Lampiran

Artikel 1

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Efektivitas Penerapan Cognitive Stimulation Therapy (CST) untuk Meningkatkan Fungsi Kognitif, Activity Daily living, Psikologis, dan Kualitas Hidup Pada Lansia

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ABSTRACT

Cognitive Decline is a significant cognitive decline from normal cognition to dementia, so interventions are needed to inhibit the development of cognitive decline so that cognitive function does not decline (Smith & Blumenthal, 2016). Various efforts can be made to prevent the decline in cognitive function, namely by pharmacological and non-pharmacological collaborative therapy. Cognitive Stimulation Therapy (CST) is a non-pharmacological therapy that is effective in specifically improving cognitive function and increasing independence, reducing depression, and improving the quality of life of the elderly with dementia. The purpose of this study was to assess the Effectiveness of the Application of Cognitive Stimulation Therapy (CST) to Improve Cognitive Function, Activity Daily living, Psychological (reducing depression), and Quality of Life. This was quasi-experimental study with Two Group (pre-test and post-test), the inclusion criteria was: elderly over 60 years old with mild to moderate dementia. Therapy was carried out in 14 sessions in intervention groups, held 2 times a week for 7 weeks with a duration of 40-45 minutes. The results showed a significant difference between the pre-test and post-test in the intervention group and the control group in 3 domains, namely cognitive function p-value (0.029), depression p-value (0.02) and quality of life p-value (0.03). It was found that there was cognitive stability and an increase in the number of scores before and after the intervention, a decrease in depression and an increase in quality of life. Suggestions for this study are expected to provide CST intervention is one of the activities that can be applied in the geriatric service unit for dementia patients

Abstrak

Cognitive Decline adalah penurunan kognitif yang signifikan dari kognisi normal menjadi demensia, sehingga diperlukan intervensi untuk menghambat perkembangan cognitive decline agar fungsi kognitif tidak menurun (Smith & Blumenthal, 2016). Berbagai upaya yang dapat dilakukan untuk mencegah penurunan fungsi kognitif yaitu dengan terapi kolaboratif farmakologis dan non-farmakologik. Cognitive Stimulation Therapy (CST) merupakan terapi non-farmakologik yang efektif meningkatkan fungsi kognitif secara spesifik serta meningkatkan kemandirian, menurunkan depresi, dan meningkatkan kualitas hidup lansia dengan demensia. Tujuan pada penetian ini adalah menilai Efektivitas Penerapan Cognitive Stimulation Therapy (CST) untuk Meningkatkan Fungsi Kognitif, Activity Daily living, Psikologis (penurunan depresi), dan Kualitas Hidup. Jenis penelitian ini adalah Quasi eksperiments Two Group (pre-test dan post-test), dengan kriteria inklusi: lansia usia ≥ 60 tahun dengan demensia ringan s/d sedang. Therapy dilakukan sebanyak 14 sesi pada kelompok intervensi, diadakan 2 kali dalam seminggu selama 7 minggu dengan durasi waktu 40 – 45 menit. Hasil penelitian menunjukan adanya perbedaan yang signikan antara pre-test dan post-test pada kelompok intervensi dan kelompok kontrol pada 3 domain yaitu fungsi kognitif p-value (0.029), depresi p-value (0.02) dan kualitas hidup p-value (0.03). Didapatkan adanya kestabilan kognitif dan peningkatan jumlah skor sebelum dan sesudah intervensi, penurunan depresi dan peningkatan kualitas hidup. Saran penelitian ini diharapkan pemberian intervensi CST menjadi salah satu kegiatan yang dapat diterapkan di unit pelayanan geriatric pada pasien demensia.

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KEYWORDS
Activity Daily Living (ADL), Cognitive Stimulation Therapy (CST), Demensia, Depresi, Quality of life.

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INTRODUCTION

Prevalensi lansia di dunia pada tahun 2015 sekitar 901 juta orang dan diperkirakan jumlah pada tahun 2030 mengalami peningkatan 1,4 miliar (Ikinovianti, 2020). Prevalensi lansia di Indonesia termasuk lima besar negara dengan jumlah penduduk lansia terbanyak di dunia yakni mencapai 18,1 juta jiwa pada tahun 2010 menjadi 28,8

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juta pada tahun 2020, atau menjadi dua kali lipat (36 juta) pada tahun 2025 (Badan Pusat Statistik, 2013). Peningkatan jumlah penduduk lansia ini menimbulkan berbagai masalah di bidang sosial, ekonomi dan kesehatan, dimana masalah kesehatan yang sering terjadi pada lanjut usia antara lain gangguan fungsi kognitif yaitu salah satu fungsi tingkat tinggi otak manusia yang terdiri dari beberapa aspek serta jika tidak dilakukan penanganan yang optimal dapat mengganggu aktifitas sehari-hari (Torech et al., 2019). Dimensi kognitif yang dapat mengalami penurunan fungsi saat menua adalah kecepatan serta ketepatan dari proses berpikir yang berkaitan dengan penggunaan panca indera, atenis, memori motorik serta visual, fungsi pembedaan, perbandingan dan kategorisasi (Riani et al., 2019). Hal tersebut sesuai dengan apa yang disampaikan oleh Sumarni et al., (2019) bahwa masalah yang seringkali muncul pada lansia salah satunya adalah kemunduran fungsi kognitif (*Cognitive Decline*) atau demensia (Octaviany, 2019).

Cognitive Decline adalah penurunan kognitif yang signifikan dari kognisi normal menjadi demensia, sehingga diperlukan intervensi untuk menghambat perkembangan *cognitive decline* agar fungsi kognitif tidak menurun (Smith & Blumenthal, 2016). Berbagai upaya yang dapat dilakukan untuk mencegah penurunan fungsi kognitif yaitu dengan terapi kolaboratif farmakologis (donezepil, galatamine, rivastigmine) namun terjadi efek samping dan non farmakologis (terapi teka teki silang, *brain gym*, *puzzle*) (Dewanto et al., 2009). Adapun terapi non-farmakologik yang direkomendasikan pada demensia antara lain manajemen perilaku (*behavioral management*), stimulasi kognitif (*cognitive stimulation*), terapi orientasi realitas (*reality orientation therapy*), aktivitas rekreasional (*recreational activity*), dan program intervensi terhadap pengasuh pasien (*caregiver intervention programme*) (SIGN, 2006). Selain itu terdapat intervensi non farmakologis lain yang telah terbukti efektif dalam meningkatkan kemampuan kognitif yaitu dengan *Cognitive Stimulation Therapy* (CST) (Spector et al., 2010). Terapi ini efektif meningkatkan fungsi kognitif lansia juga didasarkan pada pembelajaran implisit (pembelajaran suatu materi secara tersirat), merangsang bahasa, dan fungsi eksekutif otak (terkait perencanaan dan inisiasi) dengan aktivitas yang berfokus pada orientasi, kenang-kenangan atau *reminiscence*, ide-ide baru, pemikiran, serta menyatukan secara kontinu dengan sesi perawatan, adapun terapi ini diciptakan dengan lingkungan di mana penderita akan bersenang-senang, belajar, dan memperkuat kemampuan dan hubungan sosial mereka di antara anggota kelompok dan dengan operator, menjaga keterampilan sosial, serta kognitif mereka seoptimal mungkin (Aguirre et al., 2013). CST ini dapat dilakukan pada penderita demensia dengan tingkat ringan hingga sedang (Piras et al., 2017).

Berdasarkan penelitian (Piras et al., 2017) di Italia didapatkan hasil CST menunjukan adanya peningkatan yang signifikan pada fungsi kognitif lansia. Hal ini sejalan dengan penelitian Young (2019) di China bahwa CST juga efektif dalam perbaikan fungsi kognitif pada lansia dengan demensia. Diperkuat oleh (Binns et al., 2020) yang menyatakan bahwa CST efektif meningkatkan kemandirian, menurunkan depresi, dan meningkatkan kualitas hidup lansia dengan demensia. Dalam penerapan CST ini bila dilihat dari karakteristik lansia di Indonesia yang memiliki sosiodemografik, lingkungan dan latar belakang yang berbeda, hal ini berpengaruh terhadap fungsi kognitif lanjut usia. Salah satunya adalah lingkungan tempat tinggal, lansia dipanti memiliki perbedaan dengan lansia dikomunitas dalam aktivitas yang biasa dilakukan, Hal tersebut dikaitkan dengan penelitian (Wreksoatmodjo, 2015) yang mengambarkan bahwa lansia yang tidak memiliki aktivitas di masyarakatnya mempunyai kemungkinan lebih besar mengalami fungsi kognitif buruk, bila dibandingkan dengan lansia yang memiliki aktivitas di masyarakatnya baik. maka kemungkinan mempunyai fungsi kognitif baik. Dipertegas dari penelitian dari (Nurmah, 2011) menjelaskan bahwa semakin banyak aktivitas yang dilaksanakan lansia maka semakin kecil kemungkinan lansia akan mengalami penuruan fungsi kognitif Berdasarkan hal tersebut CST ini merupakan bentuk aktivitas yang dapat diterapkan dalam kehidupan sehari-hari, sehingga diharapkan penerapkan CST pada lansia dapat menghambat perkembangan *cognitive decline* dan dampak lain yang dihasilkan dari demensia.

METHODS

Jenis penelitian ini adalah Quasi eksperiment Two Group (pre-test dan post-test) Populasi pada penelitian ini yaitu lansia yang berada dikomunitas dengan tingkat demensia ringan hingga sedang. Estimasi sampel dihitung menggunakan G-power Software versi 3.1.9.4 menggunakan f-test dengan asumsi two tails, $\alpha = 0,05$, effect size = 0,5 (Cohen, 1977), power level = 0,8, yaitu minimum 34, ditambah attrition rate 10-15% dengan jumlah 4 partisipan, maka total sampel size adalah 38 partisipan terdiri dari kelompok kontrol dan intervensi. Kriteria inklusi: lansia usia $\geq$ 60 tahun dengan demensia ringan s/d sedang berdasarkan diagnosis klinis menurut kriteria DSM-IV (Diagnostic et al., 2013). Skor Mini-Mental State Examination (MMSE) antara 10 sampai 24 (demensia ringan hingga sedang). Kriteria eksklusi: adanya gangguan psikiatri, gangguan komunikasi, sensorik atau fisik yang dapat mempengaruhi partisipasi dalam penerapan CST.

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Instrument

Fungsi Cognitif

Mini-Mental State Examination (MMSE) digunakan untuk mengukur fungsi kognitif. MMSE terdiri dari 11 item penilaian yang digunakan untuk menilai memori, atensi dan orientasi, registrasi, *recall*, kalkulasi, kemampuan bahasa, dan kemampuan untuk menggambar. Rentang skor MMSE adalah 1-30, dengan *cut off* 24. Skor yang lebih rendah dari 24 menunjukkan adanya gangguan kognitif (Creavin et al., 2013). MMSE mempunyai sensitivitas dan spesifisitas yang baik, yaitu 77% dan 90% pada populasi dengan prevalensi dementia tinggi, serta 81% dan 87% pada populasi dengan prevalensi rendah (Mitchell, 2009).

Activity Daily living

Pengukuran *Activity Daily living* bertujuan untuk melihat dampak dari pemberian stimulasi kognitif. Skala ADCS-ADL digunakan untuk mengukur kompetensi penyandang disabilitas dalam ADL dasar dan instrumental. Skala tersebut memiliki 24 item, partisipan memilih opsi yang paling tepat mengenai tingkat kemampuannya. Hasil interpretasi 24 skor yaitu nilai tertinggi menunjukkan ADL mandiri (Graf & Eckstein, 2008).

Depresi

Cornell Scale digunakan sebagai alat skrining demensia bukan bersifat diagnostik, terdiri dari 19 item untuk menilai tanda dan gejala terkait suasana hati/mood, gangguan perilaku, gejala fisik, perubahan kebiasaan, idea negative. Setiap item dinilai untuk tingkat keparahan pada skala dari 0 (tidak ada) hingga 2 (berat). Interpretasi hasil di atas 10 menunjukkan kemungkinan depresi berat, dan skor di atas 18 menunjukkan depresi berat yang pasti (Salek, 2013).

