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Tesis Doctoral

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Doctorat en Psicologia Clínica i de la Salut

Departament de Psicologia Clínica i de la Salut

Universitat Autònoma de Barcelona

Bellaterra

2019

Institut Guttmann
HOSPITAL DE NEUROREHABILITACIÓ
Institut Universitari adscrit a la UAB

“Trata de acumular todas las experiencias que puedas, serán lo que te hará reír mañana”

G.P. Sanner

Agradecimientos

En primer lugar, agradecer a la dirección del Institut Guttmann y al departamento de Investigación, el darme la oportunidad de realizar esta tesis doctoral.

También dar las gracias al área de Neuropsicosocial, porque habéis estado ahí para todo (incluyendo galletas e imprimir etiquetas).

A mis compañeros de aventuras, amigos y mentores. Al "9", al café de rico, los troncos al sol y al Europa. Qué divertido ha sido el camino con vosotros. *Ohanna*.

A la jefa, por tus frases.

En especial a Alberto García, gracias capitán por llevar el barco a puerto.

Y a Adam, porque desde los *census* de ratones, la ciencia me acompaña.

A mi marido y mejor amigo, que no te has perdido ni un *p valor* de esta tesis.

A mis padres, *AGA* y Silvia, por sembrar en mi la curiosidad, el sentido del humor implacable y el "a mí que me lo expliquen", y a mis hermanos, Diana, Elsa y Antonio, por vuestro apoyo y confianza, y por los aviones, trenes y peajes.

Y con gran cariño, a todos los pacientes y familias que contestaron a nuestra llamada. Nos habéis ayudado muchísimo.

Acrónimos

GNPT®: "*Guttmann, NeuroPersonalTrainer"*®

t1: Primera valoración; t2: segunda valoración; t3: tercera valoración; t4: cuarta valoración (final de tratamientos); t5: quinta valoración (seguimiento a los 6 meses)

CPT-II: Conners Continuous Performance Test

TMT-A: Trail Making Test A

TMT-B: Trail Making Test B

WAIS-III: Wechsler Adult Intelligence Scale

RAVLT: Rey Auditory Verbal Learning

PMR: Spanish phonemic fluency test

RSAB: Rating Scale for Attentional Behavior

PRMQ: Prospective and Retrospective Memory Questionnaire

BRIEF-A: Behavior Rating Inventory of Executive Function–Adult

PCRS: Patient Competency Rating Scale

CIQ: Community Integration Questionnaire

CCT: Computerized Cognitive Training

CCT – C: Customized Computerized Cognitive Training

CCT-non-C: Non customized computerized cognitive training

INE: Instituto Nacional de Estadística

Índice

Prólogo

Este trabajo explora la aplicabilidad potencial de la rehabilitación cognitiva computerizada en pacientes de ictus en fase crónica con déficits cognitivos. Para tal propósito, se utilizó una plataforma de telerehabilitación cognitiva domiciliaria, que permite la personalización y supervisión del tratamiento. Todos los participantes habían realizado previamente, durante la fase de recuperación post-aguda (<6 meses de evolución), un programa neurorehabilitador integral en el Hospital de Neurorehabilitació Institut Guttmann que incluía el uso de la plataforma de telerehabilitación cognitiva previamente referida. Nuestro objetivo ha sido analizar si los pacientes crónicos con déficits cognitivos pueden mejorar su rendimiento cognitivo, valorado mediante pruebas de rendimiento óptimo, escalas y cuestionarios, tras trabajar de forma intensiva con un una plataforma de tele-rehabilitación domiciliaria.

Por otro lado, hemos investigado la repercusión de realizar actividades cognitivamente estimulantes en el rendimiento cognitivo de pacientes crónicos con déficit cognitivo.

El método científico seguido para abordar el eje principal de esta tesis ha sido publicado en la revista *Trials*, y se presenta como el primer artículo publicado de este compendio:

- Gil-Pagés, M., Solana, J., Sánchez-Carrión, R., Tormos, J., Enseñat-Cantallops, A., & García-Molina, A. (2018). A customized home-based computerized cognitive rehabilitation platform for patients with chronic-stage stroke: study protocol for a randomized controlled trial. *Trials, 19*(1). doi: 10.1186/s13063-018-2577-8

Los resultados finales del ensayo clínico cruzado se presentan en formato artículo, el cual está pendiente de envío para publicación (working paper):

- Gil-Pagés, M., Solana, J., Sánchez-Carrión, R., Tormos, J.M., Enseñat-Cantallops, A. & García-Molina, A. Functional improvement after home-based computerized cognitive training in young to middle aged adults with chronic-stage stroke: Results of a randomized controlled double-blind crossover clinical trial

El estudio sobre el impacto en el rendimiento cognitivo de los pacientes crónicos de las actividades cognitivamente estimulantes ha sido publicado en el *Journal of International Neuropsychological Society* y se presenta como el segundo artículo publicado de este compendio:

- Gil-Pagés, M., Sánchez-Carrión, R., Tormos, J., Enseñat-Cantallops, A., & García-Molina, A. (2019). A Positive Relationship between Cognitive Reserve and Cognitive Function after Stroke: Dynamic Proxies Correlate Better than Static Proxies. *Journal Of The International Neuropsychological Society, 25*(09), 910-921. doi: 10.1017/s1355617719000638

También, se ha dado difusión a parte de la tesis doctoral en el *II Congreso Iberoamericano de Neuropsicología* celebrado en Almería, el 4 y 5 de Mayo de 2018 mediante una comunicación oral:

- Gil-Pagés, M., Sánchez-Carrión, R., Tormos, J.M., Enseñat-Cantallops, A. & García-Molina, A. Perfil de afectación de la reserva cognitiva en pacientes con ictus crónico.

Resumen

Objetivo Los objetivos de esta tesis fueron: (I) investigar la aplicación de un tratamiento de rehabilitación cognitiva computerizada domiciliaria en pacientes de ictus con déficit cognitivo en fase crónica (II) investigar la influencia de la ejecución de actividades cognitivamente estimulantes en el rendimiento cognitivo de los pacientes en fase crónica.

Método Se realizó un estudio de dos brazos, cruzado, doble ciego y aleatorizado. Treinta pacientes de ictus en fase crónica, entre 24 y 62 años. Los participantes reclutados eran antiguos pacientes de Institut Guttmann, que habían realizado tratamiento intensivo en la fase post-aguda, y que desde el alta (t0) hasta el reclutamiento no habían mostrado cambios significativos a nivel cognitivo. En la fase I, el Grupo A recibió un tratamiento personalizado de telerehabilitación cognitiva (CCT-C) y el Grupo B realizó un tratamiento "sham", una plataforma de ejercicios no personalizada (CCT-non-C) durante 6 semanas. Después de un periodo de descanso de 3 meses, cada grupo recibió el otro tratamiento (fase II). Los participantes fueron evaluados en el reclutamiento (20 meses después del alta, t1), después de la fase I (t2), después del descanso (t3), después de la fase II (t4), y en un seguimiento 6 meses después (t5). Las evaluaciones incluyeron test, y escalas funcionales para paciente y familiar y una escala de reserva cognitiva para evaluar la frecuencia de actividades cognitivamente estimulantes (*CRS*).

Resultados Ambos grupos mostraron mejoras significativas después de los tratamientos (periodo t1 – t5). Después de la fase I, las comparaciones intergrupales revelaron que el Grupo A mostró un descenso significativo en quejas subjetivas (*RSAB*: p = 0.02, d = 0.8) y que el Grupo B mostró mejora en la puntuación de algunos test. Después de ambos tratamientos (t4), continuó observándose un descenso en las quejas subjetivas del Grupo A (*PRMQ*: p = 0.03, d = 0.9; *PCRS*: p = 0.04, d = 0.4; *BRIEF -A*: p = 0.04, d = 0.6).

Ambos grupos mostraron mejoras en pruebas de rendimiento óptimo (Grupo A en Clave de Números: p=0.01, d=1; Grupo B en *RAVLT Reconocimiento* p=0.02, d=0.6). En cuanto a la frecuencia de hábitos y rutinas, la *CRS* mostró diferencias significativas en la frecuencia de actividades cognitivamente estimulantes antes (*CRS-Pre-stroke*) y después del ictus (*CRS-Post-stroke*). Los subíndices de la *CRS- Post stroke* mostraron correlación positiva con las escalas funcionales (*RSAB, BRIEF-A y PCRS)*.

Conclusiones Los pacientes crónicos con déficits cognitivos derivados de un ictus se pueden beneficiar de un tratamiento de telerehabilitación cognitiva domiciliaria. Recibir un tratamiento basado en CCT-C y la frecuencia de actividades cognitivamente estimulantes, están relacionadas con un descenso de las quejas subjetivas.

Abstract

Objective The objectives of this thesis were: (I) to investigate the application of a home computerized cognitive rehabilitation treatment in stroke patients with chronic phase cognitive deficits (II) to investigate the influence of the execution of cognitively stimulating activities on the cognitive performance of patients in chronic phase.

Method A study of two arms, crossed, double blind and randomized, was carried out. Thirty stroke patients in chronic phase, between 24 and 62 years. The recruited participants were former patients of Institut Guttmann, who had undergone intensive treatment in the post-acute phase, and who since discharge (t0) to recruitment had not shown significant changes at the cognitive level. In phase I, Group A received a personalized cognitive telerehabilitation treatment (CCT-C) and Group B performed a "sham" treatment, a non-personalized exercise platform (CCT-non-C) for 6 weeks. After a 3-month washout period, each group received the other treatment (phase II). Participants

were evaluated in recruitment (20 months after discharge, t1), after phase I (t2), after washout (t3), after phase II (t4), and at follow-up 6 months later (t5). The evaluations included tests, and functional scales for patient and family as well as a cognitive reserve scale to assess the frequency of cognitively stimulating activities (*CRS*).

Results Both groups showed significant improvements after treatments (t1 - t5 period). After phase I, intergroup analyzes revealed that Group A showed a significant decrease in subjective complaints (*RSAB*: p = 0.02, d = 0.8). On the other hand, Group B showed improvement in some tests. After both treatments (t4), a decrease in the subjective complaints of Group A continued (*PRMQ*: p = 0.03, d = 0.9; *PCRS*: p = 0.04, d = 0.4; *BRIEF -A*: p = 0.04, d = 0.6). Both groups showed improvements in the tests (Group A *Symbol Digit*: p = 0.01, d = 1; Group B in *RAVLT Recognition* p = 0.02, d = 0.6). The *CRS* showed significant differences in the frequency of cognitively stimulating activities before (*CRS-Pre-stroke*) and after stroke (*CRS-Post-stroke*). The sub indexes of the *CRS-Post-stroke* showed a positive correlation with the functional scales (*RSAB, BRIEF-A and PCRS*).

Conclusions Chronic stroke patients with cognitive deficits can benefit from a home-based cognitive telerehabilitation treatment. Receiving a CCT-C treatment and the frequency of cognitively stimulating activities have positive correlation with a decrease in subjective complaints.

Capítulo I:
Introducción

1. El ictus

1.1 Definición del ictus

El ictus es un cuadro de inicio rápido de síntomas neurológicos que incluyen vértigo, náuseas y cefalea intensa, cuya duración es superior a 24 horas y cuyas causas son de origen vascular. Cuando los síntomas duran menos de 24 horas se considera accidente vascular transitorio o mini-ictus, y la diferencia con el ictus es que no deja secuelas a largo plazo.

El ictus causa falta de riego sanguíneo en el cerebro, muerte neuronal y secuelas neurológicas que pueden permanecer toda la vida. La interrupción de circulación sanguínea en el cerebro provoca el cese de llegada de nutrientes (glucosa principalmente) y el oxígeno a las neuronas. Las neuronas sobreviven escasos minutos sin riego, por lo que el ictus causa muerte neuronal de forma rápida. Las zonas dañadas por la muerte neuronal se llaman infarto.

Cuando tiene lugar un ictus, se inicia una serie de procesos neuroquímicos, los cuales protegen las células adyacentes al infarto (también llamada zona penumbra) y las mantienen activas, pero si no se interviene farmacológicamente, estas células también mueren y pasan a formar parte del infarto.

Son dos los mecanismos principales que provocan falta de riego: la isquemia y la hemorragia. La etiología, síntomas y tratamiento son diferentes, por lo que tradicionalmente son tratados por separado.

1.1.1 Tipos de ictus

- *Ictus isquémico*

Cuando la falta de riego se produce por la obstrucción de los vasos sanguíneos que riegan el cerebro, se llama ictus isquémico. El 80% de los ictus son isquémicos (Boehme, Esenwa & Elkind, 2017) y se pueden categorizar según las áreas vasculares implicadas: la circulación anterior (arteria carótida interna) y la circulación posterior (arteria basilar y arteria vertebral). Los mecanismos que provocan un ictus isquémico también se pueden clasificar en dos tipos: trombosis y embolia. El ictus isquémico trombótico se produce por el acumulamiento de depósitos de grasa en las paredes de las arterias, que genera placas ateroescleróticas. El crecimiento de las placas estrecha el vaso sanguíneo y aumenta la probabilidad de que se acumulen partículas de la sangre y se forme un coágulo. Cuando esto sucede, cesa el riego por la obstrucción y produce un infarto isquémico. En el caso de que el coágulo se desprenda, se incorpore a la circulación sanguínea y tapone otro vaso del sistema sanguíneo, tendrá lugar un ictus isquémico de origen embólico. Entre el 60%-70% de los ictus isquémicos son trombóticos, y el 20%-30% son embólicos.

- *Hemorragia cerebral*

El otro mecanismo que provoca un ictus es la hemorragia. La hemorragia cerebral es el tipo de ictus más devastador y de peor pronóstico. Los ictus hemorrágicos tienen una tasa de mortalidad de entre el 35% - 52% (Carhuapoma, Nyquist, Hanley & Ziai, 2016), y se trata del ictus más frecuente en pacientes menores de 40 años de edad.

El ictus hemorrágico se produce principalmente por el debilitamiento de las paredes de los vasos sanguíneos o por la ruptura de malformaciones arteriovenosas (MAV), ruptura

de aneurismas (5%-10%), tumores o alteraciones de la coagulación. Este tipo de ictus puede venir acompañados de vasoespasmo, la contracción de los vasos sanguíneos en la región donde tiene lugar la hemorragia, lo cual provoca isquemia e infarto. Por otro lado, engloba hemorragia intracerebral (HIC), la acumulación de sangre dentro del parénquima cerebral producida por la ruptura espontánea no traumática de vasos sanguíneos, y la hemorragia subaracnoidea (HSA), hemorragia en el espacio subaracnoideo (Ustrell-Roig & Serena-Leal, 2007).

1.2 Fases de evolución

Las fases de evolución del ictus se clasifican según criterios diferentes: criterio temporal o criterio de recuperación del paciente o del proceso rehabilitador.

El criterio de duración de la enfermedad establece 3 fases: (i) fase aguda durante la primera semana después del ictus, (ii) fase subaguda entre la 2º y la 4º semana, (iii) fase post-aguda entre el 1º y 6º mes y (iv) fase crónica después de seis meses de evolución (Elsner, Kugler, Pohl & Mehrholz, 2013; Timby & Smith, 2002).

Cuadrado (2009) propone una clasificación basada en la recuperación del paciente: (i) fase aguda, en la que existe una ventana terapéutica durante la cual las intervenciones terapéuticas pueden modificar el curso evolutivo del infarto cerebral y lograr una reactivación neuronal, (ii) fase subaguda en la que puede existir una mejoría a medio y largo plazo, se da reorganización cerebral que puede ser modulada por técnicas de rehabilitación a través del fenómeno de plasticidad neuronal. En la fase subaguda entra en juego el médico rehabilitador, iniciando un largo proceso de valoración y terapia continuadas hasta que el estado del paciente se estabiliza y se da por finalizado con o sin secuelas.

El criterio del proceso rehabilitador lo propone Moyano (2010): (i) fase aguda, que comprende el periodo inicial de ingreso y hospitalización en unidades especializadas de cuidados intensivos bajo la dirección de los neurólogos, (ii) fase subaguda, donde el paciente ha sobrevivido y está médicamente estable, (iii) fase crónica y de seguimiento, en la que el objetivo principal es la reinserción social y laboral del paciente, el mantenimiento de los logros obtenidos en la fase subaguda y evitar la recurrencia del ACV.

Generalmente, la evolución del paciente tras un ictus se clasifica en tres periodos: un periodo agudo que incluye desde que se inician los síntomas hasta el alta hospitalaria, un periodo subagudo en el que se presenta una mejora funcional progresiva, que se estima sucede durante los primeros 3-6 meses y posteriormente una fase crónica de estabilización funcional.

1.3 Estadísticas

De acuerdo con la Organización Mundial de la Salud (OMS, 2019), en el año 2013 entre 11 y 15 millones de personas sufrieron un ictus y al menos 1.5 millones murieron por enfermedad cardiovascular [4, 5]. El ictus es la tercera causa de muerte en la población mundial (GBD, 2017), la segunda causa de muerte en España (Brea, Laclaustra, Martorell y Pedragosa, 2013) y la primera causa de muerte entre las mujeres españolas (INE, 2016). El ictus supone el 70% de los ingresos neurológicos que se producen en España y es responsable del 3-6% del gasto total sanitario.

Según los datos del Instituto Nacional de Estadística, se dan 110.000-120.000 ictus cada año, de los cuales un 50% quedan con secuelas discapacitantes o fallecen, y se calcula que en los próximos 25 años la incidencia se incrementará un 27%. En 2016 se calculó una incidencia de 227 episodios por cada 100,000 habitantes.

El riesgo de padecer un ictus a lo largo de la vida a partir de los 25 años es del 24.9% ("*Global, Regional, and Country-Specific Lifetime Risks of Stroke*, GBD, 1990 and 2016", 2018). En los últimos 20 años los casos de ictus han aumentado un 25% entre las personas de 20 a 64, lo que supone un 31% de la incidencia a nivel mundial y actualmente más de 330.000 españoles presentan alguna limitación en su capacidad funcional por haber sufrido un ictus (GBD, 2018).

