognitive training alone and improved specific aspects of physical capacity and/or cognitive function. Physical and cognitive training conducted simultaneously or separately in older adults with normal cognition were effective, but in older adults with mild cognitive impairment (MCI), training performed separately was more effective.

On the other hand, the meta-analysis by Gheysen et al. (2018) included 41 intervention studies, 30 of which were conducted with healthy older adults. The authors investigated whether the combination of physical and cognitive interventions led to greater improvement in different cognitive processes compared to physical or cognitive interventions alone, and/or passive and active control groups. Results indicated that combining physical and cognitive training tasks in the same protocol produced larger benefits. Compared to the control condition, combined interventions produced larger cognitive gains ($g = 0.316$; $p < .001$). Combined interventions also induced significantly larger gains in cognitive functioning than physical exercise alone ($g = 0.16$; $p = .008$). However, combined and cognitive training alone did not differ ($g = 0.02$; $p = .836$). Nonetheless, the authors concluded that physical activity programs for older adults produce greater benefits when they incorporate cognitive tasks, and recommended activities such as dance and Tai-Chi that combine physical activity and cognitive training (see Muiños & Ballesteros, 2020; Muiños & Ballesteros, 2021).

Vaportzis et al. (2019) included 7 combined physical and cognitive interventions, 25 physical, and 9 cognitive intervention studies in their meta-analysis of real-world interventions with healthy older adults. Five out of the seven combined studies reported superior results in the combined intervention versus active controls. However, the meta-analysis did not find any significant difference in cognitive outcomes between combined and cognitive interventions alone.

1.5 Methodological questions and meta-analytic inconsistencies

The meta-analyses discussed in the previous section thus produced some conflicting results, especially in terms of effect sizes. The conflicting results might be due to several factors as the heterogeneity of the studies included in each meta-analysis. Moreover, as in the case of the meta-analyses on cognitive training, meta-analytic works on combined cognitive-physical training often merge nonequivalent training interventions. Different study parameters, such as the dosage and the type of physical exercise (e.g., aerobic exercise *vs* balance training), might modulate the training outcomes differentially. Also, on a within-study level, combined training is often compared with a different type of physical exercise than the one performed in the combined condition. The inclusion of a control condition in the design reduces expectation bias that could inflate training outcomes and account for other threats to internal validity (Gold et al., 2017). However, in contrast to pharmacological interventions, in behavioral studies, it is extremely difficult to find psychological placebos or "sham" interventions, as any activity might have the potential to produce unexpected effects on cognition and behavior. For example, in some studies, the training effect produced by exergames was compared with that produced by balance (Eggenberger et al., 2016; Schättin et al., 2016) or strength training (Bacha et al., 2018). In other studies, aerobic training was compared with stretching plus strength (Barnes et al., 2013), or stretching, strength, and balance training (ten Brinke et al., 2020). In other cases, both groups received a similar training part, such as aerobic and strength training, and another different one (Boa et al., 2018). Or both groups did not differ in the physical training type or load, but the single physical training group also received cognitively enhancing dual-task training (Kayama, et al., 2014). Furthermore, activities used as a control condition in some studies, as balance and/or strength training, were used in other studies as experimental conditions (Gschwind et al, 2015; Hiyamizu et al., 2012; Jehu et al., 2017; Lataar et al., 2018; Wongcharoen et al., 2017), adding a further challenge for meta-analytic analyses. It seems logical to think that aerobic exercise exerts a different effect on body and cognition than, for example, balance or strength training. Hence, the comparison of two groups that receive different training regimes does not allow to isolate the combinatory effect of physical exercise and cognitive training when both groups perform different physical or cognitive activities. Nonetheless, all meta-analyses conducted to date included at least one of the studies mentioned above, computing effect sizes from the comparison of nonequivalent physical training components.

Meta-analyses might also suffer from analytical flaws. Most interventional studies include more than one outcome measure, which produces an interdependency of effect sizes. Traditional univariate approaches often apply the *samplewise* procedure, averaging the dependent effect sizes within studies into a single effect size by computing a weighted average (Cheung, 2019). However, this method underestimates the degree of heterogeneity or the variance of the population and might lead to lower statistical power due to information loss (Cheung, 2019). A relatively novel approach for dealing with the dependency of effect sizes consists in applying a three-level structure to a meta-analytic model (Assink & Wibbelink, 2016). This approach considers three different variance components and allows effect sizes to vary between participants (sampling variance), outcomes (within-sample variance), and studies (between-study variance). The three-level meta-analytic model allows analyzing the training effects on different cognitive functions within the same study (i.e., within-study heterogeneity) and their reliability across different studies (i.e., between-study heterogeneity).

1.6 Aims and hypotheses of this multilevel meta-analysis

The primary aim of this systematic review and three-level meta-analysis was to shed light on whether combined physical and cognitive training is more effective than single-domain training (physical or cognitive alone) in maintaining and/or improving cognition in healthy older adults while controlling for the dependency of effect sizes, and differences in the training protocols. Specifically, the present multilevel meta-analysis addressed the following research questions:

(1) Does combined training produce synergistic or additive effects, i.e., are the effects obtained by the combination of cognitive and physical training larger than those obtained by each of its components separately?

(2) Are the effects of cognitive training differentially modulated when combined with aerobic versus nonaerobic exercise?

(3) Does simultaneous cognitive and physical training produce better results than sequential training performed on the same day (sequential training schedule) or different days of the week (separate training schedule)?

(4) Does the type of cognitive training (computer, interactive, such as exergames, or multicomponent training) influence the training outcomes?

(5) Does training produce better results when performed in groups than when performed individually?

(6) Finally, to what extent are the results influenced by the quality of the studies, publication bias, year of publication, sample size, age, or training duration?

2. Method

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020175632). To conduct this systematic review and multilevel meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; www.prisma-statement.org) guidelines for reporting studies (Moher et al., 2009). The objective was to ensure comprehensive and transparent reporting methods and results. The process and methods were established before conducting the review.

2.1 Literature search strategy

A systematic electronic database search was conducted to identify relevant published studies. The MEDLINE, PsycInfo, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched to identify relevant studies published up to February 2021, with no period specified for the date of publications.

The search terms were intersections of terms referring to the combination of cognitive and physical activities in older adults intended to improve cognitive and physical health. The search terms were intersections of terms referring to the combination (*combined OR combination OR simultaneous OR dual OR concurrent OR sequential OR multimodal OR multidomain OR multicomponent*) of cognitive *(cognitive OR mental OR memory OR "executive functions" OR "video games")* and physical *(physical OR exercise OR motor OR mobility OR strength OR aerobic OR endurance OR* *cardiovascular OR kinetic OR kinect OR exergame*)* interventional studies *(training OR program OR intervention OR fitness OR activity)* conducted with older adults *(older OR elderly OR elderlies OR aging or ageing OR aged OR seniors).*

For the full search strategy see Appendix C.

Next, the electronic search was complemented by reviewing the reference lists of the retrieved articles and reviews and then hand-searching cited articles considered to be of interest. Titles and abstracts were first screened by two of the authors (JAR and MM), who then individually screened the full text of relevant articles. In the event of disagreement, a consensus was achieved following a discussion with JMR and SB. If the study was relevant for our analysis but the data necessary to calculate the effect sizes were missing, the authors were contacted via email to obtain the relevant data. Of the four datasets requested, two were provided by the authors. The two remaining datasets were not provided by the authors, so we resorted to extracting the data from the graphs provided in the papers using the online tool WebPlotDigitizer version 4.3.

2.2 Selection criteria

We restricted inclusion in this review to research articles written in English and published in peer-reviewed journals. They also had to meet the following criteria:

(A) **Study participants**: Healthy older adults (mean age 60 years or older) with no known cognitive impairment or other mental illness or neurological disorder including depression, stroke, dementia, or Parkinson's disease. Studies involving both healthy and cognitively impaired older adults (with mild cognitive impairment or dementia) were only included if the results for the healthy sample were reported separately. In that case, we only used data from the healthy sample.

(B) **Combined interventions**: The studies included at least one combined physical and cognitive training group.

(C) **Comparison groups**: Studies were considered when they included, in addition to the combined training group, at least one of the following: (a) a single-physical exercise group; (b) a single-cognitive training group; (c) a passive control group (e.g., waiting list, business as usual); (d) an active control group (alternative interventions, such as leisure activities, health education or toning exercises).

(D) **Equivalent training components**: when the comparison groups consisted of single physical and/or single-cognitive training, only those studies in which the training components of the combined and the single-component training were identical (i.e., the same dosage of aerobic exercise, strength, or balance training) were included.

(E) **Study design:** We included only intervention studies with pre/post assessments of cognitive outcomes, excluding single-session trials (e.g., studies with only a post-test assessment). The studies could be randomized controlled trials (RCT), cluster-RCT, or non-RCT.

(F) **Descriptive statistics**: Studies were included if they provided the statistics needed to compute the *g* effect size index and its confidence interval or provided sufficient information to calculate at least one effect size for at least one cognitive outcome measure.

(G) The outcome measures assessed cognitive or physical functions objectively, as described in more detail below.

2.3 Data extraction

2.3.1 Outcome measures

The cognitive outcomes included objectively assessed cognitive domains of processing speed, attention, memory, executive control, verbal abilities, global cognition, as well as composite scores from test batteries. Processing speed included tests that measured reaction times. Attention included divided, selective, and sustained attention measures. The classification of executive functions assessments was based on published factor analyses (e.g., Miyake et al., 2000; Friedman & Miyake, 2004) and included tests that measured working memory, inhibition, and flexibility. Memory included short- and long-term memory tests. Language included assessments of verbal, categorical, and phonological fluency. Global cognition comprised the results of cognitive screening tools, and lastly, composite scores included z-scores from test batteries.

Objectively assessed physical measures were classified into fitness, strength, and balance. In the case of dual-task paradigms (the simultaneous performance of a physical and a cognitive task), we only computed the scores of the cognitive task, but not the physical scores. Given the close relationship between balance and gait, we coded gait parameters within the balance category, such as stride variability or step length. Results of simple motor reaction time tests were not included.

When authors provided the results of subcategories of screening tools (e.g., MMSE), we only coded the global score within the category "global cognition". Several studies included combined interventions with and without other treatments. In this case, we only computed the combined training group that did not receive other treatments. When a study included additional training groups whose training components differed from those of the combined group, we only computed the data from equivalent groups.

When a test was tailor-made or unusual, we analyzed the task paradigm in detail by examining the procedures, item-specific analyses, and online and graphic material. For a detailed description of the tests used in each study, see supplemental material S2.

2.3.2 Moderators

(a) *Mode of delivering the combined training (simultaneous, sequential, and separate).* Simultaneous training included interactive interventions, such as exergaming (e.g., pedaling and steering a bicycle in a virtual world and attainment of goals), body-mind activities in psychomotor modality, in which the cognitive training is performed while carrying out physical movements, and dual-task interventions, in which cognitive and physical components are typically separate tasks but performed at the same time. Combined interventions in sequential mode included cognitive and physical exercises performed one after the other in the same session. For combined interventions in the separate mode, the two training components were delivered on different days of the week. In square stepping exercise (SSE), the cognitive demands depend on the difficulty of the foot placement patterns being performed and progression through the stepping protocols. At beginner levels, as in Gill et al. (2016), the activity can be conceptualized as a lower extremity coordination exercise, and we considered it a physical component. In SSE with increasingly more complex stepping patterns, as in Schoene et al. (2015), the activity can be conceptualized as a visuospatial working memory task requiring a stepping response and considered a simultaneous cognitive-physical intervention. (b) *Aerobic vs non-aerobic exercise.* The aerobic intensity was classified according to the information provided by the authors. Low aerobic exercises such as walking or light group activities (e.g., catching balls) were classified as non-aerobic. (c) *Type of cognitive training.* Cognitive training was categorized either as computer training (commercial videogames or tailor-made computer tasks), interactive training (dual-task paradigms in which the cognitive training part is intrinsically associated with a motor response, as in exergames, square stepping, etc.), or multicomponent training (which could be either a mixture of different training modalities, such as paper-pencil tasks, computer games, verbal exercises, etc., or only verbal exercises, such as counting backward, naming words, etc.). Other moderators were: (d) *Number of training sessions*; (e) *Intervention length in weeks*; (f) *Minutes of training per week*; (g) *Study quality*; (h) *Mean age and its standard deviation (SD),* and (i) *Year of publication*. A couple of studies did not report the precise number, duration, and/or frequency of training sessions, but only minimum and maximum values; in these cases, we coded the mean value of each group.

2.4 Assessment of methodological quality

Two authors (SB and MM) independently conducted a qualitative assessment of the methodological quality of the studies included in this review using the Standard Quality Assessment Checklist (Kmet et al., 2004). In this checklist tool, the maximum score for study quality is 28. Methodological quality is considered excellent if the score is > 80%, good if it is 70–79%, fair if it is 50–69%, and poor if it is < 50%. When there was a disagreement in scoring a study, the authors discussed the matter until they reached an agreement. For a detailed description of the quality assessment of the reviewed articles, see Table 3 of Appendix C.

2.5 Interrater reliability

The studies were coded by two independent reviewers (JAR and JMR). Disagreements were solved by discussion. When this process was finished, a third reviewer (MM) randomly selected and coded ten studies from the whole set, and interrater reliability for this subset of studies was calculated. Cohen's Kappa for the categorical variables and intraclass correlations for continuous variables ranged from .94 (classification of measured functions) to 1 (research design).

2.6 Effect sizes

To quantify the differential training effect of combined versus cognitive and/or physical training alone, and/or active/passive control on cognitive and physical outcome measures, we computed the standardized mean differences of effect sizes and their variance for each physical and cognitive outcome of the original papers using the formula

$$g = [c_m]\left[\frac{\left(\bar{y}_{Post}^{Exp.} - \bar{y}_{Pre}^{Exp.}\right) - \left(\bar{y}_{Post}^{Cont.} - \bar{y}_{Pre}^{Cont.}\right)}{S_{pooled}}\right]$$

$$S_{pooled} = \sqrt{\frac{\left(n_{Exp.} - 1\right)\left(S_{Pre}^{Exp.}\right)^2 + \left(n_{Cont.} - 1\right)\left(S_{Pre}^{Cont.}\right)^2}{n_{Exp.} + n_{Cont.} - 2}}$$

$$c_m = \left[1 - \frac{3}{4\left(n_{Exp.} + n_{n_{Cont.}}\right) - 9}\right]$$

where $\bar{y}_{Post}^{Exp.}$ and $\bar{y}_{Pre}^{Exp.}$ are the experimental group posttest and pretest means, $(S_{Pre}^{Exp.})^2$ is the variance of the pretest scores, c_m is a bias correction factor inversely proportional to the sample size, $n_{Exp.}$ is the sample size of the experimental group, and $\bar{y}_{Post}^{Cont.}$, $\bar{y}_{Pre}^{Cont.}$, $(S_{Pre}^{Cont.})^2$, $n_{Cont.}$ are the corresponding values for the comparison group. As we used a bias correction factor, the Standardized Mean Difference (*SMD)* computed was thus

Hedge's g instead of Cohen's d. The standard deviation of Hedge's g was computed with the following equation:

$$S_g = \sqrt{c_m^2\left(\frac{n_{Exp.} + n_{Cont.}}{n_{Exp.} \cdot n_{Cont.}}\right)\left(\frac{n_{Exp.} + n_{Cont.} - 2}{n_{Exp.} + n_{Cont.} - 4}\right)\left(1 + \frac{(n_{Exp.} \cdot n_{Cont.})g^2}{n_{Exp.} + n_{Cont.}}\right) - g^2}$$

Each study usually included several dependent variables for the same outcome, either because the experiment produced several dependent variables for the same task (e.g., reaction times (RT), error rates, delayed and immediate recall, etc.), or because different assessment tools were used to evaluate the same function. We computed at least two effect sizes (ES) for each dependent variable reported in the original articles: one for the effect of the combined cognitive-physical treatment, and one for the single-cognitive and/or the single-physical and/or the active and/or passive control group. In all cases, the means and sample sizes for the combined group were the same, and only the means and sample sizes for the three possible comparison groups (cognitive, physical, and control) differed. This indicates that these ES had dependence between them stemming from two sources: several ES were computed from the same original study (for different dependent variables), and they used a common group (the combined group) as a reference point to compute ES.

2.7 Statistical analyses

Modeling ES using a three-level structure is a better approach than a two-level structure when there are several dependent effect sizes in each independent study, but only if the heterogeneity of the sampling variance is substantial. In three-level meta-analytic models, three different sources of variance are modeled: the third level describes the variance of effect sizes between studies (between-study), the second level describes the variance of effect sizes of the experiments, or measurements nested within each study (within-study), and the first level describes the sample variance. We performed the multilevel random-effects analysis with and without moderators using restricted maximum likelihood estimation. This analytical solution was specifically designed to account for the non-independence among ES, and it was the preferred methodology as the sampling variability was not too high. Heterogeneity among our effect sizes was assessed using the Q statistic. A large Q-value indicates that differences between ES do not derive from a common population mean from the original study samples but are accounted for by other reasons. The Q statistic is distributed as a χ^2 distribution. Statistical analysis was performed using the rma.mv function of the metafor package (version 2.4) (Viechtbauer, 2010) within the R software environment (version 4.0.1; Core Team 2021). We followed the analytical steps presented by Assink and Wibbelink (2016). Dot-plot figures were depicted using Mathematica (version 10.4) with software developed specifically for this study.

2.8 Outlier analysis

Outliers or influential cases are considered cases that could distort the results in one or another direction. We performed outlier and influential case diagnostics using the *influence* function of the metafor package. This function calculates the influence of deleting one case at a time on the model fit or the fitted/residual values, based on several indices: the externally standardized residual, DFFITS value, Cook's distance, covariance ratio, the leave-one-out amount of (residual) heterogeneity, the leave-one-out test statistic of the test for (residual) heterogeneity, and DFBETAS value(s). In one study, the identified influencer cases constituted the only cognitive effect sizes (Norouzi et al., 2019). Regarding the follow-up outcomes, the influence function suggested deleting all cases belonging to one specific study. Given that according to the metafor package description, the chosen cut-offs are (somewhat) arbitrary, and that substantively informed judgment should always be used when examining the influence of each case on the results, we decided not to use this function for the follow-up cases but base our decisions on the visual inspection of funnel plots. Table 4 of Appendix C summarizes the cases that were detected and removed from the database before the meta-analysis.

2.9 Publication bias

Despite our comprehensive review and systematic search strategy, it is possible that some studies were missed due to publication bias. Generally, studies that fail to produce significant results are either not submitted for publication by the authors or rejected by the editors or reviewers. This could lead to bias towards the publication of significant statistical effects, something known as the "file-drawer problem". Although there are many ways to estimate publication bias (Rothstein et al., 2006), most do not apply to multilevel studies due to dependent effect sizes. We addressed this issue with several procedures. First, we visually inspected the funnel plots of cognitive and physical functions. In the funnel plots, effect sizes were charted against the standard error around the estimated summary effect of cognitive and physical ES. An asymmetric funnel plot (e.g., usually an under-representation of non-significant and/or negative effects on the bottom left side of the plot) would suggest the existence of publication bias. To test the statistical significance of the plots, we applied Egger's test (Egger et al., 1997), which analyzes whether the standardized effect sizes can predict study precision (defined as the inverse of the standard error) in a linear regression. Furthermore, we generated fail-safe numbers (i.e., the number of non-significant ES needed to change a significant into a non-significant result) following different approaches (Orwin, 1983; Rosenberg et al., 2005; Rosenthal, 1979). Finally, we used the trim-and-fill method of Duval and Tweedie (2000a, 2000b) to determine how many ES would need to be imputed to restore the symmetry of the funnel plot.

3. Results

3.1 Search results

The initial search yielded 6,457 studies. After excluding duplicates and studies that did not meet the inclusion criteria, 50 studies were included in the analysis. **Figure 1** shows the PRISMA flow diagram of the systematic search and study selection.

3.2 Descriptive results: studies and participant characteristics

In most studies, there was more than one outcome measure. After removing 26 outliers (3.21%), our meta-analysis included a total of 783 effect sizes, of which 697 corresponded to pre-post assessments and 86 to pre/follow-up assessments. **Table 1** shows the descriptive data of all the primary studies included in our analysis. The eligible studies were published up to February 2021. The largest number of published studies was in 2015 with 10 studies, followed by 2017, 2020, and 2014 (7, 6, and 5 published studies, respectively). Four studies were published in 2012 and 2018, three in 2012 and 2021, and two in 2009 and 2016. In 2002, 2006, 2011, and 2019 there was just one published study per year. The countries with the largest number of published studies were Japan and USA

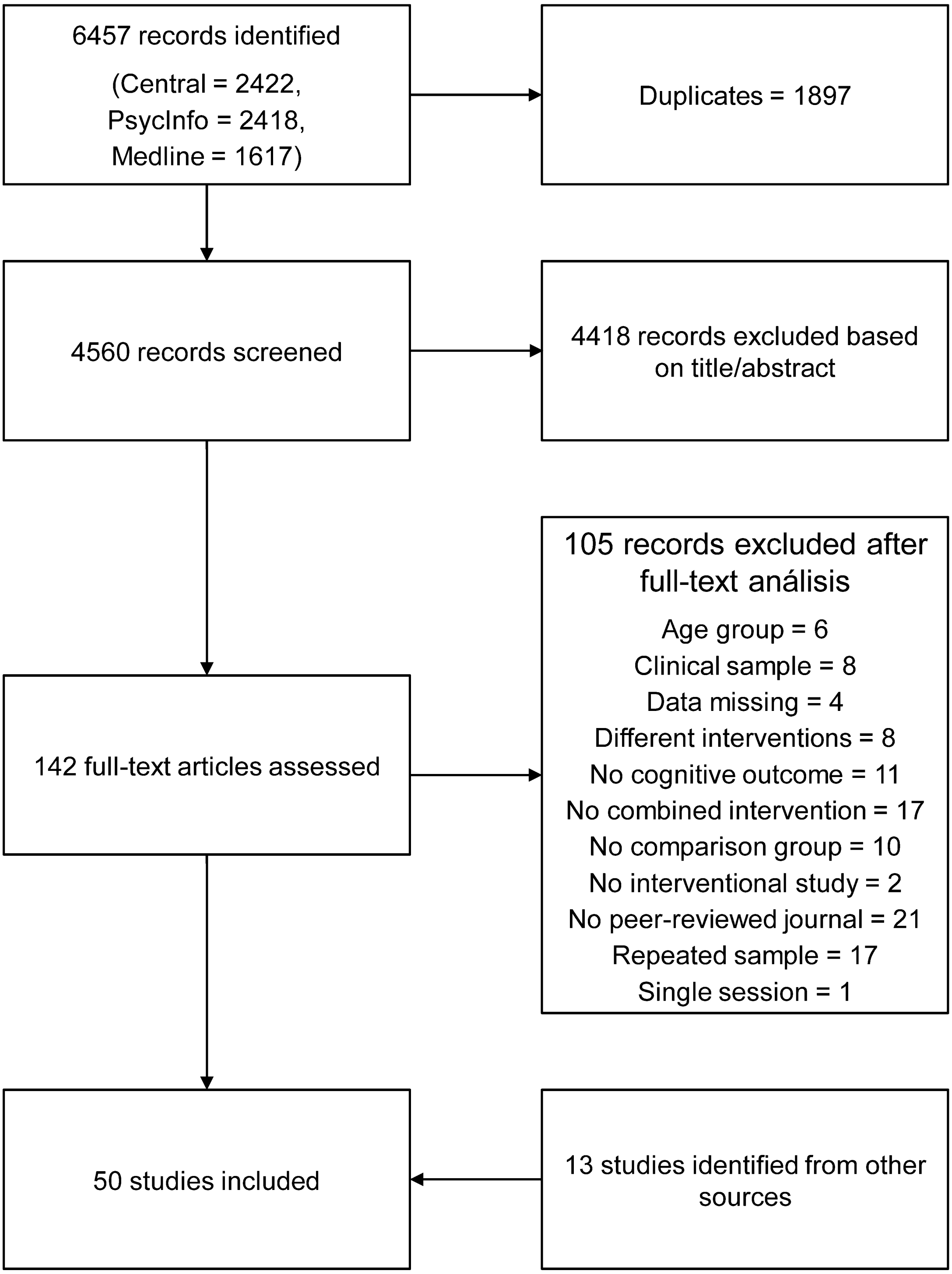

Figure 1. PRISMA flow diagram of the search strategy.

with six studies each, followed by Germany with five studies, and Switzerland and France with four studies each, Australia, and Canada with three studies each, Brazil and Thailand with two studies, and China, Finland, Greece, Iran, Italy, Mexico, Myanmar, Portugal, Singapore, South Korea, Spain, and Tunisia with one study each. Two studies were multisite, participating Italy, Greece, Spain, and Serbia in one, and Spain, Germany, and Australia in the other study. A total of 6,164 healthy older adults participated in the 50 studies with a mean age of 72.12 (*SD* = 4.51) years. Bamidis et al. (2015) did not report the mean age, but their participants were older than 55 years, so the mean age was computed over 50 studies. The number of participants in each study ranged from 13 (You et al., 2009) in a pilot study to 1,190 (Ngandu et al., 2015) with a global mean of 123.93 (*SD* = 201.86). Of all studies, six studies included a follow-up assessment. However, as the total of follow-up outcomes only summed up 86 effect sizes, these were only analyzed in a summary fashion and not by cognitive or physical functions. Twenty-seven studies reported a comparison of combined training *vs* active or passive control (*n* = 4,555), nine studies compared combined training with single cognitive training (*n* = 441), and 14 studies compared combined training with single physical training (*n* = 1,168). Two studies included two types of combined training compared with a control group (Wollesen et al., 2017) and single cognitive training (Yu et al., 2021). The combinatory mode for the combined groups was sequential (13 studies, *n* = 1,780), separate (9 studies, *n* = 2 760), or simultaneous (28 studies, *n* = 1,624). The total duration of the intervention ranged from 4 weeks (Norouzi et al., 2019 and Wongcharoen et al., 2017) to 144 weeks (Andrieu et al., 2017) with a global mean of the duration of 20.29 weeks (*SD* = 26.04). The total number of training sessions ranged from 8 (Kitazawa et al., 2015) to 745 (Andrieu et al., 2017), with a global mean of 61.9 sessions (*SD* = 124.05). The duration (in minutes) of cognitive intervention sessions ranged from 30 (Linde & Alfermann, 2014; Schoene et al., 2013; Van het Reve & de Bruin, 2014) to 360 (Pieramico et al., 2012; Shah et al., 2014), with a global mean of 114.8 minutes per week (*SD* = 64.46). The duration of physical intervention sessions ranged from 40 (Schoene et al., 2013) to 250 minutes (Shah et al., 2014), with a mean duration of 118.31 minutes (*SD* = 49.40). The studies varied in the type of physical training, and in 38 studies, the training included fitness, and/or balance, and/or strength. The aerobic exercise intensity was moderate to high in 17 studies (*n* = 1,235) and low to none in 29 (*n* = 3,176) studies. In four studies, it was not possible to determine the aerobic exercise intensity. Cognitive training included a variety of exercises (memory, planning, reasoning, visuospatial skills, attention, switching tasks, arithmetic, verbal fluency, problem-solving, and other cognitive tasks). In 15 studies (*n* = 650) the cognitive training was performed interactively (exergames, psychomotor exercises, and square stepping), in 17 studies (*n* = 3,197) via computer games or computer tasks, and in 18 studies (*n* = 2,317) via a multicomponent training (paper-pencil tasks, group games, verbal games, etc.) or verbal exercises. Outcome measures varied across the studies, with most of the studies assessing several cognitive functions, such as attention, switching, executive functions, processing speed, memory, and global cognition (see Table 2 of Appendix C), as well as physical outcomes, such as strength, endurance, frailty, gait, balance, risk of falls, functional mobility or VO_2max.

Table 1. Study designs and descriptive data of the primary studies included in the meta-analysis.

Study	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention			Aerobic intensity	Combinatory mode	Setting	Control activities	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions					
Adcock et al., 2020	Switzerland	31	EI-CI (15, 77) PC (16, 71)	48	16	-	Square stepping, 3 d/wk	95	EF, attention	Tai Chi-inspired movements and dancing 3 d/wk	105	Strength, balance, fitness	Low	Simultaneous	Individual	-	**Cognitive**: EF, PS, memory **Physical**: balance (gait), fitness
Anderson-Hanley, et al., 2012	USA	63	EI-CI (30, 76) EI (33, 82)	36	12	-	Exergames 3 d/wk, 2 months	135	Not clear	Stationary bicycle riding at 60% HRmax 3 d/wk for 3 months	135	Fitness	Moderate	Simultaneous	Individual	-	**Cognitive**: EF, global cognition, attention, language, memory
Andrieu, et al., 2017	France	722	EI-CI (356, 75) PC (366, 75)	745	144	-	Multicomponent exercises 1.5 d/wk during the first two months, 1 d/every 3rd mo. for the rest of the trial.	90	ES, PS, memory	Personalized home-based exercise program 5 d/wk	150	Fitness, balance, strength	Low	Separate	Mixed	-	**Cognitive:** global cognition, memory, PS language, attention, EF **Physical**: fitness
Bamidis, et al., 2015	Greece	90	EI-CI (69, n/a) PC (21, n/a)	37 CI: 14, EI:23	9	-	Computerized cognitive training (Posit Science), 3 d/wk	180	EF, memory	Exergames (FitForAll for Wii) at 55 – 85% HRmax, 2.3 d/wk	120	Fitness, balance, strength	Moderate	Not clear	Group	-	**Cognitive**: composite score of EF and memory
Barban et al., 2017	Italy, Greece, Spain, Serbia	481	EI-CI (121, 75) EI (119,76) CI (118, 74) CC (123, 76)	24	12	12	Computerized cognitive training 2 d/wk	EI-CI:60 CI:120	EF, memory	Supervised structured exercise program with i-walker. 2 d/wk	EI-CI:60 EI:120	Balance, fitness	Low	Sequential	Mixed	CC: entering data into computer	**Cognitive**: memory
Desjardins, et al., 2016	Canada	76	EI-CI (22, 73) EI-CC (16, 71) EC-CI (20, 73) EC-CC(18, 73)	36	12	-	Computer tasks 1 d/wk	60	EF, attention	Supervised structured exercise program and treadmill walking 2 d/wk	120	Fitness, strength	Moderate	Sequential	Group	EC: Stretching, toning CC: Computer lessons	**Cognitive**: ES, memory, PS **Physical**: fitness, balance, strength
Eggenberger, et al., 2015	Switzerland	47	EI-CI (22, 79) EI (25, 81) DANCE not incl.	52	26	24	Computer tasks 2 d/wk	120	Memory	Structured exercise program and treadmill walking 2 d/wk	120	Fitness, strength, balance	Moderate	Simultaneous	Mixed	-	**Cognitive**: memory, attention, EF, PS
Fabre, et al., 2002	France	32	EI-CI (8, 65) CI (8, 68) EI (8, 65) AC (8, 66)	24	8	-	Multicomponent exercises 1 d/wk	90	Memory, attention, language	Supervised outdoor interval training at ventilatory threshold 2 d/wk	120	Fitness	Moderate	Separate	Group	AC: leisure activities	**Cognitive**: memory **Physical**: fitness
Gill, et al., 2016	Canada	44	EI-CI (23, 73) EI (21, 75)	78	26	-	Verbal exercises 3 d/wk	45	EF, language	Structured aerobic exercise at 70-85% HRmax and beginner-level square stepping 3 d/wk	120	Fitness	Moderate	Simultaneous	Mixed	-	**Cognitive**: EF, PS, memory, language

Table 1 (continued)

Study	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention			Aerobic intensity	Combinatory mode	Setting	Control activities	Outcome measures
							Description	**min/wk**	**Trained functions**	**Description**	**min/wk**	**Trained functions**					
Gschwind et al., 2015	Spain, Germany, Australia	153	EI-CI (78, 75) PC (75, 75)	42	16	-	Computerized exercises 2.5 d/wk	100	EF, attention	Individualized training protocol embedded in home-based exergames 2.5 d/wk	112	Strength, balance	None	Simultaneous	Individual	-	**Cognitive**: EF, PS, attention. **Physical**: balance, fitness, strength
Hiyamizu, et al., 2012	Japan	36	EI-CI (17, 73) EI (19, 71)	24	12	-	Verbal exercises 2 d/wk	120	EF, attention, language	Supervised structured exercise program 2 d/wk	120	Strength, balance	None	Simultaneous	Group	-	**Cognitive**: EF, PS **Physical**: balance, strength
Htut, et al., 2018	Myanmar	42	EI-CI (21, 76) PC (21, 76)	24	8	-	Exergames 3 d/wk	90	PS, attention	Exergames 3 d/wk	90	Balance, fitness	Low	Simultaneous	Individual	-	**Cognitive**: global cognition **Physical**: balance, strength
Jardim, et al, 2021	Brazil	72	EI-CI (41, 67) PC (31, 68) EI + CI not incl..	24	12	-	Verbal exercises, psychomotor tasks 2 d/wk	150	EF, memory, attention, language	Supervised structured exercise program at 60-70% HRmax 2 d/wk	150	Fitness, balance, strength	Moderate	Simultaneous	Group	-	**Cognitive:** memory, attention **Physical:** fitness, balance, strength
Jehu, et al., 2017	Canada	41	EI-CI (14, 69) EI (15, 70) PC (12, 66)	36	12	12	Verbal exercises 3 d/wk	180	EF, language	Supervised structured exercise program 3 d/wk	180	Balance	None	Simultaneous	Individual	-	**Cognitive**: EF **Physical**: balance
Joubert, & Chainay, 2019	France	48	EI-CI (16, 69) PC (16, 70) CI (16, 70)	16	8	4	Home-based computerized cognitive training (HAPPY neuron Professional) EI-CI: 1 d/wk CI: 2 d/wk	EI-CI:60 CI:120	EF	Supervised treadmill walking 1 d/wk	60	Fitness	Moderate	Separate	Individual	-	**Cognitive**: EF, language
Kitazawa, et al., 2015	Japan	60	EI-CI (30, 77) PC (30, 76)	8	8	-	Square stepping 1 d/wk	60	Memory	Supervised square stepping 1 d/wk	60	Fitness, balance	Low	Simultaneous	Group	-	**Cognitive**: global cognition, memory **Physical**: balance
Laatar, et al., 2018	Tunisia	24	EI-CI (12, 66) EI (12, 68)	72	24	12	Verbal exercises, psychomotor tasks 3 d/wk	180	EF, memory, attention	Supervised structured exercise program 3 d/wk	180	Strength, balance	None	Simultaneous	Group	-	**Cognitive**: PS **Physical**: fitness, balance (gait), strength
Legault, et al., 2011	USA	67	EI-CI (18,75) CI (16, 76) EI (16, 78) AC (17, 77)	56	16	-	Center-based computer tasks 1,5 d/wk	100	Memory	Center-based and home-based exercises including walking or stationary cycling 2 d/wk	150	Fitness	Moderate	Separate	Mixed	AC: Health education	**Cognitive**: EF, memory
Linde, et al., 2014	Germany	55	EI-CI (16, 66) EI (15, 68) CI (11, 67) PC (13, 67)	32	16	12	Multicomponent exercises 1 d/wk	30	EF, PS, memory, attention	Supervised structured exercise program at 40% to 70% HRmax. 2 d/wk	120	Fitness, strength	Moderate	Sequential	Group	-	**Cognitive**: EF, memory, attention, PS **Physical**: fitness