Kualitas hidup

Quality of Life-Alzheimer's Disease QOL-AD dikembangkan untuk mengukur kualitas hidup lansia dengan demensia dimana terdiri dari 13 item. QOL-AD menilai hubungan seseorang dengan teman dan keluarga, kekhawatiran tentang keuangan, kondisi fisik, suasana hati, dan penilaian keseluruhan kualitas hidup. Setiap item dinilai pada skala empat poin, dengan 1 buruk dan 4 sangat baik. Rentang skor total berkisar antara 13 hingga 52, skor yang lebih tinggi menunjukkan kualitas hidup yang lebih baik (Novelli et al., 2010).

Peneliti dibantu oleh asisten peneliti dalam mengumpulkan data berupa karakteristik demografis dasar, diagnosis demensia, pre-test dan post-test dan pelaksanaan terapi pada kelompok intervensi dan p endidikan alternatif pada kelompok kontrol. Peneliti dibantu oleh tiga asisten peneliti dalam mengumpulkan data tentang karakteristik demografis dasar, diagnosis demensia, mengukur pre-test dan post-test serta penerapan program CST pada kelompok intervensi dan Pendidikan alternatif pada kelompok control.

Prosedur Pelaksanaan

Pemberian therapy dilakukan sebanyak 14 sesi pada kelompok intervensi, diadakan 2 kali dalam seminggu selama 7 minggu dengan durasi waktu 40 – 45 menit pemberian terapi stimulasi kognitif (CST) pada lansia dengan demensia ringan dan sedang. Peserta secara acak dialokasikan ke dalam kelompok intervensi CST dan kelompok kontrol. Tahap awal sebelum melakukan sesi dilakukan penilaian pre-test dan post-test. Selama 14 sesi lainnya (sesi 1 sampai dengan 14), kelompok intervensi mengikuti program penerapan CST, sedangkan kelompok kontrol mengikuti kegiatan pendidikan alternatif. Peserta secara acak dialokasikan ke dalam kelompoks intervensi dan kontrol yang masing-masing terdiri dari tiga kelompok, dimana dua kelompok sebanyak 6 partisipan dan satu kelompok 7 partisipan. Kelompok intervensi menghadiri program penerapan CST, sedangkan kelompok kontrol terlibat dalam kegiatan pendidikan, dengan sejumlah sesi yang sebanding dengan kelompok perlakuan.

Satu sesi setiap minggu di gunakan untuk membaca artikel-artikel pilihan dari koran lokal atau cerita dari buku, diikuti dengan diskusi kelompok; yang lainnya untuk kegiatan kreatif, seperti mewarnai, melukis, mendekorasi, atau memasak.

Penerapan CST dari sesi 1 sampai dengan 14 memiliki tema: permainan fisik, suara, kehidupanku, makanan, isu terkini, foto wajah atau pemandangan, pengelompokan kata, kreativitas, pengelompokan benda, orientasi, menggunakan uang, permainan angka, permainan kata dan permainan kelompok. Tehnik yang digunakan dalam setiap sesi adalah 10 menit pertama pembukaan terdiri dari perkenalan, kontrak, penjelasan tujuan dan topik umum (bernyanyi, berkenalan). 25 menit kedua masuk kedalam inti terapi sesuai dengan sesi, 10 menit terakhir penutupan terdiri dari kesimpulan, evaluasi dan kontrak yang akan datang.

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Analisis statistik

Pengolahan data pada penelitian ini menggunakan (SPSS) Versi 26 untuk meanalisis data kuantitatif. Paired sample t-testdigunakan untuk membandingkan ukuran sebelum dan sesudah diberikan intervensi , dengan tingkat signifikansi statistik ditetapkan pada *p-value* < α (0,05).

RESULTS AND DISCUSSIONS

Hasil analisis awal dari responden pada kelompok intervensi dan kontrol selama 14 kali pertemuan. Satu peserta dari kelompok intervensi tidak dapat melanjutkan program penerapan CST karena hanya menghadiri 4 kali pertemuan dari 14 sesi. kelompok kontrol dua peserta dikeluarkan karena tidak mau melanjutkan sampai akhir penelitian. kehadiran rata-rata tinggi dengan rentang 7 hingga 14 sesi, sebagian besar sampel menghadiri semua sesi. Penerapan program CST dibantu oleh *enumerator* yang sudah dilatih oleh peneliti, kepada 3 kelompok dengan jumlah rata-rata enam peserta per kelompok. Pelaksanaan kegiatan aktivitas disesuaikan dengan tingkat demensia (ringan atau sedang). Total partisipan adalah 35 terdiri dari 18 kelompok intervensi dan 17 kelompok kontrol.

Berdasarkan karakteristik demografik table.1, menunjukan bahwa rata-rata responden berusia 75.2 tahun dengan (SD = 8.1). Sebagian besar responden 62.8% berjenis kelamin perempuan dengan status pendidikan terakhir 51.4% lulusan SMP dan Partisipan dominan mengalami demensia ringan 97.1%. Hasil analisis bivariate dengan *Independent T-test* menunjukan bahwa tidak ada perbedaan yang signifikan antara kelompok intervensi dan kelompok kontrol dalam hal usia, jenis kelamin, pendidikan, dan tingkat demensia.

Tabel 1. Karakteristik Demografik Subjek (n=35)

Karakteristik	Total (N = 35) %	Kelompok Intervensi N = 18 (%)	Kelompok Kontrol N = 17 (%)	*p-value*
Usia (Mean ± SD)	(75.2 ± 8.1)	(75.7 ± 8.2)	(76.1 ± 8.5)	0.079
Jenis kelamin				
Laki-laki	13 (37.1)	8 (22.8)	5 (14.28)	0.077
Perempuan	22 (62.8)	10 (28,6)	12 (34,3)	
Pendidikan				
SD	13 (37.1)	8(22.85)	6 (17.1)	0.053
SMP	18 (51.4)	9 (25.7)	9 (25.7)	
SMA	4 (11.4)	1 (2.8)	3 (8.5)	
Demensia				
Ringan	34 (97.1)	17 (48.5)	17 (48.5)	0.213
sedang	1 (2.8)	1 (2.8)	0	

Hasil penelitian ini menunjukkan bahwa kelompok intervensi setelah diberikan CST memiliki kenaikan skor sebelum dan sesudah yaitu pada fungsi kognitif (1.54), *Activity Daily living* (0.12) dan kualitas hidup (1.1) serta penurunan skor pada depresi (0.79). Hal ini diperkuat dengan hasil yang menunjukan bahwa adanya perbedaan yang signikan antara pre-test dan post test pada kelompok intervensi dan kelompok kontrol pada 3 domain yaitu fungsi kognitif *p-value* (0.029), penurunan depresi *p-value* (0.02) dan peningkatan kualitas hidup *p-value* (0.03) Tabel.2.

Table 2. Deskriptif statistik (mean dan standar deviasi), uji-t pada pre-test dan Post-test (intervensi vs kontrol) n(35).

	Intervensi Pre-test		Kontrol Pre-test		Intervensi vs Kontrol (Pre-test)		Intervensi Post-test		Kontrol Post-test		p-value (2-tailed)
	Mean	SD	Mean	SD	t (35)	p	Mean	SD	Mean	SD	p-value
Fungsi Kognitif (MMSE)	21.29	3.72	18.73	3.96	0.81	0.27	22.83	4.45	17.69	3.47	0.029*
Activity Daily living (ADCS-ADL)	29.85	11.41	30.63	13.24	0.18	0.79	29.97	10.36	30.92	9.75	0.07
Depresi (Cornell Scale)	5.34	5.26	4.14	2.61	1.21	0.28	4.55	4.46	3.50	4.01	0.02*

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Kualitas hidup (QOL-AD)	26.75	10.08	27.43	8.82	–1.17	0.30	27.85	9.62	78.80	6.32	0.03*

CST: Cognitive stimulation therapy; MMSE: Mini-Mental State Examination; ADCS-ADL: Alzheimer's Disease Co-operative Study ADL; QOL-AD: Quality of Life-Alzheimer's Disease

Hasil penerapan program CST menunjukkan adanya peningkatan pada domain kognitif, aktivitas sehari-hari dan kualitas hidup serta penurunan pada domain depresi. Penerapan program CST dapat diterima dengan baik oleh partisipan, hal ini berdasarkan hasil uji kelayakan dimana partisipan yang mengikuti 14 sesi sangat tinggi dan partisipan yang mengundurkan diri kecil. Dari keempat domain yang diukur dihasilkan tiga domain yang sinifikan yaitu fungsi kognitif, depresi dan kualitas hidup, hal ini dikaitkan dengan karakteristi dari partisipan. Penilaian dari ke empat domain tersebut berdasarkan teori yang menyatakan bahwa 'demensia' menggambarkan sekelompok kondisi yang mengarah pada perubahan progresif dalam struktur dan fungsi otak. Perubahan ini mengubah cara orang berpikir, berperilaku dan kemampuan mereka untuk mengelola kehidupan sehari-hari. Demensia juga memiliki dampak psikologis yang mendalam pada orang-orang yang mengalaminya dan pada keluarga mereka (Woods et al., 2006). Beberapa penelitian juga menyatakan bahwa gangguan demensia pada lansia dapat mengakibatkan ketidakmampuan lansia dalam melakukan kegiatan sehari -hari (Markam et al., 2006). Dikaitkan dengan kualitas hidup lansia yang mengalami demensia disertai depresi, terjadi penurunan nilai kualitas hidup bila dibandingkan dengan lansia yang tidak menderita demensia disertai depresi (Haris et al., 2014). Jadi didalam penelitian ini keempat domain ini lah yang dilihat dalam penerapan CST

Penerapan program CST mampu menunjukan peningkatan fungsi kognitif secara spesifik serta dampak yang ditimbulkan dari demensia yaitu aktivitas kehidupan sehari-hari, depresi dan kualitas hidup. Hal ini sejalan dengan penelitian (Piras et al., 2017) dalam penelitiannya menyatakan bahwa penerapan program CST-IT secara fakta telah disarankan bahwa titik akhir yang dikembangkan untuk studi tentang Alzheimer Demensia tidak selalu berlaku untuk studi tentang gangguan kognitif terkait VaD. Variabel hasil utama dalam uji coba VaD harus multidimensi dan mencakup kognisi, fungsi global, aktivitas kehidupan sehari-hari, dan gejala perilaku.

Pada beberapa penelitian sebelumnya ditemukan lansia mendapatkan kestabilan kognitif namun ada pula yang tidak mendapatkan kestabilan kognitif seperti pada penelitian Marinho et al (2021). Pada penelitian ini didapatkan kestabilan kognitif dan peningkatan jumlah skor sebelum dan sesudah intervensi serta signifikansi pada hasil uji dua beda salah satunya dilatarbelakangi oleh karakteriktik sampel, pendekatan dan jumlah sampel. Karakteristik sampel yang didapatkan yaitu demensia ringan, hal ini memudahkan lansia untuk memahami dan mengaplikasikan CST selama penerapan program Diperkuat dari hasil studi kelayakan yang menunjukan bahwa penerapan CST dapat diterima sangat baik oleh partisipan selama 14 sesi. Diketahui bahwa pada kondisi *mild congnitive impairment* sudah mulai muncul gejala gangguan fungsi memori yang menggangu dan dirasakan oleh penderita, *mild congnitive impairment* merupakan perantara antara gangguan memori atau kognitif terkait usia dan demensia. Namun pada kondisi ini individu masih mampu memproses informasi (Strydom et al., 2013). Usia rata-rata partisipan adalah 75.7 tahun pada kelompok intervensi dan pendidikan rata-rata SD 22.85% dan SMP 25.7 %. Hal ini juga mempengaruhi peningkatan kognitif walaupun pada tingkat pendidikan tidak signifikan dalam mempengaruhi fungsi kognitif. Perbedaan-perbedaan dalam tingkat peningkatan MMSE yang dilaporkan di antara studi-studi terdahulu mungkin disebabkan oleh adanya perbedaan dalam tingkat keparahan gangguan kognitif, latar belakang demografis dan kondisi kehidupan terkait dari subjek-subjek penelitian yang terlibat (Young, 2019)