2. Rehabilitación Cognitiva Computerizada

2.1 Telerehabilitación cognitiva

La telerehabilitación consiste en la aplicación de un programa de tratamiento de supervisión remota (Peretti, Amenta, Tayebati, Nittari & Mahdi, 2017). La rehabilitación cognitiva consiste en la aplicación de actividades terapéuticas, sistematizadas y orientadas a mejorar el funcionamiento cognitivo, basadas en la evaluación neuropsicológica del paciente y en la comprensión de los déficit cognitivos, conductuales y emocionales derivados del daño cerebral adquirido (Cicerone et al, 2019).

La rehabilitación cognitiva computerizada o CCT consiste en un programa de ordenador estructurado de práctica estandarizada dirigido al entrenamiento cognitivo y que incluye un set de ejercicios cognitivamente estimulantes (Bahar-Fuchs, Clare & Woods, 2013). El eje central de la CCT es que está diseñada para involucrar activamente al paciente para que este ponga en práctica sus funciones cognitivas. Algunos programas están explícitamente diseñados para abordar un único dominio cognitivo, mientras que otros están diseñados para abordar varios dominios (plataforma multidominio) (Harvey, McGurk, Mahncke & Wykes, 2018).

2.2 Estudios de CCT en daño cerebral

La rehabilitación cognitiva es considerada el principal tratamiento para los pacientes con déficit cognitivo derivado de daño cerebral adquirido (Cicerone et al, 2019; Mellon et al, 2015). El metaanálisis llevado a cabo por Cicerone et al (2019) establece como guía para la práctica clínica la integración de sistemas computerizados para el tratamiento del déficit en atención, memoria y funciones ejecutivas en pacientes de ictus y traumatismo

craneoencefálico. Estos sistemas han de ser supervisados, con la implicación activa de un terapeuta que dirija el proceso rehabilitador, además de potenciar la generalización y la conciencia de déficit por parte del paciente. También, han de ser intensivos, dirigidos a los dominios cognitivos específicos, con una adaptación del nivel de dificultad a la ejecución del paciente, que proporcione feedback de la ejecución y que aporte datos objetivos sobre la misma. Estas conclusiones se abstraen a raíz de tres estudios realizados con un programa de rehabilitación computerizado multidominio en pacientes de daño cerebral con déficit cognitivo. Uno de ellos es el estudio de Lin et al. (2014), donde los autores encontraron mejoras en las pruebas psicométricas en memoria y atención en pacientes de ictus (6-10 meses de evolución) que realizaron 60h de tratamiento cognitivo computerizado. Estos resultados fueron replicados por el estudio de Fernández et al (2012), que utilizó el mismo programa computerizado. Por su parte, De Luca et al. (2014), encontró beneficio en medidas cognitivas y de la vida diaria en pacientes de daño cerebral adquirido (ictus y traumatismo craneoencefálico) en fase post-aguda, añadiendo un programa de CCT al tratamiento habitual, sin embargo los autores no especifican qué programa computerizado utilizaron. Un estudio más reciente de De Luca et al (2017) corroboró estos resultados en una muestra de pacientes de ictus. Otros autores han encontrado resultados similares. En el estudio de Prokopenko et al. (2013) se añadió un tratamiento CCT al protocolo habitual de tratamiento y se comparó con recibir únicamente el tratamiento habitual, y confirmaron la eficacia de añadir la CCT en los resultados obtenidos en las pruebas neuropsicológicas. Del mismo modo, Björkdahl, Akerlund, Svensson & Esbjornsson (2013) reportaron resultados positivos de CCT centrada en memoria de trabajo en una muestra de pacientes con daño cerebral adquirido en fase post-aguda. Verhelst, Linden, Vingerhoets & Caeyenberghs (2017) publicaron un estudio con una muestra de adolescentes pacientes crónicos de traumatismo

craneoencefálico a los que aplicaron un tratamiento CCT (con tecnología táctil) y cuyos resultados fueron positivos en las medidas neuropsicológicas. En el mismo sentido, un estudio piloto de Lebowitz, O´Connor y Cantor (2012) encontró efectos positivos de CCT en pacientes adultos con traumatismo craneoencefálico crónico en medidas neuropsicológicas y de autoevaluación. Coyle, Trainor & Solowij (2015) realizaron una revisión sistemática de la aplicación de CCT y realizad virtual en población con deterioro cognitivo leve y demencia, y hallaron que aquellos participantes que realizaron CCT mostraban un estancamiento del deterioro cognitivo en comparación con aquellos que no la realizaron.

2.3 CCT en el ictus crónico

En un artículo de Teasell et al (2012), se destaca el hecho de que los pacientes con accidente cerebrovascular crónico tienden a abandonar las terapias de rehabilitación, no porque no sean necesarios, sino por la falta de recursos personales y sociales. Además, Aziz (2010) explica que debido a la creencia de que la recuperación del accidente cerebrovascular más allá de la etapa post-aguda está estancada, la rehabilitación del ictus ha sido bien estudiada y estructurada en la etapa post-aguda (3-6 meses de evolución) pero es escasa la investigación sobre etapa crónica.

No obstante, algunos estudios han demostrado la efectividad de la intervención en pacientes crónicos.

El grupo de investigación Outpatient Services Trialists (OST) realizó una revisión de 14 ensayos y descubrió que a pesar de la heterogeneidad de los tratamientos proporcionados, existe una relación positiva entre recibir tratamiento 1 año después del la ocurrencia del ictus y tener mayor independencia en la vida diaria. La revisión *Long-Term Rehabilitation*

in Stroke de Aziz et al (2010) incluyó estudios sobre rehabilitación para pacientes que residían en su comunidad, con un tiempo de evolución no superior a un año y que habían completado la rehabilitación formal. La revisión concluyó que, debido a que el concepto de rehabilitación de accidente cerebrovascular a largo plazo es nuevo, no se han realizado muchos ensayos para analizar este aspecto de la atención. Se sugiere que la intervención en esta etapa es factible, pero falta evidencia sólida del beneficio general.

En su revisión, Poulin et al (2012) identificaron dos estudios de rehabilitación cognitiva computerizada en pacientes de ictus crónico. Uno de ellos es el de Westerberg et al (2007), en el cual los autores aplicaron CCT domiciliario dirigido a la estimulación de la memoria de trabajo, durante un total de 40 sesiones, 5 veces por semana durante 5 semanas, mientras que el grupo control no realizó ningún entrenamiento. Los autores hallaron diferencias estadísticamente significativas a favor del CCT en medidas de atención y memoria de trabajo. El otro estudio es un caso único reportado por Vallat et al (2005), dirigido al entrenamiento de la memoria de trabajo, 3 sesiones de 1 hora por semana, durante seis meses. Los autores hallaron beneficio en las pruebas de atención y memoria de trabajo, pero no hallaron cambios significativos en otras pruebas dirigidas a medir dominios diferentes a los entrenados. Los autores de la revisión concluyen que existe evidencia, aunque limitada, que apoya el uso de entrenamiento cognitivo computerizado de la memoria de trabajo en comparación con no intervención, en la fase crónica. Existe también evidencia preliminar que indica que puede generar generalización en el día a día.

Estas conclusiones han sido respaldadas por otros autores, como Hellgren, Samuelsson, Lundqvist & Börsbo (2015), que hallaron resultados positivos en las medidas neuropsicológicas después de aplicar un CCT dirigido a la memoria de trabajo en pacientes crónicos. Los autores concluyeron que los pacientes pueden mejorar,

independientemente del tiempo transcurrido tras la lesión, y concluyen que existe escasa pero positiva evidencia de la efectividad de la atención y la memoria de trabajo CCT en el accidente cerebrovascular crónico. Poulin, Korner-Bitensky, Bherer, Luissier & Dawson (2017) compararon la aplicación de CCT con una intervención ocupacional en pacientes con menos de un año de evolución, obteniendo resultados positivos para ambas intervenciones, por lo que concluyeron que los beneficios de la CCT se podían comparar con los de la otra intervención.

También, en Westerberg et al (2007) encontraron una mejora en las pruebas de memoria de trabajo, así como en las medidas subjetivas de atención del funcionamiento cognitivo. Johansson & Tornmalm (2012) encontraron mejoras en las tareas de memoria de trabajo y también menos problemas cognitivos en la vida diaria en las medidas autoinformadas. Lundqvist, Grundstorm, Samuelson & Ronnberg, 2010 estudiaron la aplicación de un tratamiento CCT en una muestra de pacientes de ictus de 37 meses de evolución, encontrando también resultados positivos. Estos autores concluyeron que la CCT ha de ser estructurada, intensiva e individualizada, y que tiene resultados positivos en el rendimiento cognitivo.

Por otro lado, otros autores no han podido atribuir sus hallazgos a la CCT, como por ejemplo Nyberg et al (2018), que no encontraron una mejora en el rendimiento neuropsicológico, pero sí encontraron que los pacientes mejoraron su rendimiento en las tareas cognitivas.

En resumen, si bien existe evidencia a favor de la CCT en pacientes crónicos, las revisiones sistemáticas han notado la escasez de estudios de rehabilitación cognitiva en el accidente cerebrovascular crónico (Aziz et al, 2010; Cumming et al, 2012). Además, aún es necesario demostrar el grado de mejora en la vida diaria después de CCT (Yoo, Yong, Chung y Yang, 2015).

3. Reserva cognitiva

3.1 Definición

Los pacientes con accidente cerebrovascular pueden sufrir un deterioro cognitivo con alteración de la regulación del comportamiento (Teasell y Hussein, 2016), incluidas disminuciones en la atención, la memoria y la función ejecutiva (Ma, Chan y Carruthers, 2014). La gravedad de la lesión y la ubicación de las lesiones cerebrales causadas por el accidente cerebrovascular pueden desempeñar un papel destacado en el proceso de recuperación. Sin embargo, no es posible hacer pronósticos basados solo en estos factores, ya que la práctica clínica muestra una alta variabilidad interindividual en la recuperación posterior al accidente cerebrovascular.

Esta disparidad interindividual podría explicarse a través del constructo de reserva (Stern, 2009; Umarova, 2017). El constructo de reserva generalmente se explica a través de dos modelos teóricos: reserva cerebral y reserva cognitiva. La reserva cerebral o modelo pasivo propone que las personas pueden asumir un cierto nivel de daño cerebral, más allá de los síntomas que se manifestarían (Satz, 1993). En este modelo, el potencial del cerebro para hacer frente al daño cerebral se basa en mediciones anatómicas (por ejemplo, volumen cerebral, circunferencia craneal o relación cerebro-ventrículo). La reserva cognitiva (RC) o modelo activo se refiere a la influencia de la exposición a eventos de la vida diaria y factores ambientales que configuran la eficiencia de la red, la capacidad de procesamiento y la flexibilidad (Barulli y Stern, 2013; Stern, 2002). Este modelo activo se subdivide en dos componentes: reserva neural y compensación neural (Stern, 2016). La reserva neural comprende procesos preexistentes, redes con mayor probabilidad de soportar daños sin alterar la función porque son más efectivas o tienen mayor capacidad. La compensación neural comprende circuitos alternativos que ayudan a mantener la

destreza en la ejecución de acciones diarias y cognitivamente demandantes, una vez ha tenido lugar el daño cerebral.

Nuestro objetivo era explorar los hábitos cognitivamente estimulantes y su impacto en el rendimiento cognitivo de pacientes con ictus, por lo que se realizó una revisión de la literatura para identificar los indicadores más estudiados de reserva cognitiva en la lesión cerebral adquirida y otras patologías.

3.2 Medida de la reserva cognitiva

La reserva cognitiva es un constructo hipotético, y como tal, no puede ser medida de forma directa, sino que han de utilizarse variables indirectas o indicadores. Estos indicadores son el resultado de estudios que han podido relacionar dichos indicadores con un mejor rendimiento cognitivo.

En la literatura de reserva cognitiva nos encontramos con dos tipos de indicadores: los indicadores estáticos y los dinámicos. Los indicadores estáticos son información que se puede medir de manera objetiva y cuya naturaleza hace que tiende a ser estable durante un periodo de tiempo. Existen dos indicadores dinámicos muy estudiados: el tipo de ocupación y los años de educación formal (Valenzuela & Sachdev, 2006). Se ha considerado que estos indicadores están relacionados con el desarrollo de estrategias cognitivas para resolver tareas complejas (Jones, Manly, Glymour, Rentz, Jefferson & Stern, 2012. Por otro lado, encontramos los indicadores dinámicos, estimados de forma subjetiva y con gran potencial para variar a lo largo del tiempo, y que engloban todo tipo de participación en actividades cognitivamente estimulantes (Akbaraly et al., 2009; Malek-Ahmadi et al., 2017; Scarmeas, Levy, Tang, Many & Stern, 2001; Sumowski et al., 2013).

En su revisión, Valenzuela y Sachdev (2006) encontraron que la educación, la ocupación y las actividades mentales tienen un papel protector en el desarrollo de la demencia. En una revisión reciente, Stern et al (2018) señalaron que la educación, la ocupación y las actividades de ocio se consideraron como indicadores de RC en el campo de la investigación. La investigación sobre RC y accidente cerebrovascular también incluye estas medidas indirectas. Muchos estudios han demostrado que años de educación y deterioro cognitivo después de un accidente cerebrovascular están inversamente relacionados (Sachdev et al, 2004; Elkins et al, 2006; Ojala-Oksala et al., 2012; Zieren et al., 2013). Otros encontraron una relación positiva entre la participación en actividades de ocio y la reducción del riesgo de VCI (Verghese, Wang, Katz, Sanders y Lipton, 2009). La ocupación ha sido estudiada antes incluida en el estado socioeconómico (González-Fernández et al., 2011). Existen varios cuestionarios diseñados para registrar las actividades cognitivamente estimulantes.

En cuanto a los indicadores dinámicos, existen varias herramientas para estimarlos. Por ejemplo, el *Cognitive Reserve Questionnaire* (CRC, Rami et al, 2011) o el *Life Experience Questionnaire* (*LEQ*, Valenzuela & amp; Sachdev, 2007) ambos dirigidos a investigar la reserva cognitiva en la enfermedad de Alzheimer y en estudios de envejecimiento. Otras herramientas para población general son el *Cognitive Reserve Index Questionnaire* (CRIq, Nucci, Mapelli & Mondini, 2011), validada con población italiana, y el *Cognitive Reserve Scale* (CRS, León, García-García & Roldán-Tapia, 2011), que ha sido diseñada para valorar reserva cognitiva en población española. La *CRS* es un instrumento confiable que refleja la frecuencia de participación en una amplia variedad de actividades estimulantes del cerebro a lo largo de la vida. Este cuestionario ha sido validado para su uso en adultos sanos (León, García-García y Roldán-Tapia, 2014).

Por lo tanto, tras realizar una revisión de la literatura, se decidió estudiar la reserva cognitiva a través de la educación y la ocupación (como indicadores estáticos) y actividades cognitivamente estimulantes (como indicadores dinámicos).

3.3 Reserva cognitiva y daño cerebral

Si bien el concepto de reserva debería ser relevante para cualquier situación que implique daño cerebral (Stern, 2009), se ha observado que el estudio de la RC en el ictus aún es insuficiente (Nunnari, Bramanti y Marino, 2014).

Los estudios de reserva cognitiva se han centrado mayormente en la enfermedad de Alzheimer (EA), donde la educación y la ocupación son los principales indicadores de reserva (Valenzuela y Sachdev, 2006). Se ha considerado que estos indicadores fomentan nuevas estrategias cognitivas (Jones et al., 2011). Sánchez, Rodríguez y Carro (2002) encontraron que tenían un papel protector en pacientes con EA. Se han observado resultados similares en otros estudios de EA (Garibotto et al., 2008; Stern, 1994; Stern, Albert, Tang y Tsai, 1999) y también en la enfermedad de Parkinson (Hindle, Martyr y Clare, 2010). También se ha explorado la RC en lesiones cerebrales traumáticas, encontrando efectos positivos de años de educación en la recuperación de las funciones cognitivas (Kesler, Adams, Blasey y Bigler, 2003; Schneider et al, 2014; Sumowski, Chiaravalloti, Krch, Paxton y De Luca , 2013). Alosco y col. (2017) estudiaron pacientes con encefalopatía traumática crónica y descubrieron que la complejidad del logro ocupacional predijo una edad más avanzada al inicio del déficit cognitivo. La literatura muestra los efectos positivos de la educación en la recuperación del accidente cerebrovascular (Elkins et al., 2006), el cambio cognitivo después del accidente cerebrovascular y el ataque isquémico transitorio (Sachdev et al., 2004) y la supervivencia favorable posterior al accidente cerebrovascular en el accidente cerebrovascular

isquémico leve a moderado (Ojala -Oksala et al., 2012). Zieren y col. (2013) se centró en la importancia de la gravedad de la lesión, señalando a la educación como un predictor de un mejor rendimiento cognitivo, pero solo en aquellos casos con gravedad baja o moderada.

También hay muchos estudios de indicadores dinámicos de RC en diferentes patologías. La participación en actividades de ocio se relaciona positivamente con un mejor funcionamiento cognitivo en pacientes con esclerosis múltiple (Sumowski et al., 2013) y AD (Bennet, Schneinder, Tang, Arnold & Wilson, 2006), y se asocia con un menor riesgo de desarrollo demencia (Scarmeas, Levy, Tang, Many & Stern, 2001). Un estudio centrado en indicadores dinámicos de RC y accidente cerebrovascular (Verguese et al., 2009) encontraron que la participación en actividades cognitivas de ocio se asocia con un menor riesgo de riesgo cognitivo vascular en adultos mayores.

En resumen, los estudios anteriores respaldan la idea de que las puntuaciones más altas en las medidas de proxy de reserva cognitiva (ya sea estáticas o dinámicas) generalmente se asocian con un mejor rendimiento cognitivo. Sin embargo, si bien la RC se ha explorado ampliamente en la demencia, solo unos pocos estudios han explorado la RC en la lesión cerebral adquirida (Nunnari et al., 2014).

Capítulo II:
Objetivos e hipótesis

Los objetivos generales de este trabajo fueron:

1. Estudiar si los pacientes de ictus con déficit cognitivo en fase crónica mejoran después de realizar un programa de telerehabilitación cognitiva domiciliaria y personalizada.
2. Estudiar el impacto de las variables relacionadas con los hábitos/rutinas (pre y post lesión), en el rendimiento cognitivo y funcional de los pacientes de ictus en fase crónica.