Study	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention			Aerobic intensity	Combinatory mode	Setting	Control activities	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions					
Maillot, et al., 2012	France	30	EI-CI (15, 74) PC (15, 74)	24	12	-	Exergames 2 d/wk	120	Not clear	Wii exergames 2 d/wk	120	Fitness, balance	Not clear	Simultaneous	Not clear	-	**Cognitive**: EF, PS **Physical**: fitness, strength
Marmeleira, et al., 2009	Portugal	32	EI-CI (16, 68) PC (16, 68)	36	12	-	Psychomotor tasks 3 d/wk	180	EF, PS, attention	Psychomotor responses to cognitive demands (walking, catching balls, etc.) 3 d/wk	180	Fitness	Low	Simultaneous	Group	-	**Cognitive**: attention, EF, PS **Physical**: fitness, balance
McDaniel, et al., 2014	USA	79	EI-CI (19, 65) EI-CC (23, 67) CI-EC (18, 64) CC-EC(19, 64)	96	24 (CI: 2 EI: 6)	-	Multicomponent exercises 3 d/wk	180	EF, memory, attention	Supervised treadmill walking or stationary cycling at 50% to 85% HRmax. 3 d/wk	180	Fitness	Moderate	Sequential	Group	EC: Flexibility CC: Health education	**Cognitive**: attention, memory **Physical**: VO_2peak
Morita, et al., 2018	Japan	19	EI-CI (8, 75) PC (11, 72)	96	96	-	Verbal exercises, psychomotor tasks 1 d/wk	60	EF, memory, language	Supervised structured exercise program 1 d/wk	60	Fitness, strength	Low	Simultaneous	Group	-	**Cognitive**: global cognition **Physical**: strength, fitness, balance
Ng, et al., 2017	Singapore	197	EI-CI (49, 70) EI (48, 70) CI (50, 70) AC (50, 70)	30	24	24	Multicomponent exercises 120 min, 1 d/wk for 12 weeks plus 6 booster sessions	120	EF, PS, attention, memory, language	Structured exercise program center-based:2 d/wk for 12 weeks; 12 wk. home-based sessions; number not clear.	180	Strength, balance	None	Separate	Mixed	AC: Leisure activities	**Cognitive**: global cognition, memory, language, attention, EF
Ngandu, et al., 2015	Finland	1190	EI-CI (591, 70) AC (599, 69)	538	96	-	10 group-based sessions on memory and reasoning strategies, and 2 x 6 months 72 (10-15 min, 3 d/wk) home-based, computerized training.	37	EF, PS, memory, attention	Center-based supervised, structured, and individualized exercise program 3-5 d/wk	not clear	Fitness, strength	Not clear	Separate	Mixed	AC: Health education	**Cognitive**: global cognition, EF, PS, memory
Nilsson et al., 2020	Sweden	73	EI-CI (25, 70) CI (21, 71) EI (27, 70)	30	12	-	Computerized working memory training 2.5 d/wk	75	EF	Supervised interval training on stationary bikes at 65 to 75% HRmax. 2.5 d/wk	90	Fitness	Moderate	Sequential	Group	-	**Cognitive**: EF, PS, memory, language
Nishiguchi, et al., 2015	Japan	48	EI-CI (24, 73) PC (24, 74)	12	12	-	Verbal exercises, psychomotor 1 d/wk	60	EF, language	Group classes with music soundtrack 1 d/wk	90	Fitness, strength	Not clear	Simultaneous	Group	-	**Cognitive**: global cognition, memory, EF **Physical**: fitness, balance, strength

Study	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention			Aerobic intensity	Combinatory mode	Setting	Control activities	Outcome measures
							Description	**min/wk**	**Trained functions**	**Description**	**min/wk**	**Trained functions**					
Nocera et al., 2020	USA	37	EI-CI (13, 72) EI (12, 70) CI-EC (12, 73)	36	12	-	Computerized cognitive training (Mindfit) 3 d/wk	60	EF and "other processes"	Supervised stationary bicycle riding at 50 to 75% HRmax. 3 d/wk	135	Fitness	Moderate	Sequential	Group	EC: Stretching	**Cognitive**: EF, memory, language, PS **Physical:** fitness, balance (gait)
Norouzi, et al., 2019	Iran	40	EI-CI (20, 69) AC (20, 68) EC not incl.	12	4	12	Verbal and visual tasks 3 d/wk	210	EF, memory	Supervised strength training using an isokinetic exercise device. 3 d/wk	210	Strength	None	Simultaneous	Group	AC: group discussions	**Cognitive**: EF, memory **Physical**: strength
Oswald, et al., 2006	Germany	196	EI-CI (24, 80) EI (29, 80) CI (46, 80) PC (97, 80)	30	48	48	Multicomponent exercises 1 d/wk	45	Memory, attention, PS	Supervised exercise program including gymnastics, dance, games, tennis skills, etc. 1 d/wk	45	Balance, fitness	Low	Sequential	Group	-	**Cognitive**: composite score from multiple test-domains **Physical**: composite score from multiple test-domains
Phirom et al., 2020	Thailand	39	EI-CI (19, 70) PC (20, 69)	36	12	-	Exergames 3 d/wk	180	EF, memory, attention	Center-based exergames (Xbox) 3 d/wk	180	Fitness, balance	Low	Simultaneous	Group		**Cognitive**: global cognition **Physical**: balance, strength
Pieramico, et al., 2012	Italy	30	EI-CI (15, 68) PC (15, 68)	144	24	-	Home-based cognitive activities 5 d/wk, and group activities 120 min, twice a month	300	Not clear	Structured home-based walking and dancing 2 d/wk	120	Fitness	Low	Separate	Mixed	-	**Cognitive**: global cognition, EF, memory, language, PS
Rahe, et al., 2015a	Germany	45	EI-CI (25, 68) CI (20, 68)	14	7	-	Multicomponent exercises 2 d/wk	140	Memory, EF, attention	Group classes and home exercises (walking, taking stairs) 2 d/wk	40	Fitness, balance, strength	Low	Sequential	Group	-	**Cognitive**: global cognition, memory, EF, language, attention **Physical**: fitness, strength
Rahe, et al., 2015b	Germany	30	EI-CI (15, 67) CI (15, 66)	13	6.5	48	Multicomponent exercises 2 d/wk	190	Memory, EF, attention	Supervised structured exercise program 2 d/wk	40	Fitness, balance, strength	Low	Sequential	Group	-	**Cognitive**: global cognition, EF, language, attention
Raichlen, et al., 2020	USA	51	EI-CI (12, 68) EI (17, 68) CI (10, 66) AC (12, 69)	36	12	-	Computerized cognitive training 3 d/wk	90	EF, PS, memory,	Supervised stationary bicycle riding at 40% to 80% HRmax 3 d/wk	90	Fitness	Moderate	Simultaneous	Group	AC: watching videos	**Cognitive**: EF **Physical**: balance (gait)
Romera-Liebana, et al, 2018	Spain	352	EI-CI (176, 77) PC (176 (77)	24	12	18	Multicomponent memory and verbal training 2 d/wk	180 (6 wks)	Memory, language	Supervised structured exercise program 2 d/wk	120 (6 wks)	Fitness, balance, strength	Not clear	Separate	Group	Nutritional supplement	**Cognitive**: memory, language **Physical**: fitness, balance, strength

Study	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention			Aerobic intensity	Combinatory mode	Setting	Control activities	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions					
Salazar-González, et al., 2014	Mexico	286	EI-CI (143, 71) PC (143, 74)	36	12	-	Verbal exercises, psychomotor tasks 3 d/wk	60	EF	Supervised structured exercise program 3 d/wk	180	Fitness, balance, strength	Low	Simultaneous	Group	-	**Cognitive**: EF **Physical**: Balance (gait)
Schoene, et al., 2013	Australia	32	EI-CI (15, 78) PC (17, 78)	22	8	-	Home-based exergame (Stepmania) 1,5 d/wk	30	EF	Home-based exergames involving step exercises 1,5 d/wk	30	Fitness	Low	Simultaneous	Individual	-	**Cognitive**: PS, EF **Physical:** balance (+postural stability), strength
Schoene, et al., 2015	Australia	81	EI-CI (39, 83) PC (42, 81)	48	16	-	Home-based exergames (Stepmania, Trail-Stepping, Stepper, Tetris), 3 d/wk	60	EF, PS, attention	Home-based exergames involving step exercises 3 d/wk	60	Fitness	Low	Simultaneous	Individual	-	**Cognitive**: EF, PS
Shah, et al., 2014	Australia	172	EI-CI (44, 67) EI (42, 67) CI (51, 67) PC (35, 69)	160	16	-	Computerized cognitive training (Posit Science) 5 d/wk	300	Not clear	Supervised structured exercise program 5 d/wk	250	Fitness, strength	Low	Sequential	Individual	-	**Cognitive**: memory, language, PS, attention, EF **Physical:** fitness, strength
Shatil, et al., 2013	USA	122	EI-CI (29, 79) EI (31, 79) CI (33, 80) AC (29, 81)	96	16	-	Computerized cognitive training (CogniFit) 3 d/wk	120	EF, PS, attention, language, memory	Supervied structured exercise program (FitnessForever™) 3 d/wk	135	Fitness, strength	Low	Separate	Group	AC: book reading	**Cognitive**: Memory, attention, EF, PS
Takeuchi et al., 2020	Japan	93	EI-CI (30, 68) CI (30, 69) EI (33, 69)	36	12	-	Computerized cognitive training (Brain Age, Nintendo) 3 d/wk	180	EF	Center-based supervised stationary bike riding at 40-50% HRmax 3 d/wk	90	Fitness	Low	Simultaneous	Not clear	-	**Cognitive**: Memory, attention, EF, PS, language
Teixeira, et al., 2013	Brazil	41	EI-CI (21, 68) PC (20, 68)	48	16	-	Square stepping 3 d/wk	120	Attention, memory, EF	Supervised, structured square stepping exercises 3 d/wk	120	Strength, balance	None	Simultaneous	Group	-	**Cognitive**: global cognition, EF, memory, attention, PS
Theill, et al., 2013	Switzerland	51	EI-CI (18, 72) CI (12, 73) PC (21, 71)	20	10	-	Computerized working-memory training 2 d/wk	60	EF	Supervised center-based-treadmill walking at 60% to 80% HRmax 2 d/wk	80	Fitness	Moderate	Simultaneous	Not clear	-	**Cognitive**: attention, memory, EF, PS **Physical**: balance (gait)
Van Het Reve, & de Bruin, 2014	Switzerland	145	EI-CI (69, 81) EI (76, 82)	84	12	-	Computerized cognitive training (CogniPlus) 3 d/wk	30	Attention	Progressive strength training and balance training. 2 d/wk	80	Balance, strength	None	Sequential	Not clear	-	**Cognitive**: EF, attention **Physical:** balance (gait), fitness

Table 1 (continued)

Study	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention			Aerobic intensity	Combinatory mode	Setting	Control activities	Outcome measures
							Description	**min/wk**	**Trained functions**	**Description**	**min/wk**	**Trained functions**					
Wollesen, et al., 2017	Germany	83	EI-CI[b] (30, 70) PC[b] (18, 73) EI-CI[c] (15, 72) PC[c] (20, 72)	12	12	-	Psychomotor tasks 1 d/wk	60	EF, attention	Supervised walking exercises 1 d/wk	60	Fitness	Low	Simultaneous	Group	-	**Cognitive**: EF **Physical**: balance (gait), fitness
Wongcharoen et al., 2017	Thailand	45	EI-CI (15, 72) EI (15, 74) CI (15, 72) CI dual-task not incl.	12	4	-	Cognitive tasks 3 d/wk	180	Attention, memory, language	Home-based stance and gait activities 3 d/wk	180	Balance	None	Simultaneous	Mixed	-	**Cognitive**: EF, language **Physical**: balance (gait)
Yokoyama, et al., 2015	Japan	25	EI-CI (12, 74) EI (13, 74)	48	12	-	Verbal exercises, psychomotor tasks 3 d/wk	180	EF	Supervised structured exercise program 3 d/wk	180	Fitness, balance	None	Simultaneous	Group	-	**Cognitive**: global cognition, PS **Physical:** strength, fitness, balance
You, et al., 2009	South Korea	13	EI-CI (8, 68) EI-CC (5, 68)	18	6	-	Verbal exercises 3 d/wk	90	EF, memory	Supervised fast walking 3 d/wk	90	Fitness	Moderate	Simultaneous	Not clear	CC: Music	**Cognitive**: memory **Physical:** balance (gait)
Yu, et al., 2021	China	347	EI-CI[d] (117, 65) EI-CC (114, 64) EI-CI[e] (116, 64)	24	12	-	Computerized cognitive training (Brainastic) 2 d/wk	60	EF, memory, attention	Aerobic circuit and resistance training 2 d/wk	120	Fitness, strength	Moderate	Sequential	Group	CC: DVDs	**Cognitive**: global cognition, memory

3.3 Analysis of bias

A visual inspection of the funnel plot corresponding to cognitive pre-post outcomes (number of effect sizes (k) = 507) revealed asymmetry with larger effect sizes on the right lower side of the plot, which was confirmed by the Egger's regression test ($z = 4.108$,$p < 0.001, \beta = -0.024$, 95% CI $[-0.112, 0.064]$). This test is identical to regressing effect sizes on standard errors, where weights are inversely proportional to the variance of effect sizes. In the Egger´s test a significant positive intercept means that smaller studies with less precision are associated with larger effects. The trim-and-fill method estimated that to restore symmetry are necessary to add 32 ES to the left side of the plot, which would reduce the estimated summary effect to 0.114 ($p < 0.001$, 95% CI $[0.083, 0.145]$). Even though smaller studies produced the largest effect sizes, the standard errors of effect sizes were represented uniformly in a range from 0.244 to 0.975, suggesting that the underrepresentation of negative results was not only a question of small-study effects (i.e., higher standard errors) but occurred in smaller as well as in larger samples (see **Figure 2a**). The results of the fail-safe tests indicated that it would need 21,678 ES (based on Rosenberg's approach) or 30 933 ES (following Rosenthal's approach) to increase the p value of an overall ES of 0.145 to above 0.05. According to Owen's approach, 507 ES would be necessary to reduce the average ES from 0.194 to .097.

Regarding physical functions (k = 203), the funnel plot also suggested an asymmetry skewed to the right. Again, Egger's test was significant ($z = 4.225, p < 0.001, \beta = 0.017$, 95% CI $[-0.103, 0.136]$), and the trim-and-fill method estimated that 27 ($p < 0.001$, 95% CI $[0.113, 0.234]$) ES should be added to restore the symmetry of the funnel plot, reducing the estimated summary effect to 0.174 (**Figure 2b**). In this case, the imputed effect sizes for the funnel plot to be symmetric were in a lower range of standard errors, indicating that especially negative results from studies with lower precision were needed to restore the symmetry. However, compared to the cognitive

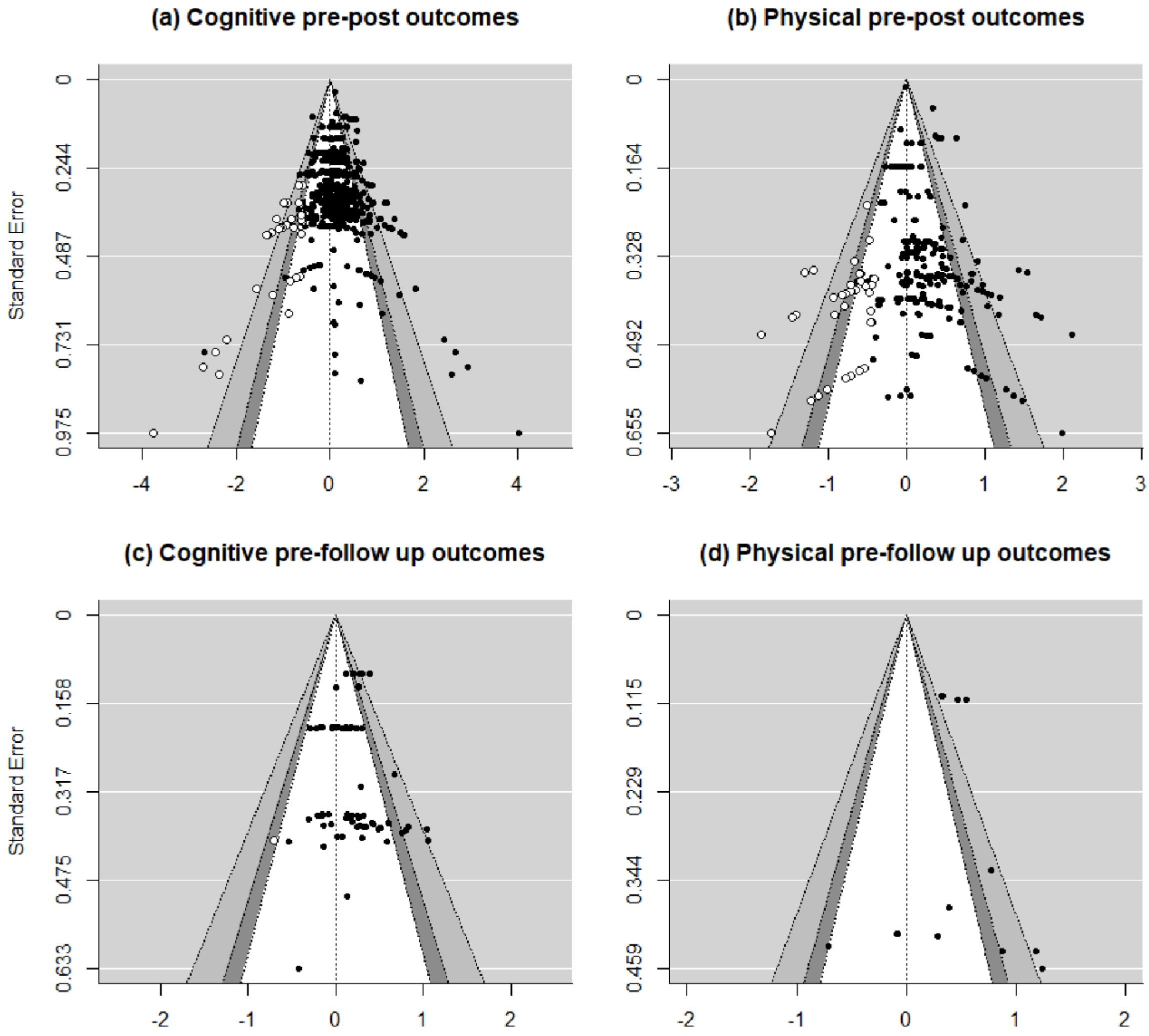

Figure 2. Funnel plots with ES on the X-axis and standard error of the ES on the Y-axis for the estimated summary effects of (A) cognitive, (B) physical pre-post outcomes, (C) cognitive, and (D) physical pre-follow up outcomes.

outcomes, the main amount of ES was in the middle of the plot, suggesting fewer studies with large samples in physical outcomes than in cognitive outcomes. To reduce the significance of an overall ES of 0.091 to a P level above 0.05, 13,326 ES would be needed taking Rosenthal's approach, or 3,540 ES taking Rosenthal's approach. According to Owen's approach, it would be necessary 203 additional ES to reduce the ES from 0.316 to 0.158.

In the case of cognitive pre/follow-up outcomes (k = 73) (**Figure 2c**), we detected no asymmetry, which was confirmed by a nonsignificant Egger's test ($z = 0.176$, $\text{n.s.}, \beta = 0.166, 95\%$ CI $[0.056, 0.277]$). The trim-and-fill method estimated that only one ES ($p < 0.001, 95\%$ CI $[0.12, 0.223]$) would be necessary to restore the symmetry of the funnel plot. According to Rosenberg, it would need 871 ES, and according to Rosenthal, 970 ES, to increase the P level of an average ES of 0.178 to above 0.05. Orwin's approach estimated that 73 ES studies would be necessary to reduce an average ES from 0.19 to 0.09.

Regarding physical pre/follow-up outcomes (**Figure 4d**), the results of the bias analysis should be taken with caution because of the reduced dataset (k = 13). Egger's test did not detect any asymmetry ($z = 0.117\ , \text{n.s}, \beta = 0.408, 95\%$ CI $[0.212, 0.6]$), and the fail-safe calculations indicated that it would be necessary 225 (Rosenberg) or 218 (Rosenthal) ES to reduce the statistical significance of an ES of 0.416 to above 0.05. According to Owen's approach, it would require 13 ES to reduce the estimated ES of 0.427 to 0.214. The trim-and-fill method estimated that no ES had to be added to restore the symmetry ($\text{n.s.}, 95\%$ CI $[0.309, 0.525]$).

3.4 Overall effect size

Figure 3 displays the summary effect of pre-post cognitive and physical outcomes by study. The estimated summary effect across all studies (n = 50) for pre-post comparison of cognitive outcomes (k = 507) was g = 0.22 ($p < 0.001$, 95% CI [0.152, 0.289]) (see **Table 2**). The summary effect of standardized mean differences differed significantly across groups ($F_{(2,\ 504)} = 11.588$, $p < 0.001$) and was highest for combined *vs* control comparisons ($g = 0.275$, $p < 0.001$, 95% CI [0.201,0.359]),

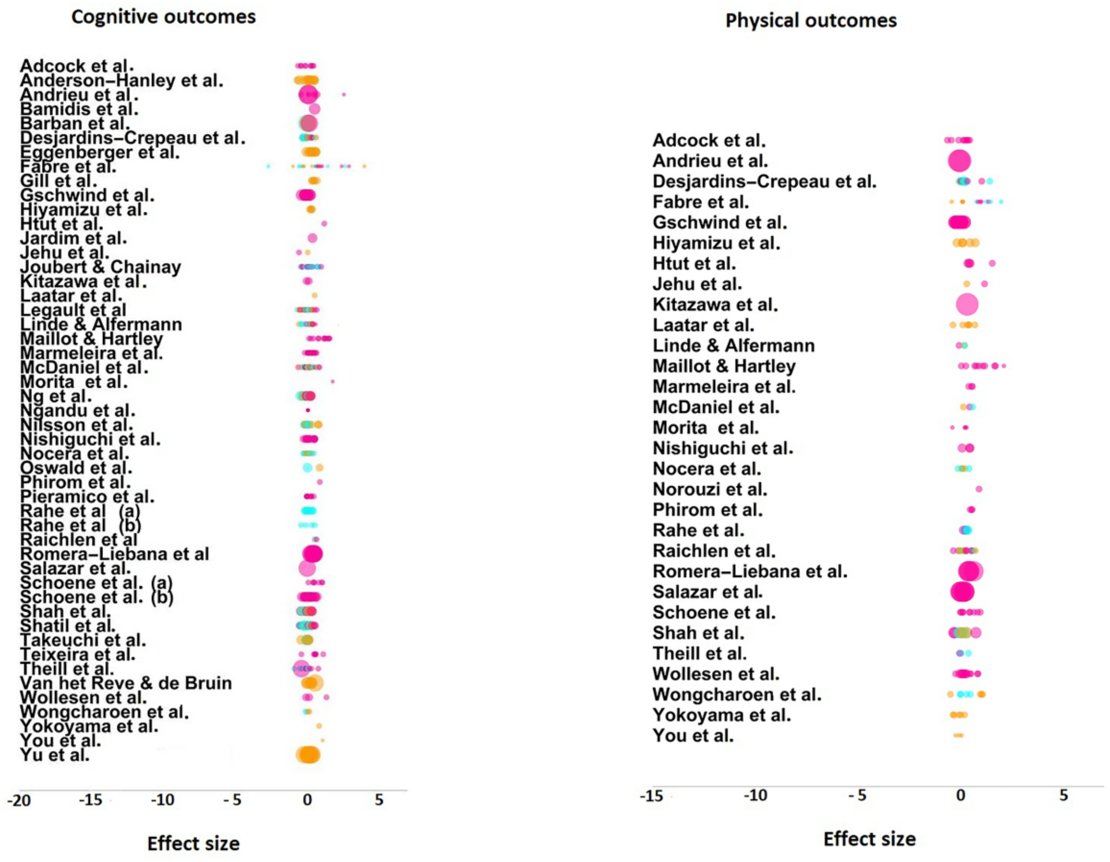

Figure 3. Dot-plot figures for effect sizes for cognitive outcomes and physical outcomes by primary studies. Pink dots represent combined training *vs* control, blue dots represent combined *vs* single cognitive training, and orange dots, combined *vs* single physical training. The size of the dot indicates the inverse of the ES variance scaled and represents the precision of the ES.

Table 2. Summary effect of pre-post and pre-follow up comparisons of pooled cognitive and physical differences of effect sizes respectively.

	Comparison	Level 2 variance (%)	Level 3 variance (%)	QE	# Studies	# ES	Mean difference in ES [95% CI]
Cognitive functions	Pre-post	0.005 (4.9)	0.041 (36.991) ***	791.173***	49	507	0.220 [0.152, 0.289]***
	Pre-follow up	0.000 (5.33e-09)	0.026 (35.619) ***	71.335	10	73	0.205 [0.073, 0.338]**
Physical functions	Pre-post	0.000 (7.65e-08)	0.045 (54.278) ***	424.825***	30	190	0.285 [0.192, 0.378]***
	Pre-follow up	0.003 (7.842)	0.00 (1.02e-07)	21.622*	4	13	0.417 [0.297, 0.538]***

Note. # Studies = Number of studies; # ES = Number of effect sizes; ES = Hedges' *g*; CI = Confidence interval; Level 2 variance = Variance in effect sizes within studies; Level 3 variance = Variance in effect sizes between studies; % = Proportion of the total variance of effect sizes attributed to this level; QE = test for heterogeneity in all effect sizes in the data set. * p < .05; ** p < .01; *** p < .001.

followed by combined *vs* single physical training ($g = 0.21\,, p < 0.001,$ 95% CI $[0.128, 0.291]$). On the other hand, the summary effect of cognitive outcomes for combined *vs* single cognitive training was similar (g = 0.083, n.s., 95% CI [-0.001, 0.169]). The summary effect for physical outcomes (k = 190) was 0.285 ($p < 0.001,$ 95% CI $[0.192, 0.378]$). Combined training produced a superior effect in all comparisons ($F_{(2,\ 187)} = 0.886, \text{n.s.}$), which was highest when compared to single cognitive training ($g = 0.33\,, p < 0.001,$ 95% CI $[0.171, 0.489]$), followed by the comparison with control groups ($g = 0.30\,, p < 0.001, 95\%$ CI $[0.198, 0.412]$), and single physical training ($g = 0.218\,, p < 0.01, 95\%$ CI $[0.073, 0.363]$).

Regarding cognitive pre-follow-up outcomes (k = 73), we found a summary effect of 0.205 ($p < 0.01, 95\%$ CI $[0.073, 0.338]$). The differential effect of combined training differed across group comparison ($F_{(2,70)} = 4.093\,, p < 0.05$), and was highest when compared to control groups ($g = 0.31, p < 0.01, 95\%$ CI $[0.107, 0.513]$), followed by single physical training ($g = 0.239, p < 0.05, 95\%$ CI $[0.037, 0.442]$). Combined training did not show superior effects at follow-up when compared to single cognitive training $(g = 0.073, \text{n.s.}, 95\%\ \text{CI}\ [-0.128, 0.275])$. Only 4 studies reported results of physical pre-follow-up assessments. Also, no ES was reported for a combined vs single cognitive comparison. For combined vs single physical training and control group comparisons, the summary effect was 0.417, with no significant group differences $(F_{(2,\ 11)} = 1.462, \text{n.s.})$. Nonetheless, due to the low number of effect sizes (k = 13), this result should be interpreted with caution. Combined training produced a significant superior effect when compared to control groups $(g = 0.584, p < 0.01, 95\%\ \text{CI}\ [0.199, 0.968])$, however, the comparison with single physical training did not reach statistical significance $(g = 0.243, p = \text{n.s.}, 95\%\ \text{CI}\ [-0.259, 0.745])$. Given the low number of ES, we did not analyze the follow-up results by functions, as most categories x group combination contained less than three ES.

According to Hunter and Schmidt (1990), heterogeneity can be regarded as substantial if sampling variance (variance explained by the specific participants sampled in the experiment) is below 75%. This criterion was achieved for both of our main conditions (cognitive and physical pre-post ES), justifying our three-level meta-analytic approach. In both cases, the three-level model provided a significantly better fit compared to a two-level model with level 3 heterogeneity constrained to zero, as indicated by the likelihood ratio test (LRT) (cognitive: $\chi^2_1 = 7.554, p < 0.001$, physical: $\chi^2_1 = 47.909$, $p < 0.001$). Also, the Akaike (AIC) and Bayesian Information Criterion (BIC) were lower for the three-level models, indicating improved model fits. On the other hand, we found in both conditions (cognitive and physical pre-post ES) a relatively high variance attributable to the estimated sampling variance and the between-study variability, but very little (4.9% for cognitive pre-post outcomes), or none of the proportion (for physical pre-post outcomes) explained by the within-study level. The low level 2 variance suggests that the differences in effect sizes within each study were consistent across the comparison groups. On the other hand, approximately half of the studies included only one type of comparison and, for the other half, two or more types of comparisons (see Table 1 with the descriptive data). Thus, the source of the level 3 variance could be attributable to a combination of the differential treatment effects (e.g., combined vs control from one study, combined vs single cognitive from another study, etc.), and different effect size magnitudes across studies (e.g., combined vs control from several studies).

3.5 Moderator analyses

3.5.1 Pre-post training effects by cognitive function

We analyzed the training effects on seven categories of cognitive functions (executive functions, attention, memory, language, processing speed, global functioning, and composite scores) using REML as the estimation method. These seven categories were crossed with the standardized mean difference of effect sizes of group comparisons (combined vs single cognitive, combined vs single physical, and combined vs control). Their means, confidence intervals, statistical significance, as well as QE-values as a test of heterogeneity for all effect sizes, and the level 2 and level 3 variances are displayed in **Table 3**. In executive functions, combined training achieved superior effects in comparison to control groups $(g = 0.201\ ,p < 0.001)$, single physical $(g = 0.199\ ,p < 0.01)$, and single cognitive training $(g = 0.144\ ,p < 0.05)$. In memory and speed, combined training produced superior training effects compared to control groups ($g = 0.204, p < 0.001$ and $g = 0.308, p < 0.001$, for memory and speed, respectively), and to single physical training ($g = 0.137, p < 0.05$ and $g = 0.258, p < 001$, for memory and speed, respectively), whereas no significant differences were found in these categories when compared to single cognitive training ($g = 0.007$, n.s., and $g = 0.046$, n.s., for memory

Table 3. Results of moderator analyses for pre-post comparisons between combined training vs. control, cognitive or physical single for cognitive and physical outcomes.

Outcomes	Level 2 variance (%)	Level 3 variance (%)	Omnibus test[a]	QE	Comparison groups	# Studies	# ES	Mean difference in ES [95% CI]
Cognitive functions								
Executive functions	0.00 (7.811e-08)	0.024 (22.971) ***	*F*(2, 161) = 0.42, *p* = .657	189.618	Combined vs control	21	80	0.2[0.103, 0.297] ***
					Combined vs cognitive	13	44	0.144 [0.021, 0.267] *
					Combined vs physical	14	40	0.199[0.081, 0.316] ***
Memory	0.000 (4.286e-08)	0.039 (36.098) ***	*F*(2,138) = 5.051, *p* = .008	251.221 ***	Combined vs control	19	50	0.204[0.088, 0.321] **
					Combined vs cognitive	15	43	0.007[-0.119, 0.134]
					Combined vs physical	17	48	0.117[-0.017, 0.256] *
Attention	0.019 (17.262)	0.02 (18.141)	*F*(2, 47) = 5.176, *p* = .009	71.632 *	Combined vs control	10	28	0.197[0.038, 0.358] *
					Combined vs cognitive	8	11	-0.166[-0.383, 0.051]
					Combined vs physical	7	11	0.19[-0.015, 0.396]
Language	0.00 (7.64e-09)	0.036 (45.287) ***	*F*(2, 31) = 3.387, *p* = .047	30.875 *	Combined vs control	6	11	0.305[0.123, 0.487] **
					Combined vs cognitive	9	11	-0.008[-0.201, 0.186]
					Combined vs physical	9	12	0.08[-0.102, 0.264]
Speed	0.00 (1.312e-08)	0.104 (54.037) ***	*F*(2, 88) = 3.481, *p* =.035	148.492 **	Combined vs control	15	47	0.308[0.129, 0.486] ***
					Combined vs cognitive	9	19	0.046[-0.163, 0.256]
					Combined vs physical	14	25	0.258[0.069, 0.447] **
Global cognition	0.000 (1.211e-08)	0.153 (86.725) *	*F*(2, 15) = 1.655, *p* = .224	44.504 ***	Combined vs control	8	10	0.525[0.172, 0.877] **
					Combined vs cognitive[a]	1	1	NA
					Combined vs physical	2	7	-0.048 [-0.621, 0.524]
Composite scores	0.052 (39.027)	0.019 (14.62)	*F*(2, 6) = 2.884, *p* = .133	16.743 *	Combined vs control	5	4	0.392 [-0.017, 0.8]
					Combined vs cognitive	3	3	NA
					Combined vs physical[a]	2	2	NA
Physical functions								
Fitness	0.00 (2.848e-08)	0.059 (61.28) ***	*F*(2, 62) = 1.917, *p* = .156	176.29 ***	Combined vs control	16	33	0.242[0.075, 0.409] **
					Combined vs cognitive	8	18	0.338[0.105, 0.571] **
					Combined vs physical	9	15	0.064[-0.185, 0.313]
Balance	0.00 (2.757e-08)	0.026 (30.205) ***	*F*(2, 92) = 0.192, *p* = .826	130.952 **	Combined vs control	17	58	0.273 [0.149, 0.396] ***
					Combined vs cognitive	4	12	0.196 [-0.052, 0.444]
					Combined vs physical	9	25	0.229 [0.045, 0.413] *
Strength	0.037 (18.584)	0.092 (46.711)	*F*(1, 27) = .266, *p* < .768	71.739 ***	Combined vs control	12	20	0.372 [0.103, 0.642] **
					Combined vs cognitive	3	5	0.463 [-0.081, 1.007]
					Combined vs physical	5	7	0.227 [-0.177, 0.632]

Note. [a] ES differences were only calculated for analyses with at least 3 ES. # Studies = Number of studies; # ES = Number of effect sizes; mean ES = mean Hedges' *g*; CI = Confidence interval; Level 2 variance = Variance in effect sizes within studies; Level 3 variance = Variance in effect sizes between studies; % = Proportion of the total variance of effect sizes attributed to this level; QE = test for heterogeneity in all effect sizes in the data set. Omnibus -test of all coefficients in the model (excluding the intercept). * $p < .05$; ** $p < .01$; *** $p < .001$.

and speed, respectively). In attention, language, and global cognition, combined training only produced superior effects when compared with control groups ($g = 0.197, p < 0.05$, $g = 0.305, p < 0.01$ and $g = 0.525$, $p < 0.01$, for attention, language, and global cognition, respectively). No other statistically significant differences were found.

3.5.2 Pre-post training effects by physical function

We analyzed the effect of the three training categories on the physical functions assessed in the original studies (balance, fitness, and strength), crossed with the type of training (combined, cognitive, and physical). Combined training showed significantly superior effects in comparison to control groups in fitness ($g = 0.242, p < 0.01$), balance ($g = 0.273, p < 0.001$), as well as in strength ($g = 0.372$, $p < 0.01$). Furthermore, combined training showed an advantage over single physical training in balance ($g = 0.229, p < 0.05$), and over single cognitive training in fitness ($g = 0.338, p < 0.01$). No other group comparisons resulted statistically significant.

3.5.3 Design, study quality, and sample characteristics

We identified several study characteristics that could potentially modify the training outcomes (see Tables 5 and 6 of Appendix C for detailed information).

Combinatory mode. Combined physical and cognitive training could be performed simultaneously (cognitive and physical training was performed at the same time), sequential (one after another) or separate (on different days). Our results indicated that the largest training effects in executive functions were produced by simultaneous training ($g = 0.208, p < 0.001$), followed by training on separate days ($g = 0.175, p < 0.05$). Sequential training did not produce a significant effect size in this case $g = 0.157, p > 0.05$). In attention, simultaneous ($g = 0.144, p < 0.05$), as well as sequential training $(g = 0.286, p < 0.05)$, had an advantage over training on separate days $(g = -0.139, \text{n.s.})$ $(F_{(2,\ 47)} = 4.483, p < .05)$. In speed, simultaneous training was related with an effect of 0.293 $(p < 0.01)$. Neither sequential training $(g = -0.007\ , \text{n.s.})$, nor training on separate days $(g = 0.138\ , \text{n.s.})$ were associated with significant training gains. In global cognition, simultaneous training resulted significantly superior $(g = 0.56, p < 0.05)$ to sequential $(g = 0.156\ , \text{n.s.})$ and separate training $(g = 0.161, \text{n.s.})$ $(F_{(2,\ 15)} = 41.064, p < 0.001.)$. As for the physical outcomes, only simultaneous training produced a significant effect size in outcomes that measured balance $(g = 0.259, p < 0.001)$ and strength $(g = 0.223,\ p < 0.05)$. No other significant differences were found.