Selama pelaksanaan penerapan CST pada penelitian ini dilakukan dengan pendekatan yang sangat nyaman, meningkatan suasana hati dan interaksi didalam kelompok. Penguatan positif dalam berpikir, bertanya, dan mengungkapkan pendapat dalam kelompok CST dapat menunjukan hasil yang signifikan dari fungsi kognitif (Spector et al., 2010). Jumlah sampel yang digunakan pada penelitian ini yaitu, 6 partisipan untuk setiap kelompoknya. Dengan jumlah yang tidak besar memudahkan peneliti untuk menerapkan CST secara efektif dan merespon hasil yang didapatkan dalam setiap sesi. Ukuran sampel untuk interaksi dalam kognisi dan kualitas hidup menunjukkan bahwa dengan sampel yang jauh lebih besar, hasil yang signifikan tidak akan ditemukan (Marinho et al., 2021)

Tidak ditemukan hasil signifikan pada domain *Activity Daily living* yang diukur dengan (ADCS-ADL) *p-value* (0.07). Hal ini sejalan dengan ulasan sebelumnya Galimberti, (2012) tidak ada perubahan yang dapat diidentifikasi dalam kecakapan peserta terhadap aktivitas kehidupan sehari-hari yang diukur dengan DAD, setelah menyelesaikan CST. Karakteristik partisipan pada penelitian ini didominasi gangguan fungsi kognitif ringan dimana hasil pre-test dengan demensia ringan belum mengalami dampak terhadap aktivitas sehari-hari. Pelaksanaan penerapan CST hanya terdiri dari beberapa sesi yang memfokuskan pada stimulasi gerak. Hal ini didukung oleh beberapa penelitian yang fokus dalam meneliti hubungan demensia dengan pemenuhan kebutuhan sehari-hari diantaranya (Nafidah, 2014) yang menyimpulkan bahwa aktifitas sehari-hari dapat mempertahankan kesehatan vaskular otak dengan menurunkan tekanan darah, meninprofil meningkatkan lipoprotein mendukung produksi endotel nitrat oksidasi

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dan memastikan perfusi otak cukup, sehingga dapat mencegah atau menunda penurunan fungsi otak (Muna et al., 2020), usia lanjut yang mengalami kesulitan melakukan pergerakkan fisik, akan menunjukan adanya perbedaan dalam interpretasi fungsi kognitifnya, sehingga apabila terdapat gangguan gerak dapat mengakibatkan penurunan gangguan fungsi kognitif yang lebih besar dibandingkan bila dibandingkan dengan yang tidak mengalami gangguan, penurunan fungsi kognitif berkaitan erat dengan penurunan kemandirian lansia. Sehingga dapat disimpulkan bahwa semakin baik fungsi kognitifnya semakin mandiri.

Masalah psikologis yang umum pada demensia adalah gejala depresi dengan etiologi multifaktor yang kompleks, termasuk genetik, psikososial, komorbiditas medis dan otak (Enache et al., 2011). Ditemukan hasil yang signifikan *p-value* (0.02) pada domain depresi dengan penurunan skor sebelum dan sesudah (0.79) menggunakan instrument *Cornell Scale*. Instrumen ini menilai tanda dan gejala terkait suasana hati/mood, gangguan perilaku, gejala fisik, perubahan kebiasaan, idea negative (Salek, 2013). Hasil menunjukan adanya peningkatan suasana hati dan perubahan kebiasaan selama penerapan program CST. Penelitian ini sejalan dengan hasil uji coba sebelumnya yang juga melaporkan manfaat dalam suasana hati setelah dilakukan penerapan terapi kenangan, terapi musik dan aktivitas fisik pada pasien demensia (Yamanaka et al., 2013). Terapi kenangan, terapi musik dan aktivitas fisik semua ini adalah komponen dari CST (Capotosto et al., 2016). Peningkatan suasana hati selama penerapan CST hasil observasi kemungkinan dapat dipengaruhi oleh jumlah anggota, dinamika kelompok dan kemampuan fasilitator dalam menyampaikan tema setiap sesi. Namun hal ini berbeda dengan penelitian (Piras et al., 2017). Dalam penelitiannya tidak ditemukan hasil yang signifikan pada domain suasana hati atau perilaku setelah penerapan CST pada demensia.

Penurunan depresi yang ditemukan dalam penelitian ini tidak dikaitkan secara langsung ke dalam peningkatan kualitas hidup. Banyak faktor yang mempengaruhi kualitas hidup pada pasien demensia, hal ini sesuai dengan penelitian sebelumnya yang dilakukan dalam pengaturan yang sama,38 menunjukkan bahwa variabel lain mungkin memiliki dampak yang lebih besar pada kualitas hidup. Pada penerapan CST kualitas hidup kemungkinan dikaitkan dengan peningkatan fungsi konitif atau kestabilan kognitif. Mekanisme yang menghubungkan peningkatan kognitif dan kualitas hidup adalah adanya peningkatan yang dirasakan dalam fungsi kognitif dapat menghasilkan evaluasi diri yang lebih positif (Young, 2019). Faktor dasar lainnya seperti jenis kelamin perempuan, kualitas hidup yang rendah pada awal, peningkatan fungsi kognitif dan penurunan depresi diprediksi peningkatan kualitas hidup dalam penelitian sebelumnya (Woods et al., 2006)

CONCLUSIONS

Hasil analisi awal berdasarkan karakteristik demografi menunjukkan tidak ada perbedaan yang signifikan antara kelompok intervensi dan kontrol. Hasil skrining MMSE awal, partisipan rata-rata mengalami demensia ringan hanya sebagian kecil yang mengalami demensia sedang. Penerapan program CST menunjukkan adanya peningkatan nilai skor sebelum dan setelah intervensi pada domain kognitif, aktivitas sehari-hari dan kualitas hidup serta penurunan pada domain depresi. Adanya perbedaan signifikan antara nilai pre-test dan post-test pada kelompok intervensi dan kelomok kontrol setelah penerapan program CST pada domain fungsi kognitif, depresi dan kualitas hidup.

Pada penelitian ini didapatkan kestabilan kognitif dan peningkatan jumlah skor sebelum dan sesudah intervensi, salah satunya dilatarbelakangi oleh karakteriktik sampel, pendekatan dan jumlah sampel. Pada penelitian ini kualitas hidup dikaitkan dengan peningkatan fungsi konitif atau kestabilan kognitif. Mekanisme yang menghubungkan peningkatan kognitif dan kualitas hidup adalah adanya peningkatan yang dirasakan dalam fungsi kognitif dapat menghasilkan evaluasi diri yang lebih positif

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The quest for synergy between physical exercise and cognitive stimulation via exergaming in people with dementia: a randomized controlled trial

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Abstract

Background: Exercise is often proposed as a non-pharmacological intervention to delay cognitive decline in people with dementia, but evidence remains inconclusive. Previous studies suggest that combining physical exercise with cognitive stimulation may be more successful in this respect. Exergaming is a promising intervention in which physical exercise is combined with cognitively challenging tasks in a single session. The aim of this study was to investigate the effect of exergame training and aerobic training on cognitive functioning in older adults with dementia.

Methods: A three-armed randomized controlled trial (RCT) compared exergame training, aerobic training and an active control intervention consisting of relaxation and flexibility exercises. Individuals with dementia were randomized and individually trained three times a week during 12 weeks. Cognitive functioning was measured at baseline, after the 12-week intervention period and at 24-week follow-up by neuropsychological assessment. The domains of executive function, episodic memory, working memory and psychomotor speed were evaluated. Test scores were converted into standardized *z*-scores that were averaged per domain. Between-group differences were analysed with analysis of covariance.

Results: Data from 115 people with dementia (mean (SD) age = 79.2 (6.9) years; mean (SD) MMSE score = 22.9 (3.4)) were analysed. There was a significant improvement in psychomotor speed in the aerobic and exergame groups compared to the active control group (mean difference domain score (95% CI) aerobic versus control 0.370 (0.103–0.637), $p = 0.007$; exergame versus control 0.326 (0.081–0.571), $p = 0.009$). The effect size was moderate (partial $\eta^2 = 0.102$). No significant differences between the intervention and control groups were found for executive functioning, episodic memory and working memory.

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Conclusions: To our knowledge, this is the first RCT evaluating the effects of exergame training and aerobic training on cognitive functioning in people with dementia. We found that both exergame training and aerobic training improve psychomotor speed, compared to an active control group. This finding may be clinically relevant as psychomotor speed is an important predictor for functional decline. No effects were found on executive function, episodic memory and working memory.

Trial registration: Netherlands Trial Register, NTR5581. Registered on 7 October 2015.

Keywords: Cognition, Dementia, Alzheimer disease, Exercise, Physical activity, Cognitive stimulation, Exergame, Neuropsychological, Randomized controlled trial

Background

The increasing prevalence of dementia greatly impacts healthcare and society, stressing the need for global action [1]. Since there is no cure or effective disease-modifying drug to treat the most common types of dementia to date [1], research should also focus on the development and implementation of non-pharmacological interventions as an alternative or add-on therapy [2]. Previous research has shown that physical exercise improves cognitive performance in older adults without dementia [3], and that physical inactivity during midlife attributes to the risk of dementia [4, 5]. However, research on cognitive effects of physical exercise in older adults with dementia has shown heterogeneous results [6, 7]. It seems that physical exercise alone may not be enough for older adults with dementia to alter or slow down cognitive decline. Previous studies suggest that combining physical exercise with cognitive stimulation may be a more successful strategy [8, 9].

Animal studies have shown that physical exercise can prime the hippocampus to increase neurogenesis elicited by cognitive stimuli [10, 11]. Furthermore, physical exercise combined with environmental enrichment positively affects hippocampal neurogenesis, possibly via separate pathways, with physical exercise influencing the proliferation of neural precursor cells and environmental enrichment fostering survival of newborn neurons [10]. In line with this, a meta-analysis [12] showed significant benefits of combined cognitive and physical interventions on cognitive function in healthy older adults. These beneficial effects significantly exceeded the effects of physical exercise training alone [12]. In addition, we recently performed a meta-analysis in older adults with mild cognitive impairment (MCI) or dementia which showed that combined cognitive and physical exercise interventions improve global cognitive performance [13]. Thus, these studies illustrate the potential of combined interventions in delaying disease progression in persons with MCI or dementia. However, the superiority of combined interventions over single physical exercise and the effects on different cognitive domains in individuals with dementia remain unknown. Hence, the aim of the current study is to investigate the effects of combined cognitive and physical exercise training on different cognitive domains in people with dementia.

Recent advances in technology present the opportunity to combine physical exercise with cognitively challenging tasks in a single session using exergames [14]. Exergaming is defined by "physical exercise interactively combined with cognitive stimulation in a virtual environment" [15]. Exergame training is a physical–cognitive dual-task training, which requires the mental flexibility to switch between concurrent tasks. Mental flexibility is a core component of executive functioning, a set of higher-order cognitive processes also including cognitive inhibition, planning and problem-solving [16]. We therefore hypothesize that exergame training will specifically benefit executive functioning. Previous research has already shown that exergames improve global cognitive function in healthy older adults and in a clinical population of patients with Parkinson's disease, schizophrenia, multiple sclerosis and MCI, compared to physical exercise training alone [17]. Moreover, older adults were found to enjoy participation in exergames, which may facilitate long-term activity participation [18]. There is also preliminary evidence that exergames are a feasible and enjoyable intervention for people with dementia [19, 20]. To our knowledge, no previous randomized controlled studies have investigated the effect of exergames on cognitive functioning, more specifically on executive functioning, in older adults with dementia.

Previous studies suggest that the gene apolipoprotein E (*APOE*) may be a moderator in the effects of exercise on cognition [21, 22]. *APOE* is a cholesterol carrier and is important for lipid transport and injury repair in the brain [23]. There are three alleles of *APOE*: *ε2*, *ε3* and *ε4*. Carrying the ε4 allele of *APOE* is a risk factor for Alzheimer's disease (AD) and carrying the ε2 allele is protective for AD [1]. Results from cohort studies are contradictory, reporting that physical exercise is both protective for cognitive decline in *APOE ε4* carriers [24, 25] as well as lowering the risk of dementia in APOE ε4 non-carriers [26]. Insight into this moderating relationship may contribute to identify people who will benefit most from our exergame intervention.