Objetivos específicos I

a) Analizar si la telerehabilitación cognitiva domiciliaria y personalizada genera mejora en el rendimiento cognitivo valorado a través de pruebas neuropsicológicas de rendimiento óptimo en pacientes crónicos con déficit cognitivo derivado de un ictus.

b) Analizar si la telerehabilitación cognitiva domiciliaria y personalizada mejora el rendimiento funcional en las actividades de la vida diaria de los pacientes de ictus en fase crónica, valorado a través escalas funcionales.

c) Analizar si el beneficio derivado de la telerehabilitación cognitiva domiciliaria y personalizada se mantiene 6 meses después de haber finalizado el tratamiento.

Hipótesis I

a) La telerehabilitación cognitiva domiciliaria y personalizada permite mejorar el rendimiento cognitivo en pruebas de rendimiento óptimo en pacientes crónicos con déficit cognitivo derivado de un ictus.

b) La telerehabilitación cognitiva domiciliaria y personalizada permite una mejora funcional, entendida como disminución de las quejas subjetivas en las actividades de la vida diaria en los pacientes crónicos con déficit cognitivo derivado de un ictus.

c) Los beneficios de realizar telerehabilitación cognitiva domiciliaria y personalizada se mantienen a largo plazo.

Los resultados del estudio han sido expuestos en formato artículo como “Estudio 1”.

Objetivos específicos II

a) Analizar si los pacientes de ictus con déficit cognitivo en fase crónica cambian la frecuencia con la que realizan hábitos/rutinas cognitivamente estimulantes respecto a antes del ictus.

b) Analizar si los hábitos y rutinas de los pacientes de ictus con déficit cognitivo en fase crónica, influyen en su rendimiento cognitivo y funcional.

Hipótesis II

a) La frecuencia de hábitos y rutinas cognitivamente estimulantes cambia en los pacientes de ictus con déficit cognitivo en fase crónica.

b) La frecuencia de hábitos y rutinas cognitivamente estimulantes influyen en el rendimiento cognitivo y funcional de los pacientes de ictus con déficit cognitivo en fase crónica.

Los resultados han sido publicados y expuestos en formato artículo como “Estudio 2”.

Capítulo III:

Método

Artículo 1

Publicado en: Trials

Volumen: 19

Páginas (inicial y final): publicación online

Editorial: BMC (BioMedCentral – parte de Springer Nature)

País de publicación: Reino Unido

ISSN: 1745-6215

Base: SCI Expanded

Área: Medicine, Research and Experimental

Índice de Impacto: 1.975

Cuartil: Q3

Gil-Pagés, M., Solana, J., Sánchez-Carrión, R., Tormos, J., Enseñat-Cantallops, A., & García-Molina, A. (2018). A customized home-based computerized cognitive rehabilitation platform for patients with chronic-stage stroke: study protocol for a randomized controlled trial. *Trials, 19(*1). doi: 10.1186/s13063-018-2577-8

https://doi.org/10.1186/s13063-018-2577-8

Trials

STUDY PROTOCOL Open Access

A customized home-based computerized cognitive rehabilitation platform for patients with chronic-stage stroke: study protocol for a randomized controlled trial

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Abstract

Background: Stroke patients usually suffer primary cognitive impairment related to attention, memory, and executive functions. This impairment causes a negative impact on the quality of life of patients and their families, and may be long term. Cognitive rehabilitation has been shown to be an effective way to treat cognitive impairment and should be continued after hospital discharge. Computerized cognitive rehabilitation can be performed at home using exercise programs that advance with predetermined course content, interval, and pace. We hypothesize that computerized rehabilitation might be improved if a program could customize course content and pace in response to patient-specific progress. The present pilot study is a randomized controlled double-blind crossover clinical trial aiming to study if chronic stroke patients with cognitive impairment could benefit from cognitive training through a customized tele-rehabilitation platform ("Guttmann, NeuroPersonalTrainer"®, GNPT®).

Methods/design: Individuals with chronic-stage stroke will be recruited. Participants will be randomized to receive experimental intervention (customized tele-rehabilitation platform, GNPT®) or sham intervention (ictus.online), both with the same frequency and duration (five sessions per week over 6 weeks). After a washout period of 3 months, crossover will occur and participants from the GNPT® condition will receive sham intervention, while participants originally from the sham intervention will receive GNPT®. Patients will be assessed before and after receiving each treatment regimen with an exhaustive neuropsychological battery. Primary outcomes will include rating measures that assess attention difficulties, memory failures, and executive dysfunction for daily activities, as well as performance-based measures of attention, memory, and executive functions.

Discussion: Customized cognitive training could lead to better cognitive function in patients with chronic-stage stroke and improve their quality of life.

Trial registration: NCT03326349. Registered 31 October 2017.

Keywords: Stroke, Chronic, Randomized controlled trial, Cognitive impairment, Computerized cognitive rehabilitation

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Background

Stroke, the most common cerebrovascular disease, is a focal neurological disorder of abrupt development due to a pathological process in blood vessels [1]. There are three main types of stroke, namely transient ischemic attack, characterized by a loss of blood flow in the brain and which reverts in less than 24 h without associated acute infarction [2]; ischemic stroke, characterized by a lack of blood reaching part of the brain due to the obstruction of blood vessels and causing tissue damage (infarction), wherein cells die in the immediate area and those surrounding the infarction area are at risk; and a hemorrhagic stroke, where either a brain aneurysm bursts or a weakened blood vessel leaks, resulting in blood spillage into or around the brain, creating swelling and pressure, and damaging cells and tissue in the brain [3].

In 2013, according to the World Health Organization (WHO) and the Global Burden of Disease study, worldwide, there were 11–15 million people affected by stroke and almost 1.5 million deaths from this cerebrovascular disease [4, 5]. Moreover, in 2013, the total Disability-Adjusted Life Years (years of healthy life lost while living with a poor health condition) from all strokes was 51,429,440. In Spain, in 2011, the National Institute of Statistics reported 116,017 cases of stroke, corresponding to an incidence of 252 episodes per 100,000 inhabitants [6]. Although stroke incidence increases with advancing age, adults aged 20–64 years comprise 31% of the total global incidence.

Stroke often results in cognitive dysfunction, and med- ical treatment may cause great expense on a personal, family, economic, and social level. Depending on the area of the brain affected and the severity of lesions, stroke patients may suffer cognitive impairment, and alteration in emotional and behavioral regulation [7]. Generally, cognitive impairment derived from stroke includes alterations in attention, memory, and executive function [8].

Recent reports have begun to show positive results from the use of computerized cognitive rehabilitation systems (CCRS) for stroke patients to improve attention, memory, and executive functions. Nevertheless, more research is needed to better control variables and improve training designs in order to reduce heterogeneity and increase control of the intensity and level of performance during treatments [9–12].

CCRS allow adjustment of the type of exercises administered to the specific cognitive impairment profile of each patient, but within a fixed set of possible exercises such that heterogeneity of therapy choice is minimized. This can improve studies by allowing better categorization of patient groups that execute similar training sessions in a similar range of responses [13]. Further, CCRS offers the possibility of applying cognitive rehabilitation at home, while patient adherence and performance can be monitored online, so that patients do not need to live near, lodge near, or travel to a rehabilitation center to receive therapy. Because CCRS therapy is entirely digitized, it generates objective data that can be analyzed to determine the relative effectiveness of these interventions. We hypothesize that by allowing a trained professional to oversee an automated customization program that stratifies the level of difficulty, duration, and stimulus speed of presentation, we will reduce the heterogeneity of traditional cognitive training and improve the efficacy of intervention in chronic stroke patients.

The first objective of this pilot study is to assess if chronic stroke patients with cognitive impairment could benefit from cognitive training through a customized tele-rehabilitation platform ("Guttmann, NeuroPersonalTrainer"®, GNPT®) [14] intended to increase the control of experimental variables (cognitive impairment profile, adherence, and performance) traditionally identified as a source of experimental heterogeneity. The study aims to assess if this benefit could translate into an improvement of the trained cognitive domains (attention, memory, and executive functions).

The second objective is focused on generalization, namely the ability to use what has been learned in rehabilitation contexts and apply it in different environments [15]. Transfer of learning is included within the concept of generalization when specifically referring to the ability to apply specific strategies to related tasks [16]. Two types of transfer have been proposed – near transfer and far transfer [17]. By near transfer we mean that, through the training of a task within a given cognitive domain, improved function in other similar, untrained tasks may be observed in the same cognitive domain. For instance, a patient who performs selective attention exercises and improves execution through the training might improve their performance in other selective attention exercises too. By far transfer we mean that training in a given cognitive domain may improve performance of tasks in other cognitive domains. Such improvement will be observable in tasks that are structurally dissimilar from the ones used in the training. For instance, if a patient performs selective attention exercises, they may also improve their performance in memory tasks.

It has been demonstrated that computerized cognitive training can lead to the phenomenon of transfer, as previously studied in stroke patients [18]. Thus, our research aims to note whether the application of patient-customized tele-rehabilitation can give rise to an improvement in other functions that are based on cognitive domains related to those that have been trained (near transfer) as well as in different ones (far transfer).

Finally, the third objective is to assess the variables of demography (age, sex, years of education) and etiology (ischemic stroke or hemorrhage) and their impact on rehabilitation outcome, given the need to understand the

patient characteristics that may influence treatment effectiveness [19].

Methods

Design

The present pilot study is a double-blind, randomized, crossover clinical trial with two arms (Figs. 1 and 2, SPIRIT). Participants will be randomly assigned to either experimental intervention (GNPT®) or sham intervention (ictus.online). In the first phase, participants in group A will start with the experimental intervention over a 6-week period (30 sessions), and participants in group B will start with the sham intervention over the same 6-week period (30 sessions). Participants will connect from their homes with their computer to the assigned intervention (experimental intervention or sham intervention). It will be indicated to them to connect once a day, from Monday to Friday, for 6 weeks. After a 3-month washout period, the second phase will commence, in which the groups will be crossed over, namely group A will receive the sham intervention and group B will receive the experimental intervention for 6 weeks each.
Evaluations will be conducted pre- and post-training by the study examiner. The examiner will be blind to the allocation of participants. Pre-testing will occur immediately before starting training (A1), and post-testing will occur immediately following both experimental and sham interventions (A2/A4) and after the 3-month washout period (A3). A follow-up neuropsychological assessment will be performed 6 months after treatment has terminated (A5).
A study researcher blinded to assessment procedure will perform the randomization of participants using the rand() function of Microsoft Excel software (Microsoft Excel 2010 for Windows), which is considered a good tool of randomization, having passed the Diehard test [20]. Each participant will have a "list entry" in our database, meaning that they will be stratified based on the two variables of interest in our study – sex (male or female) and type of stroke (ischemic or hemorrhagic). The rand() function will then assign random numbers from 0 to 1 to the stratified sample. The random numbers are ordered from lowest to highest and the first half of the list is assigned to group A and the second half to group B. A study researcher will create a letter with the information of the intervention to be performed (GNPT® or ictus.online) for each participant and will place it in a sealed envelope. The examiner will deliver the sealed envelope to each participant when the first and the third neuropsychological examinations (A1 and A3) take place.

Sample size

This is study will be an explorative pilot study. The total sample size required for a two-arm trial following some currently proposed approximation guidelines is between 24 and 70 [21]. Some recently published studies similar to this one have used sample sizes within this range

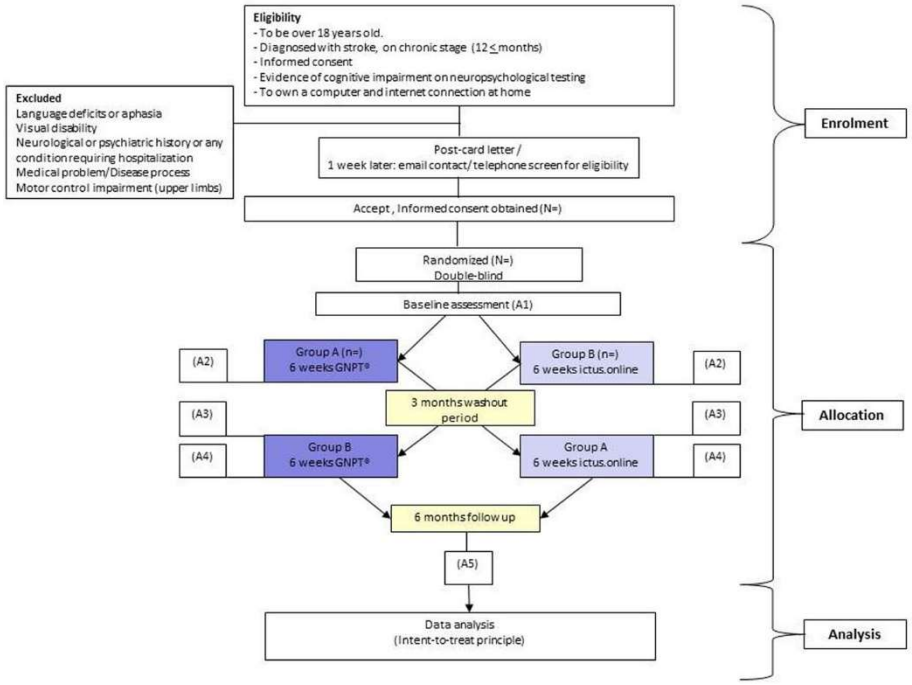
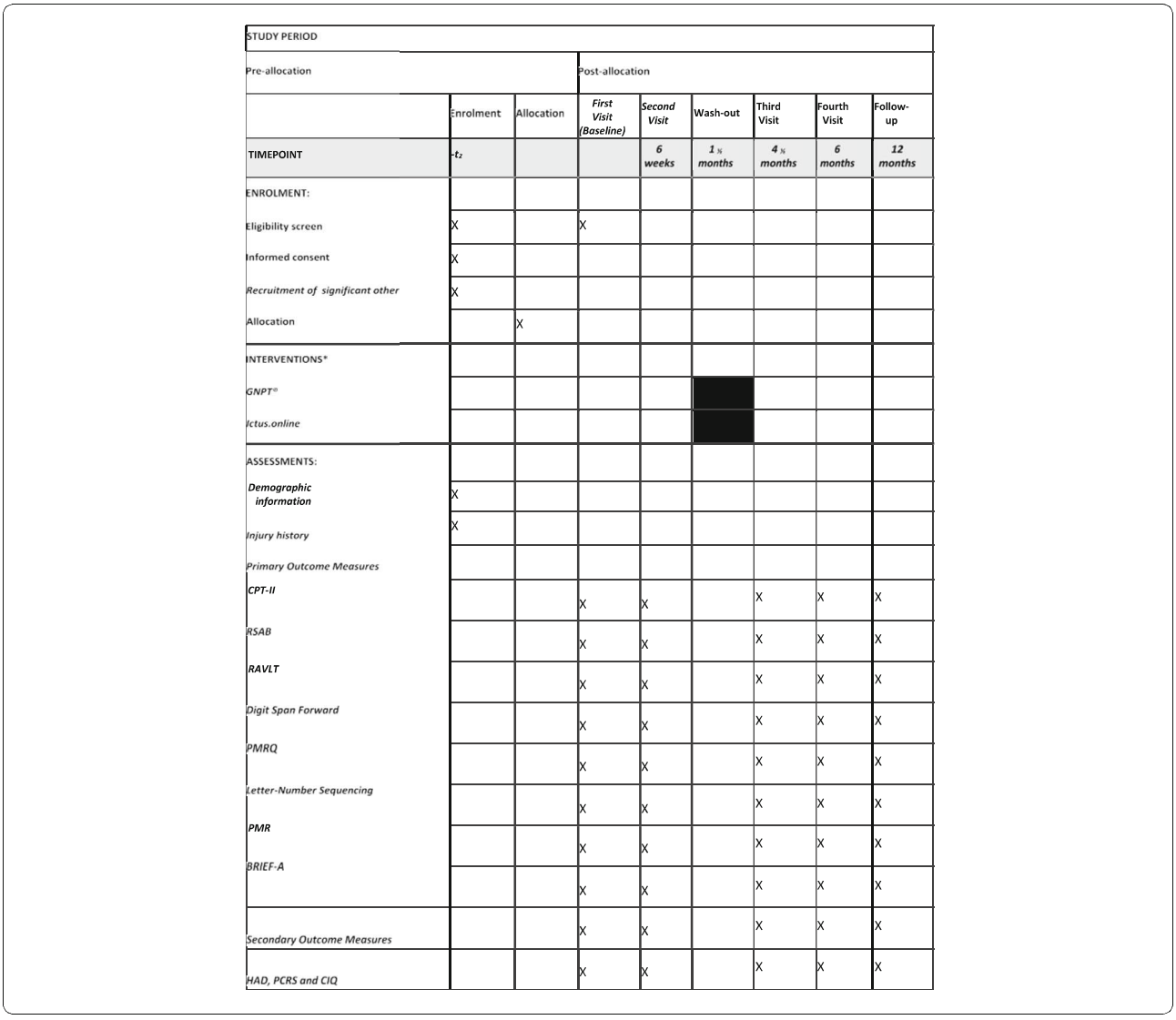


Fig. 1 Study flow diagram



STUDY PERIOD								
Pre-allocation			Post-allocation					
	Enrolment	Allocation	First Visit (Baseline)	Second Visit	Wash-out	Third Visit	Fourth Visit	Follow-up
TIMEPOINT	$-t_2$			6 weeks	1 ½ months	4 ½ months	6 months	12 months
ENROLMENT:								
Eligibility screen	X		X					
Informed consent	X							
Recruitment of significant other	X							
Allocation		X						
INTERVENTIONS*								
GNPT®								
Ictus.online								
ASSESSMENTS:								
Demographic information	X							
Injury history	X							
Primary Outcome Measures								
CPT-II			X	X		X	X	X
RSAB			X	X		X	X	X
RAVLT			X	X		X	X	X
Digit Span Forward			X	X		X	X	X
PMRQ			X	X		X	X	X
Letter-Number Sequencing			X	X		X	X	X
PMR			X	X		X	X	X
BRIEF-A			X	X		X	X	X
Secondary Outcome Measures			X	X		X	X	X
HAD, PCRS and CIQ			X	X		X	X	X

Fig. 2 SPIRIT figure: schedule of enrolment, interventions and assessments

[22–24]. The aim is to recruit 40 participants (n = 20 per group). The results of this pilot study will be used to compute sample size and conduct a power calculation to plan a full-scale study.