Aerobic vs non-aerobic training. Aerobic intensity was classified either based on objective measures provided by the authors (HRmax, velocity, etc.), or based on the description of the physical activities. Low to non-aerobic exercise, such as slow walking, strength, or balance training were classified as non-aerobic. Moderate to high aerobic intensity, such as walking at a fast pace or running were classified as aerobic. Gains in executive functions were larger for aerobic $(g = 0.20, p < 0.001\ )$ than for non-aerobic exercise $(g = 0.138, p < 0.01)$, even though the difference did not reach statistical significance $(F_{(2,\ 147)} = 0.732\ , \text{n.s.})$. Aerobic exercise $(g = 0.279, p < 0.01)$ was related to more improvement in attention than non-aerobic exercise $\big(g = 0.032, \text{n.s.}\big)$ $\big(F_{(1,\ 48)} = 5.084, p < 0.05\big)$, whereas non-aerobic exercise produced larger effects in speed $(g = 0.202, \text{p} < 0.05)$, and global cognition $(g = 0.508, p < 0.01)$. In physical categories, as could be expected, aerobic training was related to higher gains in fitness $(g = 0.257, p < 0.01)$ than non-aerobic training $(g = 0.059, \text{n.s.})$, and non-aerobic exercise produced larger gains in balance ($g = 0.272, p < 0.001$ and $g = 0.182$, n.s., for non-aerobic and aerobic, respectively). No other significant results were found in this category.

Type of cognitive training. Cognitive training was categorized as computer training (commercial videogames or tailor-made computer tasks), interactive training (dual-task paradigms in which the cognitive training part is intrinsically associated with a motor response, as in exergames, square stepping, etc.), and multicomponent training (which could be either a mixture of different training modalities, such as paper-pencil tasks, computer games, verbal exercises, etc., or only verbal exercises, such as counting backward, naming words according to a given classification, etc.). Interactive training produced a significantly higher effect on speed ($g = 0.494, p < 0.001$) than multicomponent ($g = 0.312, p < 0.05$) and computer training ($g = 0.042$, n.s.) ($F_{(2,88)} = 4.463, p < 0.05$). Regarding executive functions, interactive training produced an effect of $g = 0.322$ ($p < 0.001$), followed by computer training ($g = 0.131, p < 0.05$), and multicomponent training ($g = 0.137, \text{n.s.}$). Also, in global cognition, interactive training showed the highest effect ($g = 0.573, p < 0.001$). The ES from the interactive training type stemmed in 90% of the cases from combined *vs* control comparisons, because the cognitive activity is intrinsically associated with a motor response, so that it is impossible to perform the cognitive part separately. To confirm that the differences in training gains as a function of cognitive training type were not influenced by the underlying group comparisons, we repeated the analysis in executive functions and speed only for those cases that had been computed from combined *vs* control comparisons. In executive functions, only interactive training achieved a significant ES ($g = 0.318, p < 0.001$), whereas the training gains associated with computer training. ($g = 0.114, n.s.$), and multicomponent training ($g = 0.136, \mathrm{n.s.}$) were not significant. The same occurred with speed, with interactive training achieving a medium ES ($g = 0.475, p < 0.001$), in contrast with non-significant gains in the case of computer ($g = 0.055, \mathrm{n.s.}$), and multicomponent training ($g = 0.34, \mathrm{n.s.}$). On the other hand, multicomponent training was related with the highest effects in memory ($g = 0.196, p < 0.05$) and language ($g = 0.228, p < 0.05$), without reaching the other modalities statistical significance. In physical outcomes, interactive and multicomponent training were related with significant effects on balance (g = 0.301, p < 0.001 and g = 0.269, p < 0.01, for interactive and multicomponent training, respectively). Interactive and multicomponent training were also related with significant improvements in fitness ($g = 0.385, p < 0.01$ and $g = 0.288, p < 0.01$, for interactive and multicomponent respectively). Furthermore, interactive training was related with a significant effect in strength ($g = 0.411, p < 0.05$).

Setting. The training could either be performed in groups, individually, or in a mixed setting (some sessions group based, and others conducted individually). Group setting produced significant effects in all cognitive categories as opposed to individual or mixed setting. In executive functions, only the ES of group setting ($g = 0.162, p < 0.001$) and individual training ($g = 0.151, p < 0.05$) resulted significant. Group training was related with an effect of $g = 0.182$ ($p < 0.01$) for memory, $g = 0.189$ ($p < 0.05$) for attention, and $g = 0.482$ ($p < 0.05$) for global cognition. In language and speed, mixed training produced superior effects ($g = 0.333, p < 0.05$, and $g = 0.348, p < 0.05$, for language and speed, respectively) than group training ($g = 0.207, p < 0.05$ and $g = 0.2411, p < 0.05$, for language and speed, respectively), and in both cases significantly superior to individual training ($g = 0.086$ and $g =$

$0.08, \mathrm{n.s.}$). Group training could not be compared to the other settings in composite scores due to insufficient ES in these categories. Regarding the physical outcomes, group setting was consistently related with significant effect sizes in all physical categories (g = 0.328, p < 0.001; g = 0.255, p < 001; g = 0.291, p < 0.05, for fitness, balance, and strength, respectively), even though individual training also showed a significant effect on balance outcomes ($g = 0.242, p < 0.05$).

Continuous moderators. We analyzed the influence of several continuous moderators crossed with the different cognitive and physical outcome measures. We found a significant negative relationship between the number of participants and attention, suggesting that studies with smaller samples produced larger ES (β = -0.003, p < 0.001, CI 95% [-0.004, -0,001]). Also, studies conducted earlier achieved higher ES in fitness($\beta = -0.035, p < 0.05$, CI 95% $[-0.068, -0.002]$), and studies with lower quality ($\beta = -0.039, p < 0.05$, CI 95% $[-0.07, -0.008]$), and higher variability in the age of participants ($\beta = -0.11, p < 0.05$, CI 95% $[-0.218, -0.002]$) were related to higher gains in balance. Other moderators (year of publication, quality, mean age, number and minutes of sessions, number of weeks) were not significant.

4. Discussion

This systematic review and three-level meta-analysis investigated the effectiveness of combined physical and cognitive training on the cognitive and physical functions of healthy older adults. It included a total of 783 effect sizes from 50 intervention studies that investigated the differential effect of combining physical and cognitive training versus its components alone or control groups. The included studies varied in their experimental design, and cognitive and physical activities were performed simultaneously, sequentially, or on different days, in groups or individually. Also, the cognitive training was delivered in different ways, such as via computer games, multicomponent activities, or interactively such as in exergames.

4.1 Overall effect sizes

In line with previous meta-analyses (Gheysen et al., 2018; Guo et al., 2020; Zhu et al., 2016), our results revealed a small advantage of combined training on cognitive outcomes, which was maintained over time as shown by the follow-up effect. When analyzing the differential training effect by subcategories (executive functions, memory, attention, speed, language, and global cognition), combined training produced overall larger effects than control groups. In memory and processing speed, combined training also showed an advantage over single physical training. Combined training also had a small but significant advantage over single cognitive training in executive functions, whereas in the remaining cognitive functions, the effect of single cognitive training was not enlarged by the addition of physical exercise. This suggests that physical activation might act as an aggregate for the improvement of executive functions, independently of other cognitive processes. Executive functions, and their measurement, are closely related to certain aspects of attention, such as selective and divided attention. Nonetheless, we found no significant difference between combined and single cognitive training in attention, which might be related to a minor number of cases in this category.

4.2 Training transfer between cognitive and physical domains

In physical outcomes, combined training showed in all categories (fitness, balance, strength) an advantage over control groups. Furthermore, fitness was the only physical outcome category, in which combined training had a significant advantage over single cognitive training, indicating that combined groups, indeed, had improved their cardiovascular fitness more than single cognitive training groups. Combined training was also related to greater training gains in balance than single physical training. Given that both, combined and single physical training, performed the same type and dosage of physical exercise, and only differed in that one group additionally received cognitive training, we can speak of a transfer of cognitive training to physical balance outcomes. The transfer distance (considering near and far transfer as a continuum), depends on the degree of the interrelation of both domains. A growing body of research provides evidence of an interrelationship between cognitive processing and balance and gait in older adults (Montero-Odasso et al., 2012; Hausdorf et al., 2005; for a review, see Li, Bherer, Mirelman et al., 2018). Especially higher cognitive functions, such as executive functions and attentional control, have been investigated in relation to postural instability, showing that, as executive functions decline with age, walking and balance become less automated and more cognitively taxing (Woollacott & Shumway-Cook, 2002). This relationship becomes especially visible in dual-task paradigms (i.e., the simultaneous performance of a cognitive task and a motor task) when older adults often tend to protect their motor functioning at the expense of the cognitive task when the situation involves a threat to balance (Schaefer & Schumacher, 2011). Consistent with the existing literature, our results confirmed that the largest training gains in executive functions were obtained when the cognitive training was delivered interactively.

4.3 Cognitive training type, combinatory mode, and aerobic intensity

We considered as interactive training, dual-task paradigms in which the cognitive training part is intrinsically associated with a motor response, as in exergames or square stepping. In executive functions, interactive training more than doubled the effect achieved by computerized cognitive or multicomponent/verbal training (cognitive interventions that included verbal exercises or a mixture of different cognitive training modalities). Also, in speed measures, interactive training achieved the highest ES, which was only comparable to that obtained by multicomponent training, whereas computer training did not produce any effect on speed. In some studies, the multicomponent/verbal training was very close to interactive training (e.g., Hiyamizu et al., Jehu et al., 2017; 2012; You et al., 2009) when cognitive tasks were performed jointly with motor tasks. This suggests that the positive effect on processing speed by cognitive-physical dual tasks is boosted by situations in which cognitive challenges are intrinsically associated with functional motor responses, as it occurs in interactive training. This interpretation is also supported by our findings that simultaneous training was the only combinatory mode that was significantly related to higher gains in processing speed. Intuitively, one could postulate that processing speed would be related to cardiorespiratory fitness, in terms of more sufficient energy delivery to cerebral substrates that sustain fluid information processing. However, aerobic, and non-aerobic exercise were associated with similar training gains in processing speed. Also, in executive functions, the difference of training gains as a function of aerobic intensity was not remarkable, even though aerobic exercise was associated with slightly higher ES. Paradoxically, given the close relationship between these functions, in attention, aerobic exercise was associated with significantly higher training gains than non-aerobic exercise. Only a few studies reported and controlled the aerobic intensity with objective methods and in most cases, it was subjectively estimated. Thus, our results on the influence of the aerobic exercise intensity should be interpreted bearing in mind these limitations.

On the other hand, the mode of combining cognitive and physical activities had no significant influence on executive functions. This is an intriguing finding, as interactive training is always performed simultaneously, which, as mentioned earlier, achieved a significantly higher ES in executive functions than computer and multicomponent/verbal training. In the case of interactive training, almost 90% of the computed ES stemmed from combined *vs* control comparisons, which produced the largest between-group differences. This could undermine to a certain degree the differences found regarding the other cognitive training types, which in many cases stemmed from combined *vs* single cognitive comparisons. It is not possible to equate interactive cognitive interventions with single cognitive interventions as the first ones are intrinsically associated with motor responses. However, an additional analysis with only combined *vs* control comparisons for all three cognitive training types (interactive, computer, and multicomponent) corroborated the result that interactive training was related to significantly higher effect sizes in executive functions and speed than the other two cognitive training types.

Multicomponent/verbal training produced the highest ES in language, which might be explained by the fact that in several studies in this category, the cognitive training included verbal fluency tasks (e.g., Gill et al, 2016; Ng et al., 2018; Romera-Liebana et al, 2018; Wongcharoen et al., 2017). In memory, even though interactive and multicomponent training produced similar ES, only the latter resulted statistically significant, possibly due to a higher heterogeneity in ES in the interactive training groups. Furthermore, advantageous training gains in attention were related to aerobic exercise, as well as to sequential and simultaneous training. Within the four studies with a sequential approach, 9 out of the 14 ES stemmed from one study (McDaniel et al., 2014) and originated from a tailor-made task. Thus, this finding would require replication with standardized or more common tasks. Likewise, the results in global cognition and composite scores should be interpreted with caution due to a low number of ES. In global cognition, interactive training resulted most beneficial. However, computer and multicomponent/verbal training only reported 4 and 5 ES, respectively, leading to an extremely high between-study variance (87%). On the other hand, in composite scores, multicomponent training could not be compared to the other training types, as computer training only reported two and interactive training no ES.

Regarding the physical outcomes, simultaneous training was associated with higher gains in balance and strength, reflecting the number of studies in this category that were originally designed to investigate the influence of dual-tasking on gait and balance. In line with this finding, higher gains in balance were also related to non-aerobic exercise, whereas aerobic exercise was related to gains in fitness. Interactive and multicomponent/verbal training was associated with higher effect sizes in fitness and balance, and interactive training also with higher gains in strength, whereas there was no differential effect found in computer training. This is surprising, as in more than 75% of the physical ES from the studies with computerized training, the comparison group (control and single cognitive training) had not received any physical training, as opposed to the combined training group. A tentative interpretation for this result would be that those studies that included computer training, imposed an overall lower level of physical demands on their participants so that between-group differences diminished.

4.4 The benefits of group setting

Finally, in all cognitive outcome categories, group setting, and in some categories also mixed setting, was associated with more training gains than when performing the training individually. This finding underscores the importance of social interaction in interventions with older adults. Physical improvements were also larger when participants trained in groups, indicating that social interaction contributes as a significant motivational factor for optimum attainment.

4.5 Continuous moderators

The analysis of continuous moderators revealed a significant negative relationship between the number of participants and ES achieved in outcomes that measured attention, with studies with lower sample sizes reporting higher ES.

None of the other moderators (quality, year of publication, mean age, number of sessions, session duration, intervention length) showed a significant influence on the results, indicating that study design and sample characteristics were overall homogenous across studies. With regards to physical outcomes, our results indicated that older studies reported higher ES in fitness and that higher variability in the mean age and lower study quality were associated with higher ES in balance outcomes.

4.6 Publication bias

As mentioned above, the training effects were not influenced by study quality. However, this finding needs to be interpreted with caution, as it could be influenced by publication bias (only studies with a robust study design were accepted for publication). Our results revealed that there was a risk of publication bias for training effects on cognitive, as well as on physical functions, and our estimated effect for these groups may differ from the true training effect. In particular, the large number of small-sample studies included in our analysis may have produced an overestimation of the summary effect. Nonetheless, it has been suggested that large estimates of between-study heterogeneity can cause regression asymmetry (Ioannidis & Trikalinos, 2007; Ioannidis, 2008). Indeed, our results indicated moderate to high between-study variability for cognitive and physical functions, which was larger for the latter one. The between-study heterogeneity in our analysis included on the one hand the differences in sample sizes, and on the other hand the variability between the types of comparison groups across studies. Therefore, the symmetry of the funnel plot might not constitute the most idoneous method to analyze the risk of bias. However, there is no current consensus on techniques to assess biases in three-level meta-analyses, and these results must therefore be interpreted with caution.

As far as we know, this is the first meta-analysis that controlled for equivalence of the training components in the different comparison groups. Thus, only those studies were considered for analysis, in which the physical training part of the combined group was identical to the physical exercise performed by the comparison group. Furthermore, this is the first time, that exercise intensity, as well as the type of cognitive training, are included as moderators, leading to more specific knowledge on the effects of combining both activities. Another strength of the present study is the use of a three-level meta-analytic approach to investigate the effectiveness of training in several cognitive functions and physical variables. This approach seems an effective alternative to classic meta-analysis when there is interdependence between effect sizes. Traditional univariate meta-analytic approaches assume that there is no dependence between effect sizes, and one common solution is to average the dependent effect sizes within studies into a single effect size by calculating an unweighted, or less biased, weighted average. When averaging or eliminating effect sizes in primary studies, there may not only be the problem of a lower statistical power due to information loss but informative differences between effect sizes are also lost and can no longer be identified in the analyses.

In sum, the results of this three-level meta-analysis indicate that even in advanced age, cognitive functioning can be improved by training, and that combined training produces a small advantage over single cognitive training on executive functions. Overall, we found evidence that a simultaneous combination of cognitive and physical activity is more effective in improving executive functions, attention, and processing speed, and that the achievement is highest when the training is performed in a social context.

5. Recommendations for future research

Even though the present work may have contributed with more precise information on the combinatory effect of physical exercise and cognitive training on cognitive functions in healthy older adults, several issues remain unexplained issues and should be addressed in future research. Most importantly, to truly differentiate between mere learning effects and synergistic training benefits, it is necessary to disentangle the transfer effects and separate between near and fare transfer. Furthermore, dual-task investigations have shown that concurrent physical and cognitive activity might produce conflicts in attentional resource allocation. Therefore, future studies should control for this potential influence in their research designs, because, depending on the complexity of the physical exercise, the exercise could either boost or debilitate the effect of the cognitive training part. Lastly, an emerging field investigates the effects of immersive virtual reality (IVR) on cognitive functions (Burin, et al., 2021), where physical activity is experienced by virtual simulation. The inclusion of this type of research could provide information on the cognitive contributions to the effects of physical exercise and should be included in future meta-analytic research.

Chapter 9

Conclusions

This Doctoral Thesis had two main goals, both embedded in the research on the prevention of age-related decline. The first goal was to investigate the influence of bilingualism as a life-long proxy of cognitive reserve on executive control in older adults. The second goal was to investigate the effects of multidomain training in comparison to cognitive and physical training alone on cognitive functions of older adults.

The first objective was addressed by conducting an experimental study in which we compared the task-switching abilities of bilingual and monolingual older adults. The second objective was addressed with two different approaches. First, we designed and implemented an RCT to investigate the effects of multidomain training in comparison to cognitive and physical training alone on cognitive functions of older adults.

The implementation of the trial had to be suspended due to the COVID-19 pandemic, for which a second approach to this objective was to conduct a systematic review and multi-level meta-analysis on multidomain interventions compared to single-domain interventions on the same topic.

The results obtained in these investigations contribute to the knowledge of different factors that positively influence later-life cognitive functioning. Our results show that long-term L2-immersion, as well as short-term multidomain training, enhance executive functions in older adults. The results show that the beneficial effects of bilingualism are not reserved for early childhood bilingualism, but also can be developed at later stages in life, that brain plasticity remains functional in later life and that executive functions can be improved in in older adults via training interventions. In what follows, we will present the conclusions from these studies in detail.

In the first study, we analyzed the effect of bilingualism on cue-based versus memory-based task switching in older adults (Chapter 6). We were specifically interested in investigating the effect of bilingualism as a function of different attentional reorientation processes. Language switches mainly occur in a random fashion in response to environmental cues and are more frequent in dual-language contexts. Therefore, we adapted a task-switching paradigm that contained two conditions requiring different types of attentional control: first, a memory-based switching condition in which the task alternated every N-trial; and second, a cued switching condition in which task rules randomly changed in response to an external cue.

Task-switching paradigms typically consist of blocks of switch and repeat trials, and blocks of non-switch trials where only single-task sets are performed. The difference in performance between switch and repeat trials is called "switch cost" and reflects task-set reconfiguration processes associated with changing task sets across trials (Monsell, 2003). The difference in performance between repeat trials in the switch block and trials in the single-task block is called "mixing cost". This difference is thought to reflect the active maintenance of multiple task configurations in working memory and is more sensitive to age-related cognitive changes (Kray & Lindenberger, 2000).

Given the similarity of language-switching in a dual-language context and attentional task-shifting in a random order, we expected bilinguals to produce lower switch costs than monolinguals in the cued-switching condition, whereas both groups would perform similarly in the memory-based condition. On the other hand, given the detrimental effects of cognitive aging on working memory, we expected to find higher mixing costs in the memory-based switching condition, and that mixing costs would be higher for monolinguals. Our results showed that bilinguals produced more efficient task-set reconfigurations (lower RT and higher accuracy) than monolinguals when task switches were aleatory and externally cued. On the other hand, the performance of both groups did not differ when task switches were memory-based. The most interesting finding of this study was that, whereas monolinguals experienced a pronounced decrease in performance in the cued condition, the performance of bilinguals remained stable across conditions. The cued condition imposes additional attentional demands (unpredictability, cue interpretation, and updating), for which this condition can be considered the more complex task.

Several previous studies have found that the bilingual advantage is especially evident with increasing task demands (Bialystok, 2006; Costa et al., 2009; Hernández et al., 2013; Qu et al., 2015). However, to our knowledge, this is the first study that provides a direct comparison of how bilingualism responds to two types of attentional reorientation within one task paradigm. On the other hand, we did not find any group differences in the magnitude of the composite switch and mixing costs, suggesting that composite scores might not sufficiently capture fine-grained differences in performance. Exogenous and endogenous reorientation involves slightly different control mechanisms. Whereas the monitoring in WM is mainly managed by frontoparietal areas, context-dependent reorientation (as in cued task switching) strongly relies on interaction with subcortical areas (Shulman et al., 2009; Van Schouwenburg et al., 2010).

To sum up, the results of this experiment suggest that processes that rely heavily on WM are affected in a similar way in monolinguals and bilinguals, but that bilingualism might improve processes that require a flexible reorientation to environmental cues. Furthermore, our results show that the beneficial effects of bilingualism can also be developed at a later age, not necessarily bound to critical periods during early childhood. Our participants had learned their L2 as adults but have been immersed in the L2 environment for several decades. This indicates that the neuroprotective benefits of bilingualism could be understood as long-term dual-language exposure which could be fostered from later stages in life.

The second investigation of this Thesis (Chapter 7) consisted in the design of a study protocol for a randomized controlled trial, investigating the effects of multidomain versus single-domain training on executive control and memory in older adults. The study protocol set the stage for a single-blind, randomized controlled trial with a factorial design with four treatment arms (multidomain, single-cognitive, single physical, and active control), controlling for potential bias and confounding factors. The trial was registered in the registry of clinical trials (ClinicalTrials.gov) of the United States National Library of Medicine (NLM) at the National Institutes of Health, which is the largest clinical trials database in the world.

The protocol provided detailed information in terms of the timelines, execution, and conduct of the trial as well as the analysis of the data. For its elaboration, we carefully analyzed the target population and treatment components. We decided on the assessment tools based on the functions they measured and the time it took to complete them. The timing was overall a crucial aspect of the whole planning. Given the limitations in space and timelines, we divided the trial into three training waves, which permitted us to fit training and assessment periods in the established time frame. For the cognitive training, we reached a research agreement with a commercial brain-training platform and for the physical training we hired a team of professional fitness instructors. The experimental physical intervention consisted of fixed protocol of interval training of moderate to high aerobic intensity, combining aerobic, strength and balance exercises to a music soundtrack. A crucial aspect of the design was the choice of the respective control activities of the cognitive and physical training components. As the physical training involved intense aerobic exercise, its control activity was decided to be nonaerobic, involving relaxation and balance exercises. On the other hand, cognitive training was based on an enhancement of executive functions with an emphasis on flexibility and WM. As cognitive control activity, we choose verbal functions and general knowledge, as these functions show less decline with age (see Chapter 1). The trial was implemented from January 2019 to March 2020, when due to the Covid-19 pandemic, it had to be suspended. By this moment, we had carried out about 200 assessments sessions, corresponding to approximately 1 000 hour of laboratory work, and 64 hours of training interventions. As seen, this was a very ambitious trial and without the pandemic interruption, we would have accomplished all trial phases within the established timeframes. Nonetheless, even though we could not finish the trial, this project still contributed in a very important way to this doctoral journey, in that it generated deep knowledge on how to plan and execute a complex RCT.

The third study of this Doctoral Dissertation consisted of a systematic review and three-level meta-analysis on the effects of combined cognitive-physical interventions on cognitive and physical functions in healthy older adults (Chapter 8). After a systematic search in the most relevant databases, we identified 50 published intervention studies that fulfilled our inclusion criteria (healthy adults, at least one combined training group, at least one comparison group, equivalent training components), involving 6,164 participants. The outcome measures were classified, according to their assessment tools, into seven cognitive domains (executive functions, memory, language, speed, global cognition, and composite scores) and three physical domains (fitness, balance, and strength). Further moderators were the mode in which cognitive and physical training were combined (simultaneous, sequential, on separate days), aerobic vs. non-aerobic exercise, type of cognitive training, the length of training (total of weeks, days per week, and minutes per session), mean age and standard deviation, year of publication, and study quality. For each dependent variable, we computed the standardized mean differences (SMD), as expressed by the bias-corrected Hedges' *g*, of the differential training effect of combined training *vs.* its comparison group (i.e., single-cognitive training, single-physical training, active, and/or passive control). After the elimination of influential cases, we submitted a total of 783 effect sizes (ES) to a three-level meta-analysis. Analyses were performed separately for cognitive and physical functions and for pre-post and pre-follow-up comparisons. In a first step, we calculated the summary effects (with ES pooled across cognitive and across physical functions). Then we computed the SMD for each group comparison for cognitive and physical subcategories, and in the last step, we added categorical and continuous moderators to the model.

This study contributed three novelties to the research area: (1) The type of statistical analysis, (2) the comparison of only equivalent training conditions, and (3) the inclusion of novel moderators. Instead of applying a traditional samplewise procedure (pooling of effect sizes), we opted for a three-level random-effects structure which allowed us to analyze the training effects on different cognitive functions within the same study (i.e., within-study heterogeneity), as well as their reliability across different studies (i.e., between-study heterogeneity) and control thereby for the dependency of effect sizes. Furthermore, contrary to previous meta-analyses on this topic, we only computed the SMD from group comparisons in which both groups performed either the same physical activity (combined *vs.* single-physical) or the same cognitive (combined *vs.* single-cognitive) activity. Regarding the moderators, we included for the first time the effect of exercise intensity (aerobic *vs.* nonaerobic) and the type of cognitive training (computer *vs.* interactive *vs.* multicomponent).

The results of this study showed that combined training produced superior training effects as opposed to active or passive control groups, in all cognitive and physical subcategories. The analysis of the effects of the different training combinations showed that combined training produces a small advantage over single-cognitive training on executive functions. In the remaining cognitive functions, combined cognitive-physical training produced the same effect as cognitive training alone. Combined training also produced superior effects to single-physical training on executive functions, memory, and processing speed, whereas no significant difference was found in attention and language. Regarding the physical outcomes, the most interesting finding is that combined training produces superior effects on balance than physical training alone, underscoring the contribution of executive control to physical stability in older adults. This result could be relevant, especially to clinicians interested in fall prevention and mobility improvement of elderlies. Furthermore, group setting, and in some cases mixed setting, was related to the highest training gains in all cognitive and physical categories. This confirms the importance of social interaction as a strong moderator of the effectiveness of training outcomes.

Taken together, the findings of this thesis contribute to the existent literature on cognitive reserve and on the improvement of cognitive functions in older healthy adults via training interventions, as well as to the knowledge on the design and preparation of a clinical trial. It seems that especially executive functions are susceptible to be modified, either by life-long CR proxies such as bilingualism or by short-term effects of training interventions.

Chapter 10

Conclusiones

Esta Tesis Doctoral tenía dos objetivos principales, ambos enmarcados en la investigación sobre la prevención del deterioro cognitivo en el envejecimiento normal. El primer objetivo fue investigar la influencia del bilingüismo sobre el control ejecutivo en adultos mayores, como indicador de la reserva cognitiva a largo plazo. El segundo objetivo fue investigar los efectos del entrenamiento multidominio, en comparación con el entrenamiento cognitivo y físico de forma separada, en las funciones cognitivas de los adultos mayores. Para lograr el primer objetivo realizamos un experimento en el que comparamos las habilidades de cambio de tarea de adultos mayores bilingües y monolingües. El segundo objetivo se abordó con dos metodologías diferentes. Primero, diseñamos e implementamos un ensayo clínico aleatorizado para analizar los efectos del entrenamiento multidominio en comparación con el entrenamiento cognitivo y físico solo en las funciones cognitivas de los adultos mayores. Este ensayo clínico controlado aleatorizado tuvo que suspenderse debido a la pandemia de COVID-19, por lo que decidimos abordar este objetivo mediante una revisión sistemática y un metaanálisis de tres niveles. Los resultados obtenidos en estas investigaciones contribuyen al conocimiento sobre diferentes factores que influyen positivamente en el funcionamiento cognitivo en personas mayores.

Nuestros resultados muestran que la exposición intensiva y prolongada a una segunda lengua, así como el entrenamiento multidominio, tienen un efecto positivo en las funciones ejecutivas de adultos mayores. Los resultados muestran que el bilingüismo produce cambios en el funcionamiento ejecutivo de personas mayores, aunque hayan aprendido la segunda lengua siendo ya adultos. Los resultados de esta investigación aportan además evidencia sobre los efectos positivos de intervenciones multidominio en el funcionamiento cognitivo de personas mayores, lo que indica que la plasticidad cerebral sigue activa hasta una edad avanzada. A continuación, presentaremos en detalle las conclusiones de estos estudios.

En el primer estudio analizamos el efecto del bilingüismo sobre el cambio de tarea señalizado *versus* el cambio de tarea basado en series alternantes en adultos mayores (Capítulo 6). Específicamente nos interesaba investigar el efecto del bilingüismo en función de diferentes procesos de reorientación atencional. En bilingües, los cambios de idioma ocurren principalmente de manera aleatoria en respuesta a señales ambientales y son más frecuentes en entornos en los que se usan ambas lenguas de forma indistinta. Para reproducir este proceso de reorientación en un experimento controlado, adaptamos un paradigma de cambio de tarea que contenía dos condiciones que requerían diferentes tipos de control atencional: en una condición el cambio de tarea estaba basado en el mantenimiento de una secuencia en la memoria de trabajo, en la que la tarea alternaba cada *N*-ensayos. En la otra condición, el cambio de tarea se producía de forma aleatoria en respuesta a señales externas.

Los paradigmas de cambio de tarea generalmente consisten en bloques que mezclan ensayos de repetición (repetir la misma regla que en el ensayo anterior) con ensayos de cambio (ejecutar una regla distinta que en el ensayo anterior) y de bloques de ensayos en los que hay que ejecutar solamente un tipo de regla (no requieren un cambio de tarea). La diferencia en el rendimiento entre los ensayos de cambio y los de repetición se denomina "costo de cambio local" y refleja el proceso de reconfiguración del *set* de tarea a nivel de ensayos (Monsell, 2003). La diferencia de rendimiento entre los ensayos de repetición de los bloques mixtos y los ensayos del bloque de tarea única se denomina "costo por cambio global". Se cree que esta diferencia refleja el mantenimiento activo de múltiples *sets* de tarea en la memoria de trabajo y es más sensible a los cambios cognitivos relacionados con la edad (Kray y Lindenberger, 2000). Dada la similitud del cambio de idioma y el cambio de tarea aleatorio, esperábamos que los bilingües produjeran costes de cambio locales más bajos que los monolingües en la condición de cambio señalizado, mientras que ambos grupos no se diferenciarían en los cambios de tarea basada en memoria. Por otro lado, teniendo en cuenta los efectos negativos del envejecimiento cognitivo sobre la memoria de trabajo, esperábamos encontrar en ambos grupos costos globales más altos en los cambios de tarea en series alternantes que cuando los cambios fuesen aleatorios y señalizados y que éstos serían mayores para los monolingües.

Nuestros resultados mostraron que los bilingües tuvieron un rendimiento más eficiente que los monolingües (tiempos de reacción más bajos y mayor precisión) cuando los cambios de tarea fueron aleatorios y señalizados. Por otro lado, no hubo diferencias entre bilingües y monolingües en la condición de cambio en series alternantes. El resultado más interesante de este estudio fue que, mientras el rendimiento de los monolingües bajó significativamente en la condición de cambios señalizados, en los bilingües el rendimiento fue similar en ambas condiciones experimentales. Los cambios aleatorios y señalizados exigen una demanda atencional adicional (imprevisibilidad e interpretación y actualización de las señales), por lo que esta condición puede considerarse la tarea más compleja. Varios estudios previos encontraron una ventaja bilingüe especialmente cuando la dificultad de la tarea era elevada (Bialystok, 2006; Costa et al., 2009; Hernández et al., 2013; Qu et al., 2015). Sin embargo, hasta donde sabemos, este es el primer estudio que proporciona una comparación directa del efecto del bilingüismo sobre dos tipos de reorientación atencional dentro de una única tarea experimental.

Por otro lado, no encontramos ninguna diferencia significativa entre ambos grupos en la magnitud de los costos por cambio globales y locales. Estos resultados sugieren que las puntuaciones compuestas podrían no captar diferencias sutiles en el funcionamiento cognitivo. La reorientación exógena y endógena se procesan en redes neuronales ligeramente diferentes. Mientras que la monitorización en la memoria de trabajo es sustenida principalmente por áreas frontoparietales, la reorientación aleatoria y dependiente del contexto involucra también una interacción con áreas subcorticales (Van Schouwenburg et al., 2010; Shulman et al., 2009).

En resumen, los resultados de este experimento sugieren que los cambios atencionales que responden a una monitorización en la memoria de trabajo están afectados de manera similar en monolingües y bilingües, pero que el bilingüismo podría modular los procesos que requieren una reorientación flexible en respuesta a señales ambientales. Además, nuestros resultados muestran que los efectos cognitivos del bilingüismo se pueden desarrollar también a una edad más avanzada, y que no necesariamente están condicionados por haber aprendido una segunda lengua durante períodos críticos en la primera infancia. Nuestros participantes aprendieron su segunda lengua siendo ya adultos, pero han estado inmersos en el contexto bilingüe durante varias décadas. Esto indica que los efectos del bilingüismo sobre el funcionamiento de los procesos ejecutivos surgen a raíz de una exposición continuada a ambas lenguas, por lo que también podría fomentarse durante de la etapa adulta.

La segunda investigación de esta Tesis (Capítulo 7) consistió en el diseño de un protocolo para la realización de un ensayo clínico controlado, aleatorizado que tenía como objetivo investigar los efectos del entrenamiento multidominio versus el unidominio sobre el control ejecutivo y la memoria en adultos mayores. Este protocolo sentó las bases para la ejecución de un ensayo clínico aleatorizado simple ciego, con un diseño factorial con cuatro condiciones de tratamiento (multidominio, solo cognitivo, solo físico y control activo). El estudio se registró en el registro de ensayos clínicos de la Biblioteca Nacional de Medicina de los Estados Unidos (U.S. National Library of Medicine, NLM) dependiente del Instituto Nacional de Salud de los Estados Unidos, que es la base de datos de ensayos clínicos más grande del mundo.

El protocolo incluyó información detallada en cuanto a los plazos, la ejecución y la realización del ensayo, y también a cómo se iban a analizar y guardar los datos. Para su elaboración, analizamos cuidadosamente la población diana y los diferentes componentes de la intervención. Analizamos y decidimos las pruebas a utilizar para evaluar las diferentes funciones cognitivas y físicas y cronometramos los tiempos que se tardaba en la realización cada prueba. El factor tiempo fue un aspecto crucial, tanto en la planificación como en la ejecución del estudio. Dado las limitaciones de espacio y tiempo, dividimos el ensayo en tres tandas de entrenamiento. Esto permitió ajustar los períodos de entrenamiento y evaluación en los cronogramas establecidos con anterioridad, para así llegar a incluir el número de participantes necesarios para obtener una aceptable potencia estadística. Para el entrenamiento cognitivo, llegamos a un acuerdo de investigación con una plataforma comercial de entrenamiento cognitivo. Para el entrenamiento físico contratamos a un equipo profesional de instructores deportivos. La actividad física experimental consistió en un protocolo de entrenamiento de intervalo, de intensidad cardiovascular moderada a alta, que combinaba movimientos aeróbicos atléticos con ejercicios de fuerza y estabilización postural.

Un aspecto crucial del diseño fue la elección de las respectivas actividades de control físico y cognitivo. Como el entrenamiento físico involucraba ejercicio aeróbico intenso, se decidió que su actividad de control fuera no aeróbica, consistiendo en un protocolo de ejercicios de relajación y equilibrio. Por otro lado, el entrenamiento cognitivo se centró en el entrenamiento de las funciones ejecutivas con énfasis en la flexibilidad y la memoria de trabajo. Como actividad de control cognitivo elegimos juegos que implicaban funciones verbales y de conocimiento general. Por un lado, estas funciones muestran un menor deterioro con la edad y por otro, se sustentan en un procesamiento cerebral diferente. El ensayo se implementó desde enero de 2019 hasta marzo de 2020, cuando debido a la pandemia de Covid-19 tuvo que ser suspendido. Para entonces habíamos realizado más de 200 sesiones de evaluación, lo que corresponde a unas 1000 horas de trabajo de laboratorio y 64 horas de sesiones de intervención. Como se puede apreciar, se trataba de un estudio muy ambicioso y de no ser por la pandemia, se habrían alcanzado los objetivos dentro de los plazos establecidos. Aún sin poder terminar el estudio, este proyecto aportó algo fundamental a esta Tesis Doctoral, que es la gran riqueza de conocimiento y destreza que ha generado.