The primary aim of the current study is to investigate the efficacy of a 12-week exergame training and aerobic training compared to a control group on executive functioning in older adults with dementia. We hypothesize that exergame training results in greater improvement on executive functioning than aerobic training. Secondary aims are: to assess the feasibility of exergames; to compare effects of exergame training with single aerobic training on the cognitive domains of psychomotor speed, episodic memory and working memory; to measure the follow-up effects of exergame training and aerobic training; and to determine whether the cognitive effects of training are modified by the *APOE ε4* carrier state.

Methods

Study design

The current study was a 12-week single-blind randomized controlled trial (RCT) with two experimental intervention groups and one active control group. Participants were included from January 2016 to September 2017. The Medical Ethics Committee of Radboud University Medical Center in Nijmegen, the Netherlands approved the research protocol, which was published previously [27]. The study was conducted in compliance with Declaration of Helsinki ethical standards. Participants all verbally agreed to participate in the study and gave written informed consent. The trial is registered at the Dutch trial register (http://www.trialregister.nl) with identification number NTR5581.

Participants and study procedures

Participants were approached via the memory clinic of Radboudumc Alzheimer Center, day care centres for older adults with cognitive disorders, advertisement in local newspapers and word of mouth. Eligibility criteria for inclusion were: clinically confirmed diagnosis of dementia following the DSM-IV criteria [28] (vascular, Alzheimer or mixed type) with a Mini Mental Status Examination (MMSE) [29] score ≥ 17; aged 60 years or older; if using anti-dementia medication, a stable dose for at least 3 months before the start of the trial; and being capable of giving informed consent [30]. Exclusion criteria were: co-morbidity that limited exercising, including severe cardiovascular, musculoskeletal or neurological disease; diagnosis of a depression, bipolar disorder or psychotic disorder at the moment of inclusion; current drug or alcohol dependency; exercising more than five times per week for at least 30 min at a moderate intensity; wheelchair bound; and severe hearing or visual problems that could not be corrected with the use of hearing aids/glasses. When participants were recruited by newspaper advertisement or word of mouth, we confirmed the dementia diagnosis by investigating their medical record before planning a screening visit. The study was conducted in community centres in Nijmegen, the Netherlands. Participants were randomly assigned to one of the intervention groups or the control group by an independent statistician. The minimization method [31] was used to balance groups for gender, severity of cognitive impairment (MMSE ≥ 20 or < 20), use of medication for Alzheimer's disease, training location and level of education. The Dutch classification of education levels [32] was used to classify the educational attainment of participants as low (levels 1–3), average (levels 4–5) or high (levels 6–7).

Interventions

The study included three arms: exergame training, aerobic training and active control. Participants in each arm received three training sessions per week for 12 weeks. Training sessions were given on a one-on-one basis, and trained students or research assistants supervised the participants. Adherence to the intervention was calculated by dividing the number of sessions the participant followed by the total number of sessions that were offered.

The exergame training consisted of a combined cognitive–aerobic bicycle training developed by Bike Labyrinth (www.bikelabyrinth.com). The aerobic training component consisted of cycling on a stationary bike, 30–50 min per session. The aerobic exercise was tailored to an individual fitness level and health status, and aimed to achieve an intensity of 65–75% of heart rate reserve after 12 weeks of training [27]. For participants on medication that attenuates heart rate (e.g. beta-blockers), the Borg Rating of Perceived Exertion (RPE) [33] was used to ensure that the intended training intensity was achieved. In addition, the stationary bike was connected to a video screen. Participants followed a route through a digital environment and simultaneously performed cognitive tasks targeting response inhibition, task switching and processing speed. The exergame training consisted of seven different cognitive training levels. The difficulty of the cognitive tasks increased per level to ensure that the training remained cognitively challenging. The exergame training and different training levels are described extensively in our protocol paper [27].

The single aerobic exercise group consisted of cycling on a stationary bike that was not connected to a video screen. The aerobic training was identical to the exergame training already described. Participants in the active control group received training that consisted of relaxation and flexibility exercises with a duration of 30 min and the same frequency as the training regimes of the intervention groups. The exercises required minimal muscle strength and aerobic capacity and were easy to perform. The level of social engagement was similar to the intervention groups.

Outcomes

Full assessments were carried out before training (T0), after the 12-week training phase (T2) and 12 weeks thereafter at the 24-week follow-up (F1). Intermediate measurements were performed after 6 weeks of training (T1). Trained research assistants with a background in neuropsychology assessed cognitive performance using a test battery that was described previously [27], and they were blinded to group allocation. The primary outcome measure was objective executive functioning, which was measured by four neuropsychological tasks that were averaged into one domain score: a short form of the Trail Making Test part B [34], the abbreviated 5-line Stroop Color Word Test interference score [35, 36], Letter Fluency [37, 38], and the Rule Shift Cards Test [39]. All tests, except for letter fluency, were also administered after 6 weeks (T1). Secondarily, the following cognitive domains were assessed: episodic memory (Location Learning Test—Revised [40]), working memory (WAIS-III Digit Span [41] and WMS-III Spatial Span [42]), and psychomotor speed (short form of Trail Making Test part A [34] and the abbreviated Stroop Color Word Test parts I and II [35]). Only all psychomotor speed tests were also performed after 6 weeks (T1). Tests were categorized into cognitive domains a priori using the conventional classification described by Lezak et al. [43]. In order to calculate domain scores, test scores were converted into *z*-scores based on the mean and standard deviation of the total sample at baseline [44]. Subsequently, these individual test *z*-scores were averaged per domain.

After inclusion, saliva samples were taken with buccal swabs for *APOE* genotyping. Samples were stored at −20 °C and analysed using real-time polymerase chain reaction (PCR) [45]. This results in different *APOE* gene phenotypes: three homozygous (*ε2/ε2, ε3/ε3, ε4/ε4*) and three heterozygous (*ε2/ε3, ε2/ε4, ε3/ε4*) [45].

Statistical analysis

Socio-demographic and clinical characteristics at baseline were presented using descriptive statistics. Feasibility measures (e.g. adherence to the exercise programme, measures of exercise intensity and rating of the exercise sessions) were compared between the groups with one-way analysis of variance (ANOVA) and independent-sample *t* test.

To assess the effect of training on cognitive performance in each domain (i.e. executive function, episodic memory, working memory and psychomotor speed), analysis of covariance (ANCOVA) was performed with post-training cognitive domain *z*-scores as dependent variables, baseline *z*-scores as covariates and group (exergame training, aerobic training and active control) as between-subject factors. To specify significant group effects, Bonferroni-corrected post-hoc tests were performed. To investigate follow-up effects of the intervention for each cognitive domain, we used mixed-model ANCOVA. Variables included in the model were cognitive domain *z*-scores at T2 and F1 as dependent variables, group as between-subject factors, time as within-subject factors, and the corresponding baseline measure as covariates. Additionally, a time × group interaction term was added as a fixed effect. To assess a moderating effect of *APOE ε4*, an interaction term between *APOE ε4* and group was added separately as a predictor.

If a participant had missing data because he/she was cognitively incapable to perform a certain test, the worst possible score for this test was awarded. Afterwards, the domain *z*-score was calculated. If there were missing data due to drop-out and the reason for missingness was at random, missing data were substituted using the multiple imputation method. Characteristic variables of the sample, cognitive domain scores at baseline and training group were included in the imputation model. The following imputation settings were used: automatic model setting, 15 iterations and 5 imputations. If a participant had missing data due to drop-out because of cognitive decline, the criterion for missing at random was not fulfilled. Use of multiple imputation would in this case have been inappropriate as violation of the missing at random assumption biases the estimates [46]. We expected that the cognitive decline would be larger in these participants than the mean decline in the entire group, as it was their reason for drop-out. We decided to use a single value imputation approach for these participants, in which we replaced the missing values by a single value, in our case the greatest decline in the group. To prevent imputing non-realistic values, the lowest possible score was used as a cut-off score. We performed additional sensitivity analyses to check whether this alternative method of dealing with missing data influenced our results.

All statistical analyses were performed as intention-to-treat analyses, including all participants irrespective of adherence to intervention. Additionally, we performed per-protocol analyses including only those participants who successfully completed the intervention period and all measurements. SPSS 22 was used for all analyses with α set at 0.05.

Results

Patient flow and sample characteristics

In total, 307 participants were screened for eligibility and 121 participants eventually enrolled in the study. Six participants refused to participate during baseline measurements and the remaining 115 participants

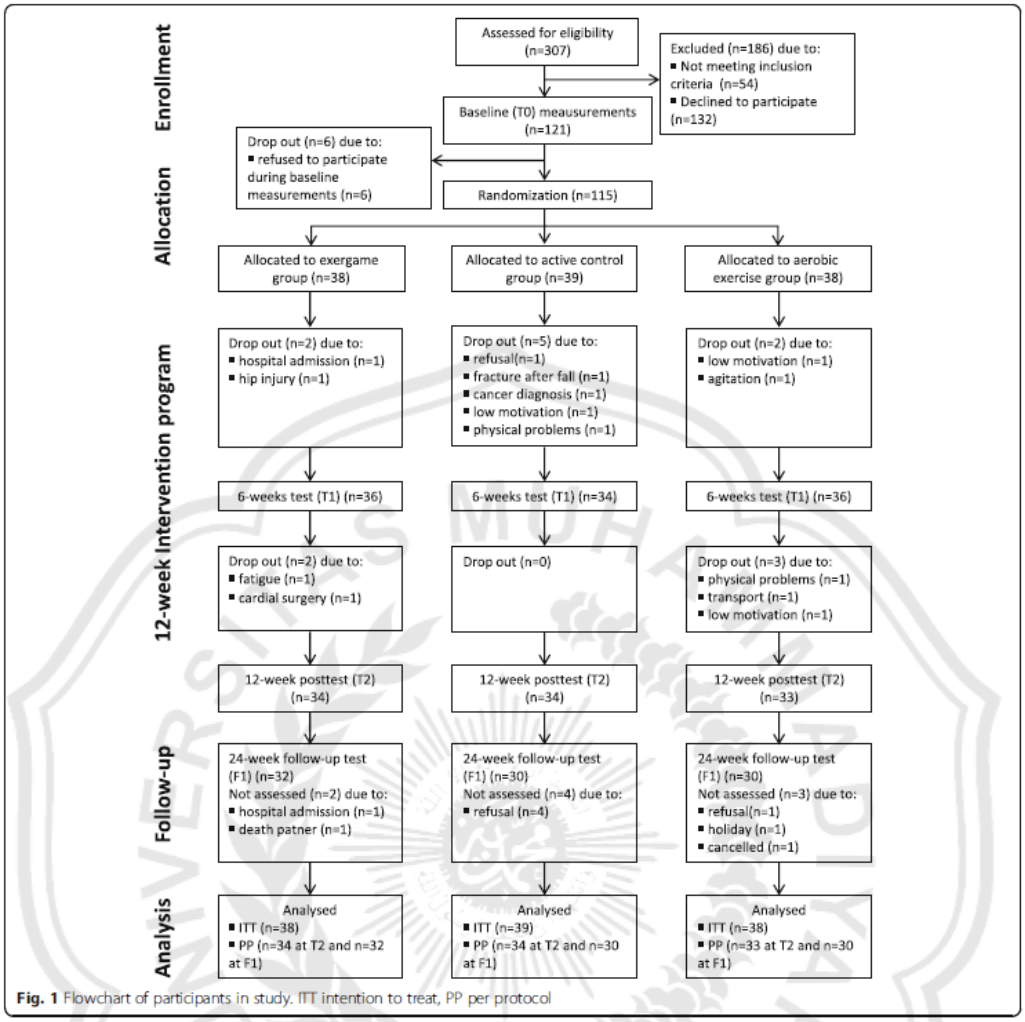

Fig. 1 Flowchart of participants in study. ITT intention to treat, PP per protocol

were randomized. Fourteen participants did not complete the 12-week intervention (12%). The number of drop-outs did not differ significantly between the groups ($p = 0.930$). The enrolment, allocation process and reasons for drop-out are presented in Fig. 1. Baseline characteristics for the randomized sample were well matched between the groups (Table 1). The included participants had a mean (SD) age of 79.9 (6.5) years and a mean (SD) MMSE score of 22.4 (3.2). There were no differences in age, MMSE score and Katz index between the different dementia types (see Additional file 1).