Participants

Forty chronic-stage stroke patients with cognitive impairment involving alteration in attention, memory, and/or executive functions will be recruited. The sample will be composed of former patients of Institut Guttmann who have previously received cognitive rehabilitation in the sub-acute phase of evolution.

Recruitment will include postal, email, and telephone contact with participants. Participants will be informed about the study features, goals, and implications of their participation, the duration of the study and the type of procedures that will be applied. Informed consent will be obtained in order to include them in our database. After providing informed consent to participate, participants will schedule an appointment at our center for a baseline testing session.

Inclusion criteria for the trial are (1) age over 18 years old, (2) a stroke diagnosis (ischemic stroke or hemorrhagic stroke); (3) a time of evolution of 12 months or more since stroke occurred (chronic-stage); (4) cognitive impairment confirmed by pre-intervention neuropsychological assessment; and (5) willingness to give written informed consent to participate in the study. Exclusion criteria are (1) diagnosis of language deficits or aphasia; (2) motor impairment concerning upper limbs that may incapacitate them for computer use; (3) severe alteration of the visual field or perceptual problems; (4) health status that may require

further intervention or admission to a medical center during the study; (5) neurological or psychiatric history; or (6) substance abuse.

A neuropsychological screen evaluation to check exclusion criteria (1) and (3) will be applied. It will consist of an orientation and language test (orientation, word-repetition, visual-naming, and order comprehension subtests of Test Barcelona-R) [25]. The cutoff needed to participate in the study is 100% proficiency on these tests.

In addition, we will recruit a next-of-kin for each participant, to whom we will administer questionnaires about the impact of attention, memory, and executive function impairment on the patient's daily life at pre-training, post-training, and follow-up testing stages.

All recruited patients to date are able to consent and understand the implications of the study. Additionally, relatives are involved in both the process of patient consent and patient performance in the study. At the time of recruitment, next-of-kin have been included and informed of the study and its characteristics and implications. This reference next-of-kin collaborates in the study by completing questionnaires about how the participant functions in daily life.

Ethical considerations and informed consent

Ethics approval has been received from the Care Ethics Committee of Fundació Institut Guttmann and the study will be conducted in accordance with the Declaration of Helsinki [26]. A neuropsychologist will explain the study to each participant by phone and in person. An information letter will be given to participants. Participants will be free to ask any question about study treatments and under no circumstances will study professionals imply that certain cognitive results will occur as a result of study participation. Further, a participant may resign from the study at any time.

The protocol follows the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT) 2013 [27] (Additional files 1 and 2).

Setting

The study requires that five neuropsychological assessments be held in a hospital setting at the Institut Guttmann. The Institut Guttmann is a hospital and academic institution located in Badalona (Barcelona, Spain). The hospital is specialized in the medical and surgical treatment and comprehensive rehabilitation of people with spinal cord injury, acquired brain injury, or other neurological disabilities. The institute's main objective is to provide specialized, comprehensive, continuous, and personalized care, incorporating the highest levels of science and technology. In the case of patients with acquired brain injury, part of the rehabilitation includes cognitive rehabilitation, which is performed by neuropsychologists.

Participants will perform home-based interventions (GNPT® and ictus.online).

Intervention

Experimental intervention

GNPT® is a tele-rehabilitation platform that allows therapists to configure and schedule rehabilitation sessions, consisting of a set of personalized computerized cognitive exercises. The examiner from the study will perform the initial neuropsychological assessment and the results of this assessment will be stored in the GNPT® system by a study researcher. The program will then calculate a cognitive profile using these results, taking into account the patient's age and educational level. Using this profile, the program will assign a set of computerized tasks to a certain day, configuring the input parameters of each task in order to personalize treatments. The neuropsychological assessment done at A1 (for group A) and A3 (for group B) will be used to establish the cognitive profile. Starting from each patient's initial cognitive capacity, therapeutic plans will be adjusted to the level of execution and adapted to the patient's evolution according to the obtained results. The adjustment is performed by GNPT® using an automated process. The difficulty level of the tasks will vary and will be adapted according to the participant's performance. Once a rehabilitation session is defined, the participant executes the assigned tasks, sending the results back to the server located at Institut Guttmann, such that therapists can asynchronously see the performance. A researcher from the study group will be exclusively dedicated to supervising this process.

The treatment consists of a set of 1-h sessions, five sessions per week during 6 weeks. A series of cognitive exercises of attention, memory, and executive functions will be conducted in each session (Fig. 3).

Sham intervention

For the sham intervention, a web platform has been developed and is available online through a the domain ictus.online (Fig. 4). This web platform has a graphic interface design similar to GNPT®. After login, it allows participants to access a daily session, which presents four videos of 10 minutes each. After each video, the participant must complete a three-question quiz about the contents of the video (for example, "What animal appears in the video?"). This makes each session last approximately 1 hour in total. The difficulty level of the questions is minimal and independent of the results of the neuropsychological assessment and will remain stable regardless of the execution of the participants. The quality of execution of this condition will be monitored.

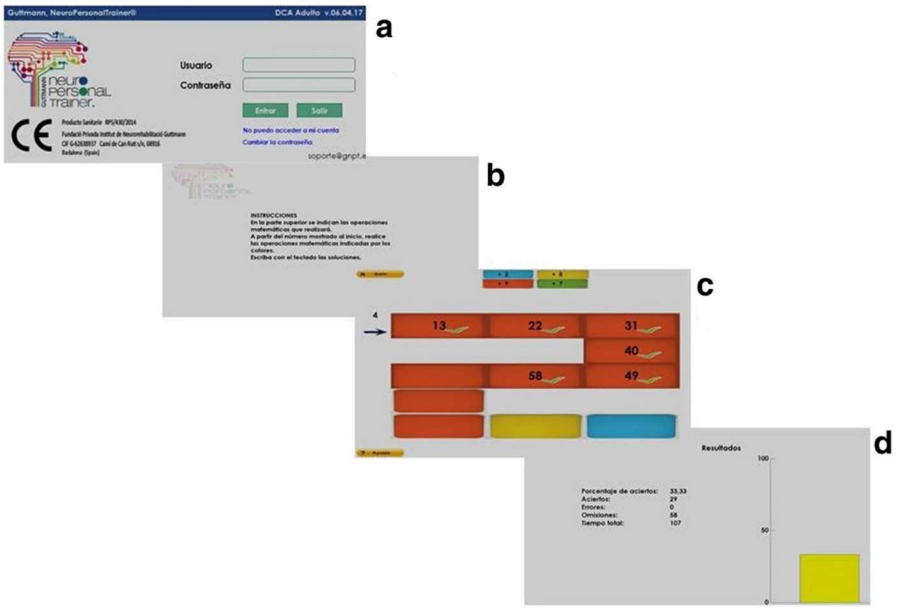


Fig. 3 Experimental intervention (GNPT®) screenshots. a To access to the platform, the user must enter their username and password. b Each exercise begins with an instruction screen. c Example of a cognitive rehabilitation exercise. d At the end of each exercise, a results screen is displayed

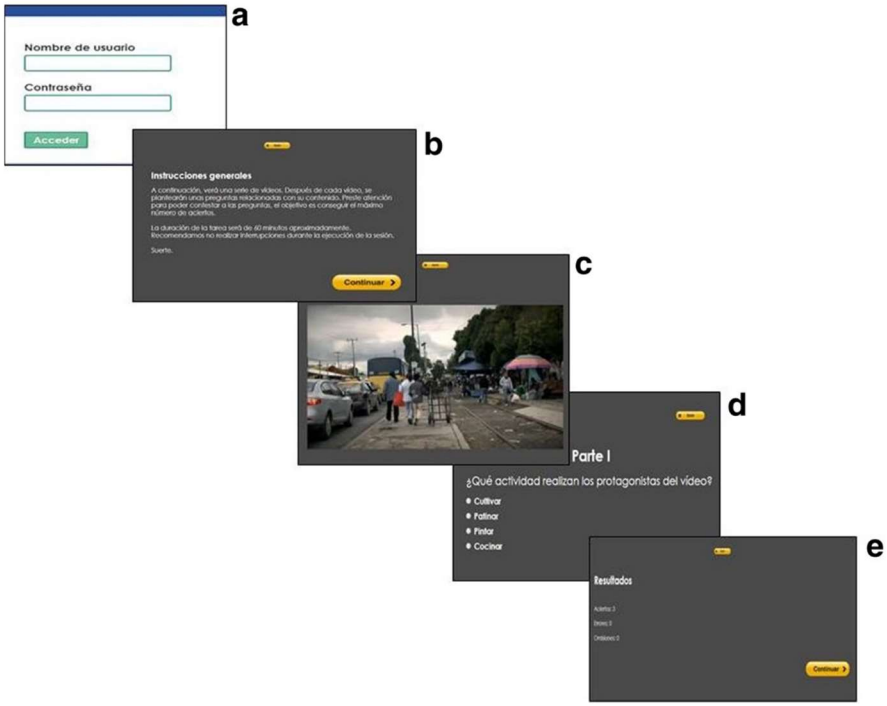


Fig. 4 Sham intervention (ictus.online) screenshots. a To access to the platform, the user must enter their username and password. b Each exercise begins with an instruction screen. c The user watches a 10-min video. d When finished, the user accesses a three-question quiz with four response options. e When the quiz is finished, a results screen is displayed. In each session, three videos with their corresponding quiz are presented

Both the experimental intervention group and the sham intervention group will receive a username and password for logging in.
As adherence strategies, the organizers will offer flexible schedules to perform the exercises, phone calls to confirm appointment dates, and periodic progress reports to keep participants informed on their personal progress in the study (i.e., how much work they have completed, how much longer the study will last, etc.). Additionally, connection frequency will be supervised. To reduce risk, a member of the organizing team will contact the participants if they do not perform any exercise at any of the platforms of treatment for 3 consecutive days (GNPT® or ictus.online) and will reinforce treatment compliance. Attrition will be considered when (1) presence of a new neurological condition appears during the study, or (2) loss of contact with participants occurs during the study and follow-up.

Measures

Demographic information (age, sex, marital status, occupation, education level) and injury history (time of evolution, type of stroke) from all participants will be collected. Whether they have received or are currently receiving any kind of neuropsychological or functional rehabilitation at the moment of joining the study will be also recorded. The information collection method will be a personal interview. A comprehensive neuropsychological battery will be used to assess the participants. This battery is comprised of performance-based measures to assess attention (Conners Continuous Performance, CPT-II) [28], Trail Making Test A and B [29]), memory (Digit Span forward from the Wechsler Adult Intelligence Scale (WAIS-III) [30], Rey Auditory Verbal Learning Test [31]), speed of processing (Digit Symbol-Coding test from WAIS-III), visuoconstruction (Block Design test from WAIS-III), and executive functions (Digit Span backwards and Letter-Number Sequencing from WAIS-III, Stroop Color and Word test [32], Wisconsin Card Sorting Test – computerized version [33], and a Spanish phonemic fluency test – PMR [34]). Administered rating measures (Rating Scale for Attentional Behavior (RSAB) [35]; Prospective and Retrospective Memory Questionnaire (PRMQ) [36]; Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)) [37] will be administered alongside the performance-based measures. All these rating measures will be applied to the patient (self-report) and their recruited next-of-kin (informant-report). Finally, a psychological well-being self-rating scale (Hospital Anxiety and Depression Scale [38]), Patient Competency Rating Scale [39], and the Community Integration Questionnaire [40] will be administered. The Hospital Anxiety and Depression scale will be used to detect participants with emotional disorders. The Patient Competency Rating Scale comprises 30 items, spanning a range of everyday situations and behaviors, and for each item, the patient must make judgment about their own level of competency. The Community Integration Questionnaire is a self-rating scale developed to measure community integration that comprises three subscales (home integration, social integration, and productive activities). These rating measures have been used before in other studies involving stroke patients [41–43].

Primary outcome measures

The primary outcome measures are performance-based measures and rating measures of attention, memory, and executive functions. Since they are different cognitive domains, we need to use different measures for attention (two primary outcomes: the CPT-II and RSAB), memory (Rey Auditory Verbal Learning Test, Digit Span forward from WAIS-III, and the PRMQ), and executive functions (Spanish phonemic fluency test – PMR, Digit Span backward, and the Letter-Number Sequencing Subtests from the WAIS-III and the BRIEF-A). CPT-II is a task-oriented computerized assessment of sustained attention; the Rey Auditory Verbal Learning Test assesses short- and long-term verbal memory and recognition; the PMR test assesses capacity of word generation according to an initial letter (P, M and R); the Digit Span forward test measures the span of immediate verbal recall; Digit Span backward and Letter Number assess working memory; and the RSAB comprises 14 items aimed to identify attentional difficulties on daily routines. The PRMQ includes 16 items, and was designed to evaluate prospective and retrospective memory in the short and long term. The BRIEF-A is designed to assess executive function behaviors on day-to-day activities.
In order to reduce the number of analyses, we will cre- ate composite cognitive indices – one for attention, another for memory, and another for executive functions, using sub-scores from the various performance-based measurements of the primary outcome. Composite cognitive indices will include sub-scores on CPT-II, namely number of omissions, number of commissions, and hit of response for attention; sub-scores on Rey Auditory Verbal Learning Test (Trials 1–5 recall, long-delay free recall and recognition) and Digit Span forward from WAIS-III (immediate recall of a series of numbers) for memory; and scores on Spanish phonemic fluency test – PMR (phonemic word fluency), Digit Span backward from the WAIS-III (immediate recall of a sequence of numbers in reverse order in which it was presented), and Letter-Number Sequencing Subtests from the WAIS-III (recall of progressively longer lists of intermixed letters and numbers in alphabetical and then numerical order) for executive functions.

Secondary outcome measures

Secondary outcomes are the Digit Symbol-Coding and the Block Design Subtests from the WAIS-III, Trail Making Test A and B (TMT-A and TMT-B), Wisconsin Card Sorting Test, and Stroop Color and Word Test. The Digit Symbol-Coding assesses the speed of processing; Block Design evaluates visuoconstruction and planning; TMT-A measures visual attention, while TMT-B measures task-switching; the Wisconsin Card Sorting Test is a measure of cognitive flexibility; and the Stroop Color and Word test is used as a measure of inhibitory control.

Statistical analysis

Analysis Data analysis will be based on the intention-to-treat principle, which means that all participants who were randomized will be included in the final analysis, regardless of their adherence to any of the interventions. To avoid the problems derived from missing data (no attendance to neuropsychological assessments), blank spots will be filled with missing data imputation technique last value carried forward.

In order to detect changes in the variables recorded for the primary outcome and secondary outcome, a within-subject comparison pre-/post-intervention in both groups after both interventions will be made, as well as comparisons between groups (group A and group B).

Our null hypothesis is that a difference between baseline scores (A1 for group A and A3 for group B) and scores post-treatment (A2 for group A and A4 for group B) will not be significantly different from zero. Therefore, the Kolmogorov–Smirnov test will be used to examine the data for normality, and either ANOVA (parametric test) or Kruskal–Wallis (non-parametric test) will be used to analyze the measurements. A significance level of 95% will be used ($P < 0.05$ cutoff). Demographic (age, sex, years of education) and etiologic characteristics (ischemic stroke or hemorrhage) will be described using descriptive statistics for each group (group A and group B). The Bonferroni method will be applied to adjust the overall level of significance for multiple outcomes.

Alternatively, composite indices will be created by transforming raw neuropsychological test scores into z scores using published normative data. Domains will be created by averaging the z scores for each test within the domain ($M = 0$; $SD = 1$). This system has been used before in similar studies [44, 45].

If the sample size of this pilot study allows, a longitudinal mixed model will be applied.

Data analysis will be performed by an analyst outside the study with the statistical analysis software R and appropriate packages ("lmm" and "psych") [46].

Discussion

The first objective of this research is to study the effectiveness of a patient-customized computerized cognitive training program (GNPT®) as a home-based cognitive stimulation tool for stroke patients in the chronic stage of recovery. We hypothesize that training cognitive functions of attention, memory, and executive functions with GNPT® could lead to better function of those cognitive domains post-therapy. Furthermore, we want to study whether customized cognitive training could lead to an improvement in other contexts different from the examination tests, improving performance in both related (near transfer) and unrelated (far transfer) tasks. Finally, we want to study the impact of variables such as demography and etiology on rehabilitation outcome.

The strengths of our study include that it is designed to (1) be easily replicated in new patient cohorts, (2) minimize unintended variability by reducing intervention heterogeneity, (3) adjust the type and difficulty of exercises to the specific cognitive impairment profile of patients, and (4) monitor adherence and performance of each exercise during the whole treatment.

Furthermore, our study focuses on targeting cognitive rehabilitation toward the improvement of the quality of life of the patient. In this sense, we include in our primary outcome measures an assessment of functioning in daily life, before, during, and after the performance of both interventions. Additionally, our design is longitudinal, which offers the possibility of studying the maintenance of the results over time (over 3 and 6 months). The timing of the primary outcome is 3 months. The purpose of the follow-up at 6 months is to check the evolution of patients once they have stopped receiving any type of intervention.

Furthermore, the execution of both interventions will be remotely monitored and we will be able to record the quantity and quality of the execution of the participants. Nevertheless, we consider a limitation the fact that we will not be able to control the environmental conditions in which participants perform the tasks. Another limitation is that the battery assessment will be the same throughout the study, which might create a learning effect and/or ceiling effect in some evaluation tasks.

Trial status

This article was submitted on January 3, 2018. Recruitment is ongoing.