El tercer trabajo de esta tesis consistió en una revisión sistemática y un meta-análisis de tres niveles sobre los efectos de intervenciones de entrenamiento cognitivo y físico sobre las funciones cognitivas en adultos mayores sanos (Capítulo 8). Después de realizar una búsqueda sistemática en las bases de datos más relevantes, identificamos 50 estudios de intervención que cumplieron con nuestros criterios de inclusión (adultos sanos, al menos un grupo de entrenamiento combinado, al menos un grupo de comparación, componentes de entrenamiento equivalentes) y que incluyeron un total de 6.164 participantes. Las variables de interés se clasificaron en siete dominios cognitivos (funciones ejecutivas, memoria, lenguaje, velocidad de procesamiento, cognición global y puntuaciones compuestas) y tres dominios físicos (fitness, equilibrio y fuerza).

Otros moderadores fueron el modo en que se combinaron el entrenamiento cognitivo y físico (simultáneo, secuencial, días separados), si el entrenamiento físico era aeróbico o no aeróbico, el tipo de entrenamiento cognitivo, la duración del entrenamiento (total de semanas, días por semana y minutos por sesión), la edad media y desviación estándar, el año de publicación y la calidad del estudio. Para cada variable dependiente, calculamos las diferencias de medias estandarizadas (*g* de Hedges con corrección de sesgo) del efecto diferencial entre el entrenamiento físico-cognitivo combinado versus el grupo de comparación (entrenamiento cognitivo, entrenamiento físico, control activo y/o pasivo). Después de la eliminación de los casos influyentes, incluimos un total de 783 tamaños del efecto a un meta-análisis de tres niveles. Los análisis se realizaron por separado para las funciones cognitivas y físicas y para las comparaciones pretest, postest y de seguimiento. En un primer paso, calculamos los efectos globales y después calculamos la diferencia de los tamaños de efecto para cada comparación de grupos para las subcategorías cognitivas y físicas y en el último paso, añadimos los moderadores categóricos y continuos al modelo.

Este estudio aportó tres novedades al área de investigación: (1) el tipo de análisis estadístico, (2) la comparación exclusiva de entrenamiento equivalentes, y (3) la inclusión de moderadores novedosos. En lugar de utilizar el procedimiento meta-analítico tradicional basado en un efecto promedio ponderado, optamos por un modelo multivariado de tres niveles Este modelo permite computar todos los tamaños de efecto de cada estudio, mientras se modelan tres componentes de varianza, distribuidos sobre tres niveles: la varianza de muestreo (nivel 1), la varianza “intra-estudios” (nivel 2) y la varianza “inter-estudios” (nivel 3), lo que permite controlar la interdependencia de los tamaños del efecto. Además, a diferencia de meta-análisis previos sobre este tema, solo computamos la diferencia de tamaños de efecto cuando las comparaciones provenían de grupos que realizaron, o bien el mismo entrenamiento cognitivo (para comparaciones entre entrenamientos combinados *vs* entrenamiento cognitivo), o la misma actividad física (para comparaciones entre entrenamientos combinados versus entrenamiento físico). En cuanto a los moderadores, incluimos por primera vez el efecto de la intensidad aeróbica del ejercicio físico (aeróbico *vs* no aeróbico) y el tipo de entrenamiento cognitivo (ordenador *vs* interactivo *vs* multicomponente).

Los resultados de este estudio mostraron que el entrenamiento combinado, comparado con el control activo y pasivo, produce efectos superiores en todas las categorías de funciones cognitivas y físicas. El entrenamiento combinado también produce un mayor efecto sobre las funciones ejecutivas que el entrenamiento cognitivo por sí solo. En el resto de las funciones cognitivas, el entrenamiento combinado produce resultados similares al del entrenamiento cognitivo solo. En comparación con el entrenamiento físico de forma aislada, el entrenamiento combinado produce efectos superiores en las funciones ejecutivas, la memoria y la velocidad de procesamiento, mientras que no encontramos diferencias significativas en la atención y el lenguaje.

En cuanto a los resultados físicos, el resultado más interesante de nuestro análisis fue que se producen mayores mejoras en el equilibrio cuando se combina el entrenamiento físico con ejercicios de entrenamiento cognitivo, lo que evidencia la contribución del control ejecutivo a la estabilidad postural en adultos mayores. Este resultado podría ser especialmente relevante para los profesionales clínicos interesados en la prevención de caídas y la mejora de la movilidad de los ancianos. Además, en todas las categorías cognitivas y físicas, los mayores efectos se produjeron cuando el entrenamiento se realizó en grupo, confirmando la importancia de la interacción social como potenciador de la efectividad del entrenamiento.

En conjunto, los resultados de esta Tesis Doctoral aportan resultados empíricos sobre la contribución del bilingüismo a la reserva cognitiva y sobre los efectos de intervenciones de entrenamiento cognitivo y/o físico en las funciones cognitivas y físicas de las personas mayores, además de aportar conocimiento sobre cómo ha de diseñarse un ensayo clínico. Los resultados indican que especialmente las funciones ejecutivas son susceptibles de ser modificadas en personas mayores, ya sea por factores que actúan a largo plazo, como es el caso del bilingüismo, o bien por factores que actúan a más corto plazo, como es el caso de los efectos de las intervenciones.

References

Abutalebi, J., & Green, D. (2007). Bilingual language production: The neurocognition of language representation and control. *Journal of Neurolinguistics, 20*(3), 242-275. https://doi.org/10.1016/j.jneuroling.2006.10.003

Abutalebi, J., Guidi, L., Borsa, V., Canini, M., Della Rosa, P.A., Parris, B.A., & Weekes, B.S. (2015). Bilingualism provides a neural reserve for aging populations. *Neuropsychologia*, *69*, 201-210. https://doi.org/10.1016/j.neuropsychologia.2015.01.040

Abutalebi, J., & Green, D. W. (2008). Control mechanisms in bilingual language production: Neural evidence from language switching studies. *Language and Cognitive Processes, 23*(4), 557–582. https://doi.org/10.1080/01690960801920602

*Adcock, M., Fankhauser, M., Post, J., Lutz, K., Zizlsperger, L., Luft, A.R., Guimaraes, V., Schättin, A., & de Bruin, E.D. (2020). Effects of an in-home multicomponent exergame training on physical functions, cognition, and brain volume of older adults: A randomized controlled trial. *Frontiers in Medicine*, *6*, 321. https://doi.org/10.3389/fmed.2019.00321

Adesope, O.O., Lavin, T., Thompson, T., & Ungerleider, C. (2010). A systematic review and meta-analysis of the cognitive correlates of bilingualism. *Review of Educational Research*, *80*(2), 207-245. https://doi.org/10.3102/0034654310368803

Adrover-Roig, D., & Barceló, F. (2010). Individual differences in aging and cognitive control modulate the neural indexes of context updating and maintenance during task-switching. *Cortex*, *46*(4), 434-450. https://doi.org/10.1016/j.cortex.2009.09.012

Allport, A., & Wylie, G. (2000). Task switching, stimulus-response bindings, and negative priming. In S. Monsell, & J. Driver (Eds.) *Control of cognitive processes: Attention and performance XVII* (pp. 33-70). Cambridge, MA: MIT Press.

*Anderson-Hanley, C., Arciero, P.J., Brickman, A. M., Nimon, J.P., Okuma, N., Westen, S.C., Merz, M.E., Pence, B.D., Woods, J.A., Kramer, A.F., and Zimmerman, E.A. (2012). Exergaming and older adult cognition. A cluster randomized clinical trial. *American Journal of Preventive Medicine*, *42*(2), 109-119. https://doi.org/10.1016/j.amepre.2011.10.016

*Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., Bories, L., Cufi, M.-N., Dantoine, T., Dartigues, J.-F., Desclaux, F., Gabelle, A., Gasnier, Y., Pesce, A., Sudres, K., Touchon, J., Robert, P., Rouaud, O, . . . Olivier-Abbal, P. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *The Lancet Neurology, 16*(5), 377–389. https://doi.org/10.1016/S1474-4422(17)30040-6

Anemüller, J., Sejnowski, T.J., & Makeig, S. (2003). Complex independent component analysis of frequency-domain electroencephalographic data. *Neural Networks, 16*(9), 1311-1323. https://doi.org/10.1016/j.neunet.2003.08.003

Anguera, J.A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., Kong, E., Larraburo, Y., Rolle, C., Johnston, E., and Gazzaley, A. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*(7465), 97-101. https://doi.org/10.1038/nature12486

Ansaldo, A.I., Ghazi-Saidi, L., & Adrover-Roig, D. (2015). Interference control in elderly bilinguals: Appearances can be misleading. *Journal of Clinical and Experimental Neuropsychology, 37*(5), 455–470. https://doi.org/10.1080/13803395.2014.990359

Antón, E., García, Y.F., Carreiras, M., & Duñabeitia, J.A. (2016). Does bilingualism shape inhibitory control in the elderly? *Journal of Memory and Language, 90*, 147–160. https://doi.org/10.1016/j.jml.2016.04.007

Antoniou, M. (2019). The advantages of bilingualism debate. *Annual Review of Linguistics, 5*, 395-415. https://doi.org/10.1146/annurev-linguistics-011718-011820

Assink, M., & Wibbelink, C.J.M. (2016). Fitting three-level meta-analytic models in R: A step-by-step tutorial. *The Quantitative Methods for Psychology, 12*(3), 154-174. https://doi.org/10.20982/tqmp.12.3.p154

ATS statement: guidelines for the six-minute walk test. (2002). ATS committee on proficiency standards for clinical pulmonary function laboratories. *American Journal of Respiratory and Critical Care Medicine*, *166*(1), 111-117. http://doi.org/10.1164/ajrccm.166.1.at1102

Bacha, J.M.R., Gomes, G.C.V., de Freitas, T.B., Viveiro, L.A.P., da Silva, K.G., Bueno, G.C., Varise, E.M., Torriani-Pasin, C., Castilho Alonso, A., Silva Luna, N.M., d'Andrea Greve, J., & Pompeu, J.E. (2018). Effects of kinect adventures games versus conventional physical therapy on postural control in elderly people: a randomized controlled trial. *Games for Health Journal, 7*(1), 24-36. https://doi.org/10.1089/g4h.2017.0065

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neuroscience & Biobehavioral Reviews, 30*(6), 791-807. https://doi.org/10.1016/j.neubiorev.2006.06.005

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences, 4*(11), 417-423. https://doi.org/10.1016/S1364-6613(00)01538-2

Baddeley, A. (2003). Working Memory: Looking Back and Looking Forward. *Nature Reviews Neuroscience, 4*(10), 829–839. https://doi.org/10.1038/nrn1201

Baddeley, A.D., and Hitch, G.J. (1994). Developments in the concept of working memory. *Neuropsychology, 8*(4), 485–493. https://doi.org/10.1037/0894-4105.8.4.485

Baddeley, A.D., & Logie, R.H. (1999). Working memory: The multiple component model. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 28 - 80). New York: Cambridge University Press.

De Baene, W., Duyck, W., Brass, M., & Carreiras, M. (2015). Brain circuit for cognitive control is shared by task and language switching. *Journal of Cognitive Neuroscience, 27*(9), 1752–1765. https://doi.org/10.1162/jocn_a_00817

Bak, T.H., Long, M.R., Vega-Mendoza, M., & Sorace, A. (2016). Novelty, challenge, and practice: The impact of intensive language learning on attentional functions. *PloS One, 11*(4). https://doi.org/10.1371/journal.pone.0153485

Ball, K., Berch, D.B., Helmers, K.F., Jobe, J.B., Leveck, M.D., Marsiske, M., Morris, J.N., Rebok, G.W., Smith, D.M., Tennstedt, S.L., Unverzagt, F.W., & Willis, S.L. (2002).

Effects of cognitive training interventions with older adults: a randomized controlled trial. *Journal of the American Medical Association*, *288*(18), 2271-2281. https://doi.org/10.1001/jama.288.18.2271

Ballesteros Jiménez, S. (2017). *Psicología de la memoria humana*. Madrid: Editorial Universitas, S.A.

Ballesteros S., Mayas J, Reales J.M. (2004). Cognitive function in healthy, aging and mild cognitive impaired older adults. *Psicothema*, *25*(1),18-24. http://doi.org/10.7334/psicothema2012.181

Ballesteros, S., & Reales, J. M. (2004). Intact haptic priming in normal aging and Alzheimer's disease: evidence for dissociable memory systems. *Neuropsychologia*, *42*(8), 1063-1070. http://doi.org/10.1016/j.neuropsychologia.2003.12.008

Ballesteros, S., Bischof, G.N., Goh, J. O., & Park, D.C. (2013). Neural correlates of conceptual object priming in young and older adults: an event-related functional magnetic resonance imaging study. *Neurobiology of Aging*, *34*(4), 1254-1264. http://doi.org/10.1016/j.neurobiolaging.2012.09.019

Ballesteros, S., González, M., Mayas, J., García-Rodríguez, B., & Reales, J.M. (2009). Cross-modal repetition priming in young and old adults. *European Journal of Cognitive Psychology*, *21*(2-3), 366-387. https://doi.org/10.1080/09541440802311956

Ballesteros, S., Kraft, E., Santana, S., & Tziraki, C. (2015). Maintaining older brain functionality: A targeted review. *Neuroscience and Biobehavioral Reviews*, *55*, 453–477. https://doi.org/10.1016/j.neubiorev.2015.06.008

Ballesteros, S., Mayas, J., Prieto, A., Ruiz-Marquez, E., Toril, P., & Reales, J. M. (2017). Effects of video game training on measures of selective attention and working memory in older adults: Results from a randomized controlled trial. *Frontiers in Aging Neuroscience*, *9*, 354. http://doi.org/10.3389/fnagi.2017.00354.

Ballesteros, S., Prieto, A., Mayas, J., Toril, P., Pita, C., Ponce de Leon, L., Reales, J.M., & Waterworth, J. (2014). Brain training with non-action video games enhances aspects of cognition in older adults: a randomized controlled trial. *Frontiers in Aging Neuroscience*, *6*, 277. http://doi.org/10.3389/fnagi.2014.00277

Ballesteros, S., Reales, J.M., & Mayas, J. (2007). Picture priming in normal aging and Alzheimer's disease. *Psicothema, 19*(2), 239-244. Retrieved from https://reunido.uniovi.es/index.php/PST/article/view/8572

Ballesteros, S., Reales, J.M., García, E., & Carrasco, M. (2006). Selective attention affects implicit and explicit memory for familiar pictures at different delay conditions. *Psicothema*, *18*(1), 88-99. Retrieved from http://europepmc.org/abstract/MED/17296015

Ballesteros, S., Reales, J.M., Mayas, J., & Heller, M.A. (2008). Selective attention modulates visual and haptic repetition priming: effects in aging and Alzheimer's disease. *Experimental Brain Research*, *189*(4), 473-483. https://doi.org/10.1007/s00221-008-1441-6

Ballesteros, S., Toril, P., Mayas, J., Reales, J.M., & Waterworth, J. A. (2014). An ICT-mediated social network in support of successful ageing. *Gerontechnology*, *13*(1), 39–48. https://doi.org/10.4017/gt.2014.13.1.007.00

Ballesteros, S., Voelcker-Rehage, C., & Bherer, L. (2018). Editorial: Cognitive and brain plasticity induced by physical exercise, cognitive training, video games, and combined interventions. *Frontiers in Human Neuroscience, 12*, 169. http://doi.org/10.3389/fnhum.2018.00169

Baltes, P.B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging*, *12*(1), 12–21. https://doi.org/10.1037/0882-7974.12.1.12

*Bamidis, P.D., Fissler, P., Papageorgiou, S.G., Zilidou, V., Konstantinidis, E. I., Billis, A.S., Romanopoulou, E., Karagianni, M., Beratis, I., Tsapanou, A., Tsilikopoulou, G., Grigoriadou, E., Ladas, A., Kyrillidou, A., Tsolaki, A., Frantzidis, C., Sidiropoulos, E., Siountas, A., Matsi, S., … & Kolassa, I.T. (2015). Gains in cognition through combined cognitive and physical training: the role of training dosage and severity of neurocognitive disorder. *Frontiers in Aging Neuroscience, 7*, Article 152. https://doi.org/10.3389/fnagi.2015.00152

Bamidis, P.D., Vivas, A. B., Styliadis, C., Frantzidis, C., Klados, M., Schlee, W., Siountas, A., and Papageorgiou, S. G., (2014). A review of physical and cognitive interventions in aging. *Neuroscience & Biobehavioral Reviews, 44*, 206-20. https://doi.org/10.1016/j.neubiorev.2014.03.019

Barac, R., Bialystok, E., Castro, D.C., & Sanchez, M. (2014). The cognitive development of young dual language learners: A critical review. *Early Childhood Research Quarterly*, 29(4), 699–714. https://doi.org/10.1016/j.ecresq.2014.02.003

*Barban, F., Annichiarico, R., Melideo, M., Federici, A., Lombardi, M. G., Giuli, S., Ricci, C., Adriano, F., Griffini, I., Silvestri, M., Chiusso, M., Neglia, S., Ariño-Blasco, S., Cuevas Perez, R., Dionyssiotis, Y., Koumanakos, G., Kovačeić, M., Montero-Fernández, N., Pino, … and Caltagirone, C. (2017). Reducing fall risk with combined motor and cognitive training in elderly fallers. *Brain Sciences, 7*(2), Article 19, https://doi.org/10.3390/brainsci7020019

Barbu, C.A., Gillet, S., & Poncelet, M. (2020). Investigating the effects of language-switching frequency on attentional and executive functioning in proficient bilinguals. *Frontiers in Psychology, 11*, Article 1078. https://doi.org/10.3389/fpsyg.2020.01078

Barcelos, N., Shah, N., Cohen, K., Hogan, M.J., Mulkerrin, E., Arciero, P.J., Cohen, B.D., Kramer, A.F., & Anderson-Hanley, C. (2015). Aerobic and cognitive exercise (ACE) pilot study for older adults: Executive function improves with cognitive challenge while exergaming. *Journal of the International Neuropsychological Society, 21*(10), 768–779. https://doi.org/10.1017/S1355617715001083

Barnes, D.E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology, 10*(9), 819-828. https://doi.org/10.1016/S1474-4422(11)70072-2

Barnes, D.E., Santos-Modesitt, W., Poelke, G., Kramer, A.F., Castro, C., Middleton, L.E., & Yaffe, K. (2013). The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA Internal Medicine, 173*(9), 797-804. http://doi.org/10.1001/jamainternmed.2013.189

Bartzokis, G. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging, 25*(1), 5-18. https://doi.org/10.1016/j.neurobiolaging.2003.03.001

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, *17*(10), 502-509. doi:10.1016/j.tics.2013.08.012

Basak, C., Boot, W.R., Voss, M.W., & Kramer, A.F. (2008). Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychology and Aging, 23*(4), 765-777. https://doi.org/10.1037/a0013494

Bender, A.R., Völkle, M.C., & Raz, N. (2016). Differential aging of cerebral white matter in middle-aged and older adults: A seven-year follow-up. *NeuroImage, 125*, 74-83. https://doi.org/10.1016/j.neuroimage.2015.10.030

Bennett, I.J., & Madden, D.J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience, 276*, 187-205. http://dx.doi.org/10.1016/j.neuroscience.2013.11.026

Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., Mendes de Leon, C.F., Arnold, S.E., Barnes, L.L, & Bienias, J.L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*, *60*(12), 1909-1915. doi:10.1212/01.WNL.0000069923.64550.9F

Berggren, R., Nilsson, J., Brehmer, Y., Schmiedek, F., & Lövdén, M. (2020). Foreign language learning in older age does not improve memory or intelligence: Evidence from a randomized controlled study. *Psychology and Aging, 35*(2), 212-219. https://doi.org/10.1037/pag0000439

Bherer, L., Erickson, K.I., & Liu-Ambrose, T. (2013). Physical exercise and brain functions in older adults. *Journal of Aging Research, 2013*, Article 197326. https://doi.org/10.1155/2013/197326

Bialystok, E. (2006). Effect of bilingualism and computer video game experience on the Simon task. *Canadian Journal of Experimental Psychology, 60*(1), 68–79. https://doi.org/10.1037/cjep2006008

Bialystok, E. (2017). The bilingual adaptation: How minds accommodate experience. *Psychological Bulletin, 143*(3), 233-262. https://doi.org/10.1037/bul0000099

Bialystok, E., & Craik, F.I.M. (2006). *Lifespan cognition: Mechanisms of change*. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195169539.001.0001

Bialystok, E., Craik, F.I.M., & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia, 45*(2), 459-464. https://doi.org/10.1016/j.neuropsychologia.2006.10.009

Bialystok, E., Craik, F.I.M., Green, D., & Gollan, T. (2009). Bilingual minds. *Psychological Science in the Public Interest, 10*(3), 89-129. https://doi.org/10.1177/1529100610387084

Bialystok, E., Craik, F.I.M., Klein, R., & Viswanathan, M. (2004). Bilingualism, aging, and cognitive control: Evidence from the Simon task. *Psychology and Aging, 19*(2), 290-303. https://doi.org/10.1037/0882-7974.19.2.290

Bialystok, E., Craik, F.I.M., & Luk, G. (2008). Cognitive control and lexical access in younger and older bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 34*(4), 859–873. https://doi.org/10.1037/0278-7393.34.4.859

Bialystok, E., Craik, F.I.M., & Luk, G. (2012). Bilingualism: Consequences for mind and brain. *Trends in Cognitive Sciences, 16*(4), 240–250. https://doi.org/10.1016/j.tics.2012.03.001

Binder, J.R., & Desai, R.H. (2011). The neurobiology of semantic memory. *Trends in Cognitive Sciences, 15*(11), 527-536. https://doi.org/10.1016/j.tics.2011.10.001

Birdsong, D. (1999). *Second language acquisition and the critical period hypothesis*. Mahwah, NJ: Lawrence Erlbaum Associates.

Birdsong, D. (2006). Age and second language acquisition and processing: A selective overview. *Language Learning*, *56*, 9-49. https://doi.org/10.1111/j.1467-9922.2006.00353.x

Birdsong, D., Gertken, L.M., & Amengual, M. (2012). *Bilingual language profile: An easy-to-use instrument to assess bilingualism*. COERLL, University of Texas at Austin. Retrieved from https://sites.la.utexas.edu/bilingual/

Blanco-Elorrieta, E., & Pylkkänen, L. (2018). Ecological validity in bilingualism research and the bilingual advantage. *Trends in Cognitive Sciences*, *22*(12), 1117–1126. https://doi.org/10.1016/j.tics.2018.10.001

Boa. N.C., Gill, D.P., Gregory, M.A., Bocti, J., & Petrella, R.J. (2018). Multiple-modality exercise and mind-motor training to improve mobility in older adults: A randomized controlled trial. *Experimental Gerontology, 103,* 17–26. https://doi.org/10.1016/j.exger.2017.12.011

Bonaccorsi, J., Cintoli, S., Mastrogiacomo, R., Baldanzi, S., Braschi, C., Pizzorusso, T., Cenni, M.C., & Berardi, N. (2013). System consolidation of spatial memories in mice: Effects of enriched environment. *Neural Plasticity*, *2013*, Article 956312. https://doi.org/10.1155/2013/956312

Bongaerts, T. (1999). Ultimate attainment in L2 pronunciation: The case of very advanced late learners. In D. Birdsong (Ed.), *Second language acquisition and the critical period hypothesis* (pp. 133–159). Mahwah, NJ: Erlbaum.

Boot, W.R., Champion, M., Blakely, D.P., Wright, T., Souders, D.J., & Charness, N. (2013). Video games as a means to reduce age-related cognitive decline: Attitudes, compliance, and effectiveness. *Frontiers in Psychology, 4*, Article 31. https://doi.org/10.3389/fpsyg.2013.00031

Boot, W.R., Simons, D.J., Stothart, C., & Stutts, C. (2013). The pervasive problem with placebos in psychology: Why active control groups are not sufficient to rule out placebo effects. *Perspectives on Psychological Science, 8*(4), 445–454. https://doi.org/10.1177/1745691613491271

Bopp, K.L., & Verhaeghen, P. (2005). Aging and verbal memory span: A meta-analysis. *The Journals of Gerontology: Series B, 60*(5), 223-P233. https://doi.org/10.1093/geronb/60.5.P223

Bopp, K.L., & Verhaeghen, P. (2007). Age-related differences in control processes in verbal and visuospatial working memory: Storage, transformation, supervision, and coordination. *The Journals of Gerontology: Series B, 62*(5), 239-246. https://doi.org/10.1093/geronb/62.5.P239

Borg, G.A.V. (1982). Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise, 14*(5), 377–381. https://doi.org/10.1249/00005768-198205000-00012

Braver, T.S. (2012). The variable nature of cognitive control: a dual mechanisms framework. *Trends in Cognitive Sciences, 16*(2), 106-113. https://doi.org/10.1016/j.tics.2011.12.010

Brehmer, Y., Kalpouzos, G., Wenger, E., & Lövdén, M. (2014). Plasticity of brain and cognition in older adults. *Psychological Research, 78*(6), 790–802. https://doi.org/10.1007/s00426-014-0587-z

Brewer, W.F. (1986). What is autobiographical memory? In D. C. Rubin (Ed.), *Autobiographical memory* (pp. 25-49). New York: Cambridge University Press.

Brickman, A.M., Meier, I.B., Korgaonkar, M.S., Provenzano, F.A., Grieve, S.M., Siedlecki, K.L., Wasserman, B.T., Williams, L.M., & Zimmerman, M. E. (2012). Testing the white matter retrogenesis hypothesis of cognitive aging. *Neurobiology of Aging, 33*(8), 1699-1715. http://dx.doi.org/10.1016/j.neurobiolaging.2011.06.001

Brown, C.A., Hakun, J.G., Zhu, Z., Johnson, N.F., & Gold, B.T. (2015). White matter microstructure contributes to age-related declines in task-induced deactivation of the default mode network. *Frontiers in Aging Neuroscience, 7*, Article 194. https://doi.org/10.3389/fnagi.2015.00194

Bruderer-Hofstetter, M., Rausch-Osthoff, A.K., Meitchtry, A., Münzer, T., & Niedermann, K. (2018). Effective multicomponent interventions in comparison to active control and no interventions on physical capacity, cognitive function and instrumental activities of daily living in elderly people with and without mild impaired cognition – A systematic review and network meta-analysis. *Ageing Research Reviews, 45*, 1-14. https://doi.org/10.1016/j.arr.2018.04.002

Burin, D., & Kawashima, R. (2021). Repeated exposure to illusory sense of body ownership and agency over a moving virtual body improves executive functioning and increases prefrontal cortex activity in the elderly. *Frontiers of Human Neuroscience, 15*, Article 674326. https://doi.org/10.3389/fnhum.2021.674326

Burgaleta, M., Sanjuán, A., Ventura-Campos, N., Sebastian-Galles, N., & Ávila, C. (2016). Bilingualism at the core of the brain. Structural differences between bilinguals and monolinguals revealed by subcortical shape analysis. *NeuroImage, 125*, 437-445. doi:10.1016/j.neuroimage.2015.09.073

Butler, M., McCreedy, E., Nelson, V.A., Desai, P., Ratner, E., Fink, H.A., Hemmy, L.S., McCarten, J.R., Barclay, T.R., Brasure, M., Davila, H., & Kane, R.L. (2018). Does Cognitive Training Prevent Cognitive Decline? A Systematic Review. *Annals of Internal Medicine, 168*(1), 63-63. https://doi.org/10.7326/M17-1531

Caballero, A., Reales, J.M., & Ballesteros, S. (2018). Taste priming and cross-modal taste-olfactory priming in normal aging and in older adults with mild cognitive impairment. *Psicothema, 30*(3), 304. https://doi.org/10.7334/psicothema2017.382

Cabeza, R., Anderson, N.D., Locantore, J.K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage, 17*(3), 1394-1402. https://doi.org/10.1006/nimg.2002.1280

Cabeza, R., Daselaar, S.M., Dennis, N.A., Fleck, M.S., & Davis, S.W. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex, 18*(5), 1201-1209. https://doi.org/10.1093/cercor/bhm155

Calvo, N., García, A.M., Manoiloff, L., & Ibáñez, A. (2016). Bilingualism and cognitive reserve: A critical overview and a plea for methodological innovations. *Frontiers in Aging Neuroscience, 7*, Article 249. https://doi.org/10.3389/fnagi.2015.00249

Carlson, S.M., & Meltzoff, A.N. (2008). Bilingual experience and executive functioning in young children. *Developmental Science, 11*(2), 282–298. https://doi.org/10.1111/j.1467-7687.2008.00675.x

Casey, B.J., Giedd, J.N., & Thomas, K.M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology, 54*(1-3), 241–257. https://doi.org/10.1016/S0301-0511(00)00058-2

Cassilhas, R.C., Tufik S., & de Mello M.T. (2016). Physical exercise, neuroplasticity, spatial learning, and memory. *Cellular and Molelcular Life Science. 73*, 975–83. https://doi.org/10.1007/s00018-015-2102-0

Chan, A. W., Tetzlaff, J.M., Gøtzsche, P.C., Altman, D.G., Mann, H., Berlin, J.A., Dickersin, K., Hróbjartsson, A., Schulz, K.F., Parulekar, W.R., Krleza-Jeric, K., Laupacis, A., & Moher, D. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ, 346*, Article e7586. https://doi.org/10.1136/bmj.e7586

Cheung, M. (2019). A guide to conducting a meta-analysis with non-independent effects sizes. *Neuropsychological Reviews. 29*, 387-396. https://doi.org/10.1007/s11065-019-09415-6

Chiu, H.L., Chu, H., Tsai, J.C., Liu, D., Chen, Y.R., Yang, H.L., & Chou, K.R. (2017). The effect of cognitive-based training for healthy older people: A meta-analysis of randomized controlled trials. *PLoS One, 12*, Article e0176742. https://doi.org/10.1371/journal.pone.0176742

Chomsky, N. (1965) *Aspects of the Theory of Syntax*. Cambridge, Mass., MIT Press.

Chomsky, N. (2007). Approaching UG from below. In U. Sauerland, G. Hans-Martin (Eds.), *Interfaces + recursion = Language? Chomsky's minimalism and the view from syntax-semantics* (pp. 1 - 30). Berlin: De Gruyter Mouton.

Chow, S.C., & Liu, J.P. (2004). *Design and analysis of clinical trials. Concepts and methodologies (2nd edition).* Hoboken, New Jersey: John Wiley & Sons.

Christoffels, I.K., Firk, C., & Schiller, N.O. (2007). Bilingual language control: An event-related brain potential study. *Brain Research, 1147,* 192-208. https://doi.org/10.1016/j.brainres.2007.01.137

Clare, L., Wu, Y. T., Teale, J. C., MacLeod, C., Matthews, F., Brayne, C., Woods, B., & CFAS-Wales Study Team (2017). Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. *PLoS Medicine, 14*(3), e1002259. https://doi.org/10.1371/journal.pmed.1002259

Coderre, E.L., Smith, J.F., Van Heuven, W.J.B., & Horwitz, B. (2016). The functional overlap of executive control and language processing in bilinguals. Bilingualism: *Language and Cognition, 19*(3), 471–488. https://doi.org/10.1017/S1366728915000188

Coderre, E.L., & van Heuven, W.J.B. (2014). Electrophysiological explorations of the bilingual advantage: Evidence from a Stroop task. *PLoS One, 9*(7), Article e103424. https://doi.org/10.1371/journal.pone.0103424

Colcombe, S., & Kramer, A.F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14*(2), 125-130. https://doi.org/10.1111/1467-9280.t01-1-01430

Concato, J., Shah, N., & Horwitz, R.I. (2000). Randomized, controlled trials, observational studies, and the hierarchy of research designs. *The New England Journal of Medicine, 342(25),* 1887–1892. https://doi.org/10.1056/NEJM200006223422507

Conway, M.A. (2001). Sensory–perceptual episodic memory and its context: autobiographical memory. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 356*(1413), 1375-1384. https://doi.org/10.1098/rstb.2001.0940

Cools, R., Van Schouwenburg, M., & Ouden, H.D. (2010). The human basal ganglia modulate frontal-posterior connectivity during attention shifting. *Journal of Neuroscience, 30*(29), 9910-9918. https://doi.org/10.1523/jneurosci.1111-10.2010

Costa, A., Hernández, M., & Sebastián-Gallés, N. (2008). Bilingualism aids conflict resolution: Evidence from the ANT task. *Cognition, 106*(1), 59–86. https://doi.org/10.1016/j.cognition.2006.12.013

Costa, A., Hernandez, M., Costa-Faidella, J., & Sebastian-Galles, N. (2009). On the bilingual advantage in conflict processing: Now you see it, now you don't. *Cognition, 113*(2), 135-149. https://doi.org/10.1016/j.cognition.2009.08.001

Corbetta, M., Patel, G., & Shulman, G.L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron, 58*(3), 306-324. https://doi.org/10.1016/j.neuron.2008.04.017

Craik, F.I.M., Bialystok, E., & Freedman, M. (2010). Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve. *Neurology, 75*(19), 1726-1729. https://doi.org/10.1212/WNL.0b013e3181fc2a1c

Crinion, J., Turner, R., Grogan, A., Hanakawa, T., Noppeney, U., Devlin, J. T., Aso, T., Urayama, S., Fukuyama, H., Stockton, K., Usui,K., Green, D.W., & Price, C. J. (2006). Language control in the bilingual brain. *Science, 312*(5779), 1537-1540. https://doi.org/10.1126/science.1127761

Dahlin, E., Nyberg, L., Bäckman, L., & Neely, A.S. (2008). Plasticity of executive functioning in young and older adults: Immediate training gains, transfer, and long-term maintenance. *Psychology and Aging, 23*(4), 720–730. https://doi.org/10.1037/a0014296

Dause, T.J., & Kirby, E.D. (2019). Aging gracefully: social engagement joins exercise and enrichment as a key lifestyle factor in resistance to age-related cognitive decline. *Neural Regeneration Research, 14*(1), 39-42. http://doi.org/10.4103/1673-5374.243698.