Attendance, intensity and safety

Table 2 presents the adherence per group; a trend was found towards higher adherence in the exergame group compared to the aerobic group (mean difference (95% CI) 6.85 (– 0.09 to 13.79), $p = 0.053$). Participants rated both exercise interventions and the active control group highly (see Table 2). Training duration, training load, heart rate and rate of perceived exertion did not differ between both intervention groups. The mean training intensity was light in both intervention groups with an average of 41.8% (SD = 13.3) and 43.5% (SD = 18.2) of maximal heart rate in the exergame group and aerobic group respectively. For the exergame

Table 1 Baseline characteristics of the study population

Variable	Exergame group (*n* = 38)	Aerobic group (*n* = 38)	Control group (*n* = 39)
Age (years), mean (SD)	79.0 (6.9)	80.9 (6.1)	79.8 (6.5)
Men, *n* (%)	20 (52.6)	21 (55.3)	21 (53.8)
Educational level, *n* (%)			
Primary school education or lower	6 (15.8)	7 (18.4)	6 (15.4)
Secondary education or vocational training	23 (60.5)	22 (57.9)	22 (56.4)
Higher education	9 (23.7)	9 (23.7)	11 (28.2)
Mini Mental State Examination,[a] mean (SD)	22.9 (3.4)	22.5 (3.1)	21.9 (3.1)
Aetiology of dementia, *n* (%)			
Alzheimer's disease	22 (57.9)	16 (42.1)	21 (53.8)
Vascular dementia	4 (10.5)	4 (10.5)	3 (7.7)
Mixed dementia (Alzheimer/vascular)	5 (13.2)	8 (21.1)	11 (28.2)
Not specified	7 (18.4)	10 (26.3)	4 (10.3)
APOE carrier state, *n* (%)			
ε4/ε4	1 (2.7)	5 (13.2)	3 (7.9)
ε3/ε4	20 (54.1)	13 (34.2)	16 (42.1)
ε3/ε3	15 (40.5)	16 (42.1)	16 (42.1)
ε3/ε2	0	3 (7.9)	4 (7.9)
ε2/ε4	1 (2.7)	1 (2.6)	0
ε2/ε2	0	0	0
Duration since dementia diagnosis (months), mean (SD)	13.6 (19.9)	13.8 (12.3)	18.9 (22.4)
Functional Comorbidity Index,[b] mean (SD)	2.5 (1.9)	2.4 (1.8)	2.2 (1.4)
Katz index,[c] mean (SD)	5.2 (3.3)	4.5 (3.0)	5.1 (2.9)
Number of medications used, mean (SD)	4.9 (2.9)	5.9 (3.8)	6.1 (3.7)
Use of beta-blockers, *n* (%)	16 (42.1)	17 (44.7)	14 (35.9)
Dementia drugs, *n* (%)			
Rivastigmine	6 (15.8)	4 (10.5)	8 (20.5)
Donezepil	0	0	0
Galantamine	1 (2.6)	3 (7.9)	2 (5.1)
Memantine	0	1 (2.6)	0

SD standard deviation
[a]Scores on the Mini-Mental State Examination range from 0 (severe impairment) to 30 (no impairment)
[b]Theoretical range 0–18, higher score indicates more co-morbidities
[c]Theoretical range 0–15, higher score indicates higher dependency in activities of daily living

training, the median (interquartile range) training level after 6 weeks was 5.0 (4.3–5.8), and after 12 weeks 5.5 (5.0–6.0). After 6 weeks, 25% of the participants reached level 6 or 7, and 50% reached level 5. After 12 weeks, 50% of the participants reached level 6 or 7, and 40% reached level 5. This demonstrates that there were no floor effects for the cognitive stimulation activity and about half of the participants were able to complete the highest levels, thus showing that the exergame training was feasible and that adequate skill acquisition was present. No occurrence of serious adverse events (e.g. events leading to death, hospital admission or persistent disability) related to the exercise interventions were recorded.

Missing data

Missing data due to drop-out of participants was 0% at T0, 8.7% at T1, 9.6% at T2 and 17.5% at F1. Reasons for drop-out are described in Fig. 1. In a total of six cases, the reason for drop-out was refused participation (five out of six at follow-up measurements). Reason for refusal was cognitive decline, which led to caregivers' withdrawal of consent. As explained in Methods, we used single-value imputation for substituting missing data not at random, and performed additional sensitivity analyses to check whether this influenced our results. Data for the remaining eight drop-outs were missing at random and were substituted using multiple imputation, as explained in Methods.

Table 2 Training characteristics of the study population

Variable	Exergame group ($n = 38$)	Aerobic group ($n = 38$)	Control group ($n = 39$)
Adherence rate (%), mean (SD)	87.3 (13.6)*	81.1 (13.7)*	85.4 (12.9)
Duration training session (min), mean (SD)	32.6 (6.0)	30.5 (8.7)	30[a]
Training load (W), mean (SD)	53.7 (34.9)	51.2 (27.7)	NA
Resting heart rate (beats/min), mean (SD)	79.4 (12.1)	77.9 (10.4)	NA
Heart rate during training (beats/min), mean (SD)	105.5 (14.8)	103.9 (14.3)	NA
Heart rate difference (beats/min), mean (SD)	26.1 (15.1)	26.0 (13.8)	NA
Training intensity[b] (% of maximal heart rate), mean (SD)	41.8 (13.3)	43.5 (18.2)	NA
Rate of perceived exertion during training,[c] mean (SD)	13.1 (1.2)	12.8 (1.9)	NA
Rating of training sessions[d] (scale 1–5), Median (interquartile range)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)
Training level after 6 weeks[d] (scale 1–7), Median (interquartile range)	5.0 (4.3–5.8)	NA	NA
Training level after 12 weeks[d] (scale 1–7), Median (interquartile range)	5.5 (5.0–6.0)	NA	NA

Differences between groups tested with one-way analysis of variance (three groups) or independent-sample *t* test (two groups), if data were normally distributed. For post-hoc comparisons, Tukey honest significant difference test was performed. If data was not normally distributed, Kruskall Wallis test was performed.
NA not applicable, *SD* standard deviation
[a]All training sessions lasted for 30 min, time has not been recorded
[b]Training intensity only calculated for participants who do not use beta-blockers ($n = 21$ and $n = 20$ in the exergame group and the aerobic group respectively)
[c]Theoretical range 6–20, where 6 indicates lowest intensity level and score 20 indicates highest intensity level
[d]Data not normally distributed, therefore presented as median (interquartile range)
*A trend was found towards higher adherence in the exergame group compared to the aerobic group (mean difference (95% confidence interval) 6.85 (− 0.09 to 13.79), $p = 0.053$)

Intention-to-treat analysis

Figure 2 shows the performance on the four cognitive domains at each time point per treatment arm. No significant differences were found between the exergame group, aerobic group and control group on executive functioning after 12 weeks of training. Since after 6 weeks (T1) letter fluency was not administered as an executive function test, we decided not to include T1 data in our analyses. Significant improvement on the secondary measure psychomotor speed was found for both the aerobic and the exergame group compared to the controls after 12 weeks of training (mean difference domain score (95% CI) aerobic versus control 0.370 (0.103–0.637), $p = 0.007$; exergame versus control 0.326 (0.081–0.571), $p = 0.009$). The size of the effect was moderate (partial $\eta^2 = 0.102$). This effect was not yet present at the intermediate measurements after 6 weeks (see Fig. 2). No significant differences were found between the groups on the secondary measures of episodic memory and working memory after the 12-week intervention period. An additional sensitivity analysis yielded similar results, which shows that our findings are robust. Follow-up analysis showed that the improvement in psychomotor speed was maintained for both the aerobic group and the exergame group compared to the controls (mean difference domain score (95% CI) aerobic versus control 0.453 (0.185–0.722), $p = 0.001$; exergame versus control 0.326 (0.070–0.604), $p = 0.014$. There was no significant difference between the exergame and aerobic group (mean difference domain score (95% CI) exergame versus aerobic − 0.116 (0.399 to − 0.398), $p = 0.399$). We did not find any between-group differences in any of the other cognitive domains at follow-up. Sensitivity analysis pointed in the same direction, with a maintenance effect in the aerobic group compared to controls (mean difference domain score (95% CI) aerobic versus control 0.267 (0.048–0.486)), and no follow-up effect in any of the other cognitive domains. Moderator analysis showed that carrying *APOE ε4* did not influence the relation between training and cognitive performance. *z*-scores of the different cognitive domains per group and time point are presented in Additional file 2. Raw data of cognitive test scores are presented in Additional file 3.

Per-protocol analysis

n the per-protocol analyses, we excluded 14 participants who did not complete the 12-week intervention period. The remaining 101 participants were included in this analysis. The results of the per-protocol analyses were in line with the intention-to-treat analyses, with positive effects of exergame and aerobic training on psychomotor speed compared to controls (mean difference domain score (95% CI) aerobic versus control 0.322 (0.038–0.607), $p = 0.021$; exergame versus control 0.283 (0.002–0.563), $p = 0.047$). As in the intention-to-treat analyses, no significant between-group differences were observed in the domains of executive function, memory and working memory. At follow-up there were nine additional drop-outs, which led to inclusion of 92 participants in the follow-up analysis. We found that there was a trend for maintained improvement in psychomotor speed at 24-week follow-up in the aerobic group compared to

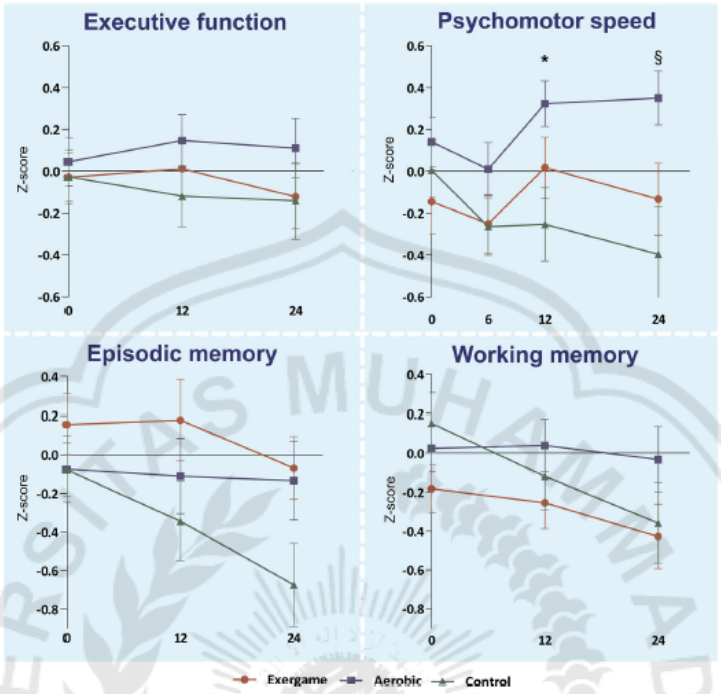

Fig. 2 Mean *z*-scores and standard errors of mean (SEM) at baseline, after 12 weeks and after 24 weeks for domains of executive function, psychomotor speed, episodic memory and working memory. Arrows represent SEM. *Significant effect ($p < 0.05$) of exergame training and aerobic training on psychomotor speed compared to controls after 12 weeks; §maintenance effect ($p < 0.05$) of aerobic and exergame training on psychomotor speed at 24-week follow-up

the control group (mean difference domain score (95% CI) aerobic versus control 0.267 (0.048–0.486), $p = 0.057$). No significant intervention effects were observed in any of the other domains.

Discussion

To our knowledge, this is the first randomized controlled trial to investigate the differential effect of exergaming versus aerobic training on cognitive functioning in people with dementia. We hypothesized that exergame training would result in greater improvement on executive functioning than single aerobic training. Although we did not find an effect of exergame training or aerobic exercise on executive function after 12 weeks, we found that psychomotor speed improved in both the exergame and the aerobic group compared to active controls. This effect was maintained at the 24-week follow-up. We did not find an effect of both intervention groups in the cognitive domains of episodic memory and working memory compared to the control group. Moderator analysis showed that *APOE ε4* carriership did not influence the relation between training and cognitive function. Finally, we demonstrated that a newly developed exergame that comprises both physical and cognitive training elements is feasible for people with dementia.