Additional files

Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*. (DOC 121 kb)

Additional file 2: CONSORT 2010 checklist of information to include when reporting a randomised trial*. (DOC 217 kb)

Abbreviations
CPT-II: Conners Continuous Performance Test; A1: first assessment;
A2: second assessment; A3: third assessment; A4: fourth assessment; A5: fifth assessment; BRIEF-A: Behavior Rating Inventory of Executive Function–Adult; GNPT®: "*Guttmann, NeuroPersonalTrainer™*"; PMR: Spanish phonemic fluency test; PRMQ: Prospective and Retrospective Memory Questionnaire;
RSAB: Rating Scale for Attentional Behavior; TMT: Trail Making Test; WAIS: Wechsler Adult Intelligence Scale

Acknowledgements
The authors are grateful to Dr. Adam G. Schrum for providing writing assistance and general support.

Funding
This study is funded by BIOCAT La Fundació BioRegió de Catalunya – Registry Number: COM15–1-0004 and Fundació Bancària "la Caixa" - Obra Social "la Caixa" Project number: LCF/PR/PR16/11110004.

Availability of data and materials
Not applicable.

Authors' contributions
AGM: trial conception, study design and reviewing of manuscript. MGP: study design, drafting and reviewing of manuscript. JS: advice in telecommunications engineering and reviewing of manuscript. RSC: refinement of the study and reviewing of manuscript. JMT: study design and reviewing of manuscript. AEC: coordination of the study and reviewing of manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval has been received from Care Ethics Committee of Fundació Institut Guttmann. Informed consent from all participants in the study will be obtained.

Consent for publication
Not applicable.

Competing interests
The GNPT® is partly property of Institut Guttmann. JS, AGM, RSC, and JMT have been involved in the development of the GNPT®.

Publisher's Note

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Received: 3 January 2018 Accepted: 6 March 2018
Published online: 22 March 2018

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Capítulo IV:
Resultados

4.1. Resumen global Estudio 1:

Se reclutó una muestra de treinta antiguos pacientes del Hospital de Neurorrehabilitación Institut Guttmann (IG) diagnosticados de ictus, con una media de 24 meses de evolución. Se llevó cabo un estudio cruzado, doble ciego, aleatorizado, con dos brazos: Grupo A y Grupo B. Se realizó un estudio intragrupo que mostró que ninguno de los grupos mostraba mejora clínica significativa desde el alta de IG (t0) y el inicio del estudio (t1). En la fase I, los integrantes del grupo A realizaron un tratamiento cognitivo computerizado domiciliario, supervisado, personalizado, (GuttmanNeuroPersonalTrainer®, GNPT®) mientras que el Grupo B realizó un tratamiento domiciliario, supervisado, no personalizado (ictus.online). Ambos tratamientos se pautaron 5 veces por semana durante seis semanas. Finalizada la fase I, ambos grupos pasaron por 12 semanas de descanso (periodo de lavado). En la fase II, el grupo A realizó el tratamiento con ictus.online y el grupo B con la plataforma GNPT®. Un examinador ciego a las condiciones experimentales (M. Gil) llevó a cabo las evaluaciones neuropsicológicas, las cuales se realizaron antes y después de cada fase, así como 6 meses después de finalizar la fase II. Las evaluaciones incluyeron pruebas de rendimiento óptimo (test neuropsicológicos) y escalas de funcionamiento cognitivo. Las escalas de funcionamiento cognitivo fueron administradas paralelamente al familiar que acompañaba al paciente al estudio. También, se administró un cuestionario para registrar la frecuencia de realización de actividades cognitivamente estimulantes antes y después de haber sufrido el ictus.

En la evaluación realizada en t0, no se identificaron diferencias estadísticamente significativas entre Grupo A y Grupo B ($p > 0.05$). Sin embargo, en la evaluación realizada en t1, se observaron diferencias estadísticamente significativas en tres pruebas tipo test (RAVLT Rec: $p=0.009$, $d=0.9$; PMR: $p=0.02$, $d=0.9$; CPT II Hit R: $p=0.03$,

d=0.8). También, se analizó la correlación entre los datos de los cuestionarios de pacientes y de los familiares, y se obtuvieron correlaciones estadísticamente significativas en todos ellos (*PCRS* r= 0.57; p<0.0001; *RSAB* r=0.52; p<0.0001; *PRMQ* r=0.24, p=0.015; *BRIEF-A* r=0.37, p=0.0001).

En primer lugar, se realizó un estudio longitudinal intragrupo para analizar si los grupos habían cambiado después de recibir ambos tratamientos. Los análisis realizados entre el inicio de fase 1 (t1) y el final de la fase 2 (t4), revelaron que Grupo A disminuyó de forma significativa las puntuaciones en *PRMQ* (p=0.02; d=0.5), lo que indica disminución de quejas a nivel de memoria. En cuanto al Grupo B, mejoró de forma significativa las puntuaciones en el subíndice *Aprendizaje* de la *RAVLT*, entre el inicio de fase I (t1) y el seguimiento a largo plazo (t5) (p=0.03; d=0.5). No se obtuvieron más diferencias estadísticamente significativas a nivel intragrupo.

También se realizó un estudio intergrupo, que reveló que entre el principio (t1) y el final de la fase I (t2), Grupo A reportó mayor cambio que Grupo B (disminución de quejas subjetivas) en el cuestionario *RSAB* (p=0.02, d=0.8). Las diferencias intergrupo detectadas en t1 desaparecieron en t2 en el subtest *Reconocimiento* de la *RAVLT* (p=0.347) y en el test de fluencia verbal *PMR* (p=0.137), donde Grupo B mejoró su ejecución. Las diferencias intergrupo en el subíndice *Hit R* de *CPT-II* permanecieron en t2 (p=0.015; d=0.9), donde Grupo B mostraba peor rendimiento en comparación con A.

Entre el inicio t(t3) y el final de la fase 2 (t4), Grupo B mostró evolución positiva en el subtest de *WAIS-III Dígitos Inversos* (p=0.005, d=1) y el índice *Hit R* de *CPT-II* (p=0.01, d=0.9) en relación con A. Grupo A mostró mejor evolución en el índice de *Comisiones* de *CPT-II* (p=0.04; d=8).

También, se estudió la diferencia entre t1 y t4, donde el grupo A reportó mayor cambio (disminución de quejas subjetivas) en *PRMQ* (p=0.01, d=1), *PCRS* (p=0.02, d=0.4) y

BRIEF-A (p=0.04, d=0.6), así como mayor incremento en las puntuaciones en *Clave de Números de WAIS III* (p= 0.01; d=1) en comparación con el grupo B. En cuanto al grupo B, tuvo mejor evolución en el subtest *Reconocimiento* de la *RAVLT* (p=0.02, d=0.6).

Por lo tanto, después de aplicar tratamiento cognitivo computerizado domiciliario, supervisado, observamos cambios estadísticamente significativos en una muestra de pacientes crónicos que no habían mostrado mejora desde el alta hospitalaria.

4.2 Resumen global Estudio 2

En el segundo estudio se correlacionaron las variables de reserva cognitiva (indicadores estáticos y dinámicos) con la evolución en las puntuaciones de las valoraciones neuropsicológicas entre el ingreso y el alta del hospital de neurorrehabilitación, y el alta y la fase crónica (t1). Además, se estudió si la frecuencia de indicadores dinámicos cambia después de un ictus.

Los resultados indicaron que los pacientes de ictus en fase crónica tienden a abandonar después de la recuperación del ictus las actividades relacionadas con las *AVDs* (p = 0.006, d = 0.64) y con la *formación/actualización* (p = 0.02; d = 0.22), mientras que recuperan la frecuencia que tenían antes del ictus en actividades relacionadas con los *hobbies* (p = 0.17; d = 0.19) y con la *vida social* (p = 0.7; d = 0.07). Por otro lado, se observó que los indicadores estáticos de reserva cognitiva no correlacionaban con el rendimiento cognitivo obtenido en la evaluación realizada al inicio del estudio. Tampoco observamos correlación estadísticamente significativa entre los indicadores dinámicos antes del ictus (*CRS – Pre stroke*) y la evolución entre el ingreso y el alta, ni entre el alta y la fase crónica. No obstante, obtuvimos correlaciones estadísticamente significativas entre los indicadores dinámicos después del ictus (RC POST) y algunas pruebas y escalas de

rendimiento cognitivo. En concreto, se observó correlación entre las puntuaciones en *CRS – Post stroke* Formación/actualización y *BRIEF-Metacognición* ($r = -0.468$; $p = 0.029$), con la *PCRS* ($r = 0.469$; $p = 0.029$), y con la *RSAB* ($r = -0.6$; $p = 0.004$). También se observó correlación significativa en CR POST Hobbies y *RSAB* ($r = -0.471$; $p = 0.029$). Por otro lado, obtuvimos correlaciones estadísticamente significativas entre el cuestionario *CIQ* y cada una de las sub-escalas de la *CRS-Post stroke: AVD*s ($r = 0.531$; $p = 0.018$), *Formación/actualización* ($r = 0.475$; $p = 0.029$), *Hobbies* ($r = 0.474$; $p = 0.029$) y *Vida Social* ($r = 0.611$; $p = 0.004$).

En resumen, podemos concluir que las personas que han sufrido un ictus disminuyen la frecuencia de participación en actividades cognitivamente estimulantes relacionadas con las AVDs y la formación/actualización pero recuperan su nivel previo en hobbies y en vida social. Estas variables correlacionan además con el rendimiento cognitivo registrado en escalas funcionales.

Estudio 1

Functional improvement after home-based computerized cognitive training in young to middle aged adults with chronic-stage stroke: Results of a randomized controlled double-blind crossover clinical trial

(Working paper)

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Functional improvement after home-based computerized cognitive training in young to middle aged adults with chronic-stage stroke: Results of a randomized controlled double-blind crossover clinical trial

Background Stroke patients usually suffer cognitive impairment. Computerized Cognitive Training (CCT) has been shown to be an effective treatment for cognitive impairment in post-acute stage of stroke, but its application has been less studied in chronic stage.

Objectives We aim to explore the extent to which chronic stroke patients with cognitive deficit can benefit from a home-based customized CCT.

Methods We identified chronic-stage stroke patients that had not participated in any CCT during their chronic phase, and had not experienced cognitive improvement over the past 20 months. Thirty patients between 24 and 62 years old were randomized in two groups. At phase I, Group A received customized CCT (CCT-C) and Group B received a non-customized CCT intervention (CCT-non-C) over 6 weeks. After a washout period of 3 months, crossover occurred wherein each group now received the other intervention (phase II). Participants were assessed at baseline (20 months after stroke, t1), after first treatment (t2), before crossover (t3), after second treatment (t4), and after six months follow-up (t5). Assessment included performance-based and next-of-kin relative's rating measures.

Results Patients in both groups showed improvement after the treatment period between t1 and t5. After phase I, between-groups analyses revealed that Group A showed a relative decrease in subjective complaints (RSAB: $p = 0.02$, $d = 0.8$). In contrast, Group B showed improvement in other performance-based measures. After all treatments were completed (t4), the decrease in subjective complaints continued in Group A (PRMQ: $p = 0.03$, $d = 0.9$; PCRS: $p = 0.04$, $d = 0.4$; BRIEF -A: $p = 0.04$, $d = 0.6$). Both groups showed improvement in performance-based measures (Group A in Digit Symbol: $p=0.01$, $d=1$; Group B in RAVLT Recognition $p=0.02$, $d=0.6$).

Conclusions Chronic stroke patients who had displayed long-term stagnation in cognitive recovery were able to improve their cognitive performance after receiving home-based CCT in either of the two treatment protocols. Group A reported better functional performance in daily life after receiving CCT-C, while both groups improved in performance-based measures after CCT-non-C. Therefore, we conclude that two protocols of CCT during chronic phase succeeded in providing measurable cognitive and functional improvement to this otherwise recalcitrant patient population. Further research is needed to determine which characteristics of home-based CCT will best address improvement in specific areas of cognitive performance during chronic stage of stroke.

Trial registration: NCT03326349. Registered 31 October 2017

Background

Approximately one third of chronic-stroke patients suffer from cognitive impairment (Douiri, Rudd & Wolfe, 2013; Middleton et al, 2014; Patel, Coshall, Rudd & Wolfe, 2003) and tend to report lower quality of life (Westerberg et al, 2007). Some studies have shown the effectiveness of home-based interventions (Chen et al, 2005) as well as the importance of rehabilitation in chronic stroke patients (Aziz, 2010; OTLS, 2003). *The Outpatient Service Trialists* (2003) conducted a review of 14 trials and found that despite the heterogeneity of treatments provided there is a positive relationship between receiving rehabilitation treatment within 1 year after stroke onset and higher level of independency in daily life functioning. However, stroke patients tend to leave rehabilitation therapies after post-acute stage, usually concurring with their discharge from rehabilitation hospitals (Gunaydin, Karatepe, Kaya, & Ulutas, 2011)

Cognitive rehabilitation addresses stroke-induced cognitive deficit (Douiri, Rudd & Wolfe, 2013) and it is a required component of stroke rehabilitation (Teasell et al, 2009). Recent reports show positive results of computerized cognitive training (CCT) in post-acute stage (Åkerlund, Esbjörnsson, Sunnerhagen, & Björkdahl, 2013; Bogdanova, Yee, Ho & Cicerone, 2016; Cicerone et al, 2019; Mellon et al, 2015; Prokopenko et al, 2013; Zuchella et al, 2014). There is little but positive evidence of effectiveness of CCT in chronic stroke, concretely in attention and working memory (Hellgren, Samuelsson, Lundqvist, & Börsbo, 2015; Johansson & Tornmalm, 2010; Lebowitz, Dams-O'Connor, & Cantor, 2012; Lundqvist et al, 2010; Poulin, Korner-Bitensky, Bherer, Lussier & Dawson, 2017; Westerberg et al, 2007). Generally, studies conclude that CCT, defined as a set of structured, intense and individualized computerized exercises that are designed to target cognitive domains, has positive results on cognitive performance (Cumming, Marshall & Lazar, 2013). Furthermore, systematic reviews have noticed the paucity of

studies of cognitive rehabilitation in chronic stroke (Johansson & Tornmalm, 2010; Lundqvist et al, 2010), and pointed that the degree of cognitive improvement in daily life after CCT is still needed to be investigated (Nordvik et al, 2014; Yoo, Yong, Chung & Yang, 2015).

The objective of this pilot study was to determine whether chronic stroke patients with cognitive impairment may improve after CCT consisting of customized home-based platform that trains multiple cognitive domains (Solana et al, 2015). The hypothesis to be tested was that chronic stroke patients are able to benefit from the CCT-C treatment, improving attention, memory, and executive functions (measured with performance-based measures) as well as performance in daily life activities (measured with rating scales).

Materials and methods

A detailed description of the design, participants, outcome measures as well as the experimental and sham interventions, have been published in a previous study (Gil-Pagés et al, 2018).

Study design

Participants were randomly assigned to two groups in a double-blind crossover clinical trial. At phase I, while Group A executed a customized CCT (CCT-C), Group B followed a non-customized CCT (CCT-non-C). Both groups connected with their computers from their homes with their computer to the assigned intervention using a personal login code. Participants were instructed to connect once a day, 5 days/week, for 6 weeks. After a 3-month washout period phase 2 commenced, where namely group A received CCT-non-

C intervention and group B received CCT-C. The protocol followed by the participants in both groups during phase II was identical to the protocol described above for phase I.

Study evaluations pre- and post-training were conducted where the examiner was blind to the allocation of participants. Baseline assessment occurred immediately before starting training (t1), and post-testing happened immediately following both experimental and sham interventions (t2 and t4) and after the 3-month washout period (t3). A follow-up neuropsychological assessment was performed 6 months after treatment terminated (t5) (see Fig.1 for study flow). As adherence strategies, we offered flexible schedules to perform the exercises, phone calls to confirm assessment appointment dates, and periodic progress reports to keep participants informed on their personal progress in the study.

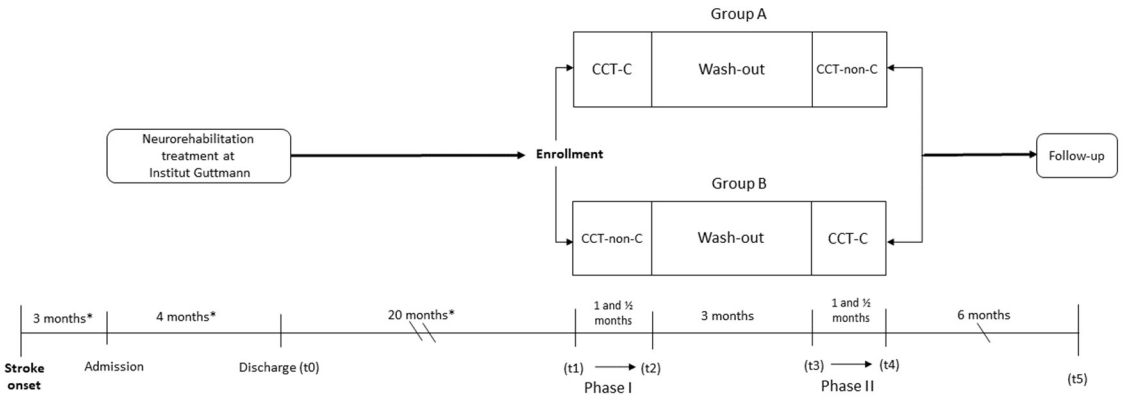

Figure 1 Study flow

(*) Time expressed as mean time, (t0) = Hospital discharge; Phase 1 = period between t1 and t2; (t1) = pre-training assessment at phase 1; (t2) = post-training assessment at phase 1; Phase 2 = period between t3 and t4; (t3) = pre-training assessment at phase 2; (t4)= post-training assessment at phase 2; (t5)= 6 month follow-up assessment after the study finished

Participants

Former patients from the neurorehabilitation hospital Institut Guttmann were recruited. All participants received CCT-C in post-acute stage of stroke during hospital admission and were evaluated at hospital discharge (t0) (see Fig.1). Initially, we recruited forty participants, but finally, thirty participants completed all neuropsychological assessments required to be included in data analysis (see Fig 2 for inclusion flow and Table 1 for demographics). A next-of-kin (of legal age) was recruited when possible for each participant (Group A n=9; Group B n=11) and participated in all assessments to rate their perception of the participants performance in specific areas of everyday life.