De Baene, W.D., Duyck, W., Brass, M., & Carreiras, M. (2015). Brain circuit for cognitive control is shared by task and language switching. *Journal of Cognitive Neuroscience, 27*(9), 1752-1765. https://doi.org/10.1162/jocn_a_00817

de Bruin, A., Bak, T.H., & Della Sala, S. (2015). Examining the effects of active versus inactive bilingualism on executive control in a carefully matched non-immigrant sample. *Journal of Memory and Language, 85,* 15–26. https://doi.org/10.1016/j.jml.2015.07.001

DeKeyser, R.M. (2003). Implicit and explicit learning. In C. J. Doughty & H. M. Long (Eds.), *The handbook of second language acquisition* (pp. 312–348). Oxford, UK: Blackwell.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9-21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Dennis, N.A., Kim, H., & Cabeza, R. (2008). Age-related differences in brain activity during true and false memory retrieval. *Journal of Cognitive Neuroscience, 20*(8), 1390–1402. https://doi.org/10.1162/jocn.2008.20096

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience, 18,* 193 - 222. https://doi.org/10.1146/annurev.ne.18.030195.001205

*Desjardins-Crépeau, L., Berryman, N., Fraser, S. A., Minh Vu, T.T., Kergoat, M.J., Li, K.Z.H, Bosqute, L., & Bherer, L. (2016). Effects of combined physical and cognitive training on fitness and neuropsychological outcomes in healthy older adults. *Clinical Interventions in Aging, 11*, 1287-99. https://doi.org/10.2147/cia.s115711

Diamond, A. (2013). Executive functions. *Annual Review of Psychology, 64*(1), 135-168. doi:10.1146/annurev-psych-113011-143750

Donnelly, S., Brooks, P. J., & Homer, B. D. (2019). Is there a bilingual advantage on interference-control tasks? A multiverse meta-analysis of global reaction time and interference cost. *Psychonomic Bulletin & Review, 26*(4), 1122–1147. https://doi.org/10.3758/s13423-019-01567-z

Douka, S., Zilidou, V.I., Lilou, O., & Tsolaki, M. (2019). Greek traditional dances: A way to support intellectual, psychological, and motor functions in senior citizens at risk of neurodegeneration. *Frontiers in Aging Neuroscience*, *11,* Article 6. https://doi.org/10.3389/fnagi.2019.00006

Duval, S.J., & Tweedie, R.L. (2000a). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56,* 455–463. https://doi.org/10.1111/j.0006-341X.2000.00455.x

Duval, S.J., & Tweedie, R.L. (2000b). A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *Journal of the American Statistical Association, 95*(449), 89-98. https://doi.org/10.1080/01621459.2000.10473905

Egeth, H.E., & Yantis, S. (1997). Visual attention: Control, representation, and time course. Annual *Review of Psychology, 48,* 269–297. https://doi.org/10.1146/annurev.psych.48.1.269

*Eggenberger, P., Schumacher, V., Angst, M., Theill, N., & de Bruin, E.D. (2015). Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. *Clinical Interventions in Aging, 10,* 1335-1349. https://doi.org/10.2147/CIA.S87732

Egger, M., Davey-Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ, 315,* 629–634. https://doi.org/10.1136/bmj.315.7109.629

Engle, R.W., Kane, M.J., & Tuholski, S.W. (1999). Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 102-134). NY, US: Cambridge University Press.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Hu, L., Morris, K.S., White, S.M., Wójcicki, T.R., McAuley, E., & Dramer, A.F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus 19*(10), 1030–1039. https://doi.org/10.1002/hipo.20547

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B. D., Woods, J.A., McAuley, E., & Kramer, A.F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America, 108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Eriksen, C.W., & James, J.D.S. (1986). Visual attention within and around the field of focal attention: A zoom lens model. *Perception & Psychophysics, 40*(4), 225-240. https://doi.org/10.3758/BF03211502

Esmail, A., Vrinceanu, T., Lussier, M., Predovan, D., Berryman, N., Houle, J., Karelis, A., Grenier, S., Minh Vu, T.T., Villalpando, J.M., & Bherer, L. (2020). Effects of Dance/Movement Training vs. Aerobic Exercise Training on cognition, physical fitness and quality of life in older adults: A randomized controlled trial. *Journal of Bodywork and Movement Therapies, 24*(1), 212-220. https://doi.org/10.1016/j.jbmt.2019.05.004

European Commission (2018). *The 2018 ageing report: economic and budgetary projections for the EU Member States (2016–2070).* Luxembourg: Publications Office of the European Union. Retrieved from https://ec.europa.eu/info/sites/info/files/economy-finance/ip079_en.pdf

Eurostat 2016. https://ec.europa.eu/eurostat/news/themes-in-the-spotlight/eu-in-the-world-2016

*Fabre, C., Chamari, K., Mucci, P., Masse-Biron, J., & Prefaut, C. (2002). Improvement of cognitive function by mental/and or individualized aerobic training in healthy elderly subjects. *International Journal of Sports Medicine. 23*(6), 415-421. https://doi.org/10.1055/s-2002-33735

Fabrigoule, C., Letenneur, L., Dartigues, J.F., Zarrouk, M., Commenges, D., & Barberger-Gateau, P. (1995). Social and leisure activities and risk of dementia: A prospective longitudinal study. *Journal of the American Geriatrics Society, 43*(5), 485-490. https://doi.org/10.1111/j.1532-5415.1995.tb06093.x

Falbo, S., Condello, G., Capranica, L., Forte, R., & Pesce, C. (2016). Effects of physical-cognitive dual task training on executive function and gait performance in older adults: A randomized controlled trial. *BioMed Research International, 2016*, 1-12. https://doi.org/10.1155/2016/5812092

Falck, R.S., Davis, J.C., Best, J.R., & Crockett, R.A. (2019). Impact of exercise training on physical and cognitive function among older adults. A systematic review and meta-analysis. *Neurobiology of Aging, 7*, 119-130. https://doi.org/10.1016/j.neurobiolaging.2019.03.007

Faul F., Erdfelder E., Buchner A., & Lang A.G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. https://doi.org/10.3758/BRM.41.4.1149

Ferreira, N., Owen, A., Mohan, A., Corbett, A., & Ballard, C. (2015). Associations between cognitively stimulating leisure activities, cognitive function and age-related cognitive decline. International *Journal of Geriatric Psychiatry, 30*(4), 422. https://doi.org/10.1002/gps.4155

Festman, J., Rodriguez-Fornells, A., & Münte, T.F. (2010). Individual differences in control of language interference in late bilinguals are mainly related to general executive abilities. *Behavioral and Brain Functions, 6*, Article 5. https://doi.org/10.1186/1744-9081-6-5

Finkel, D., Reynolds, C.A., McArdle, J.J., & Pedersen, N.L. (2007). Age changes in processing speed as a leading indicator of cognitive aging. *Psychology and Aging, 22*(3), 558-568. https://doi.org/10.1037/0882-7974.22.3.558

Flege, J.E., Yeni-Komshian, G.H., & Liu, S. (1999). Age constraints on second-language acquisition. *Journal of Memory and Language, 41*(1), 78–104. https://doi.org/10.1006/jmla.1999.2638

Fleischman, D.A. (2007). Repetition priming in aging and Alzheimer's disease: An integrative review and future directions. *Cortex, 43*(7), 889-897. https://doi.org/10.1016/S0010-9452(08)70688-9

Fleischman, D.A., & Gabrieli, J.D.E. (1998). Repetition priming in normal aging and Alzheimer's disease: A review of findings and theories. *Psychology and Aging, 13*(1), 88–119. https://doi.org/10.1037/0882-7974.13.1.88

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12(*3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fotenos, A.F., Snyder, A.Z., Girton, L.E., Morris, J.C., & Buckner, R.L. (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology, 64*(6), 1032. https://doi.org/10.1212/01.WNL.0000154530.72969.11

Fratiglioni, L., Wang, H.X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet, 355*(9212), 1315-1319. https://doi.org/10.1016/s0140-6736(00)02113-9

Freeman, S.H., Kandel, R., Cruz, L., Rozkalne, A., Newell, K., Frosch, M.P., Hedley-Whyte, T., Locascio, J.J., Lipsitz, L.A., & Hyman, B.T. (2008). Preservation of neuronal number despite age-related cortical brain atrophy in elderly subjects without Alzheimer disease. *Journal of Neuropathology & Experimental Neurology, 67*(12), 1205-1212. https://doi.org/10.1097/NEN.0b013e31818fc72f

Friederici, A.D. (2011). The brain basis of language processing: From structure to function. *Physiological Reviews, 91*(4), 1357-1392. https://doi.org/10.1152/physrev.00006.2011

Friedman, N.P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *Journal of Experimental Psychology, 133*(1), 101-135. https://doi.org/10.1037/0096-3445.133.1.101

Gajewski, P.D., & Falkenstein, M. (2012). Training-induced improvement of response selection and error detection in aging assessed by task switching: Effects of cognitive, physical, and relaxation training. *Frontiers in Human Neuroscience, 6*, Article 130. https://doi.org/10.3389/fnhum.2012.00130

Gajewski, P.D., Ferdinand, N.K., Kray, J., & Falkenstein, M. (2018). Understanding sources of adult age differences in task switching: Evidence from behavioral and ERP studies. *Neuroscience and Biobehavioral Reviews, 92*, 255–275. https://doi.org/10.1016/j.neubiorev.2018.05.029

Gajewski, P.D., Freude, G., & Falkenstein, M. (2017). Cognitive training sustainably improves executive functioning in middle-aged industry workers assessed by task switching: A randomized controlled ERP study. *Frontiers in Human Neuroscience, 11*, Article 81. https://doi.org/10.3389/fnhum.2017.00081

Gajewski, P.D., Wild-Wall, N., Schapkin, S.A., Erdmann, U., Freude, G., & Falkenstein, M. (2010). Effects of aging and job demands on cognitive flexibility assessed by task switching. *Biological Psychology, 85*(2), 187–199. https://doi.org/10.1016/j.biopsycho.2010.06.009

Gates, N.J., Rutjes, A.W., Di Nisio, M., Karim, S., Chong, L.Y., March, E., Martínez, G., & Vernooij, R.W. (2019). Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life. *Cochrane Database of Systematic Reviews, 3*(3). https://doi.org/10.1002/14651858.CD012277.pub2

Gavelin, H.M., Lampit, A., Hallock, H. Sabatés, J., & Bahar-Fuchs, A. (2020). Cognition-Oriented Treatments for Older Adults: A Systematic Overview of Systematic Reviews. *Neuropsychology Reviews. 30*(2), 167–193. https://doi.org/10.1007/s11065-020-09434-8

Gavrilov, L.A., & Heuveline, P. (2003). Aging of population. In P. Demeny & G. McNicoll (Eds.), *The encyclopedia of population (pp. 32–37).* New York, NY: Macmillan Reference.

Gertken, L.M., Amengual, M., & Birdsong, D. (2014). Assessing language dominance with the bilingual language profile. In P. Leclercq, A. Edmonds, & H. Hilton (Eds.), *Measuring l2 proficiency: Perspectives from SLA* (pp. 208-225). Bristol: Multilingual Matters.

Gheysen, F., Poppe, L., DeSmet, A., Swinnen, S., Cardon, G., De Bourdeaudhuij, I., Chastin, S., & Fias, W. (2018). 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. *The International Journal of Behavioral Nutrition and Physical Activity, 15,* Article 63. https://doi.org/10.1186/s12966-018-0697-x

*Gill, D.P., Gregory, M.A., Zou, G., Liu-Ambrose, T., Shigematsu, R., Hachinski, V., Fitzgerald, C., & Petrella, R.J. (2016). The healthy mind, healthy mobility trial: A novel exercise program for older adults. *Medicine & Science in Sports & Exercise, 48*(2), 297-306. https://doi.org/10.1249/MSS.0000000000000758

Goh, J.O., An, Y., & Resnick, S.M. (2012). Differential trajectories of age-related changes in components of executive and memory processes. *Psychology and Aging, 27*(3), 707-719. https://doi.org/10.1037/a0026715

Gold, B. (2015). Lifelong bilingualism and neural reserve against Alzheimer's disease: A review of findings and potential mechanisms. *Behavioural Brain Research, 281*, 9-15. http://dx.doi.org/10.1016/j.bbr.2014.12.006

Gold, S.M., Enck, P., Hasselmann, H., Friede, T., Hegerl, U., Mohr, D.C., & Otte, C. (2017). Control conditions for randomised trials of behavioural interventions in psychiatry: a decision framework. *Lancet Psychiatry, 4*, 725-732. https://doi.org/10.1016/S2215-0366(17)30153-0

Gold, B.T., Kim, C., Johnson, N.F., Kryscio, R.J., & Smith, C.D. (2013). Lifelong bilingualism maintains neural efficiency for cognitive control in aging. *The Journal of Neuroscience, 33*(2), 387–396. https://doi.org/10.1523/JNEUROSCI.3837-12.2013

Gollan, T.H., Montoya, R.I., Fennema-Notestine, C., & Morris, S.K. (2005). Bilingualism affects picture naming but not picture classification. *Memory & Cognition, 33*(7), 1220-1234. https://doi.org/10.3758/BF03193224

Goral, M., Campanelli, L., & Spiro, A. (2015). Language dominance and inhibition abilities in bilingual older adults. *Bilingualism, 18*(1), 79-89. https://doi.org/10.1017/S1366728913000126

Grady, C.L., Luk, G., Craik, F.I.M., & Bialystok, E. (2015). Brain network activity in monolingual and bilingual older adults. *Neuropsychologia, 66*, 170-181. https://doi.org/10.1016/j.neuropsychologia.2014.10.042

Green, D.W. (1998). Mental control of the bilingual lexico-semantic system. Bilingualism: *Language and Cognition, 1*(2), 67–81. https://doi.org/10.1017/S1366728998000133

Green, D.W., & Abutalebi, J. (2013). Language control in bilinguals: The adaptive control hypothesis. *Journal of Cognitive Psychology, 25*(5), 515-530. https://doi.org/10.1080/20445911.2013.796377

Grundy, J.G., Anderson, J., & Bialystok, E. (2017). Neural correlates of cognitive processing in monolinguals and bilinguals. *Annals of the New York Academy of Sciences, 1396*(1), 183–201. https://doi.org/10.1111/nyas.13333

*Gschwind, Y.J., Eichberg, S., Ejupi, A., de Rosario, H., Kroll, M., Marston, H.R., Drobics, M., Annegarn, J., Wieching, R., Lord, S.R., Aal, K., Vaziri, D., Woodbury, A., & Delbaere, K. (2015). ICT-based system to predict and prevent falls (iStoppFalls): results from an international multicenter randomized controlled trial. *European Review of Aging and Physical Activity, 12*(10), 1-11. https://doi.org/10.1186/s11556-015-0155-6

Guiney, H., & Machado, L. (2012). Benefits of regular aerobic exercise for executive functioning in healthy populations. *Psychonomic Bulletin & Review, 20*(1), 73–86. https://doi.org/10.3758/s13423-012-0345-4

Gunning-Dixon, F.M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology, 14*(2), 224-232. https://doi.org/10.1037/0894-4105.14.2.224

Guo, W., Zang, M., Klich, S., Kawczyński, A., Smoter, M., & Wang, B. (2020). Effect of combined physical and cognitive interventions on executive functions in older adults: a meta-analysis of outcomes. *International Journal of Environmental Research and Public Health, 17*(17), 6166. https://doi.org/10.3390/ijerph17176166

Guralnik, J.M., Simonsick, E.M., Ferrucci, L., Glynn, R.J., Berkman, L.F., Blazer, D.G., Scherr, P.A., & Wallace, R.B. (1994). A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *Journal of Gerontology, 49*(2), M85–M9. https://doi.org/10.1093/geronj/49.2.M85

Gutchess, A.H., Welsh, R.C., Hedden, T., Bangert, A., Minear, M., Liu, L.L., & Park, D.C. (2005). Aging and the neural correlates of successful picture encoding: Frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience, 17*(1), 84-96. https://doi.org/10.1162/0898929052880048

Håkansson, K., Ledreux, A., Daffner, K., Terjestam, Y., Bergman, P., Carlsson, R., Kivipelto, M., Winblad, B., Granholm, A.C., & Mohammed, A.K. (2017). BDNF responses in healthy older persons to 35 minutes of physical exercise, cognitive training, and mindfulness: Associations with working memory function. *Journal of Alzheimer's Disease, 55*(2), 645-657. https://doi.org/10.3233/JAD-160593

Harada, N.D., Chiu, V., & Stewart, A.L. (1999). Mobility-related function in older adults: assessment with a 6-minute walk test. *Archives of Physical Medicine and Rehabilitation, 80*(7), 837-841. https://doi.org/10.1016/S0003-9993(99)90236-8

Harper S. (2014). Economic and social implications of aging societies. *Science, 346*(6209), 587–591. https://doi.org/10.1126/science.1254405

Hartanto, A., & Yang, H. (2016). Disparate bilingual experiences modulate task-switching advantages: A diffusion-model analysis of the effects of interactional context on switch costs. *Cognition, 150,* 10-19. https://doi.org/10.1016/j.cognition.2016.01.016

Hartanto, A., & Yang, H. (2020). The role of bilingual interactional contexts in predicting interindividual variability in executive functions: A latent variable analysis. *Journal of Experimental Psychology, 149*(4), 609-634. https://doi.org/10.1037/xge0000672

Hasher, L., Zacks, R.T., & May, C.P. (1999). Inhibitory control, circadian arousal, and age. In D. Gopher & A. Koriat (Eds.), *Attention and performance: XVII. Cognitive regulation of performance: Interaction of theory and application* (pp. 653-675). Cambridge, MA: MIT Press.

Hausdorf, J.M., Yogev, G., Springer, S., Simon, E.S., & Giladi, N. (2005). Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Experimental Brain Research, 164*(4), 541-548. https://doi.org/10.1007/s00221-005-2280-3

Hernández, M., Martin, C.D., Barceló, F., & Costa, A. (2013). Where is the bilingual advantage in task-switching? *Journal of Memory and Language, 69*(3), 257–276. https://doi.org/10.1016/j.jml.2013.06.004

Hervais-Adelman, A.G., Moser-Mercer, B., & Golestani, N. (2011). Executive control of language in the bilingual brain: integrating the evidence from neuroimaging to neuropsychology. *Frontiers in Psychology, 2*. https://doi.org/10.3389/fpsyg.2011.00234

Hindin, S.B., & Zelinski, E.M. (2012). Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: A meta-analysis. *Journal of the American Geriatrics Society, 60*(1), 136-141. https://doi.org/10.1111/j.1532-5415.2011.03761.x

Hirase, H., & Shinohara, Y. (2014). Transformation of cortical and hippocampal neural circuit by environmental enrichment. *Neuroscience, 280,* 282-298. http://dx.doi.org/10.1016/j.neuroscience.2014.09.031

*Hiyamizu, M., Morioka, S., Shomoto, K., & Shimada, T. (2012). Effects of dual task balance training on dual task performance in elderly people: A randomized controlled trial. *Clinical Rehabilitation, 26*(1), 58–67. https://doi.org/10.1177/0269215510394222

Hong, Z., Ng, K.K., Sim, S.K.Y., Ngeow, M.Y., Zheng, H., Lo, J.C., Chee, M.W.L, & Zhou, J. (2015). Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults. *NeuroImage, 123,* 42-50. http://dx.doi.org/10.1016/j.neuroimage.2015.08.034

Hötting, K., & Röder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neuroscience & Biobehavioral Reviews, 37,* 2243-2257. http://doi.org/10.1016/j.neubiorev.2013.04.005

*Htut, T., Hiengkaew, V., Jalayondeja, C., & Vongsirinavarat, M. (2018). Effects of physical, virtual reality-based, and brain exercise on physical, cognition, and preference in older persons: a randomized controlled trial. *European Review of Aging and Physical Activity, 15,* Article 10. https://doi.org/10.1186/s11556-018-0199-5

Houtzager, N., Lowie, W., Sprenger, S., & de Bot, K. (2017). A bilingual advantage in task switching? Age-related differences between German monolinguals and Dutch-

Frisian bilinguals. *Bilingualism: Language and Cognition, 20*(1), 69–79. https://doi.org/10.1017/S1366728915000498

Huff, M.J., Balota, D.A., Minear, M., Aschenbrenner, A.J., & Duchek, J.M. (2015). Dissociative global and local task-switching costs across younger adults, middle-aged adults, older adults, and very mild Alzheimer's disease individuals. *Psychology and Aging, 30*(4), 727-739. https://doi.org/10.1037/pag0000057

Hunter, J.E., and Schmidt, F.L. (1990). *Methods of meta-analysis: Correcting error and bias in research findings*. Newbury Park, CA: Sage.

Hurd, M.D., Martorell, P., Delavande, A., Mullen, K.J., & Langa, K.M. (2013). Monetary costs of dementia in the United States. *The New England Journal of Medicine, 368*(14), 1326–1334. https://doi.org/10.1056/NEJMsa1204629

Hyltenstam, K., & Abrahamsson, N. (2003). Maturational constraints in SLA. In C. J. Doughty & M. H. Long (Eds.), *The handbook of second language acquisition* (pp. 539–588). Malden, MA: Blackwell.

Ikier, S., Yang, L., & Hasher, L. (2008). Implicit proactive interference, age, and automatic versus controlled retrieval strategies. *Psychological Science, 19*(5), 456–461. https://doi.org/10.1111/j.1467-9280.2008.02109.x

Ioannidis, J.P.A. (2008). Interpretation of tests of heterogeneity and bias in meta-analysis. *Journal of Evaluation in Clinical Practice, 14*(5), 951–957. https://doi.org/10.1111/j.1365-2753.2008.00986.x

Ioannidis, J.P.A., & Trikalinos, T.A. (2007). The appropriateness of asymmetry tests for publication bias in meta-analyses: A large survey. *Canadian Medical Association Journal, 176*(8), 1091–1096. https://doi.org/10.1503/cmaj.060410

*Jardim, N., Bento-Torres, N., Costa, V. O., Carvalho, J., Pontes, H., Tomás, A.M., Sosthenes, M., Erickson, K.I., Bento-Torres, J., & Diniz, C. (2021). Dual-task exercise to improve cognition and functional capacity of healthy older adults. *Frontiers in Aging Neuroscience, 13*, Article 589299. https://doi.org/10.3389/fnagi.2021.589299

Jaroslawska, A.J., & Rhodes, S. (2019). Adult age differences in the effects of processing on storage in working memory: A meta-analysis. *Psychology and Aging, 34*(4), 512-530. https://doi.org/10.1037/pag0000358

*Jehu, D.A., Paquet, N., & Lajoie, Y. (2017). Balance and mobility training with and without concurrent cognitive training improves the time up and go (TUG), TUG cognitive, and TUG manual in healthy older adults: an exploratory study. *Aging Clinical and Experimental Research, 29*, 711-720. https://doi.org/10.1007/s40520-016-0618-2

Jimura, K., & Braver, T.S. (2010). Age-related shifts in brain activity dynamics during task switching. *Cerebral Cortex, 20*(6), 1420–1431. https://doi.org/10.1093/cercor/bhp206

*Joubert, C., & Chainay, H., 2019. Effects of cognitive and aerobic training on working memory and executive function in aging, a pseudo-randomized trial: Pilot study. *Journal of Ageing Research and Healthcare, 2*(3), 46-70. https://doi.org/10.2147/CIA.S165399

Jung T., Makeig S., McKeown M.J., Bell A.J., Lee T., & Sejnowski T.J. (2001). Imaging brain dynamics using dependent component analysis. *Proceedings of the IEEE, 89*(7), 1107-1122. http://doi.org/10.1109/5.939827

Jung T.P, Makeig S., Stensmo M., & Sejnowski T.J. (1997). Estimating alertness from the EEG power spectrum. *IEEE Transactions on Biomedical Engineering, 44*(1), 60-9. http://doi.org/10.1109/10.553713

Kałamała, P., Szewczyk, J., Chuderski, A., Senderecka, M., & Wodniecka, Z. (2020). Patterns of bilingual language use and response inhibition: A test of the adaptive control hypothesis. *Cognition, 204,* Article 104373. http://doi.org/10.1016/j.cognition.2020.104373

Kane, M.J., Bleckley, M.K., Conway, A.R., & Engle, R.W. (2001). A controlled-attention view of working-memory capacity. *Journal of Experimental Psychology, 130*(2), 169-183. doi:10.1037//0096-3445.130.2.169

Kapa, L.L., & Colombo, J. (2013). Attentional control in early and later bilingual children. *Cognitive Development, 28*(3), 233–246. https://doi.org/10.1016/j.cogdev.2013.01.011

Kattenstroth, J.C., Kolankowska, I., Kalisch, T., & Dinse, H.R. (2010). Superior sensory, motor, and cognitive performance in elderly individuals with multi-year dancing activities. *Frontiers in Aging Neuroscience, 2,* Article 31. http://doi.org/10.3389/fnagi.2010.00031.

Kattenstroth, J.C., Kalisch, T., Holt, S., Tegenthoff, M., & Dinse, H. R. (2013). Six months of dance intervention enhances postural, sensorimotor, and cognitive performance in elderly without affecting cardio-respiratory functions. *Frontiers in Aging Neuroscience, 5,* Article 5. http://doi.org/10.3389/fnagi.2013.00005.

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Renbing, X., & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology, 23*(2), 138-144. https://doi.org/10.1002/ana.410230206

Kayama, H., Okamoto, K., Nishiguchi, S., Yamada, M., Kuroda, T., & Aoyama, T. (2014). Effect of a Kinect-based exercise on improving executive cognitive performance in community-dwelling elderly: Case control study. *Journal of Medical Internet Research, 16*(2), Article e61. https://doi.org/10.2196/jmir.3108

Keller, J.N. (2006). Age-related neuropathology, cognitive decline, and Alzheimer's disease. *Ageing Research Reviews, 5*(1), 1-13. http://dx.doi.org/10.1016/j.arr.2005.06.002

Keller, J.B., Hedden, T., Thompson, T.W., Anteraper, S.A., Gabrieli, J.D.E., & Whitfield-Gabrieli, S. (2015). Resting-state anticorrelations between medial and lateral prefrontal cortex: Association with working memory, aging, and individual differences. *Cortex, 64,* 271-280. https://doi.org/10.1016/j.cortex.2014.12.001

Kelly, M.E., Loughrey, D., Lawlor, B.A., Robertson, I.A., Walsh. C., & Brennan, S. (2014). The impact of cognitive training and mental stimulation on cognitive a everyday functioning of healthy older adults: a systematic review and a meta-analysis. *Ageing Research Reviews, 15,* 28-43. http://dx.doi.org/10.1016/j.arr.2014.02.004

Kempermann G., Fabel K., Ehninger D., Babu H., Leal-Galicia P., Garthe A., & Wolf S.A. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Frontiers in Neuroscience, 8,* Article 189. https://doi.org/10.3389/fnins.2010.00189

Kempermann, G., Kuhn, H.G., & Gage, F.H. (1998). Experience-induced neurogenesis in the senescent dentate gyrus. *The Journal of Neuroscience, 18*(9), 3206. https://doi.org/10.1523/JNEUROSCI.18-09-03206.1998

Kim, S.H., Kim, M., Ahn, Y.B., Lim, H.K., Kang, S.G., Cho, J.H., Park, S.J., & Song, S.W. (2011). Effect of dance exercise on cognitive function in elderly patients with metabolic syndrome: a pilot study. *Journal of Sports Science & Medicine, 10*(4), 671–678. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761497/

*Kitazawa, K., Showa, S., Hiraoka, A., Fushiki, Y., Sakauchi, H., & Mori, M. (2015). Effect of a dual-task net-step exercise on cognitive and gait function in older adults. *Journal of Geriatric Physical Therapy, 38*(3), 133–140. https://doi.org/10.1519/JPT.0000000000000029

Kmet, L.M., Lee, R.C., & Cook, L. S. (2004). Standard quality assessment criteria for evaluating primary research papers from a variety of fields. Alberta Heritage Foundation for Medical Research (AHFMR). https://doi.org/10.7939/R37M04F16

Knopman, D.S., Parisi, J. E., Salviati, A., Floriach-Robert, M., Boeve, B. F., Ivnik, R.J., Smith, G.E., Dickson, D.W., Johnson, K.A., Petersen, L.E., McDonald, W.C., Braak, H., & Petersen, R.C. (2003). Neuropathology of Cognitively Normal Elderly. *Journal of Neuropathology & Experimental Neurology, 62*(11), 1087-1095. https://doi.org/10.1093/jnen/62.11.1087

Kopp, B., Lange, F., Howe, J., & Wessel, K. (2014). Age-related changes in neural recruitment for cognitive control. *Brain and Cognition, 85,* 209-219. https://doi.org/10.1016/j.bandc.2013.12.008

Kosmat, H., & Vranic, A. (2017). The efficacy of a dance intervention as cognitive training for the old-old. *Journal of Aging and Physical Activity*, 25(1), 32–40. https://doi.org/10.1123/japa.2015-0264

Kraft, E. (2012). Cognitive function, physical activity, and aging: Possible biological links and implications for multimodal interventions. *Aging, Neuropsychology, and Cognition, 19*(1-2), 248–263. https://doi.org/10.1080/13825585.2011.645010

Kramer, A.F., Hahn, S., & Gopher, D. (1999). Task coordination and aging: explorations of executive control processes in the task switching paradigm. *Acta Psychologica, 101*, 2–3, 339-378. https://doi.org/10.1016/S0001-6918(99)00011-6

Kramer, A. F., & Madden, D. J. (2008). Attention. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition (3rd ed.)* (pp. 189–250). Psychology Press. https://doi.org/10.4324/9780203837665

Krampe, R.T., Smolders, C., Doumas, M. (2014). Leisure sports and postural control: Can a black belt protect your balance from aging? *Psychology and Aging, 29*(1), 95-102. http://doi.org/10.1037/a0035501.

Kray, J. (2006). Task-set switching under cue-based versus memory-based switching conditions in younger and older adults. *Brain Research, 1105*(1), 83-92. http://dx.doi.org/10.1016/j.brainres.2005.11.016

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging, 15*(1), 126-147. https://doi.org/10.1037/0882-7974.15.1.126

Kroll, J.F., Bobb, S.C., & Hoshino, N. (2014). Two languages in mind: Bilingualism as a tool to investigate language, cognition, and the brain. *Current Directions in Psychological Science, 23*(3), 159-163. https://doi.org/10.1177/0963721414528511

Kronenberg, G., Bick-Sander, A., Bunk, E., Wolf, C., Ehninger, D., & Kempermann, G. (2006). Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiology of Aging, 27*(10), 1505-1513. https://doi.org/10.1016/j.neurobiolaging.2005.09.016

*Laatar, R., Kachouri, H., Borji, R., Rebai, H., & Sahli, S. (2018). Combined physical-cognitive training enhances postural performances during daily life tasks in older adults. *Experimental Gerontology, 107*, 91-97. https://doi.org/10.1016/j.exger.2017.09.004

Lamme, V.A.F. (2003). Why visual attention and awareness are different. *Trends in Cognitive Sciences*, 7(1), 12-18. https://doi.org/10.1016/S1364-6613(02)00013-X

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLOS Medicine, 11,* Article e1001756. https://doi.org/10.1371/journal.pmed.1001756

Lauenroth, A., Ioannidis, A.E., & Teichmann, B. (2016). Influence of combined physical and cognitive training on cognition: a systematic review. *BMC Geriatrics, 16,* 141. http://doi.org/10.1186/s12877-016-0315-1

Law, L.L., Barnett, F., Yau, M.K., & Gray, M.A. (2014). Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: a systematic review. *Ageing Research Review, 15,* 61-75. https://doi.org/10.1016/j.arr.2014.02.008

Lee, T.W., Girolami, M., & Sejnowski, T.J. (1999). Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Computation, 11*(2), 417-441. https://doi.org/10.1162/089976699300016719

*Legault, C., Jennings, J.M., Katula, J.A., Dagenbach, D., Gaussoin, S.A., Sink, K.M., Rapp, S. R., Rejeski, W.J., Shumaker, S.A., & Espeland, M.A. (2011). Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: the Seniors Health and Activity Research Program Pilot (SHARP-P) study, a randomized controlled trial. *BMC Geriatrics, 11,* Article 27. https://doi.org/10.1186/1471-2318-11-27

Lehtonen, M., Soveri, A., Laine, A., Järvenpää, J., de Bruin, A., & Antfolk, J. (2018). Is bilingualism associated with enhanced executive functioning in adults? A meta-analytic review. *Psychological Bulletin, 144*(4), 394–425. https://doi.org/10.1037/bul0000142

Li, K., Bherer, L., Mirelman, A., Maidan, I., and Hausdorff, J.M. (2018). Cognitive involvement in balance, gait and dual-tasking in aging: A focused review from a neuroscience of aging perspective. *Frontiers in Neurolology, 9*, Article 913. https://doi.org/10.3389/fneur.2018.00913

Li, P., Legault, J., & Litcofsky, K.A. (2014). Neuroplasticity as a function of second language learning: anatomical changes in the human brain. *Cortex, 58*, 301-324. https://doi.org/10.1016/j.cortex.2014.05.001

Li, S.-C., Brehmer, Y., Shing, Y.L., Werkle-Bergner, M., & Lindenberger, U. (2006). Neuromodulation of associative and organizational plasticity across the life span: Empirical evidence and neurocomputational modeling. *Neuroscience and Biobehavioral Reviews, 30*(6), 775–790. https://doi.org/10.1016/j.neubiorev.2006.06.004

Li, S.-C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: from neuromodulation to representation. *Trends in Cognitive Sciences, 5*(11), 479-486. https://doi.org/10.1016/S1364-6613(00)01769-1

Lieberman, P. (2000). *Human language and our reptilian brain: The subcortical bases of speech, syntax, and thought*. Cambridge: Harvard University Press.

*Linde, K., & Alfermann, D. (2014). Single versus combined cognitive and physical activity effects on fluid cognitive abilities of healthy older adults: a 4-month randomized controlled trial with follow-up. *Journal of Aging and Physical Activity, 22*, 302-313. https://doi.org/10.1123/japa.2012-0149

Lindenberger, U., Mayr, U., & Kliegl, R. (1993). Speed and intelligence in old age. *Psychology and Aging, 8*(2), 207-220. https://doi.org/10.1037/0882-7974.8.2.207

Lintern, G., & Boot, W.R. (2019). Cognitive Training: Transfer Beyond the Laboratory? *Human Factors, 63*, 531-547. https://doi.org/10.1177/0018720819879814

Liu-Ambrose, T., Nagamatsu, L.S., Graf, P., Beattie, B.L., Ashe, M.C., & Handy, T.C. (2010). Resistance Training and Executive Functions: A 12-Month Randomized Controlled Trial. *Archives of Internal Medicine, 170*(2), 170-178. https://doi.org/10.1001/archinternmed.2009.494

Liu-Ambrose, T., Nagamatsu, L.S., Voss, M.W., Khan, K.M., & Handy, T.C. (2012). Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiology of Aging, 33*, 1690-1698. https://doi.org/10.1016/j.neurobiolaging.2011.05.010

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., & Buckner, R.L. (2002). Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron, 33*(5), 827-840. https://doi.org/10.1016/S0896-6273(02)00612-8

Lopez-Calderon, J., & Luck, S.J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience, 8*, Article 213. https://doi.org/10.3389/fnhum.2014.00213

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin, 136*(4), 659-676. http://doi.org/10.1037/a0020080.