Interpretation of results and comparison with previous research

Contrary to our hypothesis, the current results did not show a larger effect of exergame training compared to aerobic training on cognitive functioning. Comparable research on the differential effects of combined cognitive and physical training versus only cognitive or physical interventions in people with dementia is scarce. There is one previously published paper reporting that neither a 12-week combined cognitive–aerobic training nor aerobic training only improved global cognitive function in a smaller sample of 80 individuals with AD [47]. However, the type of intervention and used outcome measures are incomparable to the current study. Research in individuals with MCI showed inconsistent

findings regarding the cognitive benefits of combined interventions and its potential superiority compared to physical exercise or cognitive training alone [48]. In contrast, for older adults without cognitive impairment there is converging evidence that combined interventions (including exergames) are superior to physical or cognitive training alone [48], with larger effect sizes for interventions that are performed simultaneously compared to sequential interventions [12].

In healthy older adults, evidence for the efficacy of physical exercise and combined cognitive and physical interventions on executive functions [12, 49], memory [12, 49], working memory [12, 50] and attention [51] have been well established. In our current study, both exergame and aerobic-only training did not positively affect executive functions, working memory or episodic memory. This seems partly in line with previous research. A meta-analysis performed by our group [13] demonstrated positive effects of combined interventions on global cognitive function in older adults with MCI or dementia, but no effects in the domains of executive function and memory. In contrast, a recently published RCT showed that both a mentally challenging exergame and a passive exergame improve executive functioning in people with MCI [52]. However, the more challenging exergame only yielded significant effects after 6 months of training, while the passive exergame already produced gains after 3 months [52]. A possible explanation for this discrepancy is that participants in the mentally challenging exergame group needed more time to master the intervention, which may have delayed triggering the synergistic effects of the combined intervention [52]. This might also explain the negative findings in our study, since a mentally challenging exergame was used for a relative short intervention period of 12 weeks.

There is evidence that the severity of neurocognitive disorder has a moderating impact on the cognitive effects of combined cognitive and physical training [53]. An increase in the severity of neurocognitive disorder may lead to a decrease of the intervention effect [53]. This could be explained by a reduced structural brain capacity (e.g. reduced number of neurons and synapses) in participants with more severe neurocognitive disorder, which may lead to limited resources necessary for training-induced gains [53]. Therefore, it may be more difficult to induce cognitive benefits in people with dementia compared to those with MCI or healthy older adults. Moreover, the complexity to obtain valid neuropsychological outcomes that are sensitive to change in persons who already have severe cognitive deficits due to their dementia complicates the assessment of cognitive functioning in this group. Even though we carefully selected and adjusted tests for use in mild-to-moderate dementia, it is particularly challenging to assess executive functions in this group. Executive functions include higher-order processes such as inhibitory control, mental flexibility and planning, which are already affected in the early stages of dementia [54, 55]. Assessment of executive function in people with dementia may consequently result in floor effects or missing data, which make it difficult to measure change over time.

In our study we found a moderate effect of exergame training and aerobic training on psychomotor speed after a 12-week training period in people with dementia. This effect was not yet present after 6 weeks of training. Firstly, this may imply that the improvement is due to the training and not due to non-specific treatment or practice effects. Secondly, this suggests that a longer training duration is necessary to improve psychomotor speed. Although still under debate, there is some evidence that physical exercise leads to improved cognitive function through promotion of hippocampal neurogenesis [56], brain angiogenesis [57] and synaptic plasticity [58] elicited by an increased expression of neurotrophic factors [59]. In cognitively healthy older adults, physical exercise interventions have the largest gains on executive control processes, psychomotor speed and attention [49, 51, 60, 61]. In people with dementia there is little research about the benefits for different cognitive domains. From a neurobiological perspective, however, we do not have an explanation for why exercise would only improve psychomotor speed, but not the other cognitive skills assessed. We hypothesize, that only finding an effect on psychomotor speed, and not on executive functioning, may be related to domain-specific responsiveness of the selected outcome measures. Processing speed tests typically are continuous outcome measures without ceiling or floor effects that are highly sensitive [62], which may explain the sensitivity to change even in a dementia sample. In contrast, tests that measured executive functioning resulted in floor effects in our dementia sample, which made it difficult to measure change over time. Alternatively, one could also hypothesize that mood may be a mediating factor for improvement on speed measures, as previous research showed that exercise and exergame training can reduce depressive symptoms in healthy older adults [63, 64]. The positive effect on psychomotor speed was consistent across the different neuropsychological tests used to measure psychomotor speed (short form of Trail Making Test part A and the abbreviated Stroop Color Word Test parts I and II), which shows that the effect was robust and reliable. Its moderate effect size is slightly larger than to the small-to-moderate effect sizes commonly found in studies examining the effects of cholinesterase inhibitors on cognitive function [65, 66]. Given that interventions to ameliorate cognitive decline of people with

dementia are scarce, this effect size may be clinically relevant. Poor processing speed is a predictor of functional decline in basic and instrumental activities of daily living [67]. In addition, poor processing speed is reported to be a predictor for incident dementia [68] and was found to be associated with shorter survival among older adults in Japan [69]. Furthermore, late-life cognitive decline is attributable to slower processing speed [70]. Thus, the reported improvement in processing speed may be clinically relevant.

The mean training intensity was light in both intervention groups, with an average of 41.8% (SD = 13.3) and 43.5% (SD = 18.2) of maximal heart rate in the exergame group and the aerobic group respectively. We expected that improved cardiorespiratory fitness would be a requirement to improve cognitive function [51], and therefore we aimed to achieve moderate exercise intensity (e.g. 65–75% of maximal heart rate) during the training sessions. However, the exercise training was tailored to an individual fitness level and health status, and most participants were not able to achieve a moderate training intensity. The recently published Dementia and Physical Activity (DAPA) trial [71] showed that moderate to high-intensity aerobic and strength exercise training did not slow cognitive decline in people with mild to moderate dementia, and even worsened cognitive impairment in those who complied with the intervention, despite an improvement in physical fitness. It is therefore unlikely that the light training intensity in our study limited the beneficial effects of exercise on cognitive functioning.

Strengths and limitations

The strengths of our study include the inclusion of a relatively large sample of people with dementia, a high adherence rate, the use of a comprehensive neuropsychological assessment and follow-up measurement for long-term maintenance effects. However, some limitations need to be taken into account when interpreting our results. Firstly, only participants who were mobile and motivated enrolled in our study, which may limit the external validity of the current findings. Secondly, participants were not blinded to allocation, which is an unavoidable limitation of exercise studies. Outcome assessors were masked for intervention allocation. Thirdly, although we used adapted versions of executive tests, making administration in people with dementia more feasible, a floor performance was still found in a number of individuals. This may have reduced the sensitivity to measure change over time, obscuring potential positive results. Fourthly, the intervention period was only 12 weeks, which may have been too short to show beneficial effects of exergames on executive functioning. Lastly, future studies should include measures of mood, since this might be a potential mediating factor for the improvement in processing speed measures.

Clinical relevance and feasibility

Both exergame training and aerobic training improved psychomotor speed after 12 weeks, with a moderate effect size. This finding may be clinically relevant as psychomotor speed is an important predictor for functional decline. In our study, exergame training was not superior to aerobic training. However, there was a trend for higher adherence in the exergame group compared to the aerobic group. Additionally, trainers who individually guided the training sessions reported that it was easier to motivate participants in the exergame group and to increase duration of the training sessions. This was confirmed by our finding that no participants dropped out in the exergame group due to low motivation (see Fig. 1). Accordingly, exergaming seems to be an effective method to stimulate long-term physical activity participation in people with dementia.

Future directions

Future studies should examine whether certain individual characteristics (e.g. type of dementia) moderate the effect of physical activity on cognition. Insight into these individual differences is important because it can determine which people are most likely to benefit from physical activity. It can also help to personalize interventions, thereby stimulating physical activity. Moreover, additional studies are needed to explore the optimal intervention design and dose–response for eliciting beneficial cognitive effects in people with dementia. Future intervention trials should include measures of psychomotor speed as these can reliably and validly be assessed in people with dementia and are closely related to everyday activities. Furthermore, studies should also focus on investigating neurophysiological mechanisms that underlie the cognitive effects of exercise, for example by including neuroimaging measures.

Conclusions

Exergaming is a feasible and highly appreciated exercise method to engage older adults with dementia in physical exercise, mixed with cognitive stimulation. Both exergame training and aerobic training can improve psychomotor speed, which may be clinically relevant as psychomotor speed is an important predictor for functional decline. Although no effects were found on executive function, episodic memory and working memory, the potential broad range of effects of exergames for older adults with dementia (e.g. physical functioning, quality of life, activities in daily living) should be studied in future RCTs.

Artikel 3

Dement Neuropsychol 2020 June;14(2):110-117

Original Article

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Cognitive stimulation program in mild cognitive impairment

A randomized controlled trial

Isabel Gomez-Soria[1], Patricia Peralta-Marrupe[2], Fernando Plo[1]

ABSTRACT. Non-pharmacological cognitive interventions in mild cognitive impairment have demonstrated promising results in preventing or delaying cognitive impairment and functional disability. Cognitive stimulation seems to improve and maintain cognitive and social activity. **Objective:** This study aimed to evaluate the impact of a cognitive stimulation program in mild cognitive impairment (MCI) at the cognitive level on activities of daily living (ADLs), and levels of anxiety and depression. **Methods:** A randomized controlled single-blind trial involving 122 non-institutionalized elderly with a MEC-35 score of 24-27 was conducted. The intervention group (n=54) received the intervention (10-week cognitive stimulation program) and was compared with a control group (n=68) that received no intervention. Follow-up assessments were conducted post-test and at 6 months post-test. The primary outcome was cognitive function determined by changes in scores on the Spanish version (MEC-35) of the Mini-Mental State Examination, while the secondary outcomes were measured by the Barthel Index, Lawton and Brody Scale, Goldberg Questionnaire (anxiety sub-scale) and the Yesavage Geriatric Depression Scale (15-item version). **Results:** The intervention group showed a significant improvement in cognitive function at both timepoints, post-test and 6-month follow-up. The Barthel Index was higher in the intervention group, but only on the post-test analysis. The intervention did not improve the performance of instrumental ADLs or depression or anxiety levels. **Conclusion:** The findings showed cognitive improvements in an elderly population with MCI in the short and medium-term and improved basic ADLs in the short term. Clinicaltrials.gov Identifier: NCT03831061.

Key words: cognitive dysfunction, aging, randomized controlled trial, occupational therapy.

PROGRAMA DE ESTIMULAÇÃO COGNITIVA NO COMPROMETIMENTO COGNITIVO LEVE: UM ESTUDO CONTROLADO RANDOMIZADO

RESUMO. As intervenções cognitivas não farmacológicas no comprometimento cognitivo leve demonstram resultados promissores na prevenção ou retardo no comprometimento cognitivo e na incapacidade funcional. A estimulação cognitiva parece melhorar e manter a atividade cognitiva e social. **Objetivo:** Nosso objetivo foi o de avaliar um programa de estimulação cognitiva sobre o comprometimento cognitivo leve no nível cognitivo, nas atividades da vida diária, níveis de ansiedade e depressão. **Métodos:** Um estudo randomizado, controlado e cego, foi implementado em 122 idosos não institucionalizados com escore 24-27 na versão em espanhol do Mini Exame do Estado Mental (MEC-35). O grupo de intervenção (n=54) recebeu a intervenção (programa de estimulação cognitiva de 10 semanas) e foi comparado com um grupo de controle (n=68) que não recebeu nenhuma intervenção. Avaliações de acompanhamento foram realizadas pós-teste e 6 meses pós-teste. O desfecho primário foi a função cognitiva determinada pelas alterações nos escores do MEC-35 e os desfechos secundários foram medidos pelo Índice de Barthel, Escala de Lawton e Brody, Escala de Lawton e Brody, Questionário Goldberg (subescala de ansiedade)) e a Escala de Depressão Geriátrica de Yesavage (versão de 15 itens). **Resultados:** O grupo intervenção apresentou uma melhora significativa

This study was conducted at the University of Zaragoza Ringgold standard institution Zaragoza, Aragón Spain.