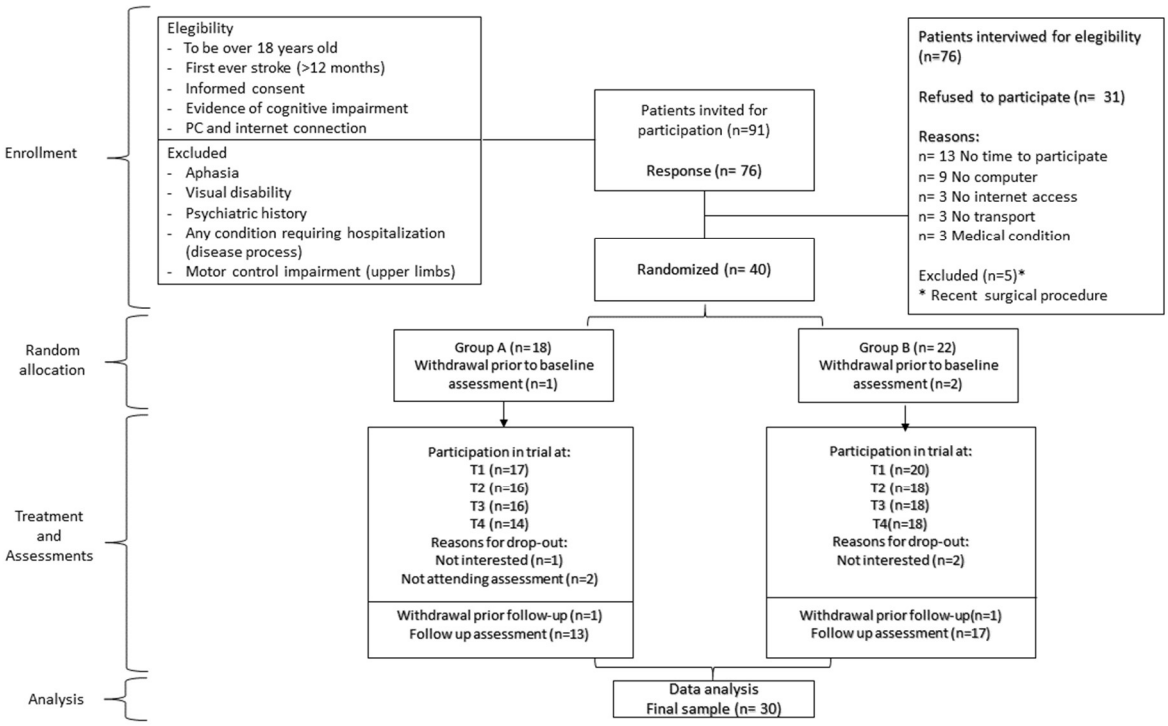

Figure 2. Inclusion flow

Table 1. Demographics distribution

Demographics	*Group A n=13*	*Group B n=17*	*p*
Gender			0.45
Male	7 (53.8%)	12 (70.6%)	
Female	6 (46.2%)	5 (29.4%)	
Mean Age at recruitment (sd)	48.1 (10.3)	52.8 (5.3)	0.23
Mean Age at stroke onset (sd)	46.2 (10.3)	51.1 (5.4)	0.22
Civil status			0.61
Single	3 (30.79%)	3 (17.68%)	
Married	8 (61.5%)	11 (64.7%)	
Divorced	1 (7.69%)	3 (17.6%)	
Mean years since stroke (sd)	1.9 (0.6)	1.8 (0.4)	0.28
Education			0.29
Primary	3 (23.1%)	6 (35.3%)	
Mid-level	5 (38.5%)	9 (52.9%)	
High	5 (38.5%)	2 (11.8%)	
Currently working			0.62
No	10 (76.9%)	15 (88.2%)	
Yes	3 (23.1%)	2 (11.8%)	
Stroke type			0.74
Hemorrahge	7 (53.8%)	7 (41.2%)	
Ischemic	6 (46.2%)	10 (58.8%)	
Computer experience			*p*>0.99
Never	1 (7.69%)	2 (11.8%)	
User	11 (84.6%)	13 (76.5%)	
Professional	1 (7.69%)	2 (11.8%)	

All recruited patients understood the objective and implications of the study and were able to give informed consent.

Ethical considerations and informed consent

Ethics approval has been received from the Care Ethics Committee of Fundació Institut Guttmann and the study has been conducted in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013). The protocol follows the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT) (Chan et al, 2013)

Interventions

CCT- C intervention consisted on the application of *Guttmann, NeuroPersonalTrainer*® (GNPT®), a CCT tele-rehabilitation platform developed by Institut Guttmann that adjusts the level of difficulty using an automated process according to patient's assessment and performance throughout the sessions (Aparicio-López et al, 2016; Solana et al, 2015). The neuropsychological assessments done at t1 (for group A) and t3 (for group B) were used to establish the cognitive profile of each participant.

For the CCT-non-C, we designed and developed a web platform, supervised but non-customized, based on the visualization of 10-minute videos and completion of a short quiz of low difficulty.

Measures

Neuropsychological performance-based measures

We used performance-based measures to assess attention (Conners Continuous Performance- CPT-II (Conners, 2000), and Trail Making Test A and B – TMT-A and TMT-B (Tombaugh, 2004)), memory (Digit Span Forward from the Wechsler Adult Intelligence Scale, WAIS-III (Wechsler, 1997), and Rey Auditory Verbal Learning Test-RAVLT (Schmid, 1996)), speed of processing (Hit response index from CPT-II, Digit Symbol-Coding test from WAIS-III, and executive functions (Digit Span Backwards and Letter-Number Sequencing from WAIS-III, Stroop Color and Word test (Golden, 2001), and a Spanish phonemic fluency test – PMR (Artiola I Fortuni et al, 1999)).

Rating measures

Rating measures were applied to the patient (self-report) and their recruited next-of-kin (informant-report) to rate subjective cognitive functioning in daily life: Patient Competency Rating Scale (PCRS) (Pritagano et al, 1986), Rating Scale for Attentional Behavior (RSAB) (Ponsford & Kinsella, 1991), Prospective and Retrospective Memory Questionnaire (PRMQ) (Crawford, Smith, Maylor, Della Sala & Logie, 2003), Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) (Roth, Isquith, & Goia, 2005)

Statistics

Comparisons between group A and group B at each assessment and within groups were performed. Non-parametric statistics were applied as Shapiro-Wilk test showed that our data were not normally distributed. We used U-Mann Whitney test to study differences between groups (independent samples). For within-group analyses we used Signed-rank Wilcoxon test for paired samples. For these analyses we also used Spearman correlation to study the relationship between next-of-kin reports and patient's reports on functional questionnaires for controlling deficit awareness.

All statistical analyses were performed with "R" (r-project). The level of significance was set at $p < 0.05$. We used Cohen's d to calculate effect size when appropriate.

Results

Sample characteristics

Demographic variables were analyzed, and no significant differences were found between group A and group B regarding gender, education, age at stroke, time since stroke and type of stroke (see Table 1).

Between groups comparison at the time point of hospital discharge revealed similar scores on all tests (see Table 2). However, significant differences were found between groups A and B at t1 in RAVLT Recognition (p=0.009; d=0.9), PMR (p=0.02; d=0.9) and Hit Response of CPT-II (p=0.035; d=0.8), where Group A performed significantly better than Group B on these three tests. Additional tests performed at t1 did not find significant differences between Group A and Group B (see Table 3). Finally, no differences were found across individuals in a group (within-group analysis) when comparing them at t0 and t1 (see Table 4).

Table 2. Between groups differences in tests at IG discharge (t0)

	Grupo A n=13	Grupo B n=17	*p*
Digit Forward	5.62 (1.19)	5.65 (1.41)	0.983
Digit Backwards	4.15 (1.07)	4.06 (1.20)	0.811
TMTA	89.7 (111)	66.8 (49.4)	0.867
TMTB	102 (57.2)	129 (65.4)	0.257
Stroop (Inhibition)	4.50 (10.3)	0.67 (6.71)	0.383
Digit Symbol	52.4 (15.7)	40.8 (18.1)	0.229
Letter-Number Seq.	9.15 (2.94)	9.64 (2.84)	0.434
RAVLT Learning	47.9 (12.0)	42.6 (8.90)	0.224
RAVLT Long Term	10.4 (3.84)	8.35 (4.40)	0.239
RAVLT Recognition	12.6 (2.69)	12.1 (2.75)	0.538
PMR	43.8 (15.5)	34.5 (13.9)	0.107
CPT Hit Response	57.1 (9.75)	61.1 (15.2)	0.573
CPT Omissions	75.7 (54.1)	71.1 (40.2)	0.751
CPT Commissions	49.9 (10.5)	50.5 (11.9)	0.751

(*) Significance $p < 0.05$

Values expressed in mean (sd)

Table 3. Between groups differences in tests at recruitment (t1)

	Group A n=13	Group B n=17	*p*	*d*
Digit Forward	5.31 (1.44)	5.24 (1.35)	0.948	0,05
Digit Backwards	4.23 (1.09)	4.00 (1.22)	0.594	0,20
TMTA	51.9 (36.4)	49.6 (26.3)	0.785	0,07
TMTB	104 (58.5)	101 (47.9)	0.828	0,06
Stroop (Inhibition)	1.27 (8.81)	-2.07 (7.32)	0.310	0,43
Digit Symbol	56.6 (19.5)	47.3 (15.9)	0.210	0,54
Letter-Number Seq.	8.54 (2.44)	8.25 (3.00)	0.658	0,10
RAVLT Learning	47.0 (8.55)	42.4 (11.6)	0.142	0,45
RAVLT Long Term	10.1 (2.81)	7.82 (3.80)	0.092	0,68
RAVLT Recognition	12.8 (2.70)	9.35 (4.42)	0.009*	0,95
PMR	46.1 (12.3)	34.4 (13.2)	0.020*	0,94
CPT Hit Response	49.6 (9.06)	61.2 (16.5)	0.035*	0,85
CPT Omissions	50.5 (12.2)	57.8 (26.4)	0.373	0,34
CPT Commissions	52.0 (15.5)	50.7 (10.3)	1	0,10

(*) Significance $p < 0.05$

Values expressed in mean (sd)

Table 4. Differences between hospital discharge and recruitment

	Group A (n=13)			Group B (n=17)		
Tests	t0	t1	*p*	t0	t1	*p*
Digit Forwards	5.62 (1.19)	5.31 (1.44)	0.395	5.65 (1.41)	5.24 (1.35)	0.38
Digit Backwards	4.15 (1.07)	4.23 (1.09)	0.979	4.06 (1.20)	4.00 (1.22)	0.72
TMTA	89.7 (111)	51.9 (36.4)	0.626	66.8 (49.4)	49.6 (26.3)	0.42
TMTB	102 (57.2)	104 (58.5)	1	129 (65.4)	101 (47.9)	0.24
Stroop	4.50 (10.3)	1.27 (8.81)	0.523	0.67 (6.71)	-2.07 (7.32)	0.43
Symbol Digit	52.4 (15.7)	56.6 (19.5)	0.518	40.8 (18.1)	47.3 (15.9)	0.37
Letter-Number Seq	9.15 (2.94)	8.54 (2.44)	0.756	9.64 (2.84)	8.25 (3.00)	0.12
RAVLT Learning	47.9 (12.0)	47.0 (8.55)	0.817	42.6 (8.90)	42.4 (11.6)	0.50
RAVLT Long Term	10.4 (3.84)	10.1 (2.81)	0.587	8.35 (4.40)	7.82 (3.80)	0.66
RAVLT Recognition	12.6 (2.69)	12.8 (2.70)	0.854	12.1 (2.75)	9.35 (4.42)	0.05
PMR	43.8 (15.5)	46.1 (12.3)	0.837	34.5 (13.9)	34.4 (13.2)	1
CPT HitR	57.1 (9.75)	49.6 (9.06)	0.151	61.1 (15.2)	61.2 (16.5)	0.97
CPT-Omissions	75.7 (54.1)	50.5 (12.2)	0.240	71.1 (40.2)	57.8 (26.4)	0.51
CPT-Comissions	49.9 (10.5)	52.0 (15.5)	0.970	50.5 (11.9)	50.7 (10.3)	0.85

(*) Significance $p < 0.05$

Values expressed in mean (sd)

Analyses of next-of-kin and patient's report in rating-scales showed positive and significant correlations between both groups (PCRS r= 0.57; p<0.0001; RSAB r=0.52; p<0.0001; PRMQ r=0.24, p=0.015; BRIEF-A r=0.37, p=0.0001).

Study 1. Within-group analyses

Within groups analyses revealed no differences between t1 and t2, and neither between t1 and t3 nor between t2 and t3 (see Appendices Tables A1, A2 & A3). Within group significant differences were found in the decrease of scores in PMRQ in group A between t1 and t4 (p=0.02, d=0.5) (see Table 5).

Table 5. Differences throughout the study

	Group A				Group B			
Questionnaires	t1	t4	*p*	*d*	t1	t4	*p*	*d*
PCRS	124 (20.1)	131 (14.5)	0.35	0,44	126 (18.1)	125 (16.6)	0.59	0,03
RSAB	20.2 (11.0)	14.6 (9.18)	0.15	0,57	21.5 (7.23)	18.8 (7.53)	0.10	0,37
PRMQ	32.5 (12.2)	25.8 (12.2)	0.02*	0,56	31.9 (9.07)	31.0 (9.08)	0.11	0,10
BRIEF-A	110 (25.1)	102 (18.9)	0.45	0,37	111 (25.4)	112 (24.5)	0.70	0,05

(*) Significance $p < 0.05$
Values expressed in mean (sd)

This difference remained at follow-up, since mean differences between t4 and t5 in PMRQ were not statistically significative (p > 0.05) (see Table 6):

Table 6. Follow-up within group differences

	Group A			Group B		
Questionnaires	t4	t5	*p*	t4	t5	*p*
PCRS	131 (14.5)	129 (17.1)	0.73	125 (16.6)	129 (14.3)	0.54
RSAB	14.6 (9.18)	15.2 (9.33)	0.81	18.8 (7.53)	20.8 (9.66)	0.49
PRMQ	25.8 (12.2)	26.5 (10.5)	0.57	31.0 (9.08)	31.4 (10.7)	0.97
BRIEF-A	102 (18.9)	102 (20.8)	0.79	112 (24.5)	112 (27.5)	0.83

(*) Significance $p < 0.05$
Values expressed in mean (sd)

Also, results showed significant differences between t1 and t5 in RAVLT Learning in group B (p=0.03; d=0.5). (See Table 7).

Table 7. Differences between recruitment and follow-up

	Group A				Group B			
Test	t1	t5	*p*	*d*	t1	t5	*p*	*d*
Digit Forwards	5.31 (1.44)	5.69 (1.03)	0.34	0,32	5.24 (1.35)	6.00 (1.00)	0.05	0,66
Digit Backwards	4.23 (1.09)	4.46 (1.05)	0.45	0,22	4.00 (1.22)	4.12 (1.11)	0.67	0,10
TMTA	51.9 (36.4)	50.6 (44.5)	0.64	0,03	49.6 (26.3)	54.5 (34.9)	0.91	0,16
TMTB	104 (58.5)	92.4 (35.6)	0.95	0,24	101 (47.9)	137 (119)	0.77	0,41
Stroop	1.27 (8.81)	0.64 (7.99)	1	0,07	-2.07 (7.32)	-1.07 (8.33)	0.77	0,13
Symbol Digit	56.6 (19.5)	66.1 (16.8)	0.24	0,54	47.3 (15.9)	49.7 (18.6)	0.42	0,14
Letter-Number Seq	8.54 (2.44)	8.85 (3.13)	0.93	0,11	8.25 (3.00)	7.94 (3.01)	0.97	0,10
RAVLT Learning	47.0 (8.55)	52.3 (7.77)	0.18	0,67	42.4 (11.6)	48.5 (10.2)	0.03*	0,57
RAVLT Long Term	10.1 (2.81)	10.6 (2.69)	0.69	0,20	7.82 (3.80)	9.65 (3.20)	0.12	0,53
RAVLT Recognition	12.8 (2.70)	12.7 (1.55)	0.30	0,07	9.35 (4.42)	12.1 (2.28)	0.05	0,79
PMR	46.1 (12.3)	47.1 (21.3)	0.62	0,06	34.4 (13.2)	36.8 (12.8)	0.41	0,19
CPTHitR	49.6 (9.06)	45.9 (9.48)	0.32	0,43	61.2 (16.5)	55.1 (15.8)	0.30	0,38
CPT-Omissions	50.5 (12.2)	45.6 (8.59)	0.18	0,48	57.8 (26.4)	54.1 (19.2)	0.30	0,16
CPT-Comissions	52.0 (15.5)	49.1 (10.5)	1	0,22	50.7 (10.3)	55.5 (12.5)	0.34	0,43

(*) Significance $p < 0.05$

Study2. Between group analyses

We found significant mean differences between group A and B between t1 and t2 in RSAB (p=0.02, d=0.8), where group A decrease its mean compared to group B (see Table 8).

Table 8. Between group differences after Phase I

Time frame		Group A (n=13)		Group B (n=17)			
t1 vs t2	Questionnaires	Mean	sd	Mean	sd	*p*	*d*
	PCRS	-0,08	8,12	-0,41	17,80	0,74	0,02
	RSAB	-3,15	3,95	-0,06	3,88	0,03*	0,82
	PRMQ	-4,31	3,99	-0,47	6,10	0,13	0,75
	BRIEF-A	-3,00	11,00	4,65	16,61	0,14	0,55

(*) Significance $p < 0.05$

Initial differences at t1 between groups disappeared in RAVLT Recognition (p=0.347) and PMR (p=0.137). Between-group differences in CPT-II Hit Response remained at t2 (p=0.015; d=0.9) (see Appendices Table A7). Also, group A presented significantly decreased scores in PRMQ than group B (p = 0.03; d=0. 9) (see Table 9) when comparing individuals at t1 and t3.