Luk, G., Bialystok, E., Craik, F.I.M., & Grady, C.L. (2011). Lifelong bilingualism maintains white matter integrity in older adults. *The Journal of Neuroscience, 31*(46), 16808-16813. https://doi.org/10.1523/JNEUROSCI.4563-11.2011

Luk, G., Green, D., Abutalebi, J., & Grady, C. (2012). Cognitive control for language switching in bilinguals: A quantitative meta-analysis of functional neuroimaging studies. *Language and Cognitive Processes, 27*(10), 1479-1488. https://doi.org/10.1080/01690965.2011.613209

Lustig, C., Hasher, L., & Zacks, R.T. (2007). Inhibitory deficit theory: Recent developments in a "new view" In D. S. Gorfein & C. M. MacLeod (Eds.), *Inhibition in cognition* (pp. 145–162). American Psychological Association. https://doi.org/10.1037/11587-008

Lustig, C., Shah, P., Seidler, R., & Reuter-Lorenz, P.A. (2009). Aging, training, and the brain: A review and future directions. *Neuropsychology Review, 19*(4), 504–522. https://doi.org/10.1007/s11065-009-9119-9

Mahncke, H.W., Connor, B.B., Appelman, J., Ahsanuddin, O.N., Hardy, J.L., Wood, R.A., Joyce, N.M., Boniske, T., Atkins, S.M., & Merzenich, M.M. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: A randomized, controlled study. *Proceedings of the National Academy of Sciences, 103*(33), 12523. https://doi.org/10.1073/pnas.0605194103

Maillet, D., Yu, L., Hasher, L., & Grady, C. L. (2020). Age-related differences in the impact of mind-wandering and visual distraction on performance in a go/no-go task. *Psychology and Aging, 35*(5), 627-638. https://doi.org/10.1037/pag0000409

*Maillot, P., Perrot, A., & Hartley, A. (2012). Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. *Psychology and Aging, 27,* 589. https://doi.org/10.1037/a0026268

Makeig, S., Jung, T. P., Bell, A.J., Ghahremani, D., & Sejnowski, T.J. (1997). Blind separation of auditory event-related brain responses into independent components. *Proceedings of the National Academy of Sciences, 94*(20), 10979-10984. https://doi.org/10.1073/pnas.94.20.10979

Mar, J., Soto-Gordoa, M., Arrospide, A., Moreno-Izco, F., & Martinez-Lage, P. (2015). Fitting the epidemiology and neuropathology of the early stages of Alzheimer's disease to prevent dementia. *Alzheimer's Research & Therapy, 7*(1), 1-8. https://doi.org/10.1186/s13195-014-0079-9

Marinova-Todd, S.H., Marshall, D.B., & Snow, C.E. (2000). Three misconceptions about age and L2 learning. *TESOL Quarterly*, 34(1), 9-34. https://doi.org/10.2307/3588095

*Marmeleira, J.F., Godinho, M.B., & Fernandes, O.M. (2009). The effects of an exercise program on several abilities associated with driving performance in older adults. *Accident Analysis & Prevention, 41*, 90-97. https://doi.org/10.1016/j.aap.2008.09.008

Martínez de la Iglesia, J., Onís Vilches, M., Dueñas Herrero, R., Albert Colomer, C., Aguado Taberné, C., & Luque Luque, R. (2002). Versión española del cuestionario de Yesavage abreviado (GDS) para el despistaje de depresión en mayores de 65 años: adaptación y validación. *Medifam, 12*(10), 26-40. Retrieved from https://scielo.isciii.es/scielo.php?pid=s1131-57682002001000003&script=sci_arttext&tlng=en

May, C.P., & Hasher, L. (1998). Synchrony effects in inhibitory control over thought and action. *Journal of Experimental Psychology: Human Perception and Performance, 24*(2), 363–379. https://doi.org/10.1037/0096-1523.24.2.363

Mayas, J., Parmentier, F.B.R., Andres, P., & Ballesteros, S. (2014). Plasticity of Attentional Functions in Older Adults after Non-Action Video Game Training: A Randomized Controlled Trial. *PloS One, 9*(3), Article e92269. https://doi.org/10.1371/journal.pone.0092269

McAvinue, L.P., Golemme, M., Castorina, M., Tatti, E., Pigni, F.M., Salomone, S., Brennan, S., & Robertson, I.H. (2013). An evaluation of a working memory training scheme in older adults. *Frontiers in Aging Neuroscience, 5*, Article 20. https://doi.org/10.3389/fnagi.2013.00020

*McDaniel, M. A., Binder, E.F., Bugg, J.M., Waldum, E.R., Dufault, C. Meyer, A., Johanning, J., Zheng, J., Schechtman, K.B., & Kudelka, C. (2014). Effects of cognitive training with and without aerobic exercise on cognitively-demanding everyday activities. *Psychology and Aging, 29*(3), 717-730. https://doi.org/10.1037/a0037363

McEwen, S. C., Siddarth, P., Abedelsater, B., Kim, Y., Mui, W. L., Wu, P., . . . Merrill, D. A. (2018). Simultaneous aerobic exercise and memory training program in older adults with subjective memory impairments. *Journal of Alzheimers Disease, 62*(2), 795-806 https://doi.org/10.3233/JAD-170846

McIsaac, T.L., Lamberg, E.M., & Muratori, L.M. (2015). Building a framework for a dual task taxonomy. *BioMed Research International, 2015*, article 591475. https://doi.org/10.1155/2015/591475

Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. *PloS One, 7*(6), e38268. https://doi.org/10.1371/journal.pone.0038268

Mesulam, M.M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology, 28*(5), 597-613. https://doi.org/10.1002/ana.410280502

Meuter, R.F.I., & Allport, A. (1999). Bilingual language switching in naming: Asymmetrical costs of language selection. *Journal of Memory and Language, 40*(1), 25–40. https://doi.org/10.1006/jmla.1998.2602

Mireles, D.E., & Charness, N. (2002). Computational explorations of the influence of structured knowledge on age-related cognitive decline. *Psychology and Aging, 17*(2), 245–259. https://doi.org/10.1037/0882-7974.17.2.245

Mitchell, D.B., & Bruss, P.J. (2003). Age Differences in Implicit Memory: Conceptual, Perceptual, or Methodological? *Psychology and Aging, 18*(4), 807–822. https://doi.org/10.1037/0882-7974.18.4.807

Miyake, A., Friedman, N.P., Emerson, M.J., & Witzki, A.H. (2000). The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: A latent variable analysis. *Cognitive Psychology, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med, 6*, Article e1000097. https://doi.org/10.1136/bmj.b2535

Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin card sorting revisited: Distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 21*(19), 7733–7741. https://doi.org/10.1523/JNEUROSCI.21-19-07733.2001

Monsell, S. (2003). Task switching. *Trends in Cognitive Sciences, 7(*3), 134-140. https://doi.org/10.1016/S1364-6613(03)00028-7

Monsell, S., Sumner, P., & Waters, H. (2003). Task-set reconfiguration with predictable and unpredictable task switches. *Memory & Cognition, 31*(3), 327–342. https://doi.org/10.3758/BF03194391

Montero-Odasso, M., Verghese, J., Beauchet, O., & Hausdorff, J.M. (2012). Gait and cognition: A complementary approach to understanding brain function and the risk of falling. *Journal of the American Geriatrics Society, 60*(11), 2127–2136. https://doi.org/10.1111/j.1532-5415.2012.04209.x

Montgomery, A.A., Peters, T.J., & Little, P. (2003). Design, analysis and presentation of factorial randomised controlled trials. *BMC Medical Research Methodology, 3*(1), 1-5. https://doi.org/10.1186/1471-2288-3-26.

Morcom, A.M., Li, J., & Rugg, M.D. (2007). Age effects on the neural correlates of episodic retrieval: Increased cortical recruitment with matched performance. *Cerebral Cortex, 17*(11), 2491-2506. https://doi.org/10.1093/cercor/bhl155

*Morita, E., Yokoyama, H., Imai, D., Takeda, R., Ota, A., Kawai, E., Suzuki, Y., & Okazaki, K. (2018). Effects of 2-Year Cognitive–Motor Dual-Task Training on Cognitive Function and Motor Ability in Healthy Elderly People: A Pilot Study. *Brain Science, 8*, Article 86. https://doi.org/10.3390/brainsci8050086

Mozolic, J.L., Long, A.B., Morgan, A.R., Rawley-Payne, M., & Laurienti, P.J. (2011). A cognitive training intervention improves modality-specific attention in a randomized controlled trial of healthy older adults. *Neurobiology of Aging, 32*(4), 655–668. https://doi.org/10.1016/j.neurobiolaging.2009.04.013

Muiños, M., & Ballesteros, S. (2014). Peripheral vision and perceptual asymmetries in young and older martial arts athletes and nonathletes. *Attention, Perception, & Psychophysics, 76*(8), 2465–2476. https://doi.org/10.3758/s13414-014-0719-y

Muiños, M., & Ballesteros, S. (2015). Sports can protect dynamic visual acuity from aging: A study with young and older judo and karate martial arts athletes. *Attention, Perception, & Psychophysics, 77*(6), 2061–2073. https://doi.org/10.3758/s13414-015-0901-x

Muiños, M., & Ballesteros, S. (2018). Does physical exercise improve perceptual skills and visuospatial attention in older adults? A review. *European Review of Aging and Physical Activity, 15*. Article 2. https://doi.org/10.1186/s11556-018-0191-0

Muiños, M., & Ballesteros, S. (2020). Tai Chi to improving brain and cognition. In D. Hackfort, R. Schinke (Eds.). *The routledge international encyclopedia of sport and exercise psychology* (pp. 626-644), Vol. 2. Abingdon, Oxon: Routledge (Taylor & Francis Group)

Muiños, M., & Ballesteros, S. (2021). Does dance counteract age-related cognitive and brain declines in middle-aged and older adults? A systematic review. *Neuroscience & Biobehavioral Reviews, 121*, 259-276. https://doi.org/10.1016/j.neubiorev.2020.11.028

Netz, Y. (2019). Is there a preferred mode of exercise for cognition enhancement in older age? A narrative review. *Frontiers in Medicine, 6*, 57. https://doi.org/10.3389/fmed.2019.00057

Neugarten, B.L., Havighurst, R.J., & Tobin, S.S. (1961). The measurement of life satisfaction. *Journal of Gerontology, 16,* 134–143. https://doi.org/10.1093/geronj/16.2.134

*Ng, T.P., Ling, L.H.A., Feng, L., Nyunt, M.S.Z., Feng, L., Niti, M., Tan, B.Y., Chan, G., Khoo, S.A., Chan, S.M., Yap, P., & Yap, K.B. (2018). Cognitive effects of multi-domain interventions among pre-frail and frail community-living older persons: randomized controlled trial. *The Journals of Gerontology, 73*(6), 806-812. https://doi.org/10.1093/gerona/glx207

*Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., . . . Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet, 385*(9984), 2255–2263. https://doi.org/10.1016/S0140-673

Niemann, C., Godde, B., & Voelcker-Rehage, C. (2014). Not only cardiovascular, but also coordinative exercise increases hippocampal volume in older adults. *Frontiers in Aging Neuroscience, 6*, Article 170. https://doi.org/10.3389/fnagi.2014.00170

*Nilsson, J., Ekblom, Ö., Ekblom, M., Lebedev, A., Tarassova, O., Moberg, M., & Lövdén, M. (2020). Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. *Scientific Reports, 10*(1), 4395. https://doi.org/10.1038/s41598-020-60124-0

Nilsson, L.-G. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica, 107*, 7–13. https://doi.org/10.1034/j.1600-0404.107.s179.5.x

*Nishiguchi, S., Yamada, M., Tanigawa, T., Sekiyama, K., Kawagoe, T., Suzuki, M., Yoshikawa, S., Abe, N., Otsuka, Y., Nakai, R., Aoyama, T., & Tsuboyama, T. (2015). A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: a randomized controlled trial. *Journal of the American Geriatrics Society, 63*(7), 1355-1363. https://doi.org/10.1111/jgs.13481

*Nocera, J.R., Mammino, K., Kommula, Y., Wharton, W., Crosson, B., & McGregor, K.M. (2020). Effects of combined aerobic exercise and cognitive training on verbal Fluency in older adults. *Gerontology and Geriatric Medicine, 6*, 1 – 11. https://doi.org/10.1177/2333721419896884

Nolla, M.D.C., Queral, R., & Miró, J. (2014). Las escalas panas de afecto positivo y negativo: Nuevos datos de su uso en personas mayores [The Positive and Negative Affect Schedule: Further examination of the questionnaire when used with older patients]. *Revista de Psicopatología y Psicología Clínica, 19*(1), 15–21. https://doi.org/10.5944/rppc.vol.19.num.1.2014.12931

*Norouzi, E., Vaezmosavi, M., Gerber, M., Pühse, U., & Brand, S. (2019). Dual-task training on cognition and resistance training improved both balance and working memory in older people. *The Physician and Sportsmedicine, 47*(4), 471-478. https://doi.org/10.1080/00913847.2019.1623996

Northey, J.M., Cherbuin, N., Pumpa, K.L., Smee, D.J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *British Journal of Sports Medicine, 52*(3), 154-160. https://doi.org/10.1136/bjsports-2016-096587

Nyberg, L., Bäckman, L., Erngrund, K., Olofsson, U., & Nilsson, L.G. (1996). Age differences in episodic memory, semantic memory, and priming: Relationships to demographic, intellectual, and biological factors. *The Journals of Gerontology, 51(*4), 234-240. https://doi.org/10.1093/geronb/51B.4.P234

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences, 16*(5), 292-305. https://doi.org/10.1016/j.tics.2012.04.005

O'Sullivan, M., Jones, D.K., Summers, P.E., Morris, R.G., Williams, S.C.R., & Markus, H.S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology, 57*(4), 632–638. https://doi.org/10.1212/WNL.57.4.632

Onton, J., Delorme, A., & Makeig, S. (2005). Frontal midline EEG dynamics during working memory. *Neuroimage, 27*(2), 341-356. http://doi.org/10.1016/j.neuroimage.2005.

Orwin, R.G. (1983). A fail-safe N for effect size in meta-analysis. *Journal of Educational Statistics, 8*(2), 157–159. https://doi.org/10.2307/1164923

Osorio, A., Ballesteros, S., Fay, S., & Pouthas, V. (2009). The effect of age on word-stem cued recall: A behavioral and electrophysiological study. *Brain Research, 1289*, 56-68. https://doi.org/10.1016/j.brainres.2009.07.013

Osorio, A., Fay, S., Pouthas, V., & Ballesteros, S. (2010). Ageing affects brain activity in highly educated older adults: An ERP study using a word-stem priming task. *Cortex, 46*(4), 522-534. https://doi.org/10.1016/j.cortex.2009.09.003

*Oswald, W.D., Gunzelmann, T., Rupprecht, R., & Hagen, B. (2006). Differential effects of single versus combined cognitive and physical training with older adults: The SimA study in a 5-year perspective. *European Journal of Ageing, 3*(4), 179–192. https://doi.org/10.1007/s10433-006-0035-z

Owsley, C., Sloane, M., McGwin, G., Jr., & Ball, K. (2002). Timed instrumental activities of daily living tasks: Relationship to cognitive function and everyday performance assessments in older adults. *Gerontology, 48*(4), 254–265. https://doi.org/10.1159/000058360

Paap, K.R., & Greenberg, Z.I. (2013). There is no coherent evidence for a bilingual advantage in executive processing. *Cognitive Psychology, 66*(2), 232–258. https://doi.org/10.1016/j.cogpsych.2012.12.002

Paap, K.R., Johnson, H.A., & Sawi, O. (2016). Should the search for bilingual advantages in executive functioning continue? *Cortex, 74,* 305-314. https://doi.org/10.1016/j.cortex.2015.09.010

Paap, K.R., Mason, L., Zimiga, B., Ayala-Silva, Y., & Frost, M. (2020). The alchemy of confirmation bias transmutes expectations into bilingual advantages: A tale of two new meta-analyses. *Quarterly Journal of Experimental Psychology, 73*(8), 1290-1299. https://doi.org/10.1177/1747021819900098

Packard, M.G., & Knowlton, B.J. (2002). Learning and memory functions of the basal ganglia. Annual *Review of Neuroscience, 25,* 563–593. https://doi.org/10.1146/annurev.neuro.25.112701.142937

Park, D.C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology, 60,* 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., & Smith, P.K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging, 17*(2), 299-320. https://doi.org/10.1037/0882-7974.17.2.299

Park, D.C., Lodi-Smith, J., Drew, L., Haber, S., Hebrank, A., Bischof, G.N., & Aamodt, W. (2014). The impact of sustained engagement on cognitive function in older adults: The Synapse Project. *Psychological Science, 25*(1), 103–112. https://doi.org/10.1177/0956797613499592

Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., & Smith, M.R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences of the United States of America, 101*(35), 13091-13095. https://doi.org/10.1073/pnas.0405148101

Park, D., Polk, T., Hebrank, A., & Jenkins, L. (2010). Age differences in default mode activity on easy and difficult spatial judgment tasks. *Frontiers in Human Neuroscience, 3,* Article 75. https://doi.org/10.3389/neuro.09.075.2009

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L.B. (2005). The plastic human brain cortex. *Annual Review of Neuroscience, 28,* 377-401. http://doi.org/10.1146/annurev.neuro.27.070203.144216.

Peel, N.M., McClure, R.J., & Bartlett, H.P. (2005). Behavioral determinants of healthy aging. *American Journal of Preventive Medicine, 28*(3), 298-304. https://doi.org/10.1016/j.amepre.2004.12.002

Pelham, S.D., & Abrams, L. (2014). Cognitive advantages and disadvantages in early and late bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *40*(2), 313–325. https://doi.org/10.1037/a0035224

Perani, D., Farsad, M., Ballarini, T., Lubian, F., Malpetti, M., Fracchetti, A., Magnani, G., March, A., & Abutalebi, J. (2017). The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. *PNAS Proceedings of the National Academy of Sciences of the United States of America, 114*(7), 1690–1695. https://doi.org/10.1073/pnas.1610909114

Peter C., Kreisner A., Schröter M., Kim H., Bieber G., Öhberg F., Hoshi K., Waterworth E.L., Waterworth J., & Ballesteros, S. (2013). AGNES: Connecting people in a multimodal way. *Journal on Multimodal User Interfaces, 7*(3), 229-245. https://doi.org/10.1007/s12193-013-0118-z

Pfefferbaum, A., Mathalon, D. H., Sullivan, E. V., Rawles, J. M., Zipursky, R. B., & Lim, K. O. (1994). A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Archives of Neurology, 51*(9), 874-887. https://10.1001/archneur.1994.00540210046012

*Phirom, K., Kamnardsiri, T., & Sungkarat, S. (2020). Beneficial effects of interactive physical-cognitive game-based training on fall risk and cognitive performance of older adults. *International Journal of Environmental Research and Public Health, 17*(17), Article 6079. https://doi.org/10.3390/ijerph17176079

*Pieramico, V., Esposito, R., Sensi, F., Cilli, F., Mantini, D., Mattei, P.A., Frazzini, V., Ciavardelli, D., Gatta, V., Ferretti, A., Romani, G.L., & Sensi, S.L. (2012). Combination training in aging individuals modifies functional connectivity and cognition, and is potentially affected by dopamine-related genes. *PLoS One, 7*(8), Article e43901. https://doi.org/10.1371/journal.pone.0043901

Pliatsikas, C., DeLuca, V., Moschopoulou, E., & Saddy, J.D. (2016). Immersive bilingualism reshapes the core of the brain. *Brain Structure and Function, 222*(4), 1785-1795. https://doi.org/10.1007/s00429-016-1307-9

Pons Van Dijk, G., Huijts, M., & Lodder, J. (2013). Cognition improvement in Taekwondo novices over 40. Results from the SEKWONDO study. *Frontiers in Aging Neuroscience. 5*, 74. https://doi.org/10.3389/fnagi.2013.00074

Porat, S., Goukasian, N., Hwang, K.S., Zanto, T., Do, T., Pierce, J., Joshi, S., Woo, E., & Apostolova, L.G. (2016). Dance experience and associations with cortical gray matter thickness in the aging population. *Dementia and Geriatric Cognitive Disorders Extra*, 6(3), 508–517. https://doi.org/10.1159/000449130

Posner, M.I. (1994). Attention: the mechanisms of consciousness. *Proceedings of the National Academy of Sciences, 91*(16), 7398 - 7403. https://doi.org/10.1073/pnas.91.16.7398

Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. Annual Review of *Neuroscience, 13*, 25–42. https://doi.org/10.1146/annurev.ne.13.030190.000325

Posner, M.I., Snyder, C.R., & Davidson, B.J. (1980). Attention and the detection of signals. *Journal of Experimental Psychology: General, 109*(2), 160–174. https://doi.org/10.1037/0096-3445.109.2.160

Pot, A., Keijzer, M., & de Bot, K. (2018). Intensity of multilingual language use predicts cognitive performance in some multilingual older adults. *Brain Science, 8*(5), 92. https://doi.org/10.3390/brainsci8050092

Powers, K.L., Brooks, P.J., Aldrich, N.J., Palladino, M.A., & Alfieri, L. (2013). Effects of video-game play on information processing: A meta-analytic investigation.

Psychonomic Bulletin & Review, 20(6), 1055–1079. https://doi.org/10.3758/s13423-013-0418-z

Prakash, R.S., Voss, M.W., Erickson, K.I., & Kramer, A.F. (2015). Physical activity and cognitive vitality. *Annual Review of Psychology, 66,* 769-797. https://doi.org/10.1146/annurev-psych-010814-015249

Prince, M., Prina, M., & Guerchet, M. (2013). *World Alzheimer Report 2013: Journey of Caring: An analysis of long-term care for dementia*. Alzheimer's Disease International. http://www.alz.co.uk/research/WorldAlzheimerReport2013.pdf

Prior, A., & Gollan, T.H. (2011). Good language-switchers are good task-switchers: Evidence from Spanish-English and Mandarin-English bilinguals. *Journal of the International Neuropsychological Society, 17*(4), 682–691. https://doi.org/10.1017/S1355617711000580

Qu, L., Low, J.J.W., Zhang, T., Li, H., & Zelazo, P.D. (2015). Bilingual advantage in executive control when task demands are considered. *Bilingualism: Language & Cognition, 19*(2), 277-293. https://doi.org/10.1017/S1366728914000376

R Core Team. (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org

*Rahe, J., Becker, J., Fink, G.R., Kessler, J., Kukolja, J., Rahn, A., Rosen, J.B., Szabados, F., Wirth, B., & Kalbe, E. (2015a). Cognitive training with and without additional physical activity in healthy older adults: cognitive effects, neurobiological mechanisms, and prediction of training success. *Frontiers in Aging Neuroscience, 7*, Article 187. https://doi.org/10.3389/fnagi.2015.00187

*Rahe, J., Petrelli, A., Kaesberg, S., Fink, G.R., Kessler, J., & Kalbe, E. (2015b). Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults. *Clinical Interventions in Aging, 10*, 297-310. https://doi.org/10.2147/CIA.S74071

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience, 38*, 433-447. https://doi.org/10.1146/annurev-neuro-071013-014030

*Raichlen, D.A., Bharadwaj, P.K., Nguyen, L.A., Franchetti, M.K., Zigman, E.K., Solorio, A.R., & Alexander, G.E. (2020). 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, 20,* Article 83. https://doi.org/10.1186/s12877-020-1484-5

Ramos, S., Fernández García, Y., Antón, E., Casaponsa, A., & Duñabeitia, J.A. (2017). Does learning a language in the elderly enhance switching ability? *Journal of Neurolinguistics, 43,* 39-48. https://doi.org/10.1016/j.jneuroling.2016.09.001

Ransdell, S.E., & Fischler, I. (1987). Memory in a monolingual mode: When are bilinguals at a disadvantage? *Journal of Memory and Language, 26*(4), 392-405. https://doi.org/10.1016/0749-596X(87)90098-2

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., Secher, N. H., Pedersen, B. K., & Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology, 94*(10), 1062–1069. https://doi.org/10.1113/expphysiol.2009.048512

Raz, N., & Daugherty, A.M. (2018). Pathways to Brain Aging and Their Modifiers: Free-Radical-Induced Energetic and Neural Decline in Senescence (FRIENDS) Model - A Mini-Review. *Gerontology, 64*(1), 49-57. https://doi.org/10.1159/000479508

Raz, N., & Lindenberger, U. (2013). Life-span plasticity of the brain and cognition: from questions to evidence and back. *Neuroscience & Biobehavioral Reviews, 37*(9), 2195-2200. http://doi.org/10.1016/j.neubiorev.2013.10.003.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., & Acker, J.D. (2005). Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cerebral Cortex, 15*(11), 1679–1689. https://doi.org/10.1093/cercor/bhi044

Reales, J.M., & Ballesteros, S. (1999). Implicit and explicit memory for visual and haptic objects: Cross-modal priming depends on structural descriptions. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 25*(3), 644–663. https://doi.org/10.1037/0278-7393.25.3.644

Rechel, B., Grundy, E., Robine, J.-M., Cylus, J., Mackenbach, J. P., Knai, C., & McKee, M. (2013). Ageing in the European Union. *The Lancet, 381*(9874), 1312-1322. https://doi.org/10.1016/S0140-6736(12)62087-X

Redondo, M.T., Beltrán-Brotóns, J.L., Reales, J.M., & Ballesteros, S. (2015). Word-stem priming and recognition in type 2 diabetes mellitus, Alzheimer's disease patients and healthy older adults. *Experimental Brain Research, 233*(11), 3163–3174. https://doi.org/10.1007/s00221-015-4385-7

Redondo, M.T., Beltrán-Brotóns, J.L., Reales, J.M., & Ballesteros, S. (2016). Executive functions in patients with Alzheimer's disease, type 2 diabetes mellitus patients and cognitively healthy older adults. *Experimental Gerontology, 83,* 47-55. http://doi.org/10.1016/j.exger.2016.07.013

Rehfeld, K., Müller, P., Aye, N., Schmicker, M., Dordevic, M., Kaufmann, J., Hökelmann, A., & Müller, N.G. (2017). Dancing or fitness sport? The effects of two training programs on hippocampal plasticity and balance abilities in healthy seniors. *Frontiers in Human Neuroscience,* 11, Article 305. https://doi.org/10.3389/fnhum.2017.00305

Reimers, S., & Maylor, E.A. (2005). Task Switching Across the Life Span: Effects of Age on General and Specific Switch Costs. *Developmental Psychology, 41*(4), 661–671. https://doi.org/10.1037/0012-1649.41.4.661

Resnick, S.M., Pham, D. L., Kraut, M.A., Zonderman, A.B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *The Journal of Neuroscience, 23*(8), 3295. doi:10.1523/JNEUROSCI.23-08-03295.2003

Reuter-Lorenz, P.A., & Cappell, K.A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science, 17*(3), 177-182. https://doi.org/10.1111/j.1467-8721.2008.00570.x

Reuter-Lorenz, P.A., & Lustig, C. (2005). Brain aging: reorganizing discoveries about the aging mind. *Current Opinion in Neurobiology, 15*(2), 245-251. https://doi.org/10.1016/j.conb.2005.03.016

Reuter-Lorenz, P.A., and Park, D.C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review, 24*(3), 355-370. https://doi.org/10.1007/s11065-014-9270-9

Richmond, L.L., Morrison, A.B., Chein, J.M., & Olson, I.R. (2011). Working memory training and transfer in older adults. *Psychology and Aging, 26*(4), 813-822. https://doi.org/10.1037/a0023631

Riley, K.P., Snowdon, D.A., & Markesbery, W.R. (2002). Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Annals of Neurology, 51*(5), 567–577. https://doi.org/10.1002/ana.10161

Rodríguez-Pujadas, A., Sanjuán, A., Ventura-Campos, N., Román, P., Martin, C., Barceló, F., Costa, A., & Avila, C. (2013). Bilinguals use language-control brain areas more than monolinguals to perform non-linguistic switching tasks. *PloS One, 8*(9). Article 73028. https://doi.org/10.1371/journal.pone.0073028

*Romera-Liebana, L., Orfila, F., Segura, J.M., Real, J., Fabra, M.L., Möller, M., Lancho, S., Ramirez, A., Marti, N., Cullell, M., Bastida, N., Martinez, D., Giné, M., Cendrós, P., Bistuer, A., Perez, E., Fabregat, M.A., & Foz, G. (2018). Effects of a primary care-based multifactorial intervention on physical and cognitive function in frail, elderly individuals: A randomized controlled trial. *The Journals of Gerontology: Series A, 73*(12), 1688–1674. https://doi.org/10.1093/gerona/gl

Rönnlund, M., Lövdén, M., & Nilsson, L.G. (2007). Cross-sectional versus longitudinal age gradients of Tower of Hanoi performance: The role of practice effects and cohort differences in education. *Aging, Neuropsychology, and Cognition, 15*(1), 40-67. https://doi.org/10.1080/13825580701533751

Rönnlund, M., Nyberg, L., Bäckman, L., & Nilsson, L.-G. (2005). Stability, growth, and fecline in adult life span development of declarative memory: Cross-sectional and longitudinal data from a population-based study. *Psychology and Aging, 20*(1), 3–18. https://doi.org/10.1037/0882-7974.20.1.3

Rosenberg, M.S. (2005). The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. *Evolution, 59*, 464-468. https://doi.org/10.1111/j.0014-3820.2005.tb01004.x

Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin, 86*(3), 638–641. https://doi.org/10.1037/0033-2909.86.3.638

Rothstein, H.R., Sutton, & A.J., Borenstein, M. (Eds.). (2006). Publication bias in meta-analysis. New York, NY: John Wiley & Sons.

Rubin, O., & Meiran, N. (2005). On the origins of the task mixing cost in the cuing task-switching paradigm. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*(6), 1477–1491. https://doi.org/10.1037/0278-7393.31.6.1477

Runnqvist, E., Fitzpatrick, I., Strijkers, K., & Costa, A. (2012). An appraisal of the bilingual language production system: Quantitatively or qualitatively different from monolinguals? In T. K. Bhatia & W. C. Ritchie (Eds.), *The handbook of bilingualism and multilingualism* (Second edition., pp. 244-265). Chichester, UK: John Wiley & Sons.

Ruscheweyh, R., Willemer, C., Krüger, K., Duning, T., Warnecke, T., Sommer, J., Völker, K., Ho, H.V., Mooren, F., Knecht, S., & Flöel, A. (2011). Physical activity and memory functions: An interventional study. *Neurobiology of Aging, 32*(7), 1304–1319. https://doi.org/10.1016/j.neurobiolaging.2009.08.001

Sadat, J., Martin, C.D., Alario, F.X., & Costa, A. (2012). Characterizing the bilingual disadvantage in noun phrase production. *Journal of Psycholinguistic Research, 41*(3), 159-179. https://doi.org/10.1007/s10936-011-9183-1

Sala, G., Tatlidil, K.S., & Gobet, F. (2018). Video game training does not enhance cognitive ability: A comprehensive meta-analytic investigation. *Psychological Bulletin, 144*(2), 111–139. https://doi.org/10.1037/bul0000139

Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S.R., Busa, E., Morris, J.C., Dale, A.M., & Fischl, B. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex, 14*(7), 721-730. https://doi.org/10.1093/cercor/bhh032

*Salazar-González, B.C., Cruz-Quevedo, J.E., Gallegos-Cabriales, E.C., Villarreal-Reyna, M.D. L.A., Ceballos-Gurrola, O., Hernández-Cortés, P.L., Garza-Elizondo, M.E., Gómez-Meza, M.V., & Enriquez-Reyna, M.C. (2015). A physical-cognitive intervention to enhance gait speed in older Mexican adults. *American Journal of Health Promotion, 30*(2), 77-84. https://doi.org/10.4278/ajhp.130625-QUAN-329

Saldanha, I.J., Dickersin, K., Wang, X., & Li, T. (2014). Outcomes in Cochrane systematic reviews addressing four common eye conditions: an evaluation of completeness and comparability. *PloS one, 9*(10). Article 109400. doi: 10.1371/journal.pone 0109400.

Salthouse, T. (2012). Consequences of age-related cognitive declines. *Annual Review of Psychology, 63*, 201–226. https://doi.org/10.1146/annurev-psych-120710-100328

Salthouse, T.A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428. https://doi.org/10.1037/0033-295X.103.3.403

Salvatierra, J.L., & Rosselli, M. (2010). The effect of bilingualism and age on inhibitory control. *International Journal of Bilingualism, 15*(1), 26-37. https://doi.org/10.1177/1367006910371021

Sambataro, F., Murty, V.P., Callicott, J.H., Tan, H.-Y., Das, S., Weinberger, D.R., & Mattay, V. S. (2010). Age-related alterations in default mode network: Impact on working memory performance. *Neurobiology of Aging, 31*(5), 839-852. https://doi.org/10.1016/j.neurobiolaging.2008.05.022

Sandín, B., Chorot, P., Lostao, L., Joiner, T. E., Santed, M.A., & Valiente, R.M. (1999). Escalas PANAS de afecto positivo y negativo: Validación factorial y convergencia transcultural [The PANAS Scales of Positive and Negative Affect: Factor analytic validation and cross-cultural convergence*]. Psicothema, 11*(1), 37–51. Retrieved from https://www.redalyc.org/pdf/727/72711104.pdf

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273–295. https://doi.org/10.1037/0894-4105.7.3.273

Scaltritti, M., Peressotti, F., & Miozzo, M. (2017). Bilingual advantage and language switch: What's the linkage? *Bilingualism, 20*(1), 80. https://doi.org/10.1017/S1366728915000565

Schaefer, S., & Schumacher, V. (2011). The interplay between cognitive and motor functioning in healthy older adults: findings from dual-task studies and suggestions for intervention. *Gerontology, 57*, 239–246. https://doi.org/10.1159/000322197

Schättin, A., Arner, R., Gennaro, F., & de Bruin, E.D. (2016). Adaptations of prefrontal brain activity, executive functions, and gait in healthy elderly following exergame and balance training: A randomized-controlled study. *Frontiers in Aging Neuroscience, 8*, Article 278. https://doi.org/10.3389/fnagi.2016.00278

Schipolowski, S., Wilhelm, O., & Schroeders, U. (2014). On the nature of crystallized intelligence: the relationship between verbal ability and factual knowledge. *Intelligence, 46,* 156-168. https://doi.org/10.1016/j.intell.2014.05.014

Schlegel, A.A., Rudelson, J.J., & Tse, P. U. (2012). White matter structure changes as adults learn a second language. *Journal of Cognitive Neuroscience, 24*(8), 1664-1670. https://doi.org/10.1162/jocn_a_00240

Schmitt, F. A., Davis, D. G., Wekstein, D. R., Smith, C. D., Ashford, J. W., & Markesbery, W. R. (2000). "Preclinical" AD revisited: Neuropathology of cognitively normal older adults. *Neurology, 55*(3), 370 - 376. https://doi.org/10.1212/WNL.55.3.370

*Schoene, D., Lord, S.R., Delbaere, K., Severino, C., Davies, T.A., & Smith, S.T. (2013). A randomized controlled pilot study of home-based step training in older people using videogame technology. *PloS One, 8.* Article 57734. https://doi.org/10.1371/journal.pone.0057734

*Schoene, D., Valenzuela, T., Toson, B., Delbaere, K., Severino, C., Garcia, J., Davies, T.A., Russell, F., Smith, S.T, & Lord, S.R. (2015). Interactive cognitive-motor step training improves cognitive risk factors of falling in older adults–a randomized controlled trial. *PLoS One, 10.* Article 0145161. https://doi.org/10.1371/journal.pone.0145161

Schweizer, T.A., Ware, J., Fischer, C.E., Craik, F.I., & Bialystok, E. (2012). Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease. *Cortex, 48*(8), 991-996. https://doi.org/10.1016/j.cortex.2011.04.009

Sebastián, M., & Ballesteros, S. (2012). Effects of normal aging on event-related potentials and oscillatory brain activity during a haptic repetition priming task. *NeuroImage, 60*(1), 7–20. https://doi.org/10.1016/j.neuroimage.2011.11.060

Sebastián, M., Reales, J.M., & Ballesteros, S. (2011). Ageing affects event-related potentials and brain oscillations: a behavioral and electrophysiological study using a haptic recognition memory task. *Neuropsychologia, 49*(14), 3967-3980. https://doi.org/10.1016/j.neuropsychologia.2011.10.013ç

Segalowitz, N., & Hulstijn, J. (2005). Automaticity in bilingualism and second language learning. In J.F. Kroll & A.M.B. de Groot (Eds.), *Handbook of bilingualism: Psycholinguistic approaches*, (pp. 371-388). New York, NY: Oxford University Press.

*Shah, T., Verdile, G., Sohrabi, H., Campbell, A., Putland, E., Cheetham, C., Dhaliwal, S., Weinborn, M., Maruff, P., Darby, D., & Martins, R. N. (2014). A combination of physical activity and computerized brain training improves verbal memory and increases cerebral glucose metabolism in the elderly. *Translational Psychiatry, 4*(12). Article 487. https://doi.org/10.1038/tp.2014.122

*Shatil, E. (2013). Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. *Frontiers in Aging Neuroscience, 5*. Article 8. https://doi.org/10.3389/fnagi.2013.00008

Shulman, G.L., Astafiev, S.V., Franke, D., Pope, D.L.W., Snyder, A.Z., McAvoy, M.P., & Corbetta, M. (2009). Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. *The Journal of Neuroscience, 29*(14), 4392–4407. https://doi.org/10.1523/JNEUROSCI.5609-08.2009

Simons, D.J., Boot, W.R., Charness, N., Gathercole, S.E., Chabris, C.F., Hambrick, D.Z., & Stine-Morrow, E.A. (2016). Do "brain-training" programs work? *Psychological Science in the Public Interest, 17*(3), 103-186. https://doi.org/10.1177/1529100616661983

Sinha, S. R., Sullivan, L. R., Sabau, D., Orta, D., Dombrowski, K. E., Halford, J. J., Hani, A. J., Drislane, F. W., & Stecker, M. M. (2016). American Clinical Neurophysiology Society Guideline 1: minimum technical requirements for performing clinical electroencephalography. *The Neurodiagnostic Journal, 56*(4), 235–244. https://doi.org/10.1080/21646821.2016.1245527

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Browndyke, J.N., & Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*(3), 239–252. https://doi.org/10.1097/PSY.0b013e3181d14633

Souders, D.J., Boot, W.R., Blocker, K., Vitale, T., Roque, N.A., & Charness, N. (2017). Evidence for narrow transfer after short-term cognitive training in older adults. *Frontiers in Aging Neuroscience, 9*, Article 41. https://doi.org/10.3389/fnagi.2017.00041

Soveri, A., Rodriguez-Fornells, A., & Laine, M. (2011). Is there a relationship between language switching and executive functions in bilingualism? Introducing a within group analysis approach. *Frontiers in Psychology, 2*, 183. https://doi.org/10.3389/fpsyg.2011.00183

Squire, L.R. (1987). Memory and brain. New York, NY, US: Oxford University Press.

Squire, L.R. (1992). Declarative and nondeclarative memory: Multiple brain systems supporting learning and memory. *Journal of Cognitive Neuroscience, 4(*3), 232-243. https://doi.org/10.1162/jocn.1992.4.3.232

Squire, L.R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory, 82*(3), 171-177. https://doi.org/10.1016/j.nlm.2004.06.005

Stanmore, E., Stubbs, B., Vancampfort, D., de Bruin, E. D., & Firth, J. (2017). The effect of active video games on cognitive functioning in clinical and non-clinical populations: A meta-analysis of randomized controlled trials. *Neuroscience and Biobehavioral Reviews, 78,* 34–43. https://doi.org/10.1016/j.neubiorev.2017.04.011

Stein, M., Federspiel, A., Koenig, T., Wirth, M., Strik, W., Wiest, R., Brandeis, D., & Dierks, T. (2012). Structural plasticity in the language system related to increased second language proficiency. *Cortex, 48*(4), 458–465. https://doi.org/10.1016/j.cortex.2010.10.007

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028. https://doi.org/10.1016/j.neuropsychologia.200

Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., & the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association, 16*(9), 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.