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na função cognitiva nas duas medidas de tempo, pós-teste e 6 meses de acompanhamento. O Índice de Barthel foi encontrado mais alto no grupo de intervenção, mas apenas na análise pós-teste. A intervenção não melhorou o desempenho de atividades instrumentais da vida diária e níveis de depressão ou ansiedade. **Conclusão:** Os achados mostram melhorias cognitivas no comprometimento cognitivo leve da população idosa em curto e médio prazo e melhoraram as atividades básicas da vida diária em curto prazo. Identificador do Clinicaltrials.gov: NCT03831061.
Palavras-chave: disfunção cognitiva, envelhecimento, estudo controlado randomizado, terapia ocupacional, estimulação cognitiva, comprometimento cognitivo leve.

We are experiencing a huge demographic shift, with an increase in the elderly population and prevalence of ageing-related diseases.[1] Mild cognitive impairment (MCI) reflects a level of cognitive functioning between ageing and dementia. MCI is an especially big challenge and the development of non-pharmacological interventions is critically needed.[2] MCI prevalence is increasing with age and has an incidence of between 21.5 and 71.3 per 1,000 population/year.[3] The annual rate of progression to dementia ranges from 8% to 15%.[4]

The MCI concept has led to debate regarding the value of non-pharmacologic interventions.[5] Non-pharmacological cognitive interventions could be key in preventing or delaying cognitive impairment and functional disability.[6] Clare & Woods (2004)[7] describe three different types of cognitive intervention: cognitive training, cognitive rehabilitation and cognitive stimulation. Cognitive training refers to guided standard tasks to develop cognitive function. Cognitive rehabilitation focuses on the improvement of some cognitive goals. Finally, cognitive stimulation includes participation in cognitive activities, mainly in groups, designed to improve and maintain social and cognitive activity. Cognitive stimulation includes activities such as orientation, reminiscence, memorization, association and leisure activities. These three types of intervention are based on unimodal interventions (focusing on one domain). Multimodal cognitive interventions are generally more complex interventions (encompassing physical, social or psychological components).[8]

A number of studies based on cognitive stimulation have shown improvements in cognitive function in healthy older people, elderly with MCI and with dementia.[9-15] The findings of Alves et al.[15] suggest that cognitive stimulation can lead to high values of experiential relevance, even in the absence of cognitive or functional improvements. The study of Schultheisz et al.[16] supports cognitive stimulation programs as a resource for improving cognition and quality of life for the elderly. The prevention of dementia should be taken into account in health systems given the severity of this pathology.[17]

This study seeks to determine the effectiveness of a cognitive stimulation program using a randomized controlled trial (RCT). More specifically, there were three objectives: (i) to ascertain efficacy at the cognitive level using the 35-point Cognitive Mini-Exam (MEC-35); i.e. the Spanish version of Folstein's Mini-Mental State Examination (MMSE); (ii) to measure changes in activities of daily living (ADLs) using the Barthel Index and the Brody and Lawton Scale; (iii) to examine effects on levels of anxiety using the anxiety sub-scale, Goldberg questionnaire (EADG), and on depression using the Yesavage Geriatric Depression Scale (15-item version).

METHODS

Design setting

A randomized controlled trial (RCT) was performed in non-institutionalized elderly people. The inclusion criteria were being over 65 years old, not being institutionalized, not having received cognitive stimulation in the last year, scoring >60 points on the Barthel Index, and presenting no deafness, no blindness, no neuropsychiatric disorders or motor difficulties, and having a MEC-35 score of between 24 and 27 points. MEC-35 scores of less than 27 denote cognitive deficits.[18] The optimal cut-off point on the MEC-35 to establish the presence of cognitive impairment in the population over 65 years is 24 points for a low educational level and 27 points for a medium-high level.[19] A sample size >53 in each group guaranteed that an increase of 1.5 points on the MEC-35 could be detected with a level of significance of 5% and statistical power of 80%, assuming a standard deviation ≤2.5 points and a rate of abandonment of 35%. The CONSORT standards[20] and the Declaration of Helsinki of the World Medical Association - Ethical Principles for Medical Research in Humans 2013[21] were observed during the study. This study was approved by the Ethical Committee of Clinical Studies of Aragón in Act No. 18/2011, under study registration number PI11/00091 and registered on ClinicalTrials.gov Identifier (NCT03831061).

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Participant selection

The participants were recruited from San José Norte-Centro Health Center in Zaragoza (Spain). For randomization, an opaque urn was used into which the participants' file numbers were placed and an anonymous person drew the selected numbers. The first author verified the inclusion criteria of the participants. A total of 416 candidates were evaluated. Following inclusion, the 122 patients were allocated into two groups: 54 participants in the Intervention group and 68 participants in the Control group. The evaluators and the occupational therapist who performed the intervention were different.

The randomized controlled trial was single-blind, as the persons responsible for the assessments were blinded and different from those responsible for the intervention. The sample size was calculated in such a way that an increase of 1.5 points on the MEC-35 could be detected with a level of significance of 5% and a statistical power of 80%, assuming a standard deviation ≤2.5 points and a rate of abandonment of 35%. The flow of participants including the number of dropouts and their causes are shown in Figure 1. As expected, the number of dropouts was high (22.1% between pre-test and post-test). Differences in the baseline values (pre-test) of participants who stayed until the last assessment versus those who had left at some stage during follow-up were analyzed. No statistically significant differences in age or in any of the other outcome variables were found.

Intervention

Eight occupational therapists performed the assessments (pre-test, post-test and 6-month post-test) and were all blinded. Two trained occupational therapists performed the intervention. The intervention was carried out at the Foundation La Caridad, Zaragoza (Spain) in two subgroups of 27 participants each using the red notebook of mental activation.[22] The difficulty of the exercises was adapted to take into account cognitive level, interests and gender, as per the Spector et al.[23] programme.

The intervention consisted of 10 sessions of 45 min/week for 10 weeks. Each session included four parts: (a) Reality orientation: questions about date, time and place, using calendars, clock and posters indicating the place and address where the participants were situated; (b) Explanation of the cognitive aspect that was going to be focused on in each session; with alternatives including: 1) "memory" (changes withj aging, types of memory, strategies such as association and categorization); 2) "orientation" (temporary, spatial and personal); 3) "language"; 4) "praxis" (ideomotor, ideational and constructive); 5) "gnosis"; 6) "calculation"; 7) "perception"; 8) "reasoning"; 9) "visual attention"; 10) "executive functions" (planning capacity, training in social skills and association with activities of daily living); (c) Individual practical work, in which 4 exercises of the cognitive aspect corresponding to each session were performed; (d) Group correction of practical exercises. The objectives and types of cognitive stimulation exercises used in the intervention are given in Figures 2 and 3.

The conceptual framework of this intervention was formed from the framework for practice of Occupational Therapy,[24] the cognitive model[25] and the human occupation model of Gary Kielhofner.[26]

Outcomes

Main outcome

The Mini-Mental State Examination (MEC-35) is the Spanish version of the MMSE.[27] It is a standardized screening instrument widely used in the detection of cognitive deterioration that explores a set of cognitive functions.[19] Scores ≤27 denote cognitive deficits. Test-retest reliability: weighted kappa = 0.667, sensitivity = 89.8%, and specificity = 83.9%.[18] The 35-point questionnaire consists of 11 items in which 8 cognitive areas are assessed: space-temporal orientation, fixation and recent memory, attention-concentration and calculation, comprehensive and expressive language, abstract thinking and visuospatial construction.

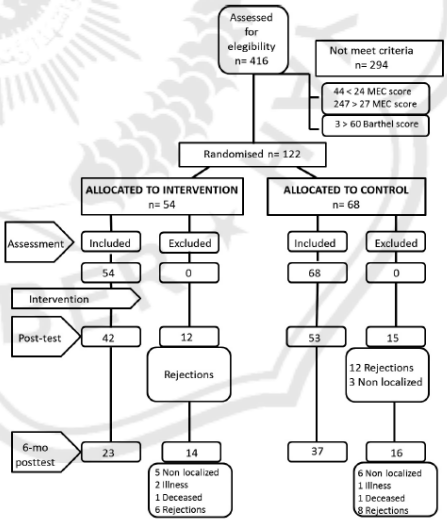

Figure 1. Flow chart of participation and study design.

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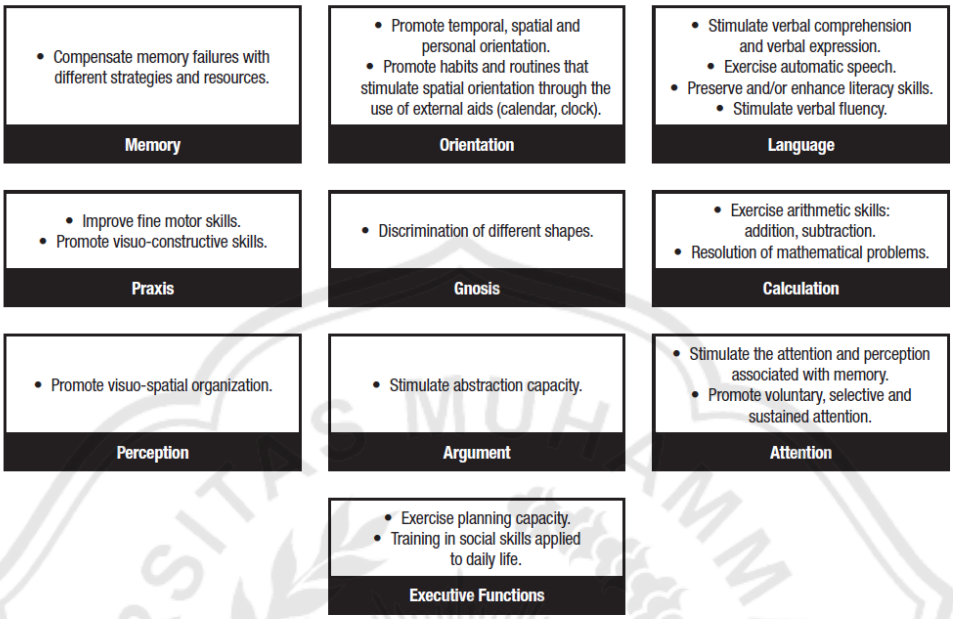

Figure 2. Development objectives following the red mental activation notebook guidelines.

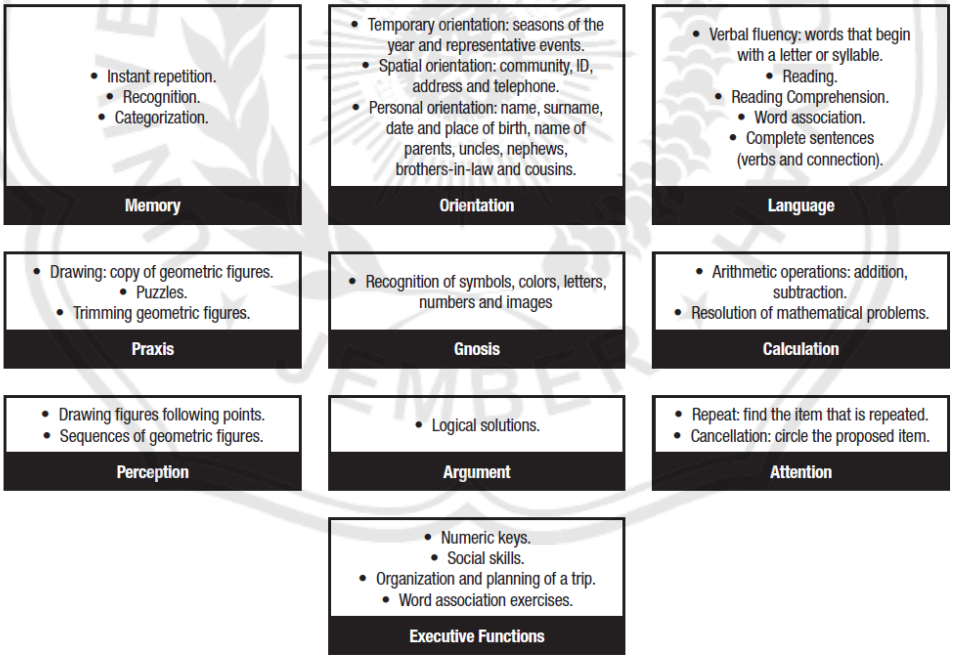

Figure 3. Cognitive stimulation exercises used based on red mental activation notebook guidelines.