Table 9. Between groups differences after Phase I and washout

Time frame		Group A (n=13)		Group B (n=17)			
t1 vs t3	Questionnaires	Mean	sd	Mean	sd	*p*	*d*
	PCRS	4,08	8,71	2,41	19,15	0,82	0,11
	RSAB	-4,15	4,39	-0,94	6,71	0,09	0,57
	PRMQ	-5,54	4,86	-0,94	5,48	0,03*	0,91
	BRIEF-A	-3,38	11,57	2,29	17,02	0,34	0,39

(*) Significance $p < 0.05$

Results observed in phase I remained, since between groups analyses at t3 revealed that group A and group B kept the same performance in RAVLT Recognition and PMR, but differences in Hit Response remained (p=0.02; d=1) (see Table 10).

Table 10. Between groups differences before Phase II (t3)

	Group A n=13	Group B n=17	*p*	*d*
Digit Forward	5.62 (0.87)	5.65 (1.50)	0.56	0,03
Digit Backwards	4.54 (0.88)	3.76 (1.25)	0.06	0,72
TMTA	54.1 (58.9)	53.8 (39.0)	0.46	0,01
TMTB	99.9 (45.0)	115 (55.8)	0.64	0,31
Stroop (Inhibition)	-0.45 (8.25)	-0.50 (7.11)	0.60	0,01
Digit Symbol	60.0 (20.3)	48.6 (14.7)	0.09	0,68
Letter-Number Seq.	8.77 (3.35)	8.56 (2.83)	0.72	0,07
RAVLT Learning	50.3 (10.1)	47.0 (11.8)	0.27	0,31
RAVLT Long Term	10.7 (3.30)	9.18 (3.15)	0.12	0,49
RAVLT Recognition	12.6 (2.96)	10.9 (3.22)	0.07	0,58
PMR	47.9 (15.9)	38.5 (14.4)	0.11	0,65
CPT Hit Response	46.9 (7.78)	62.9 (19.6)	0.02*	1,04
CPT Omissions	58.5 (38.6)	60.4 (31.0)	0.95	0,06
CPT Commissions	51.9 (9.26)	47.6 (9.53)	0.34	0,48

(*) Significance $p < 0.05$

Values expressed in mean (sd)

After Phase II, we studied differences between t1 and t4 and found significant mean differences in PCRS (p=0.02, d=0.4), PRMQ (p=0.01, d=1), BRIEF -A (p=0.04, d=0.6) and Digit Symbol (p=0.01, d=1), where group A had greater performance than group B. On the other hand, group B had better evolution in RAVLT Recognition (p=0.02, d=0.6) than group A (see Tables 11 and 12).

Table 11. Between group differences throughout the study

Time frame		Group A (n=13)		Group B (n=17)			
t1 vs t4	Test	Mean	sd	Mean	sd	*p*	*d*
	Digit Forwards	0,69	1,32	0,53	1,42	0,65	0,12
	Digit Backwards	-0,08	0,95	0,41	0,80	0,23	0,58
	TMTA	-1,77	44,06	-5,35	16,75	0,43	0,12
	TMTB	-0,67	43,75	15,08	43,36	0,53	0,38
	Stroop	1,45	6,47	3,14	6,42	0,43	0,27
	Symbol Digit	6,27	4,43	0,88	5,95	0,01*	1
	Letter-Number Seq	1,15	3,21	1,19	1,80	0,44	0,01
	RAVLT Learning	-0,54	8,23	4,06	10,00	0,08	0,51
	RAVLT Long Term	0,38	2,33	2,00	2,67	0,08	0,66
	RAVLT Recognition	-0,31	1,97	2,24	5,24	0,02*	0,63
	PMR	4,62	9,55	4,47	7,04	0,97	0,02
	CPTHitR	-1,76	8,10	-4,03	11,43	0,63	0,23
	CPT-Omissions	-1,57	8,80	0,44	34,12	0,28	0,08
	CPT-Comissions	-5,06	14,77	-0,40	7,89	0,23	0,43

(*) Significance $p < 0.05$

Table 12. Between groups differences throughout the study

Time frame		Group A (n=13)		Group B (n=17)			
t1 vs t4	Questionnaires	Mean	sd	Mean	sd	*p*	*d*
	PCRS	7,54	10,67	-0,59	21,25	0,02*	0,48
	RSAB	-5,54	5,32	-2,71	5,68	0,17	0,53
	PRMQ	-6,62	4,96	-0,88	5,95	0,01*	1
	BRIEF-A	-8,00	17,12	1,24	11,36	0,04*	0,68

(*) Significance $p < 0.05$

Group B showed significant mean differences between t3 and t4 compared with group A in Digit Backwards (p=0.01, d=1) and Hit R (p=0.01, d=0.9) (see Table 13).

Table 13. Between groups differences after Phase II

Time frame		Group A (n=13)		Group B (n=17)			
t3 vs t4	Test	Mean	sd	Mean	sd	*p*	*d*
	Digit Forwards	0,38	0,65	0,12	1,05	0,24	0,31
	Digit Backwards	-0,38	0,96	0,65	0,79	0,01*	1
	TMTA	-3,92	11,12	-9,47	24,29	1,00	0,29
	TMTB	-7,00	63,90	-0,07	66,35	0,98	0,11
	Stroop	3,18	7,69	1,00	2,56	0,36	0,43
	Symbol Digit	2,55	3,45	-0,06	7,26	0,76	0,44
	Letter-Number Seq	0,92	1,44	0,88	2,22	0,86	0,03
	RAVLT Learning	-3,85	9,03	-0,53	8,66	0,23	0,39
	RAVLT Long Term	-0,23	2,24	-0,94	6,74	0,35	0,14
	RAVLT Recognition	-0,08	4,13	0,88	3,60	0,36	0,26
	PMR	2,77	6,19	1,65	10,23	0,92	0,13
	CPTHitR	1,02	3,74	-6,25	10,12	0,01*	0,93
	CPT-Omissions	-9,57	32,83	-2,50	16,36	0,88	0,30
	CPT-Comissions	-5,03	8,39	3,10	10,15	0,05	0,90

(*) Significance $p < 0.05$

Finally, differences observed at t1 between groups disappeared at t4 (see Table 14).

Table 14. Between groups differences after Phase II (t4)

Test	Group A n=13	Group B n=17	*p*
Digit Forward	6.00 (1.08)	5.76 (1.56)	0.453
Digit Backwards	4.15 (0.80)	4.41 (1.18)	0.525
TMTA	50.2 (65.8)	44.3 (36.6)	0.258
TMTB	103 (64.5)	127 (82.5)	0.714
Stroop (Inhibition)	2.73 (7.24)	0.00 (7.33)	0.311
Digit Symbol	66.2 (18.0)	48.6 (18.6)	0.022
Letter-Number Seq.	9.69 (3.73)	9.44 (3.16)	0.877
RAVLT Learning	46.5 (6.46)	46.5 (9.37)	0.834
RAVLT Long Term	10.5 (2.26)	9.82 (2.98)	0.735
RAVLT Recognition	12.5 (3.50)	11.6 (2.94)	0.189
PMR	50.7 (19.3)	38.8 (13.3)	0.082
CPT Hit Response	47.9 (7.94)	57.2 (15.3)	0.114
CPT Omissions	49.0 (9.07)	59.2 (34.0)	0.953
CPT Commissions	46.9 (7.47)	51.1 (9.88)	0.412

(*) Significance $p < 0.05$

Values expressed in mean (sd)

At follow-up, results showed significant mean differences between t4 and t5 in Digit Backwards (p=0.04; d=0.8) where mean in Group B decreased and mean in Group A increased. The rest of the scores showed no differences between groups in tests and neither in questionnaires (see Tables 15 and 16):

Table 15. Evolution differences at follow-up

Time frame		Group A (n=13)		Group B (n=17)		
t4 vs t5	Test	Mean	sd	Mean	sd	*p*
	Digit Forwards	-0,31	0,63	0,24	0,97	0,06
	Digit Backwards	0,31	0,75	-0,29	0,77	0,05
	TMTA	0,46	25,51	10,41	26,76	0,56
	TMTB	-10,83	36,16	-8,23	71,62	0,62
	Stroop	-2,09	5,30	-1,50	5,36	0,70
	Symbol Digit	-0,09	4,76	0,13	5,33	1,00
	Letter-Number Seq	-0,85	2,08	2,94	15,87	1,00
	RAVLT Learning	5,85	7,21	2,06	8,43	0,13
	RAVLT Long Term	0,15	1,77	-0,18	2,48	0,66
	RAVLT Recognition	0,15	3,74	0,47	3,34	0,67
	PMR	-3,62	9,67	-2,06	7,83	0,63
	CPTHitR	-2,20	4,59	-0,20	6,01	0,38
	CPT-Omissions	-3,57	7,74	-6,35	26,27	0,92
	CPT-Comissions	3,02	8,18	3,26	9,09	0,79

(*) Significance $p < 0.05$

Table 16. Between groups mean differences after follow-up

Time frame		Group A (n=13)		Group B (n=17)		
t4 vs t5	Questionnaires	Mean	sd	Mean	sd	*p*
	PCRS	-2,54	7,41	3,71	16,10	0,31
	RSAB	0,62	3,95	2,06	5,19	0,47
	PRMQ	0,69	4,89	0,35	6,65	0,61
	BRIEF-A	0,08	10,39	-0,76	11,46	0,54

(*) Significance $p < 0.05$

Discussion

The aim of this study was to determine whether chronic stroke patients could benefit from a home-based CCT. Pre-treatment data showed no differences in both groups within the time between discharge and recruitment, so cognitive performance was stable before therapy. Comparison of pre and post-treatment results showed benefit in both groups after both treatments. Additionally, we obtained positive evolution in Group A after CCT-C in rating measures and Group B after CCT-non-C in some performance-based measures.

Both groups showed better cognitive outcome after CCT (CCT-C and CCT-non-C). We found similar results as Westerberg et al (2007), where chronic stroke patients improved after CCT in working memory tests and fewer cognitive problems in daily life in rating measures. In Johansson & Tornmalm (2010) and Lebowitz et al (2012) authors found positive effects of CCT in neuropsychological and self-rating measures in chronic patients with acquired brain injury. However, in Nyberg et al (2018) there was no improvement in neuropsychological tests, and participants improved their performance on trained tasks. Poulin et al (2012) concluded that the improvement after CCT may be caused by the remediation of cognitive skills. Other authors shed light over different factors of the CCT that could explain this benefit, as the fact of participating in a study helps patients to develop self-awareness and therefore get to know better their own limitations (Buitenberg, Murre & Ridderinkhof, 2012). Spikman et al (2010) stated that the immediate feedback of CCT leads to a better sense of self-efficacy. It has been stated that home-based CCT must be supervised in order to create benefit (Cicerone et al, 2019). Since both groups got benefit after both types of CCT, we propose, based on the characteristics of both treatments, and on previous studies by other authors (van de Ven et al, 2017) that our sham treatment might have functioned as a therapeutic protocol. Both CCT programs tested in this study were home-based, provided feedback and were

supervised, with a therapist actively involved in giving support and keeping participant's adherence. As a matter of fact, participants showed good adherence with both types of CCT (Group A completed a mean of 26 sessions of CCT-C 24 of CCT-non-C, while Group B completed a mean of 25 sessions of CCT-C and 19 of CCT-non-C).

We administered each type of CCT for six weeks (30h in total, 5 sessions of CCT per week), while the total time spent in both treatments was 6 months. Others have studied CCT dose before. A meta-analysis carried out by Lampit, Hallock & Valenzuela (2014) recommended CCT no more than 3 per week, but this studies just included healthy adults. Others studied patients with mild cognitive decline and risk of dementia and found that total intervention time did not mediate efficacy of treatments (Coyle, Traynor & Solowij, 2015). Our preliminary results point that the amount of time needed for the treatments to create benefit, and for it to be reflected in cognitive measures, is higher than expected. More research is needed to state CCT dose effects in chronic stroke patients with cognitive deficit.

We observed that Group A showed greatest benefit regarding functional measures of attention, memory, and executive functioning on daily life activities meanwhile, group B did not show the same benefit. The difference between those groups was the order of treatments. Group A did first the CCT-C, followed by the sham CTC-non-, while Group B did receive those same protocols in reversed order. The CCT-C used in this study was not only customized for patient´s cognitive performance, it was also multidomain, as it attempted to train attention, memory and executive functions. Others have stated that training multiple cognitive domains is necessary to promote generalization of abilities beyond the trained task, and to achieve better performance on daily life tasks (Green & Bavelier, 2008; Sohlberg & Mateer, 2001). Accordingly, we suggest that receiving first a CCT-C say here when could be causing the improvement in functional measures, and it

might potentiate the results of subsequent CCTs, including our sham as described here. This would explain why Group A got more benefit regarding functional measures. Furthermore, all participants received CCT-C during admission in post-acute stage of stroke, so it is formally possible that the effectiveness of the CCT-non-C treatment studied here was the result of some synergistic effect resulting from being given after the post-acute CCT-C treatment. Future studies should focus on which features of CCTs tested here may be responsible of such benefits, and what temporal sequences for the administration of CCT treatments may result in synergistic benefits as the ones described above.

There were some limitations in our study. The absence of a passive control group limits the inferences that can be made about whether the CCT is creating a differential benefit compared to not to do any treatment at all. To avoid initial differences, baseline assessments should have been done before the randomization of participants in two groups. Also, repeated measures along time enhanced the possibility of learning effect in tests. The variable of multidomain treatment was not properly isolated. We recruited patients diagnosed of moderate to severe stroke, who may not be representative of community-dwelling individuals with stroke, representing sample bias. Finally, we did not relate assessment measures to the performance on cognitive training tasks, which could have helped to determine the "patient profile" that fits better to cognitive treatment.

Conclusions

This study demonstrates that home-based computerized cognitive training improves cognitive and functional performance in chronic stroke patients. Customized and multidomain home-based computerized cognitive training seems to be related to the benefits in subjective complaints. Therefore, to best optimize the potential benefits of

CCT therapies, further research will be needed to establish key features to be included in the CCTs, as well as the temporal sequences and frequencies administration, to obtain the best neuropsychological outcome in chronic stroke patients.

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Estudio 2 (Artículo 2):

Publicado en: Journal of the International Neuropsychological Society

Páginas (inicial y final): 1-12

Editorial: Cambridge University Press

País de publicación: Estados Unidos

ISSN: 1355-6177

Base: SCI

Área: Psicología Clínica

Índice de Impacto: 3.098

Cuartil: Q1

Gil-Pagés, M., Sánchez-Carrión, R., Tormos, J., Enseñat-Cantallops, A., & García-Molina, A. (2019). A Positive Relationship between Cognitive Reserve and Cognitive Function after Stroke: Dynamic Proxies Correlate Better than Static Proxies. Journal of The International Neuropsychological Society, 25(09), 910-921. doi: 10.1017/s1355617719000638

A positive relationship between cognitive reserve and cognitive function after stroke: Dynamic proxies correlate better than static proxies

(Accepted manuscript)

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Word count for the abstract: 217

Word count for the manuscript: 4.738

Abstract

Objectives: How brain damage after stroke is related to specific clinical manifestation and recovery is incompletely understood. We studied cognitive reserve (CR) in stroke patients by two types of measurements: (i) objectively verifiable static proxies (i.e., education, occupational attainment), and (ii) subjective, dynamic proxies based on patient testimony in response to a questionnaire. We hypothesized that one or both of these types of CR measurements might correlate positively with patient cognitive performance during the post-acute and chronic phases of recovery.

Method: Thirty-four stroke patients underwent neuropsychological assessment at 2, 6 and 24 months after stroke onset. In chronic stage at 24+ months, self-rating assessments of cognitive performance in daily life and social integration were obtained. CR before and after stroke was estimated using static proxies and dynamic proxies were obtained using the Cognitive Reserve Scale (*CRS-Pre-stroke, CRS-Post-stroke*).

Results: CRS-Pre-stroke and CRS-Post-stroke showed significant mean differences**.** Dynamic proxies showed positive correlation with self-assessment of attention, metacognition, and functional ability in chronic stage**.** In contrast, significant correlations between static proxies and cognitive recovery were not found.

Conclusions: Dynamic proxies of CR were positively correlated with patients' perception of their functional abilities in daily life. To best guide cognitive prognosis and treatment, we propose that dynamic proxies of CR should be included in neuropsychological assessments of patients with brain damage.

Key words: brain injury, daily living, self-assessment, prognosis, cognition, neuropsychological tests

INTRODUCCTION

Stroke is a focal neurological disorder of abrupt development due to a pathological process in blood vessels and is the most common cerebrovascular disease that causes brain damage (Donaghy, 2009). The two main types are ischemic and hemorrhagic stroke (Lezak, 2012). A stroke caused by lack of blood reaching part of the brain due to the obstruction of blood vessels is called an ischemic stroke. Hemorrhagic stroke is either a brain aneurysm burst or a weakened blood vessel leak, where blood spills into or around the brain and creates swelling and pressure, damaging cells and tissue in the brain (Sacco et al., 2013).

Stroke stages of evolution are classified following different criteria (e.g. duration of illness or rehabilitation process). The duration of illness criterion establishes (i) acute phase in the first week after stroke, (ii) sub-acute phase in the second to the fourth weeks after stroke, (iii) post-acute phase from the first to the sixth month after stroke, and (iv) chronic phase more than six months after stroke onset (Bouffioulx, Thonnard, Arnould & Vandervelde, 2010; Elsner, Kugler, Pohl & Mehrholz, 2013). The rehabilitation process criterion proposes (i) acute stage, which comprises the initial period of hospitalization in specialized units to manage cerebrovascular disease under the direction of neurologists, (ii) post-acute stage, where patients who survive the acute phase of stroke achieve neurological stabilization of their condition, and (iii) chronic stage where the objectives are the optimal reinsertion at family, social and work levels (Moyano, 2010). In the present study, post-acute stage was defined as 2-6 months post-stroke (including in-patient and out-patient rehabilitation phases), while chronic stage was defined as > 12 months post-stroke (during in-home phase).

Stroke patients may suffer cognitive impairment with alteration of behavioral regulation (Teasell & Hussein, 2016), including decreases in attention, memory, and executive

function (Ma, Chan & Carruthers, 2014). The severity of lesion and the location of brain injuries caused by the stroke may play prominent roles in the recovery process. However, it is not possible to make prognoses based just on these factors since clinical practice shows high inter-individual variability in post-stroke recovery. This inter-individual disparity could be explained through the reserve construct (Stern, 2009; Umarova, 2017).