Stern, Y., Gazes, Y., Razlighi, Q., Steffener, J., & Habeck, C. (2018). A task-invariant cognitive reserve network. *NeuroImage, 178,* 36-45. https://doi.org/10.1016/j.neuroimage.2018.05.033

Stocco, A., Lebiere, C., & Anderson, J.R. (2010). Conditional routing of information to the cortex: A model of the basal ganglia’s role in cognitive coordination. *Psychological Review, 117*(2), 541–574. https://doi.org/10.1037/a0019077

Stocco, A., Yamasaki, B., Natalenko, R., & Prat, C.S. (2014). Bilingual brain training: A neurobiological framework of how bilingual experience improves executive function. *International Journal of Bilingualism, 18*(1), 67-92. https://doi.org/10.1177/1367006912456617

Styliadis, C., Kartsidis, P., Paraskevopoulos, E., Ioannides, A.A., & Bamidis, P.D. (2015). Neuroplastic effects of combined computerized physical and cognitive training in elderly individuals at risk for dementia: An eLORETA controlled study on resting states. *Neural Plasticity, 2015,* Article 172192. https://doi.org/10.1155/2015/172192

Sullivan, M.D., Janus, M., Moreno, S., Astheimer, L., & Bialystok, E. (2014). Early stage second-language learning improves executive control: Evidence from ERP. *Brain and Language, 139,* 84–98. https://doi.org/10.1016/j.bandl.2014.10.004

Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research, 60,* 56–64. https://doi.org/10.1016/j.jpsychires.2014.10.003

*Takeuchi, H., Magistro, D., Kotozaki, Y., Motoki, K., Nejad, K.K., Nouchi, R., Jeong, H., Sato, C., Sessa, S., Nagatomi, R., Zecca, M., Takanishi, A., & Kawashima, R. (2020). Effects of simultaneously performed dual-task training with aerobic exercise and working memory training on cognitive functions and neural systems in the elderly. *Neural Plasticity, 2020,* Article 3859824. https://doi.org/10.1155/2020/3859824

Taubert, M., Roggenhofer, E., Melie-Garcia, L., Muller, S., Lehmann, N., Preisig, M., Vollenweider, P., Marques-idal, P., Lutti, A., Kherif, F., & Draganski, B. (2020). Converging patterns of aging-associated brain volume loss and tissue microstructure differences. *Neurobiology of Aging, 88,* 108-118. https://doi.org/10.1016/j.neurobiolaging.2020.01.006

*Teixeira, C.V.L., Gobbi, S., Pereira, J.R., Vital, T.M., Hernandéz, S.S.S., Shigematsu, R., & Gobbi, L. T. B. (2013). Effects of square-stepping exercise on cognitive functions of older people. *Psychogeriatrics, 13,* 148-156. https://doi.org/10.1111/psyg.12017

Ten Brinke, L.F., Best, J.R., Chan, J., Ghag, C., Erickson, K.I., Handy, T.C., & Liu-Ambrose, T. (2020). The effects of computerized cognitive training with and without physical exercise on cognitive function in older adults: An 8-week randomized controlled trial. *The Journals of Gerontology, 75*(4), 755–763. https://doi.org/10.1093/gerona/glz115

Terry, C., & Sliwinski, M. (2012). Aging and random task switching: The role of endogenous versus exogenous task selection. *Experimental Aging Research, 38*(1), 87-109. https://doi.org/10.1080/0361073X.2012.637008

Tetlow, A M., & Edwards, J.D. (2017). Systematic literature review and meta-analysis of commercially available computerized cognitive training among older adults. *Journal of Cognitive Enhancement, 1*(4), 559-575. https://doi.org/10.1007/s41465-017-0051-2

Tettamanti, M., Moro, A., Messa, C., Moresco, R.M., Rizzo, G., Carpinelli, A., Matarrese, M, Fazio, F., & Perani, D. (2005). Basal ganglia and language: Phonology modulates dopaminergic release. *Neuroreport, 16*(4), 397-401. doi:10.1097/00001756-200503150-00018.

*Theill, N., Schumacher, V., Adelsberger, R., Martin, M., & Jäncke, L.J. (2013). Effects of simultaneously performed cognitive and physical training in older adults. *BMC Neuroscience, 14*, Article 103. https://doi.org/10.1186/1471-2202-14-103

Toril, P., Reales, J.M., & Ballesteros, S. (2014). Video game training enhances cognition of older adults: A meta-analytic study. *Psychology and Aging, 29*(3), 706–716. https://doi.org/10.1037/a0037507

Toril, P., Reales, J. M., Mayas, J., & Ballesteros, S. (2016). Video game training enhances visuospatial working memory and episodic Memory in older adults. *Frontiers in Human Neuroscience, 10*, 206. https://doi.org/10.3389/fnhum.2016.00206

Tornay, F.J., & Milán, E.G. (2001). A more complete task-set reconfiguration in random than in predictable task switch. *The Quarterly Journal of Experimental Psychology A: Human Experimental Psychology, 54*(3), 785–803. https://doi.org/10.1080/02724980042000499

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381-423). Oxford, England: Academic Press.

Tulving, E. (1985). How many memory systems are there? *American Psychologist, 40*(4), 385-398. doi:10.1037/0003-066X.40.4.385

Ullman, M.T. (2001). A neurocognitive perspective on language: The declarative/procedural model. *Nature Reviews Neuroscience, 2*(10), 717-726. https://doi.org/10.1038/35094573

Valenzuela, M.J., & Sachdev, P. (2006). Brain reserve and dementia: a systematic review. *Psychological Medicine, 36*(4), 441-454. doi:10.1017/S0033291706007744

van den Heuvel, M.P., & Hulshoff Pol, H.E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology, 20*(8), 519-534. https://doi.org/10.1016/j.euroneuro.2010.03.008

van den Noort, M., Vermeire, K., Bosch, P., Staudte, H., Krajenbrink, T., Jaswetz, L., Struys, E., Yeo, S., Barisch, P., Perriard, B., Lee, S.H., & Lim, S. (2019). A systematic review on the possible relationship between bilingualism, cognitive decline, and the onset of dementia. *Behavioral Sciences, 9*(7), Article 81. https://doi.org/10.3390/bs9070081

*van Het Reve, E., & de Bruin, E.D. (2014). Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults: a multicenter randomized-controlled trial. *BMC Geriatrics, 14,* Article 134. https://doi.org/10.1186/1471-2318-14-134

van Praag, H., Kempermann, G., & Gage, F.H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience, 2*(3), 266-270. https://doi.org/10.1038/6368

Van Schouwenburg, M. R., den Ouden, H.E.M., & Cools, R. (2010). The human basal ganglia modulate frontal-posterior connectivity during attention shifting. *Journal of Neuroscience, 30*(29), 9910-9918. doi:10.1523/jneurosci.1111-10.2010

Vaportzis, E., Niechcial, M.A., & Gow, A.J. (2019). A systematic literature review and meta-analysis of real-world interventions for cognitive ageing in healthy older adults. *Ageing Research Reviews, 50,* 110–130. https://doi.org/10.1016/j.arr.2019.01.006

Vázquez, F.L., Otero, P., García-Casal, J.A., Blanco, V., Torres, Á.J., & Arrojo, M. (2018). Efficacy of video game-based interventions for active aging. A systematic literature review and meta-analysis. *PLoS One 13,* Article e0208192. https://doi.org/10.1371/journal.pone.0208192

Verhaeghen, P. (2003). Aging and vocabulary score: A meta-analysis. *Psychology and Aging, 18*(2), 332–339. https://doi.org/10.1037/0882-7974.18.2.332

Verhaeghen, P., & Salthouse, T.A. (1997). Meta-analyses of age-cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models. *Psychological Bulletin, 122*(3), 231-249. https://doi.org/10.1037/0033-2909.122.3.231

Verhaeghen, P., Kliegl, R., & Mayr, U. (1997). Sequential and coordinative complexity in time-accuracy functions for mental arithmetic. *Psychology and Aging, 12*(4), 555-564. https://doi.org/10.1037//0882-7974.12.4.555

Verreyt, N., Woumans, E., Vandelanotte, D., Szmalec, A., & Duyck, W. (2016). The influence of language-switching experience on the bilingual executive control advantage. *Bilingualism: Language and Cognition, 19*(1), 181–190. https://doi.org/10.1017/S1366728914000352

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software, 36*(3), 1-48. https://doi.org/10.18637/jss.v036.i03

Voelcker-Rehage, C., & Niemann, C. (2013). Structural and functional brain changes related to different types of physical activity across the life span. *Neuroscience and Biobehavioral Reviews, 37*(9), 2268–2295. https://doi.org/10.1016/j.neubiorev.2013.01.028

Voelcker-Rehage, C., Godde, B., & Staudinger, U.M. (2010). Physical and motor fitness are both related to cognition in old age. *European Journal of Neuroscience, 31(*1), 167–176. https://doi.org/10.1111/j.1460-9568.2009.07014.x

Voelcker-Rehage, C., Godde, B., & Staudinger, U.M. (2011). Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. *Frontiers in Human Neuroscience, 5*, Article 26. https://doi.org/10.3389/fnhum.2011.00026

Voss, M.W., Erickson, K.I., Chaddock, L., Prakash, R.S., Colcombe, S.J., Morris, K.S., Doerksen, S., Hu, L., McAuley, E., & Kramer, A.F. (2008). Dedifferentiation in the visual cortex: an fMRI investigation of individual differences in older adults. *Brain Research, 1244*, 121–131. https://doi.org/10.1016/j.brainres.2008.09.051

Walsh, J. J., Scribbans, T. D., Bentley, R. F., Kellawan, J. M., Gurd, B., & Tschakovsky, M. E. (2016). Neurotrophic growth factor responses to lower body resistance training in older adults. *Applied Physiology, Nutrition, and Metabolism, 41*(3), 315-323. https://doi.org/10.1139/apnm-2015-0410

Walsh, J. J., & Tschakovsky, M. E. (2018). Exercise and circulating BDNF: Mechanisms of release and implications for the design of exercise interventions. *Applied Physiology, Nutrition, and Metabolism, 43*(11), 1095–1104. https://doi.org/10.1139/apnm-2018-0192

Wang, M.Y., Chang, C.Y., & Su, S.Y. (2011). What's cooking? – Cognitive training of executive function in the elderly. *Frontiers in Psychology, 2*, Article 228. https://doi.org/10.3389/fpsyg.2011.00228

Wang, P., Liu, H.H., Zhu, X. T., Meng, T., Li, H.J., & Zuo, X.N. (2016). Action video game training for healthy adults: A meta-analytic study. *Frontiers in Psychology, 7*, Article 907. https://doi.org/10.3389/fpsyg.2016.00907

Wasylyshyn, C., Verhaeghen, P., & Sliwinski, M. J. (2011). Aging and task switching: A meta-analysis. *Psychology and Aging, 26*(1), 15-20. doi:10.1037/a0020912

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063–1070. https://doi.org/10.1037/0022-3514.54.6.1063

Watson, C. W.M., Manly, J.J., & Zahodne, L.B. (2016). Does bilingualism protect against cognitive aging? Methodological issues in research on bilingualism, cognitive reserve, and dementia incidence. *Linguistic Approaches to Bilingualism, 6*(5), 590-604. https://doi.org/10.1075/lab.15043.wat

Wayne, P.M., Walsh, J.N., Taylor-Piliae, R.E., Wells, R.E., Papp, K.V., Donovan, N.J., & Yeh, G.Y. (2014). Effect of Tai Chi on cognitive performance in older adults: Systematic review and meta-analysis. *Journal of the American Geriatrics Society, 62*(1), 25–39. https://doi.org/10.1111/jgs.12611

Wechsler, D. (1997). *Wechsler Memory Scale (WMS-III).* San Antonio, USA: Psychological Corporation. Spanish Edition 2004 by TEA Ediciones, SA, Madrid (Spain)

Wechsler, D. (1999). *WAIS-III: Wechsler adult intelligence scale. Administration and scoring manual (*3rd ed.*).* San Antonio, TX: Psychological Corporation: Harcourt Brace.

Wen, C.P., Wai, J.P.M., Tsai, M.K., Yang, Y.C., Cheng, T.Y.D., Lee, M.-C., Chan, H.T., Tsao, C.K., Tsai, S.P., & Wu, X. (2011). Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *The Lancet*, 378(9798), 1244–1253. https://doi.org/10.1016/S0140-6736(11)60749-6

Whitson, L.R., Karayanidis, F., & Michie, P.T. (2012). Task practice differentially modulates task-switching performance across the adult lifespan. *Acta Psychologica, 139*(1), 124-136. https://doi.org/10.1016/j.actpsy.2011.09.004

Willis, S.L., Tennstedt, S.L., Marsiske, M., Ball, K., Elias, J., Koepke, K.M., Morris, J.N., Rebok, G.W., Unverzagt, F.W., Stoddard, A.M., Wright, E., & ACTIVE Study Group (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *Journal of the American Medical Association, 296*(23), 2805–2814. https://doi.org/10.1001/jama.296.23.2805

*Wollesen, B., Schulz, S., Seydell, L., & Delbaere, K. (2017). Does dual task training improve walking performance of older adults with concern of falling? *BMC Geriatrics, 17*(1), Article 213. https://doi.org/10.1186/s12877-017-0610-5

*Wongcharoen, S., Sungkarat, S., Munkhetvit, P., Lugade, V., & Silsupadol, P. (2017). Home-based interventions improve trained, but not novel, dual-task balance performance in older adults: A randomized controlled trial. *Gait & Posture 52,* 147–152. https://doi.org/10.1016/j.gaitpost.2016.11.036

Woollacott, M., & Shumway-Cook, A. (2002). Attention and the control of posture and gait: A review of an emerging area of research. *Gait & Posture 16*, 1–14. https://doi.org/10.1016/S0966-6362(01)00156-4

World Health Organization. (2012). Dementia: A public health priority. Available online at: https://www.who.int/mental_health/publications/dementia_report_2012/en/. Accessed October 15, 2018.

World Health Organization (2017). Global action plan on the public health response to dementia 2017-2025. (Licence: CC BY-NC-SA 3.0 IGO). Geneva: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/259615/9789241513487-eng.pdf

World Health Organization (2019). Global action plan on physical activity 2018-2030: more active people for a healthier world (Licence: CC BY-NC-SA 3.0 IGO). Geneva: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/272722/9789241514187-eng.pdf

Woumans, E.V.Y., Santens, P., Sieben, A., Versijpt, J.A.N., Stevens, M., & Duyck, W. (2015). Bilingualism delays clinical manifestation of Alzheimer's disease. *Bilingualism: Language and Cognition, 18*(3), 568-574. https://doi.org/10.1017/S136672891400087X

Xu, W., Yu, J.-T., Tan, M.-S., & Tan, L. (2015). Cognitive reserve and Alzheimer’s disease. *Molecular Neurobiology, 51*(1), 187-208. https://doi.org/10.1007/s12035-014-8720-y pmid

Yang, H., Hartanto, A., & Yang, S. (2016). The complex nature of bilinguals' language usage modulates task-switching outcomes. *Frontiers in Psycholology, 7*, 560. https://doi.org/10.3389/fpsyg.2016.00560

Yankner, B.A., Lu, T., & Loerch, P. (2008). The aging brain. *Annual Review of Pathology: Mechanisms of Disease, 3*(1), 41-66. https://doi.org/10.1146/annurev.pathmechdis.2.010506.092044

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., & Leirer, V.O. (1983). Development and validation of a Geriatric Depression Screening Scale: A preliminary report. *Journal of Psychiatric Research, 17*(1), 37–49. https://doi.org/10.1016/0022-3956(82)90033-4

*Yokoyama, H., Okazaki, K., Imai, D., Yamashina, Y., Takeda, R., Naghavi, N., Ota, A., Hirasawa, Y., & Miyagawa, T. (2015). 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, 15*. Article 60. https://doi.org/10.1186/s12877-015-0058-4

*You, J.H., Shetty, A., Jones, T., Shields, K., Belay, Y., & Brown, D. (2009). Effects of dual-task cognitive-gait intervention on memory and gait dynamics in older adults with a history of falls: a preliminary investigation. *NeuroRehabilitation 24*, 193-198. https://doi.org/10.3233/NRE-2009-0468

*Yu, R., Leung, G., & Woo, J. (2021). Randomized controlled trial on the effects of a combined intervention of computerized cognitive training preceded by physical exercise for improving frailty status and cognitive function in older adults. *International Journal of Environmental Research and Public Health, 18*(4), Article 1396. https://doi.org/10.3390/ijerph18041396

Zanesco, A.P., Witkin, J.E., Morrison, A.B., Denkova, E., & Jha, A.P. (2020). Memory load, distracter interference, and dynamic adjustments in cognitive control influence working memory performance across the lifespan. *Psychology and Aging, 35*(5), 614-626. https://doi.org/10.1037/pag0000434

Zarin, D.A., Tse, T., Williams, R.J., & Rajakannan, T. (2017). Update on Trial Registration 11 Years after the ICMJE Policy Was Established. *The New England Journal of Medicine, 376*(4), 383–391. https://doi.org/10.1056/NEJMsr1601330

Zhang, H., Wu, Y.J., & Thierry, G. (2020). Bilingualism and aging: A focused neuroscientific review. *Journal of Neurolinguistics, 54*, Article 100890. https://doi.org/10.1016/j.jneuroling.2020.100890

Zelazo, P.D., Craik, F.I.M., & Booth, L. (2004). Executive function across the life span. *Acta Psychologica, 115*(2), 167-183. https://doi.org/10.1016/j.actpsy.2003.12.005 pmid:

Zhu, X., Yin, S., Lang, M., He, R., & Li, J. (2016). The more the better? A meta-analysis on effects of combined cognitive and physical intervention on cognition in healthy older adults. *Ageing Research Reviews, 31,* 67-79. https://doi.org/10.1016/j.arr.2016.07.003

Zhu, Z., Johnson, N.F., Kim, C., & Gold, B.T. (2015). Reduced frontal cortex efficiency is associated with lower white matter integrity in aging. *Cerebral Cortex, 25*(1), 138–146. https://doi.org/10.1093/cercor/bht212

Zilidou, V.I., Frantzidis, C.A., Romanopoulou, E.D., Paraskevopoulos, E., Douka, S., & Bamidis, P.D. (2018). Functional re-organization of cortical networks of senior citizens after a 24-week traditional dance program. *Frontiers in Aging Neuroscience, 10*, Article 422. https://doi.org/10.3389/fnagi.2018.00422

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*References marked with an asterisk indicate studies included in this meta-analysis.

APPENDIX A. Description of the submodules of the Bilingual Language Profile questionnaire (BLP; Birdsong et al., 2012).

Module	Scoring	Weighting factor	Cronbach's alpha	Items
Language History	Six questions, scored from zero to 20.	0.454	.663	• Age of acquisition • Age at which you became comfortable using each language • Years of schooling in each language • Years spent in a country or region where each language is spoken • Years spent in a family where each language is spoken • Years spent in a work or school environment where each language is spoken
Language Use	Five questions, scored from zero to 10.	1.09	.841	• Percentage of use in an average week with friends • Percentage of use in an average week with family • Percentage of use in an average week at school or work • How often you talk to yourself in each language • How often you use each language when counting
Language Proficiency	Four questions, scored from zero to six.	2.27	.914	• How well you speak each language • How well you understand each language • How well you write each language • How well you read each language
Language Attitudes	Four questions, scored from zero to six.	2.27	.729	• Degree to which you feel like yourself when speaking each language • Identification with cultures that speak each language • Importance of using each language like a native speaker • Importance of being mistaken for a native speaker

APPENDIX B. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist

Section/item	Item Nº	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_______1______
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_______2______
	2b	All items from the World Health Organization Trial Registration Data Set	_______x______
Protocol version	3	Date and version identifier	_______x______
Funding	4	Sources and types of financial, material, and other support	______20______
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	______21______
	5b	Name and contact information for the trial sponsor	_______x______
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_not applicable_

APPENDIX B (continued)

Section/item	**Item Nº**	**Description**	**Addressed on page number**
Introduction			
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_______x______
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	______4-7_____
	6b	Explanation for choice of comparators	________7_____
Objectives	7	Specific objectives or hypotheses	________7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	______8-9_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	________9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_______10_____

APPENDIX B (continued)

Section/item	Item Nº	Description	Addressed on page number
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_______x______
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_______x______
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__not applicable_
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____13-19_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figures 1 and 2_
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____10_______
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____10_______
Methods: Assignment of interventions (for controlled trials)			

APPENDIX B (continued)

Section/item	Item Nº	Description	Addressed on page number
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____11_______
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____11_______
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____11_______
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____11_______
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	______x_______
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13_______

APPENDIX B (continued)

Section/item	Item Nº	Description	Addressed on page number
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	______x_______
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	______x_______
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____19_______
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____19_______
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	______x_______
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	______x_______
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	______x_______

APPENDIX B (continued)

Section/item	Item Nº	Description	Addressed on page number
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	______x_______
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____x________
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____21-22_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	______x_______
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	______x_______
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	______x_______
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	______x_______
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____22_______
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	______x_______

APPENDIX B (continued)

Section/item	Item Nº	Description	Addressed on page number
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	______x_______
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	______x_______
	31b	Authorship eligibility guidelines and any intended use of professional writers	______x_______
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	______x_______
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	______x_______
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_not applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

APPENDIX C – TABLE 1. Search Strategy

((((“cognitive training” or “brain training” or “attention training” or “reasoning training” or “memory training” or “mental training” or “mental skills training” or “neurocognitive training” OR “executive function training” OR “attentional control training”) OR (“cognitive exercise” or “brain exercise” or “memory exercise” or “attention exercise” or “reasoning exercise”) OR (“cognitive stimulation” or “memory stimulation” or “memory enhance$” or “cognitive enhanc$” OR “executive function enhancement”) OR (“cognitive activit$” or “mental activit$”)

OR (speed and processing and training) OR mnemonic$ OR (“video game$” or videogame$ or wii or “computer game$” or “virtual reality”) OR (“cognitive intervention$” or “neurocognitive intervention$”)) AND ((exercis$ OR sport$ OR “physical fitness”) OR (“aerobic exercis$” or “aerobic train$” or “aerobic fitness” or “aerobic program$”) OR (“resistance exercis$” or “resistance train$” or “anaerobic exercis$” or “anaerobic train$” or “resistance program$”) OR (physical or aerobic or endurance or cardiorespiratory or cardiovascular or resistance or strength) OR (bicycl$ or “bike rid$” or “bicycle rid$”)))

OR

(((multimodal or multidomain or multicomponent or “multi-modal” or “multi-domain” or “multi-component” or “dual task” or “dual-task” or “tai chi” or danc$) OR (exergame$ or “active video game$” or “active videogame$” or kinect or “active play” or “interactive video”)) AND (cognitive adj2 physical) AND (cognition or cognitive or memory or executive function$ or “executive control” or attention or visuospatial or “processing speed” or language)))

AND (“older adults” or elder$ or senior$ or adult$ or older or ag?ing)

APPENDIX C – TABLE 2. Assessment tools used in the included studies and their classification into cognitive (executive functions, memory, speed, attention, global cognition, and composite scores), and physical functions (fitness, balance, and strength).

Authors	Year	Test	Function
Adcock et al	2020	2min stepping test	fitness
Adcock et al	2020	30 s chair rises test	strength
Adcock et al	2020	Cycle duration CV [%]	balance
Adcock et al	2020	Digit span backward score	executive
Adcock et al	2020	Digit span forward	memory
Adcock et al	2020	Digit span forward score	memory
Adcock et al	2020	Extended balance test of SPPB	balance
Adcock et al	2020	Gait Speed mean [m/s]	fitness
Adcock et al	2020	Stride length CV [%]	balance
Adcock et al	2020	Stride length mean [m]	balance
Adcock et al	2020	TMT A -s	speed
Adcock et al	2020	TMT B-s	executive
Adcock et al	2020	Toe clearance CV [%]	balance
Adcock et al	2020	Toe clearance mean [cm]	balance
Adcock et al	2020	Victoria 3-2	executive
Adcock et al	2020	Victoria Stroop 1 – time	speed
Adcock et al	2020	Victoria Stroop 2 – time	speed
Adcock et al	2020	Victoria Stroop 3 – time	executive
Anderson-Hanley et al	2012	Clock drawing	global
Anderson-Hanley et al	2012	Color trail test	executive
Anderson-Hanley et al	2012	COWAT-categories	language
Anderson-Hanley et al	2012	COWAT-total	language
Anderson-Hanley et al	2012	Digit Span backward	executive
Anderson-Hanley et al	2012	Figure copy	global
Anderson-Hanley et al	2012	Figure copy delayed	global
Anderson-Hanley et al	2012	Letter Digit Symbol Test	attention
Anderson-Hanley et al	2012	RAVLT delayed	memory
Anderson-Hanley et al	2012	RAVLT immediate	memory
Anderson-Hanley et al	2012	RAVLT_5trials	memory
Anderson-Hanley et al	2012	Stroop	executive
Andrieu et al	2017	Category Naming Test	language
Andrieu et al	2017	Composite z score	composite
Andrieu et al	2017	COWAT	language
Andrieu et al	2017	DSST	speed
Andrieu et al	2017	Free and Cued Selective Reminding	memory
Andrieu et al	2017	Gait speed	fitness
Andrieu et al	2017	MMSE	global
Andrieu et al	2017	MMSE orientation	global
Andrieu et al	2017	SPPB	Fitness

APPENDIX C – TABLE 2 (continued)

Andrieu et al	2017	TMT-A	speed
Andrieu et al	2017	TMT-B	executive
Andrieu et al	2017	visual analogue scale	memory
Bamidis et al	2015	Composite z score	composite
Barban et al	2017	RAVLT delayed	memory
Desjardins-Crepeau et al	2016	6-min walk	fitness
Desjardins-Crepeau et al	2016	Baddeley dual task - single	speed
Desjardins-Crepeau et al	2016	Baddeley dual-task interfern index	executive
Desjardins-Crepeau et al	2016	Chair stand test	strength
Desjardins-Crepeau et al	2016	Color-word inhibition	executive
Desjardins-Crepeau et al	2016	Color-word interference_color	speed
Desjardins-Crepeau et al	2016	Color-word interference_reading	speed
Desjardins-Crepeau et al	2016	Color-word task switching	executive
Desjardins-Crepeau et al	2016	Handgrip strength	strength
Desjardins-Crepeau et al	2016	Modified phys performance test	fitness
Desjardins-Crepeau et al	2016	RAVLT delayed	memory
Desjardins-Crepeau et al	2016	RAVLT immediate	memory
Desjardins-Crepeau et al	2016	RAVLT total	memory
Desjardins-Crepeau et al	2016	TMT A	speed
Desjardins-Crepeau et al	2016	TMT B	executive
Desjardins-Crepeau et al	2016	TUG	balance
Eggenberger et al	2015	Age concentration A	attention
Eggenberger et al	2015	Age concentration B	attention
Eggenberger et al	2015	Digit Span forward	memory
Eggenberger et al	2015	DSST	speed
Eggenberger et al	2015	Executive control task	executive
Eggenberger et al	2015	PALT	memory
Eggenberger et al	2015	Story recall	memory
Eggenberger et al	2015	TMT A	speed
Eggenberger et al	2015	TMT B	executive
Fabre et al	2002	Digit Span forward	memory
Fabre et al	2002	Logical memory - immediate	memory
Fabre et al	2002	Logical memory information	memory
Fabre et al	2002	Logical memory mental control	executive
Fabre et al	2002	Logical memory orientation	memory
Fabre et al	2002	Logical memory visual reprod	memory
Fabre et al	2002	O2 pulse	fitness
Fabre et al	2002	O2pulse max	fitness
Fabre et al	2002	PALT	memory
Fabre et al	2002	VO2	fitness
Fabre et al	2002	VOX2max	fitness
Fabre et al	2002	Wais memory quotient	memory
Gill et al	2016	Auditory verbal learning-learning	memory
Gill et al	2016	Autitory verbal learning-recall	memory

APPENDIX C – TABLE 2 (continued)

Gill et al	2016	DSST	speed
Gill et al	2016	Verbal fluency category	language
Gill et al	2016	Verbal fluency letter	language
Gschwind et al	2015	10-m walk-single task	fitness
Gschwind et al	2015	Attention network test-alert	attention
Gschwind et al	2015	Attention network test-conflict	attention
Gschwind et al	2015	Attention network test-orient	attention
Gschwind et al	2015	Attention network test-RT	attention
Gschwind et al	2015	Coordinated stability	balance
Gschwind et al	2015	Digit Span backward	executive
Gschwind et al	2015	DSST	speed
Gschwind et al	2015	Handgrip strength	strength
Gschwind et al	2015	Knee extension	strength
Gschwind et al	2015	Maximum balance range-antero posterior	balance
Gschwind et al	2015	Melbourne edge test	balance
Gschwind et al	2015	Propioception	balance
Gschwind et al	2015	Sensor-based chair stand test	strength
Gschwind et al	2015	Sensor-based full tandem stance	balance
Gschwind et al	2015	Sensor-based near tandem stance	balance
Gschwind et al	2015	Sensor-based semi tandem stance	balance
Gschwind et al	2015	SPPB	fitness
Gschwind et al	2015	Sway-area	balance
Gschwind et al	2015	TMT A	speed
Gschwind et al	2015	TMT B	executive
Gschwind et al	2015	TUG	balance
Gschwind et al	2015	Victoria Stroop-efficacy score	executive
Gschwind et al	2015	Victoria Stroop-intrusions	executive
Hiyamizu et al	2012	Chair stand test	strength
Hiyamizu et al	2012	Functional reach test	balance
Hiyamizu et al	2012	Stroop ACC	executive
Hiyamizu et al	2012	Sway - eyes closed	balance
Hiyamizu et al	2012	Sway - eyes open	balance
Hiyamizu et al	2012	TMT A	speed
Hiyamizu et al	2012	TMT B	executive
Hiyamizu et al	2012	TMT B-A	executive
Hiyamizu et al	2012	TUG	balance
Htut et al	2018	Five times sit to stand	strength
Htut et al	2018	Handgrip left	strength
Htut et al	2018	Handgrip right	strength
Htut et al	2018	MoCA	global
Htut et al	2018	TUG	balance
Jardim et al	2021	30-s chair stand	strength
Jardim et al	2021	6-m walk	fitness
Jardim et al	2021	CERARD word list - evocation	memory

APPENDIX C – TABLE 2 (continued)

Jardim et al	2021	CERARD word list - inm	memory
Jardim et al	2021	CERARD word list - recognition	memory
Jardim et al	2021	PALT - nº of patterns	memory
Jardim et al	2021	PALT - stages completed	memory
Jardim et al	2021	PALT – total	memory
Jardim et al	2021	Rapid visual processing	attention
Jardim et al	2021	TUG	balance
Jardim et al	2021	Walking m/s	fitness
Jehu et al	2017	Counting backward (TUGcog)	executive
Jehu et al	2017	TUG	balance
Joubert & Chainay	2019	Complex Span task - ACC	executive
Joubert & Chainay	2019	Complex Span task - RT	executive
Joubert & Chainay	2019	Flanker task - ACC	executive
Joubert & Chainay	2019	Flanker task - RT	executive
Joubert & Chainay	2019	Plus Minus task - ACC	executive
Joubert & Chainay	2019	Plus Minus task - RT	executive
Joubert & Chainay	2019	RAVLT- lexical	memory
Joubert & Chainay	2019	RAVLT-categories	memory
Joubert & Chainay	2019	TMT B-A	executive
Joubert & Chainay	2019	Updated Span task - ACC	executive
Joubert & Chainay	2019	Updated Span task - RT	executive
Kitazawa et al	2015	Dementia Assessment Scale	global
Kitazawa et al	2015	Touch-M - visuospatial	memory
Kitazawa et al	2015	TUG	balance
Laatar et al	2018	30-s chair stand test	strength
Laatar et al	2018	CoP x	balance
Laatar et al	2018	CoP y	balance
Laatar et al	2018	Functional reach test	balance
Laatar et al	2018	Gait speed	fitness
Laatar et al	2018	Simple reaction time	speed
Laatar et al	2018	TUG	balance
Legault et al	2011	1-back	memory
Legault et al	2011	2-back	executive
Legault et al	2011	Flanker task	executive
Legault et al	2011	HVLT delayed	memory
Legault et al	2011	HVLT immediate	memory
Legault et al	2011	HVLT suppl score	memory
Legault et al	2011	HVTL total	memory
Legault et al	2011	Self-ordered pointing task	executive
Legault et al	2011	Task switching	executive
Legault et al	2011	TMT B-A	executive
Linde & Alfermann	2014	d2 test of attention	attention
Linde & Alfermann	2014	DSST	speed
Linde & Alfermann	2014	Leistungs-Pruf-System 50+ Reasoning	speed

APPENDIX C – TABLE 2 (continued)

Linde & Alfermann	2014	Leistungs-Pruf-System 50+ Spatial relatio	speed
Linde & Alfermann	2014	TMT A	speed
Linde & Alfermann	2014	V02max	fitness
Linde & Alfermann	2014	Word list test	memory
Maillot & Hartley	2012	6-Min Walk test-distance	fitness
Maillot & Hartley	2012	6-Min Walk test-max HR	fitness
Maillot & Hartley	2012	6-Min Walk test-mean HR	fitness
Maillot & Hartley	2012	8-Foot Up-and Go test	fitness
Maillot & Hartley	2012	Arm curls	strength
Maillot & Hartley	2012	Back Scratch test – lower left	fitness
Maillot & Hartley	2012	Back Scratch test – lower right	fitness
Maillot & Hartley	2012	Back Scratch test – upper left	fitness
Maillot & Hartley	2012	Back Scratch test – upper right	fitness
Maillot & Hartley	2012	Cancellation test	speed
Maillot & Hartley	2012	Chair stand test	strength
Maillot & Hartley	2012	Directional Headings test	executive
Maillot & Hartley	2012	DSST	speed
Maillot & Hartley	2012	Letter Sets test	executive
Maillot & Hartley	2012	Matrix reasoning test	executive
Maillot & Hartley	2012	Mental rotation test	executive
Maillot & Hartley	2012	Number comparison test	speed
Maillot & Hartley	2012	Reaction time test – choice	speed
Maillot & Hartley	2012	Reaction time test – simple	speed
Maillot & Hartley	2012	Spatial Span test	executive
Maillot & Hartley	2012	Spatial Span test - backward	executive
Maillot & Hartley	2012	Stroop incongruent	executive
Maillot & Hartley	2012	Stroop switching	executive
Maillot & Hartley	2012	TMT B-A	executive
Marmeleira et al.	2009	Dual-task movement time	attention
Marmeleira et al.	2009	Dual-task reaction time	attention
Marmeleira et al.	2009	Dual-task response time	attention
Marmeleira et al.	2009	Foot tap test (Lower limb mobility)	fitness
Marmeleira et al.	2009	Functional reach test	balance
Marmeleira et al.	2009	Self-only in motion. Absolute errors	attention
Marmeleira et al.	2009	Self-only in motion. Constant errors	attention
Marmeleira et al.	2009	Self-only in motion. Variable errors	attention
Marmeleira et al.	2009	Single-task. Movement time	speed
Marmeleira et al.	2009	Single-task. Reaction time	speed
Marmeleira et al.	2009	Single-task. Response time	speed
Marmeleira et al.	2009	Stroop - incongruent	executive
Marmeleira et al.	2009	Stroop - interference	executive
Marmeleira et al.	2009	Target-only in motion. Absolute errors	attention
Marmeleira et al.	2009	Target-only in motion. Constant errors	attention
Marmeleira et al.	2009	Target-only in motion. Variable errors	attention

APPENDIX C – TABLE 2 (continued)