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Secondary outcomes

The Barthel Index (BI) assesses the level of independence for ten basic Activities of Daily Living (ADLs). Its internal consistency is 0.90; interobserver reliability, Kappa index is between 0.47 and 1.00, and intraobserver reliability Kappa index is between 0.84 and 0.97. Regarding the evaluation of internal consistency, a Cronbach's alpha of 0.90-0.92[28] was obtained. Maximum score on the Barthel Index is 100, where scores >60 indicate low dependence for ADLs and scores <20 demonstrate a high dependence level for ADLs.[28]

The Lawton and Brody Scale assesses the degree of autonomy for eight instrumental ADLs necessary for living independently in the community. Score ranges from 0 (dependent) to 8 (independent) points. The scale's sensitivity is 0.57 and specificity is 0.92.[29]

The Goldberg questionnaire (EADG) consists of two sub-scales, one for anxiety and the other for depression. Each sub-scale has 9 dichotomous response items (Yes / No). An independent score is given for each scale, with one point for each affirmative answer. Goldberg et. al.[30] proposed a cut-off point of ≥4 for the anxiety scale. In the present study, the anxiety sub-scale was used, which has overall specificity of 91% and sensitivity of 86%.

The Yesavage Geriatric Depression Scale (15-item version) evaluates depression level. The abbreviated version has 15 questions and is adequate for elderly people living in the community. It was highly correlated with the original version consisting of 30 items (r=0.84, p<0.001). The authors found that a cut-off score of 11 on the GDS yielded an 84% sensitivity rate and 95% specificity rate.[31]

Besides these outcome variables, other socio-demographic variables such as age, sex, marital status (single, married, widowed/separated) and educational level (primary, secondary) were collected using a structured interview.

Data analysis

The IBM SPSS Statistics v. 22 software package was used for statistical analysis. In addition to the usual descriptive tools and Fisher's exact test, Student's *t*-test for equal means was used and, when statistically significant differences were found, effect size was calculated using Cohen's d, providing both a point estimate and confidence interval. Analysis of covariance was used to control the effect of the sex variable on the main outcome variable, and the partial eta-squared statistic was used to report effect size. The significance level for statistical tests was 5% (p<0.05).

RESULTS

The frequencies and proportions for the sociodemographic variables are shown in Table 1. Participant age was similar for both groups, ranging from 65 to 88 years (74.3±5.8 years in the intervention group and 75.6±6.2 years in the control group), with a higher proportion of women in both groups (87.0% in the intervention group and 69.1 in the control group). Randomization did not produce statistically significant discrepancies except for sex (p=0.029), but this discrepancy had no effect on the results for the effect of the intervention, as will be discussed later.

Comparison of intervention and control groups

Means and standard deviations of the outcome variables in the three assessments (pre-test, post-test and 6-month post-test) are presented in Table 2.

On the MEC-35 scale, both groups scored 25 at baseline, demonstrating low cognitive impairment. During the course of the study, the Intervention group improved their MEC-35 score, with an increase to 29 points. Surprisingly, the Control group improved their score from 25 to 27 points (cut-off score).

Table 1. Frequencies and percentages for sociodemographic variables.

Variables		Intervention Group (n=54)	Control Group (n=68)
Sex	Male	7 (13.0)	21 (30.9)
	Female	47 (87.0)	47 (69.1)
Marital status	Single	3 (5.6)	7 (10.3)
	Married	33 (61.1)	42 (61.8)
	Widowed. Separated	18 (33.3)	19 (27.9)
Educational Level	Primary	50 (92.6)	58 (85.3)
	Secondary	4 (7.4)	10 (14.7)

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Table 2. Mean±SD of outcome variables.

Variables	Intervention Group			Control Group		
	Pre-test n=54	Post-test n=42	6-month post-test n=28	Pre-test n=68	Post-test n=53	6-month post-test n=37
MEC-35	25.91±1.03	28.85±2.95	29.64±2.60	25.62±1.02	26.60±4.03	27.08±4.07
Barthel	95.93±7.65	96.43±6.27	95.89±8.50	95.74±6.18	94.28±7.64	93.74 ±8.71
Lawton-Brody	7.26±1.28	7.26±1.23	7.29±1.33	6.51±1.93	6.36±1.87	6.70±1.76
Goldberg	3.22± 2.29	2.89±2.34	2.61±1.90	2.78±2.55	2.94±2.31	2.85±2.28
GDS-15	2.93±2.60	2.83±2.97	2.13±1.86	3.14±2.89	3.62±3.35	3.12±3.52

Outcome variables expressed in points on respective scales. MEC-35: Mini-Examen Cognoscitivo-35 points (Spanish version of MMSE). Barthel: Barthel Index. Lawton-Brody: Lawton and Brody Scale. Goldberg: Goldberg Anxiety Sub-scale. GDS-15: Yesavage Geriatric Depression Scale, 15-item version.

Table 3. Mean±SD of increases in outcome variables relative to baseline levels.

Variables	Post-test				6-month post-test			
	IG n=42	CG n=53	IG-CG	p	IG n=28	CG n=37	IG-CG	P
MEC-35	2.89±2.65	0.98±3.87	1.91	0.005	3.78±2.49	1.44±3.43	2.34	0.009
Barthel	0.71±4.49	–1.30±5.08	2.01	0.048	–0.18±7.00	–1.49±7.42	1.21	0.506
Lawton-Brody	–0.05±0.44	–0.15±0.97	0.10	0.491	–0.04±0.88	0.11±1.24	–0.15	0.604
Goldberg	0.03±2.26	–0.01±2.48	0.04	0.927	–0.52±2.36	–0.12±2.42	–0.40	0.619
GDS-15	–0.12±1.91	0.13±2.73	–0.25	0.600	–0.73± 2.82	–0.39±2.64	–0.34	0.600

Outcome variables expressed in points on respective scales. MEC-35: Mini-Examen Cognoscitivo-35 points (Spanish version of MMSE). Barthel: Barthel Index. Lawton-Brody: Lawton and Brody Scale. Goldberg: Goldberg Anxiety Sub-scale. GDS-15: Yesavage Geriatric Depression Scale, 15-item version. IG-CG: difference in means between Intervention and Control Groups. p: p-value of Student's t-test of equal means.

Regarding both instrumental and basic ADLs, measured by the Lawton & Brody Scale and Barthel Index, respectively, participants had no dependence at study baseline. The intervention did not improve the performance of ADLs. However, the Control group showed a decline in scores during the intervention period, while the Intervention group maintained their score on the Barthel Index.

The analysis of anxiety and depression levels revealed no difference between the Intervention and Control groups. At study baseline, the Intervention group had a score of 3 on the Goldberg questionnaire, close to the cut-off point of 4. However, the intervention was able to reduce anxiety levels with score decreasing to 2.

Randomization produced no statistically significant discrepancies for any of these variables. Therefore, pre-test values were very similar for all variables, but better behavior was evident in the Intervention group on the MEC-35, both at post-test and 6-month post-test. To assess the effect of the intervention, increments over the baseline level of the outcome variables were calculated along with their differences between Intervention and Control group, both after the intervention (post-test) and after 6 months (6-month post-test), as presented in Table 3. Statistically significant differences were found in MEC-35 post-test scores (1.91 points, p=0.005) with Cohen's d of 0.564 and 95% confidence interval (0.150, 0.975), and in MEC-35 6-month post-test scores (2.34 points, p=0.009) with d=0.764 and 95% confidence interval (0.253, 1.270). Analysis of covariance was used to control the effect of the sex variable for these increases on the MEC-35, and this analysis ruled out interaction between participant sex and the effect of the intervention on both the post-test assessment (F=0.807, p=0.371) and 6-month post-test assessment (F=1.749, p=0.191). The linear model used estimated the effect of the intervention, after controlling for sex, at 1.63 points for the post-test evaluation and at 2.06 points for the 6-month post-test follow-up. A statistically significant difference was also found in performance on the Barthel post-test (2.01 points, p=0.048) with Cohen's d of 0.416 and 95% confidence interval

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(0.004, 0.826). This difference decreased to 1.12 points on the 6-month post-test assessment and was no longer statistically significant. No statistically significant difference in performance was observed on the Lawton-Brody, Goldberg or GDS-15 instruments.

DISCUSSION

The aim of this study was to assess the results of a cognitive intervention program in elderly people. Our results demonstrate that the intervention may help participants' cognitive performance and basic activities of daily living. The Intervention group showed a significant improvement in cognitive function, as measured by the MEC-35 scale, after the intervention both at post-test and 6-month follow-up. The Barthel Index was also higher in the Intervention group, but only on the post-test analysis. However, no significant differences were found for the Lawton and Brody Scale. There were no statistically significant differences between Intervention and Control groups on the Goldberg Questionnaire or the Yesavage Geriatric Depression Scale. It should be noted that the pre-test scores in both groups were relatively low, meaning that participants did not present anxiety or depression.

Both post-test and 6-month post-test results showed that the program produced positive results in the Intervention group, with statistically significant improvements in general cognitive state, as measured with the Spanish version of the MMSE (MEC-35). The effect size of the post-test analysis was Cohen's d=0.564, a medium size according to Belleville et al..[32] Our results are in line with some previously published studies. Llanero-Luque et al.[14] reported a similar post-test effect size for the MEC-35 (d=0.45) after performing a cognitive stimulation program. Polito et al.[13] reported statistically significant short-term gains on the MMSE after applying this in MCI participants living in the community, as did the study by Alves et al.[15] of institutionalized participants with either MCI or mild/moderate dementia, both through a cognitive stimulation program.

Our medium-term effect size at the 6-month post-test on the MEC-35 was Cohen's d=0.764, a large value according to Belleville et al.[32]. Hwang, et al.[33] described a cognitive training program involving MCI participants, but did not report a statistically significant improvement in the medium term on the MMSE.

We found statistically significant post-test improvements in basic ADLs measured with the Barthel Index for the Intervention group, but this improvement was small and no longer significant on the 6-month post-test. A longer intervention could be required to improve physical status and ADL development in the long term.

By contrast, no statistically significant improvement was obtained in instrumental ADLs, as measured with the Lawton and Brody scale, over short or medium-terms. No statistically significant improvements in ADLs are reported by similar studies that used cognitive rehabilitation.[34,35]

As we have indicated previously, none of the groups presented depression or anxiety. Consequently, no statistically significant differences were found in levels of anxiety or depression, as measured by the Goldberg and GDS-15 scales. This corroborates other studies that also found no short-term differences after a program of cognitive stimulation on the Goldberg[12] or GDS-15.[14] However, Talassi et al.,[35] in a cognitive rehabilitation program, reported statistically significant differences in short-term assessments, but employed other instruments, using the STA for anxiety level and the GDS-30 for depression level.

Therefore, our hypothesis is that the present program may improve participants' cognitive performance and basic activities of daily living in the short term.

Limitations

First, we could not access patients' medical history or clinical diagnosis, and pharmacological treatments were not recorded. Second, we had a high number of dropouts, but this problem is difficult to avoid, and has occurred in other studies.[12] Third, the therapists who performed the intervention and the participants could not be blinded.

Future research

Most MCI studies involve small samples[35,36] therefore studies with a larger sample of participants are necessary to be able to expand the knowledge in this field. There are few RCTs and their designs vary greatly[33] with high heterogeneity in cognitive intervention techniques, time and duration of sessions, involving treatment of not only older people with MCI, but also patients with dementia and Alzheimer's disease, whose results are evaluated by means of different questionnaires, and follow-up applied at different timepoints. This lack of methodological uniformity could explain the variability of results. It would be useful to implement RCTs with a multimodal intervention, a wider range of assessment instruments and more assessment periods. It would also be valuable to study ways of fostering participant adherence to the program in order to reduce dropouts.

In conclusion, people over 65 with MCI benefited from a cognitive stimulation program. This program may increase cognitive levels and delay cognitive impairment progression. We found that this program also improved basic ADLs of the participants in the short term.

Author contributions. Isabel Gomez-Soria, Patricia Peralta-Marrupe: conceptualization, investigation, methodology, writing-original draft, writing-review & editing; Fernando Plo: conceptualization, formal analysis, supervision, validation, writing-review & editing.

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