Marmeleira et al.	2009	Three-choice reaction time	speed
Marmeleira et al.	2009	TMT B errors	executive
Marmeleira et al.	2009	TMT B s	executive
Marmeleira et al.	2009	TUG	balance
Marmeleira et al.	2009	Two-choice reaction time	speed
Marmeleira et al.	2009	Useful Field of View - divided att	attention
Marmeleira et al.	2009	Useful Field of View - selective att	attention
Marmeleira et al.	2009	Useful Field of View - speed	speed
McDaniel et al	2014	Cooking Breakfast Task- Ideal Performance	memory
McDaniel et al	2014	Cooking Breakfast Task- Number of Table S	memory
McDaniel et al	2014	Cooking Breakfast Task- Stopping Time Ran	memory
McDaniel et al	2014	Memory for Health Information Task- Corre	memory
McDaniel et al	2014	Memory for Health Information Task- FAs t	memory
McDaniel et al	2014	Memory for Health Information Task- Sourc	memory
McDaniel et al	2014	Virtual Week Task - irregular	attention
McDaniel et al	2014	Virtual Week Task - regular	attention
McDaniel et al	2014	Virtual Week Task – time based	attention
McDaniel et al	2014	VO2peak	fitness
Morita et al	2018	Maximal step length	fitness
Morita et al	2018	Modified Mini-Mental State (3MS)	global
Morita et al	2018	Quad. Muscle strength	strength
Morita et al	2018	Single-leg standing	balance
Morita et al	2018	TUG	balance
Ng et al	2018	RBANS - attention	attention
Ng et al	2018	RBANS - language	language
Ng et al	2018	RBANS – total	composite
Ng et al	2018	RBANS - visuospatial	executive
Ng et al	2018	RBANS – delayed	memory
Ng et al	2018	RBANS – immediate	memory
Ngandu et al	2015	Neuropsychological test battery - Executive Functions	executive
Ngandu et al	2015	Neuropsychological test battery - Memory	memory
Ngandu et al	2015	Neuropsychological test battery - Processing speed	speed
Ngandu et al	2015	Neuropsychological test battery – Memory short version	memory
Ngandu et al	2015	Neuropsychological test battery (NTB) – total	composite
Nilsson et al	2020	Episodic memory spatial + verbal	memory
Nilsson et al	2020	ETS kit verbal inference + BIS analogies + Syllogisms	language
Nilsson et al	2020	n-back + Running span trained	speed
Nilsson et al	2020	n-back + Running span untrained	speed
Nilsson et al	2020	Numerical and spatial updating	speed
Nilsson et al	2020	Perceptual matching 1+ 2	speed

APPENDIX C – TABLE 2 (continued)

Nilsson et al	2020	Raven's Progressive Matrices	executive
Nilsson et al	2020	Task switching 1 + 2	speed
Nishiguchi et al	2015	0-back - face-ACC	speed
Nishiguchi et al	2015	0-back - face-ms	speed
Nishiguchi et al	2015	0-back - face+location ACC	speed
Nishiguchi et al	2015	0-back - face+location-ms	speed
Nishiguchi et al	2015	0-back - location-ACC	speed
Nishiguchi et al	2015	0-back - location-ms	speed
Nishiguchi et al	2015	1-back face+location-ms	executive
Nishiguchi et al	2015	1-back - face-ms	executive
Nishiguchi et al	2015	1-back - face+location-ms	executive
Nishiguchi et al	2015	1-back - location-ACC	executive
Nishiguchi et al	2015	1-back - location-ms	executive
Nishiguchi et al	2015	10-m walk test	fitness
Nishiguchi et al	2015	Chair stand test	strength
Nishiguchi et al	2015	Daily steps	fitness
Nishiguchi et al	2015	Logical memory - delayed	memory
Nishiguchi et al	2015	Logical memory - immediate	memory
Nishiguchi et al	2015	MMSE	global
Nishiguchi et al	2015	TMT B-A	executive
Nishiguchi et al	2015	TUG	balance
Nocera et al	2020	Digit Span backward	executive
Nocera et al	2020	Digit Span forward	memory
Nocera et al	2020	Letter fluency	language
Nocera et al	2020	n-back-ACC	executive
Nocera et al	2020	n-back-ms	executive
Nocera et al	2020	Semantic fluency	language
Nocera et al	2020	Single gait	fitness
Nocera et al	2020	SPPB	fitness
Nocera et al	2020	Stroop	executive
Nocera et al	2020	TMT A	speed
Nocera et al	2020	TMT B	executive
Nocera et al	2020	VO2	fitness
Norouzi et al	2019	Berg Balance Scale	balance
Norouzi et al	2019	n-back	executive
Oswald et al	2006	Composite z score - cognitive	composite
Phirom et al	2020	MoCA	global
Phirom et al	2020	Physiological Profile Assessment – knee extension strength	strength
Phirom et al	2020	Physiological Profile Assessment – Sway	balance
Phirom et al	2020	TUG – single task	balance
Pieramico et al	2012	Babcock Story – Delayed Recall	memory
Pieramico et al	2012	Babcock Story – Immediate Recall	memory
Pieramico et al	2012	Babcock Story Recall Test	memory
Pieramico et al	2012	Frontal Assessment Battery	global

APPENDIX C – TABLE 2 (continued)

Pieramico et al	2012	MMSE	global
Pieramico et al	2012	Phonological Fluency test	language
Pieramico et al	2012	TMT A	speed
Pieramico et al	2012	TMT B	executive
Pieramico et al	2012	TMT B-A	executive
Rahe et al (a)	2015	30 s Chair stand	strength
Rahe et al (a)	2015	6 minute walk test/2Min step test	fitness
Rahe et al (a)	2015	8 foot up and go test	fitness
Rahe et al (a)	2015	Arm curl	strength
Rahe et al (a)	2015	Brief Test of Attention	attention
Rahe et al (a)	2015	Chair sit and reach test	fitness
Rahe et al (a)	2015	Complex Figure Test- memory	memory
Rahe et al (a)	2015	DemTect - composite	composite
Rahe et al (a)	2015	DemTect subtest supermarket/animal	language
Rahe et al (a)	2015	DemTect-delayed recall	memory
Rahe et al (a)	2015	DemTect-immediate recall	memory
Rahe et al (a)	2015	Digit Span backward	executive
Rahe et al (a)	2015	Overal fitness	fitness
Rahe et al (a)	2015	Regensburger Wort Flüssigkeits-Test – Fluidez verbal	language
Rahe et al (a)	2015	Stroop	executive
Rahe et al (b)	2015	Brief Test of Attention	attention
Rahe et al (b)	2015	Complex Figure Test- memory	global
Rahe et al (b)	2015	COWAT	language
Rahe et al (b)	2015	TMT B/A	executive
Raichlen et al	2020	serially subtract 7's beginning at 500	executive
Raichlen et al	2020	Stride duration	balance
Raichlen et al	2020	Stride duration variability	balance
Raichlen et al	2020	Stride length	balance
Raichlen et al	2020	Stride length variability	balance
Raichlen et al	2020	Stride velocity	balance
Raichlen et al	2020	Stride velocity variability	balance
Romera-Liebana et al	2018	Abstraction of word pairs	language
Romera-Liebana et al	2018	Animal naming test	language
Romera-Liebana et al	2018	Designation of images	language
Romera-Liebana et al	2018	Designation of names	language
Romera-Liebana et al	2018	Evocation of words	language
Romera-Liebana et al	2018	Functional reach test	fitness
Romera-Liebana et al	2018	Handgrip	strength
Romera-Liebana et al	2018	SPPB	fitness
Romera-Liebana et al	2018	Unipodal station	fitness
Romera-Liebana et al	2018	Verbal memory delayed	memory
Romera-Liebana et al	2018	Verbal memory immediate	memory
Salazar et al	2014	Cadence	balance
Salazar et al	2014	Double support	balance

APPENDIX C – TABLE 2 (continued)

Salazar et al	2014	Step width	balance
Salazar et al	2014	Stride length	balance
Salazar et al	2014	Substracting digits backwards	executive
Salazar et al	2014	Swing	balance
Salazar et al	2014	Walk speed	fitness
Schoene et al (a)	2013	Alternate Step test	balance
Schoene et al (a)	2013	Chair stand test	strength
Schoene et al (a)	2013	Choice stepping reaction time. Movement time.	speed
Schoene et al (a)	2013	Choice stepping reaction time. Reaction time.	speed
Schoene et al (a)	2013	Choice stepping reaction time. Total response time.	speed
Schoene et al (a)	2013	Physiological Profile Assessment (PPA). anteroposterior	balance
Schoene et al (a)	2013	Physiological Profile Assessment (PPA). central	balance
Schoene et al (a)	2013	Physiological Profile Assessment (PPA). medio-lateral	balance
Schoene et al (a)	2013	Physiological Profile Assessment (PPA). Global	balance
Schoene et al (a)	2013	Physiological Profile Assessment (PPA). Lower extremity strength	strength
Schoene et al (a)	2013	Physiological Profile Assessment (PPA). Propioception of lower extremities	balance
Schoene et al (a)	2013	Step inhibition test - s	executive
Schoene et al (a)	2013	Step inhibition test errors	executive
Schoene et al (a)	2013	Step inhibition test time/trials	executive
Schoene et al (a)	2013	TMT A	speed
Schoene et al (a)	2013	TUG	balance
Schoene et al (b)	2015	Attentional network test - alert	attention
Schoene et al (b)	2015	Attentional network test - executive	executive
Schoene et al (b)	2015	Attentional network test - orientation	attention
Schoene et al (b)	2015	Choice stepping movement time test	speed
Schoene et al (b)	2015	Choice stepping reaction time test	speed
Schoene et al (b)	2015	Digit letter maximum	speed
Schoene et al (b)	2015	Digit letter mean	speed
Schoene et al (b)	2015	Digit letter minimum	speed
Schoene et al (b)	2015	Digit Span backward	executive
Schoene et al (b)	2015	Hand reaction time test	speed
Schoene et al (b)	2015	Mental rotation - errors	executive
Schoene et al (b)	2015	Mental rotation - TR	executive
Schoene et al (b)	2015	Stroop - errors	executive
Schoene et al (b)	2015	Stroop – TR	executive
Schoene et al (b)	2015	Stroop Stepping Test - TR	executive
Schoene et al (b)	2015	Stroop Stepping Test -errors	executive
Schoene et al (b)	2015	TMT A	speed

APPENDIX C – TABLE 2 (continued)

Schoene et al (b)	2015	TMT B	executive
Schoene et al (b)	2015	TMT B/A	executive
Shah et al	2014	1-back	memory
Shah et al	2014	Borg's scale	balance
Shah et al	2014	COWAT	language
Shah et al	2014	Detection (DET)	speed
Shah et al	2014	Groton Maze learning	memory
Shah et al	2014	Immediate Recall	memory
Shah et al	2014	Incremental Shuttle Walk test	fitness
Shah et al	2014	long term delayed recall	memory
Shah et al	2014	short term delayed recall	memory
Shah et al	2014	Sum of Strength (kgs.)	strength
Shah et al	2014	Visual Memory - index score	memory
Shatil et al	2013	CogniFit avoiding distractors	executive
Shatil et al	2013	CogniFit divided attention	attention
Shatil et al	2013	CogniFit global visual memory	memory
Shatil et al	2013	CogniFit inhibition	executive
Shatil et al	2013	CogniFit naming	language
Shatil et al	2013	CogniFit planning	executive
Shatil et al	2013	CogniFit processing speed	speed
Shatil et al	2013	CogniFit self-awareness	executive
Shatil et al	2013	CogniFit shifting	executive
Shatil et al	2013	CogniFit time estimation	executive
Shatil et al	2013	CogniFit visual scanning	attention
Shatil et al	2013	CogniFit working memory	executive
Takeuchi et al	2020	0-back	memory
Takeuchi et al	2020	2-back	executive
Takeuchi et al	2020	Digit cancellation task	attention
Takeuchi et al	2020	Digit span	executive
Takeuchi et al	2020	Frontal lobe and executive function	executive
Takeuchi et al	2020	Logical memory	memory
Takeuchi et al	2020	Raven's Progressive Matrices	executive
Takeuchi et al	2020	Semantic fluency	language
Takeuchi et al	2020	Symbol search	speed
Teixeira et al	2013	Digit Span backward	executive
Teixeira et al	2013	Digit Span forward	memory
Teixeira et al	2013	MMSE	global
Teixeira et al	2013	Modified Card Sorting Test - errors	executive
Teixeira et al	2013	Modified Card Sorting Test - errors adjusted for age	executive
Teixeira et al	2013	Toulouse-Pierón Concentrated Attention Test - hits	attention
Teixeira et al	2013	Toulouse-Pierón Concentrated Attention Test - TR	attention
Theill et al.	2013	Continuous Performance task	attention

APPENDIX C – TABLE 2 (continued)

Theill et al.	2013	DSST	speed
Theill et al.	2013	Dual task (WM+gait) - errors	executive
Theill et al.	2013	Dual task (WM+gait) - hits	executive
Theill et al.	2013	Executive control task	executive
Theill et al.	2013	Gait variability – single task	fitness
Theill et al.	2013	Gait velocity – single task	fitness
Theill et al.	2013	Operation span test	memory
Theill et al.	2013	PALT	memory
Theill et al.	2013	Raven's Progressive Matrices	executive
Van het Reve & de Bruin	2014	TMT A	speed
Van het Reve & de Bruin	2014	TMT B	executive
Van het Reve & de Bruin	2014	Vienna Test System – divided attention, lower channel	attention
Van het Reve & de Bruin	2014	Vienna Test System – divided attention, upper channel	attention
Wollesen et al (a)	2017	Gait-line left	balance
Wollesen et al (a)	2017	Gait-line right	balance
Wollesen et al (a)	2017	SPPB	balance
Wollesen et al (a)	2017	Step length left	balance
Wollesen et al (a)	2017	Step length right	balance
Wollesen et al (a)	2017	Step width	balance
Wollesen et al (a)	2017	Stroop	executive
Wollesen et al (a)	2017	Stroop dual-task (during walking)	executive
Wollesen et al (b)	2017	Gait-line left	balance
Wollesen et al (b)	2017	Gait-line right	balance
Wollesen et al (b)	2017	SPPB	balance
Wollesen et al (b)	2017	Step length left	balance
Wollesen et al (b)	2017	Step length right	balance
Wollesen et al (b)	2017	Step width	balance
Wollesen et al (b)	2017	Stroop	executive
Wollesen et al (b)	2017	Stroop dual-task (during walking)	executive
Wongcharoen et al	2017	Counting backwards	speed
Wongcharoen et al	2017	Step width	balance
Wongcharoen et al	2017	Stride length	balance
Wongcharoen et al	2017	Verbal fluency test	language
Wongcharoen et al	2017	XcoM-BoS - Narrow walk distance	balance
Wongcharoen et al	2017	XcoM-BoS - Narrow walk speed	balance
Yokoyama et al	2015	Maximal step length	fitness
Yokoyama et al	2015	Modified Mini-Mental State (3MS)	global
Yokoyama et al	2015	Muscle strength - legs	strength
Yokoyama et al	2015	Muscle strength – cuadr.	strength
Yokoyama et al	2015	Single leg standing	balance
Yokoyama et al		TMT A	speed
Yokoyama et al	2015	TUG	balance
You et al	2009	Gait stability - AP COP	balance

APPENDIX C – TABLE 2 (continued)

You et al	2009	Gait stability - ML COP	balance
You et al	2009	Gait velocity	fitness
You et al	2009	Memory recall	memory
Yu et al (dual-cognitive)	2021	Frontal Assessment Battery	global
Yu et al (dual-cognitive)	2021	Hong Kong List Learning Test-Delay Recall Trial	memory
Yu et al (dual-cognitive)	2021	Hong Kong List Learning Test-Total Learning	memory
Yu et al (dual-cognitive)	2021	Rapid Cognitive Screen	global
Yu et al (multicognitive)	2021	Frontal Assessment Battery	global
Yu et al (multicognitive)	2021	Hong Kong List Learning Test-Delay Recall Trial	memory
Yu et al (multicognitive)	2021	Hong Kong List Learning Test-Total Learning	memory
Yu et al (multicognitive)	2021	Rapid Cognitive Screen	global

APPENDIX C – TABLE 3. Quality assessment of the reviewed articles using the Checklist for Assessing the Quality of Quantitative Studies (Kmet, Lee, and Cook (2004).

Criteria	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Quality score**	**Groups**
Fabre et al. (2002)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	22	Combined; single physical; single cognitive; active control
Oswald et al. (2006)	Y	Y	Y	Y	N	N	N	Y	P	Y	Y	P	Y	Y	20	Combined; single physical, single cognitive, passive control; psychoeducation (not incl.); psychoeducation + physical (not incl.)
Marmeleira et al. (2009)	Y	P	Y	Y	P	N	N	Y	N	Y	Y	P	Y	Y	19	Combined; passive control
You et al. (2009)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	P	Y	Y	21	Combined; physical + cognitive control
Legault et al. (2011)	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	P	Y	Y	23	Combined; single physical; single cognitive; active control
Anderson-Hanley et al. (2012).	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	P	Y	Y	23	Combined; single physical
Hiyamizu et al. (2012).	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	P	Y	Y	23	Combined; single physical
Maillot et al. (2012)	Y	P	Y	Y	P	N	N	Y	N	Y	Y	Y	Y	Y	20	Combined; passive control
Pieramico et al. (2012)	Y	y	Y	Y	P	N	N	Y	N	Y	Y	P	Y	Y	20	Combined; passive control
Schoene et al. (2013)	Y	Y	y	Y	P	Y	N	Y	P	Y	Y	Y	Y	Y	24	Combined, passive control
Shatil (2013)	Y	y	y	Y	Y	N	N	Y	P	Y	Y	P	Y	Y	22	Combined; single physical, single cognitive, passive control
Teixeira et al., (2013)	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	N	Y	Y	18	Combined; passive control
Theill et al. (2013)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	P	Y	Y	17	Combined, single cognitive, passive control
Linde & Alfermann (2014)	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	P	Y	Y	23	Combined, single physical, single cognitive, passive control
McDaniel et al. (2014)	Y	Y	Y	Y	P	N	N	Y	N	Y	Y	Y	Y	Y	21	Combined, physical + cognitive control, cognitive + physical control, physical control + cognitive control
Salazar et al. (2014)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	20	Combined, passive control
Shah et al. (2014)	Y	Y	Y	Y	N	N	N	Y	P	Y	Y	P	y	Y	20	Combined, single physical, single cognitive, passive control

APPENDIX C – TABLE 3 (continued)

Criteria	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Quality score**	**Groups**
Van Het Reve & de Bruin (2014)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	24	Combined, single physical
Bamidis et al. (2015)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	22	Combined, passive control
Eggenberger et al. (2015)	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	P	Y	Y	23	Combined, single physical
Gschwind et al. (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	28	Combined, passive control
Kitazawa et al. (2015)	Y	Y	Y	P	Y	N	N	Y	N	Y	Y	P	Y	Y	18	Combined, passive control
Ngandu et al. (2015)	Y	y	y	Y	Y	y	Y	y	Y	Y	y	y	y	Y	28	Combined, active control
Nishiguchi et al (2015)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	26	Combined, passive control
Rahe et al. (2015a)	Y	P	Y	Y	N	N	N	Y	N	Y	Y	N	Y	Y	17	Combined, single cognitive
Rahe et al. (2015b)	Y	P	Y	Y	N	N	N	Y	N	Y	Y	N	Y	Y	17	Combined, single cognitive
Schoene et al. (2015)	Y	Y	y	Y	Y	Y	N	Y	Y	Y	Y	Y	y	Y	26	Combined, passive control
Yokoyama et al. (2015)	Y	P	Y	Y	Y	N	Y	Y	N	Y	Y	P	Y	Y	22	Combined, single physical
Desjardins-Crépeau et al. (2016)	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	24	Combined, single physical + cognitive control, single cognitive + physical control, physical control + cognitive control
Gill et al. (2016)	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	P	Y	Y	23	Combined, single physical
Andrieu et al. (2017)	Y	Y	Y	Y	Y	N	P	Y	Y	Y	Y	Y	Y	Y	25	Combined, passive control
Barban et al. (2017)	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	27	Combined, single physical, single cognitive, control
Jehu et al. (2017)	Y	Y	Y	Y	P	N	N	Y	N	Y	Y	P	Y	Y	20	Combined, single physical, passive control
Ng et al. (2018)	Y	P	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	23	Combined, single physical, single cognitive, active control
Wollesen et al. (2017)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	23	Combined with and without concern of falling, passive control
Wongcharoen et al. (2017)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	P	Y	Y	20	Combined, single physical, single cognitive
Htut et al. (2018)	Y	Y	Y	Y	Y	Y	N	P	Y	Y	Y	P	Y	Y	24	Combined, passive control
Laatar et al. (2018)	Y	P	Y	Y	Y	N	N	Y	N	Y	Y	P	Y	Y	2O	Combined, single physical
Morita et al. (2018)	Y	P	Y	P	N	N	N	Y	N	Y	Y	N	Y	Y	16	Combined, passive control
Romera-Liebana et al. (2018)	Y	Y	Y	Y	P	Y	N	Y	Y	Y	Y	P	Y	Y	24	Combined, passive control
Joubert & Chainay, (2019)	Y	Y	Y	Y	P	N	N	Y	N	Y	Y	P	Y	Y	20	Combined, single cognitive, passive control
Norouzi et al. (2019)	Y	Y	Y	Y	P	N	N	Y	N	Y	Y	P	Y	Y	20	Combined, passive control, single physical (not incl.: nonequivalent exercise intervention)
Adcock et al. (2020)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	20	Combined, passive control
Nilsson et al. (2020)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	26	Combined, single physical, single cognitive

APPENDIX C – TABLE 4. Results of the Influential case analysis

Authors	ES	v	Function	Comparison	Rstudent	dffits	cook.d	cov.r	tau2.del	QE.del	hat	weight	dfbs inf
Pre-post outcomes													
Oswald et al, 2016	1.0096	.057	composite	comb-control	2.1472	0.1667	0.0272	0.9824	0.0448	1204.5378	0.0025	0.2481	0.1666
Anderson-Hanley et al, 2012	-1.5200	.084	memory	comb-physical	3.5554	0.2944	0.0838	0.9593	0.0311	1264.8094	0.0017	0.1698	0.2957
Anderson-Hanley et al, 2012	1.2280	.077	executive	comb-physical	2.7594	0.2100	0.0431	0.9749	0.0326	1271.4589	0.0018	0.1804	0.2105
Maillot & Hartley, 2012	2.0486	.218	speed	comb-control	3.4601	0.1652	0.0271	0.9808	0.0332	1268.7936	0.0008	0.0800	0.1663
Maillot & Hartley, 2012	2.1280	.224	executive	comb-control	3.5739	0.1700	0.0287	0.9800	0.0332	1267.9221	0.0008	0.0780	0.1711
Schoene et al (a), 2013	3.4110	.338	executive	comb-control	5.0884	0.2171	0.0468	0.9712	0.0324	1254.1454	0.0005	0.0542	0.2196
Nishiguchi et al, 2015	-8.0860	.834	speed	comb-control	8.3542	0.2412	0.0580	0.9662	0.0319	1210.0463	0.0002	0.0233	0.2450
Nishiguchi et al, 2015	-7.6470	.754	speed	comb-control	8.2711	0.2540	0.0642	0.9639	0.0317	1211.1985	0.0003	0.0256	0.2582
Schoene et al (b), 2015	9.9500	.696	executive	comb-control	11.3233	0.4170	0.1724	0.9324	0.0288	1148.7103	0.0003	0.0277	0.4301
Yokoyama et al, 2015	2.9840	.380	global	comb-physical	4.1520	0.1524	0.0231	0.9824	0.0334	1263.9084	0.0005	0.0487	0.1535
Wollesen et al (b), 2017	1.6040	.161	executive	comb-control	2.9265	0.1553	0.0239	0.9830	0.0334	1272.2366	0.0010	0.1034	0.1560
Norouzi et al, 2019	5.5560	.534	executive	comb-control	6.9692	0.2514	0.0628	0.9646	0.0318	1231.0176	0.0004	0.0355	0.2553
Nocera et al, 2010	-2.9600	.376	executive	comb-cognitivo	4.1320	0.1523	0.0231	0.9824	0.0334	1264.0738	0.0005	0.0492	0.1534
Jardim et al, 2021	1.4150	.062	memory	comb-control	3.6317	0.3573	0.1211	0.9485	0.0301	1262.3100	0.0021	0.2082	0.3577
Jardim et al, 2021	2.0780	.089	memory	comb-control	5.1789	0.5077	0.2418	0.9188	0.0274	1246.7427	0.0016	0.1630	0.5134
Jardim et al, 2021	2.5250	.104	memory	comb-control	6.1438	0.5996	0.3355	0.9006	0.0258	1234.6876	0.0015	0.1452	0.6108
Jardim et al, 2021	2.6080	.107	memory	comb-control	6.3031	0.6119	0.3493	0.8982	0.0256	1232.5822	0.0014	0.1419	0.6241
Jardim et al, 2021	2.7550	.113	memory	comb-control	6.5727	0.6306	0.3712	0.8943	0.0252	1228.9394	0.0014	0.1364	0.6447
Jardim et al, 2021	3.1890	.132	memory	comb-control	7.2711	0.6641	0.4134	0.8872	0.0246	1219.0715	0.0012	0.1208	0.6830
Jardim et al, 2021	3.4670	.146	balance	comb-control	5.5576	0.6506	0.3528	0.8106	0.1557	741.3390	0.0044	0.4406	0.6612
Jardim et al, 2021	4.5690	.211	fitness	comb-control	7.0074	0.7842	0.5068	0.7609	0.1408	724.4046	0.0037	0.3731	0.8176
Jardim et al, 2021	4.9500	.238	fitness	comb-control	7.3955	0.8000	0.5312	0.7537	0.1386	720.0702	0.0035	0.3511	0.8408
Jardim et al, 2021	5.3960	.272	strength	comb-control	7.7886	0.8047	0.5438	0.7500	0.1376	715.7461	0.0033	0.3266	0.8527
Nishiguchi et al, 2015	2.015	.131	fitness	comb-control	2.6774	0.2435	0.0566	0.9551	0.2228	738.3822	0.0049	0.4949	0.2440
Andrieu et al, 2017	2.3437	6.67	executive	comb-control	identified based on visual inspection of the funnel plot								
Pre-follow up outcomes													
Norouzi et al, 2019	2.8620	.216	executive	comb-control	identified based on visual inspection of the funnel plot								

Note: cook.d = Cook's distance, cov.r = Covariance ratio, dfbs inf = DFBETAS, dffits = Difference in fits, ES = Effect size, hat = Diagonal of the hat matrix, Rstudent = studentized residual, QE.del = Leave-one-out test statistic of the test for (residual) heterogeneity, tau2.del = Leave-one-out amount of (residual) heterogeneity, v = Variance

APPENDIX C – TABLE 5. Results of the continuous and categorical moderator analyses by cognitive functions

	Mean difference in ES [95% CI] by moderators in cognitive outcomes						
	Executive functions	**Memory**	**Attention**	**Language**	**Speed**	**Global**	**Composite**
Continuous moderators							
Quality	-0.014 [-0.042, 0.013]	-0.022 [-0.014, 0.058]	-0.028 [-0.067, 0.012]	-0.006 [-0.057, 0.056]	-0.014 [-0.068, 0.04]	-0.029 [-0.142, 0.084]	-0.075 [-0.211, 0.061]
Year	-0.013 [-0.037, 0.011]	-0.009 [-0.033, 0.016]	0.003 [-0.044, 0.049]	0.012 [-0.037, 0.058]	-0.044 [-0.094, 0.007]	0.039 [-0.041, 0.119]	-0.053 [-0.108, -0.001]
N	-0.006 [-0.001, 0.000]	-0.000 [-0.001, 0.000]	-0.003 [-0.004, -0.001] ***	-0.000 [-0.001, 0.001]	-0.000 [-0.001, 0.001]	-0.001 [-0.002, 0.000]	-0.000 [-0.002, 0.001]
Age mean	-0.003 [-0.022, 0.016]	-0.001 [-0.022, 0.02]	-0.014 [-0.038, 0.01]	0.015 [-0.018, 0.047]	0.009 [-0.026, 0.044]	-0.025 [-0.089, 0.038]	0.043 [0.025, 0.011]
Age SD	0.013 [-0.034, 0.061]	0.043 [-0.009, 0.095]	-0.019 [-0.103, 0.064]	0.02 [-0.04, 0.08]	-0.04 [-0.123, 0.042]	-0.112 [-0.437, 0.214]	-0.001 [-0.263, 0.266]
Nº sessions	-0.000 [-0.003, 0.002]	-0.000 [-0.002, 0.000]	0.001 [-0.004, 0.006]	0.000 [-0.000, 0.001]	0.000 [-0.001, 0.002]	-0.001 [-0.002, 0.000]	-0.001 [-0.002, 0.001]
Training/wks	-0.002 [-0.014, 0.011]	-0.003 [-0.01, 0.003]	-0.004 [-0.03, 0.022]	0.001 [-0.003, 0.006]	0.003 [-0.003, 0.009]	-0.002 [-0.009, 0.005]	-0.003 [-0.013, 0.007]
Min./week	-0.001 [-0.002, 0.000]	-0.000 [-0.001, 0.001]	-0.000 [-0.002, 0.001]	-0.001 [-0.002, 0.000]	-0.001 [-0.002, 0.000]	-0.001 [-0.005, 0.001]	-0.002 [-0.006, 0.001]
Min. cogn./wk	-0.000 [-0.002, 0.001]	0.000 [-0.001, 0.002]	0.002 [-0.000, 0.005]	-0.001 [-0.003, 0.000]	-0.001 [-0.003, 0.001]	-0.001 [-0.006, 0.004]	-0.002 [-0.008, 0.007]
Min. phys/wk	0.000 [-0.002, 0.002]	-0.000 [-0.002, 0.02]	-0.000 [-0.001, 0.003]	-0.001 [-0.003, 0.001]	-0.001 [-0.004, 0.002]	-0.002[-0.012, 0.008]	-0.004 [-0.008, 0.000]
Combinatory mode							
Simultaneous	0.208 [0.098, 0.318] ***	0.154 [-0.012, 0.321]	0.144 [0.017, 0.271] *	0.06 [-0.18, 0.302]	0.293 [0.1, 0.486] **	0.56 [-0.124, 0.996] *	NA
Sequential	0.157 [-0.034, 0.348]	0.074 [-0.088, 0.237]	0.286 [0.071, 0.5] *	0.023 [-0.229, 0.275]	-0.007 [-0.276, 0.262]	0.156 [-0.592, 0.904]	0.373 [-0.001, 0.748]
Separate days	0.175 [0.001, 0.349] *	0.16 [-0.003, 0.324]	-0.139 [-0.344, 0.067]	0.176 [-0.037, 0.388]	0.138[-0.242, 0.519]	0.161 [-0.549, 0.872]	0.003 [-0.354, 0.359]
Aerobic vs non-aerobic							
Aerobic	0.2 [0.087, 0.313] ***	0.108 [-0.016, 0.233]	0.279 [0.097, 0.461] **	0.088 [-0.173, 0.348]	0.175 [-0.058, 0.407]	-0.049 [-0.627, 0.53]	0.55 [-0.179, 1.279]
Non-aerobic	0.138 [0.053, 0.223] **	0.08 [-0.066, 0.226]	0.032 [-0.094, 0.157]	0.078 [-0.094, 0.25]	0.202 [0.034, 0.37] *	0.508 [0.149, 0.868] **	0.113 [-0.24, 0.465]
Cognitive training type							
Interactive[a]	0.322 [0.179, 0.465] ***	0.258 [-0.005, 0.521]	0.158 [-0.095, 0.411]	NA	0.494 [0.257, 0.731] ***	0.56 [0.124, 0.996] *	NA
Computer	0.131 [0.025, 0.227] *	0.059 [-0.07, 0.19]	0.069 [-0.139, 0.277]	0.047 [-0.177, 0.271]	0.042 [-0.152, 0.235]	0.046 [-0.899, 0.992]	NA
Multic.[b]	0.137 [-0.037, 0.31]	0.196 [0.033, 0.358] *	0.14 [-0.081, 0.362]	0.228 [0.036, 0.421] *	0.312 [0.009, 0.614] *	0.206 [-0.409, 0.821]	0.111 [-0.218, 0.447]
Setting							
Group	0.162 [0.068, 0.256] ***	0.182 [0.058, 0.305] **	0.189 [0.047, 0.331] *	0.207 [0.012, 0.402] *	0.241 [0.038, 0.443] *	0.482 [0.027, 0.938] *	0.28 [-1.033, 1.593]
Individual	0.151 [0.022, 0.279] *	0.111 [-0.117, 0.339]	0.032 [-0.181, 0.245]	0.086 [-0.399, 0.227]	0.08 [-0.18, 0.34]	0.42 [-0.378, 1.219]	NA
Mixed	0.195 [-0.119, 0.51]	0.198 [-0.023, 0.42]	NA	0.333 [0.028, 0.638] *	0.348 [0.015, 0.68] *	0.162 [-0.592, 0.016]	NA

Note. ES = Hedges'g, CI = Confidence interval, N = Number of participants, NA = 3 or less effect sizes in this condition, SD = Standard deviation, wk = Week, wks = Weeks

[a] Interactive training refers to cognitive activities that require a body-mind interaction such as exergames, square stepping, etc.

[b] Multic. = Multicomponent which refers to a mixture of cognitive tasks and games, delivered in different modalities such as paper-pencil, verbally, computer-assisted, etc.

* $p < .05$; ** $p < .01$; *** $p < .001$.

APPENDIX C – TABLE 6. Results of the continuous and categorical moderator analyses by physical functions

	Mean difference in ES [95% CI] by moderators in physical outcomes		
	Fitness	**Balance**	**Strength**
Continuous moderators			
Quality	-0.008 [-0.057, 0.041]	-0.039 [-0.07, -0.008] *	0.015 [-0.066, 0.096]
Year	-0.035 [-0.068, -0.002] *	0.014 [-0.025, 0.053]	-0.051 [-0.155, 0.054]
N	-0.000 [-0.001, 0.000]	-0.001 [-0.002, 0.000]	-0.001 [-0.004, 0.002]
Age mean	-0.016 [-0.06, 0.028]	-0.03 [-0.066, 0.006]	0.038 [-0.041, 0.118]
Age SD	0.029 [-0.057, 0.116]	-0.11 [-0.218, 0.002] *	-0.061 [-0.25, 0.128]
Nº sessions	-0.000 [-0.001, 0.000]	-0.004 [-0.01, 0.002]	-0.012 [-0.025, 0.001]
Training/wks	-0.002 [-0.006, 0.002]	0.001 [-0.006, 0.006]	-0.01 [-0.022, 0.001]
Minutes/week	-0.000 [-0.002, 0.001]	0.000 [-0.001, 0.002]	-0.001 [-0.003, 0.001]
Min. cogn./week	-0.002 [-0.006, 0.002]	0.000 [-0.000, 0.003]	-0.001 [-0.005, 0.002]
Min. phys/week	-0.001 [-0.004, 0.002]	0.001 [-0.001, 0.003]	-0.001 [-0.005, 0.003]
Combinatory mode			
Simultaneous	0.184 [-0.021, 0.388]	0.259 [0.153, 0.364] ***	0.334 [0.045, 0.622] *
Sequential	0.151 [-0.095, 0.398]	0.308 [-0.008, 0.623]	0.177 [-0.29, 0.644]
Separate days	0.255 [-0.026, 0.537]	NA	0.147 [-0.429, 0.724]
Aerobic vs non-aerobic			
Aerobic	0.257 [0.082, 0.433] **	0.182 [-0.11, 0.475]	0.373 [-0.154, 0.9]
Non-aerobic	0.059 [-0.079, 0.197]	0.272 [0.157, 0.387] ***	0.205 [-0.01, 0.421]
Cognitive training type			
Interactive	0.385 [0.113, 0.656] **	0.301 [0.154, 0.449] ***	0.411 [0.086, 0.735] *
Computer	0.04 [-0.187, 0.268]	0.153 [-0.043, 0.343]	0.045 [-0.273, 0.563]
Multicomponent	0.288 [0.102, 0.474] **	0.269 [0.075, 0.464] **	0.4 [-0.096, 0.895]
Setting			
Group	0.328 [0.24, 0.453] ***	0.255 [0.12, 0.389] **	0.291 [0.069, 0.512] *
Individual	-0.073 [-0.256, 0.15]	0.242 [0.052, 0.432] *	0.209 [-0.034, 0.452]
Mixed	-0.011 [-0.255, 0.232]	0.394 [-0.04, 0.827]	NA

Note. ES = Hedges' g; CI = confidence interval. NA = not available due to missing effect sizes. * p < .05; ** p < .01; *** p < .001.