The construct of reserve is generally explained through two theoretical models: brain reserve and cognitive reserve. The brain reserve or passive model proposes that people can assume a certain level of brain damage, past which symptoms would be manifest (Satz, 1993). In this model, the brain's potential to cope with brain damage is based on anatomical measurements (e.g. cerebral volume, cranial circumference, or brain-ventricle ratio). Cognitive reserve (CR) or active model refers to the influence of exposure to daily life events and environmental factors which shape network efficiency, processing capacity, and flexibility (Barulli & Stern, 2013; Stern, 2002). This active model is subdivided in two components: neural reserve and neural compensation (Stern, 2016). Neural reserve comprises pre-existing processes, networks more likely to withstand harm without altering function because they are more effective or have greater capacity. Neural compensation comprises alternative circuits that help to maintain dexterity in the execution of daily actions in the presence of brain damage.

CR is a hypothetical construct and many CR proxies have been proposed. These measures include different types of data that may be considered static or dynamic. Static proxy measures are objectively verifiable data with the potential to remain stable over a period of time. In contrast, dynamic proxy measures are more subjectively gauged, with greater potential for variability over the same time frame, including various forms of participation in cognitively stimulating hobbies and leisure activities (Malek-Ahmadi et al., 2017).

Dynamic proxies are usually measured through frequency questionnaires of participation in such activities.

There are many studies of CR in Alzheimer's disease (AD), where education and occupation are the main CR proxies (Valenzuela & Sachdev, 2006). It has been considered that these proxies foster new cognitive strategies (Jones et al., 2011). Sánchez, Rodríguez & Carro (2002) found that these proxies had a protective role in patients with AD. Similar results have been observed in other AD studies (Garibotto et al., 2008; Stern, 1994; Stern, Albert, Tang & Tsai, 1999) and also in Parkinson's disease (Hindle, Martyr & Clare, 2010). CR has been explored in traumatic brain injury too, finding positive effects of years of education on recovery of cognitive functions (Kesler, Adams, Blasey, & Bigler, 2003; Schneider et al, 2014; Sumowski, Chiaravalloti, Krch, Paxton, DeLuca, 2013). Alosco et al. (2017) studied patients with chronic traumatic encephalopathy and found that occupational attainment complexity predicted later age at cognitive deficit onset. Literature shows positive effects of education in stroke recovery (Elkins et al., 2006), cognitive change after stroke and transitory ischemic attack (Sachdev et al.,2004) and favorable post-stroke survival in mild to moderate ischemic stroke (Ojala-Oksala et al., 2012). Zieren et al. (2013) focused on the importance of lesion severity, pointing to education as a predictor of better cognitive performance but only in those cases with low or moderate severity.

There are also many studies of dynamic proxies of CR in different pathologies. Participation in leisure activities is positively related to better cognitive functioning in patients with multiple sclerosis (Sumowski et al., 2013) and AD (Bennet, Schneinder, Tang, Arnold & Wilson, 2006), and is associated with reduced risk of developing dementia (Scarmeas, Levy, Tang, Many & Stern, 2001). One study focused on CR dynamic proxies and stroke (Verguese et al., 2009) found that participation in cognitive

leisure activities was associated with reduced risk of vascular cognitive impairment in older adults.

In summary, prior studies support the notion that higher scores on cognitive reserve proxy measures (whether static or dynamic) are generally associated with better cognitive performance. However, while CR has been widely explored in dementia, just a few studies have explored CR in acquired brain injury (Nunnari, Bramanti & Marino, 2014).

The main objective of the present study was to investigate the relationship between cognitive reserve and cognitive change over different stages of stroke. We have recruited 34 chronic stroke patients that were transferred to the neurorehabilitation hospital, Institut Guttmann, after the acute phase of stroke. They have been studied retrospectively when they were in post-acute stage (2-6 months, post-stroke) and after recruitment, in chronic stage (>12 months post-stroke). CR has been estimated through proxy measures previously published in the literature (static proxies: years of formal education and occupation attainment; dynamic proxies: engagement in cognitively stimulating activities). Because it is thought that different proxy measures of cognitive reserve may have independent impacts on rehabilitation (Stern, 2006), we chose to study them separately. In addition, we will separate dynamic proxy measurements referring to the time before the stroke ("pre- stroke cognitive reserve" or Pre-CR) from those referring to chronic stage of stroke ("post-stroke cognitive reserve" or Post-CR).

Cognitive function has been evaluated through information from medical records (neuropsychological assessments done at hospital admission and discharge) and through a neuropsychological assessment following recruitment to the study. The main goal was to study dynamic proxy measures before and after stroke onset and compare relationships if any between Pre- and Post-CR graded scales and static proxy measures with cognitive change in post-acute and chronic stages. We tested the following hypotheses: 1) the

frequency of activities assessed by dynamic proxies of CR decreases as a result of stroke; 2) higher pre-CR and static proxy measures correlate with rate of cognitive change after stroke in post-acute and chronic stages; 3) higher post-CR and static proxy measures correlate with better cognitive performance in patients with chronic stage stroke.

To our knowledge, this is the first study that separates pre-stroke CR from post-stroke CR, and the first to include both static and dynamic proxies of CR to explore the relationship between them and cognitive change after stroke.

METHOD

Participants

At Institut Guttmann, a neurorehabilitation hospital, a review was carried of clinical records of patients who had an ischemic or hemorrhagic stroke between August 2014 and August 2016. Those who met the inclusion criteria were selected as candidates for recruitment.

Inclusion criteria were 1) age over 18 years old, 2) to have a diagnosis of first-ever stroke, 3) to be in chronic stage of evolution at the moment of recruitment (>12 months after stroke), and 4) cognitive impairment was diagnosed by neuropsychological assessment upon hospital admission. Exclusion criteria were 1) diagnosis of aphasia, 2) to be suffering any psychiatric condition, or 3) history of substance abuse.

Thirty-four former patients from Institut Guttmann (15 women) between the ages of 28 and 64 years ($\acute{x}$ =49.7; σ=8.16) diagnosed with stroke (hemorrhage=17; ischemic=17) were recruited. At the time of stroke, patients were between 26 and 62 years old ($\acute{x}$ =47.5; σ=8.37; <50 =20, ≥50=14). See Table 1 for distribution of sample demographics. All

participants gave informant consent and were able to understand the implications of the study.

Table 1. Distribution of the sample

	Male (n=19)	Female (n=15)
Age at stroke (*)	50.05 (8.24)	44.46 (7.7)
Age at recruitment (*)	51.73 (8.13)	46.53 (7.7)
Type of stroke		
Hemorrhagic	9	8
Ischemic	10	7
Years since stroke (*)	1.88(0.45)	2.07(0.47)

(*) Data expressed as mean years and standard deviation

All recruited patients were initially assessed with a neuropsychological battery upon admission to the rehabilitation hospital ($\dot{\bar{x}}$ = 1.5 months of evolution; σ= 0.83), at the time of hospital discharge ($\dot{\bar{x}}$ = 5.9 months of evolution; σ= 2.1) and they were assessed again at the time of participating in the study ($\dot{\bar{x}}$ = 23.9 months of evolution; σ=5.7).

The study was approved by the Institute Guttmann's Research and Innovation Committee and the Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013).

Procedure

Recruitment included postal, email, and telephone contact of participants. Out of the 91 people contacted, 45 declined to participate, 41 accepted but 7 had to be excluded. Data were obtained from patients' medical records and collected in person during interview, using questionnaires and neuropsychological tests (see Fig. 1).

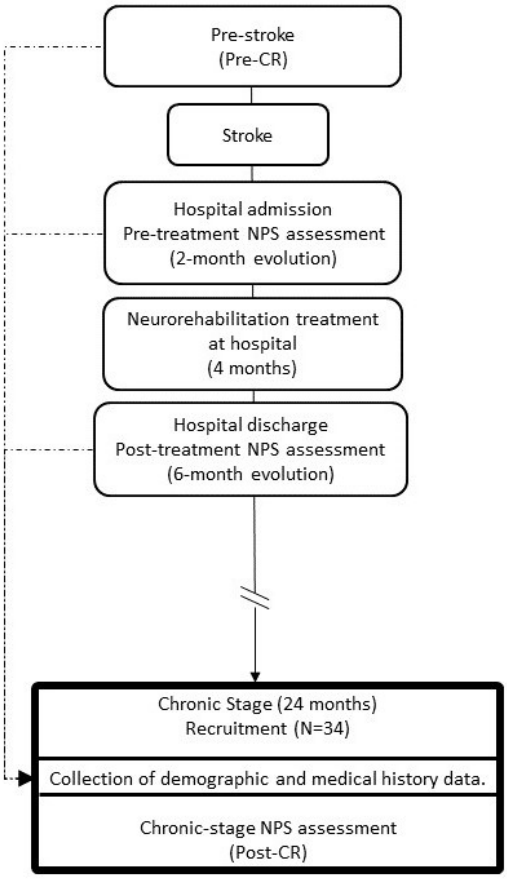


Figure 1. Study Flow

Measures

Cognitive reserve static proxies

Education was operationally defined as self-reported years of education (< 8 years – primary education n=11, 8-12 years – compulsory secondary education and Bachillerato n=17, >12 years – University education n=6), according to the structure of the education system in Spain (eacea.ec.europa.eu, 2013). Occupation complexity was operationally defined as level of occupation according to the National Catalogue of Professional Qualifications of Spain (Incual.mecd.es, 2018) (low n=6, medium n=17 and high n=11).

Cognitive reserve dynamic proxies

Cognitive Reserve Scale (CRS) (León, García-García & Roldán-Tapia, 2014) has been used to compile information of the frequency with which patients do or used to do reserve related activities identified in literature as dynamic proxies. To focus on frequency of participation in lifetime activities, we applied CRS, a measurement scheme previously validated in the Spanish population (León, García-García & Roldán- Tapia, 2011). CRS measures testimonial and remembered accounts of participation across 24 items grouped into four domains: activities of daily living (ADLs), training/formation, hobbies, and social life. In its original version, CRS aims to obtain a measure of reserve focused on healthy adults throughout different stages of life. In the present study, the same items were applied but participants were asked to indicate how often they used to engage in these activities before stroke onset (CRS pre-stroke) and how often they engage nowadays at the chronic stage of the stroke (CRS post-stroke). Therefore, "Pre-CR" represents CRS pre-stroke and "Post-CR" represents CRS post-stroke. The answers were scored in a range from 0 ("never") to 4 ("whenever it is possible") and the total score was based on the sum of all the answers for each patient.

Neuropsychological assessment

Performance-based measures

All participants were evaluated at the time of admission in the neurorehabilitation hospital (pre-treatment assessment) and at discharge (post-treatment assessment), with a neuropsychological battery. The same battery was applied to conduct the chronic stage assessment. We ran confirmatory factorial analysis using cfa() function of "R" (Rosseel, 2018) and we identified three cognitive factors from the battery tests (the methods to do this are further explained below in "Confirmatory Factorial Analysis"):

Attention factor (AT factor): Trail Making Test A (Tombaugh, 2004), reported as the number of seconds required to complete the task; therefore, higher scores mean worse performance. Digit Span Forward subtest from WAIS-III (scored from 0 to 9) (Wechsler, 1997).

Memory factor (M factor): Sub-scores from RAVLT (Schmidt, 1996), which assesses rate of learning (scored from 0 to 75 words), long-term verbal memory and verbal recognition (both scored from 0 to 15), where higher scores mean better performance.

Executive Functions factor (EF factor): PMR test (a Spanish version of FAS test) (Fortuny, 1999) which assesses phonological verbal fluency (scored as amount of words generated) and Digit Span backward (scored from 0 to 8) and Letter Number Sequencing (scored from 0 to 21) from WAIS-III, which assess verbal working memory.

Since three temporal moments have been studied (admission, discharge, and chronic stage) three cognitive factors were created for each moment in order to study cognitive change. Change in cognitive factors was obtained calculating the difference of grades in cognitive factors between discharge and admission and between chronic stage and discharge.

Self- rating scales applied in chronic stage of stroke

In addition to the neuropsychological assessment, we assessed self-rating measures to recover information about how participants perceived their performance in daily life in chronic stage of stroke.

Functional disability was measured using the Patient Competency Rating Scale (PCRS) (Prigatano & Fordyce, 1986) which comprises 30 items, spanning a range of everyday situations and behaviors, and for each item, the patient must make judgments about their own level of competency. The scores range from 1 (”I cannot do it”) to 5 (”I can do it

easily"). Additionally, the Community Integration Questionnaire (CIQ) (Willer, Rosenthal, Kreutzer, Gordon & Rempel, 1993) was used, a self-rating scale developed to measure community integration that comprises three subscales (home integration, social integration, and productive activities) The scores range from 0 to 29; a high score indicates greater integration, and a low score reflects less integration.

Also, the following self-rating questionnaires were applied to measure frequency of subjective cognitive complaints: Rating Scale for Attentional Behavior (Ponsford & Kinsella, 1991) measures frequency of attentional difficulties in daily routines and the scores ranges from 0 ("never") to 4 ("always"); Prospective and Retrospective Memory Questionnaire (Crawford, Smith, Maylor, Della Sala & Logie, 2003) evaluates prospective and retrospective memory in the short and long term, with a score range from 1 ("never") to 5 ("always"); and Behavior Rating Inventory of Executive Function – Adult Version (Roth, Isquith & Goia, 2005) assesses frequency of difficulties related to executive functions in day-to-day activities. This questionnaire uses a three-point Likert scale (1 = behavior is never observed to 3 = behavior is often observed).

Analysis

Mean differences in performance-based and self-rating scores, and between CRS-Pre stroke and CRS-Post stroke were examined using Wilcox test. To study the relationship between cognitive reserve variables (dynamic and static) and neuropsychological assessments we used Pearson correlation coefficient r and Kruskal-Wallis test. CRS domains in Pre-stroke and Post-stroke forms have been studied separately. Cohen's d has been used to measure effect size when comparing mean differences with Wilcox test (d=0.2 is considered a small effect size, d=0.5 moderate effect size and d=0.8 strong effect size) ("Effect sizes", 2018). Epsilon squared (ε^2) estimate has been used to calculate effect size in Kruskal Wallis tests ($\varepsilon^2 = 0.04$ weak, $\varepsilon^2 = 0.25$ moderate, $\varepsilon^2 = 0.36$ -0.64 strong)

(Ferguson, 2009). Since our analysis implied multiple comparisons, we used FDR ("False Discovery Rate") correction. Hence, $p < 0.05$ defined statistical significance. We used "R" (R Core Team, 2018) for statistical analyses.

Confirmatory factorial analysis was carried out using lavaan cfa () version 0.6-2 function of "R" (Rosseel, 2018). We used full information maximum likelihood (FIML) for the missing data. We standardized the latent factors, allowing free estimation of all factor loadings. The model fit was acceptable but not excellent ($\chi 2$ (17) = 67.33; $p \leq 0.001$), with a comparative fit index of 0.863 (Iacobucci, 2010) (See Appendices Figure A for a diagram of the model tested).

Cognitive factors were created following CFA. We used raw scores from all neuropsychological tests from each evaluation (admission, discharge and chronic) except from TMT-A since its grades required transformation due to deviations from normality in its native distribution. Descriptive statistics for each test are included in Appendices (Table A).

RESULTS

Study 1. Dynamic proxies of cognitive reserve before and after stroke.

Scores obtained in the four domains of CRS pre-stroke were compared with scores in CRS post-stroke. Wilcoxon test was used to compare mean differences. Influence of gender, age at stroke onset (<50, ≥50), and type of stroke (ischemic or hemorrhage) was studied too. We found significant mean differences when comparing scores of CRS pre-stroke and CRS post-stroke in the ADLs domain (p= 0.006, d=0.64) and in the training / formation domain (p= 0.02, d=0.22). There were no significant differences between CRS

pre-stroke and CRS post-stroke in Hobbies (p= 0.17; d=0.19) nor in Social Life (p=0.70; d=0.07) (see Figures 2, 3, 4 and 5). We did not find mean differences based on demographics (see Table 2).

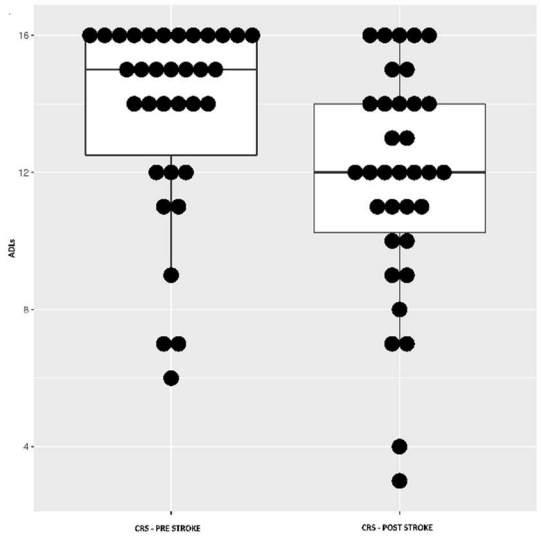


Fig 2. Mean differences between scores in CRS Pre-stroke and scores in CRS Post-stroke in ADLs domain.

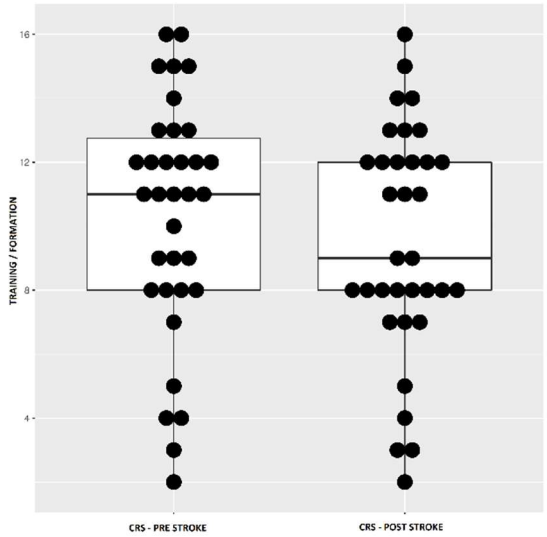


Fig 3. Mean differences between scores in CRS Pre-stroke and scores in CRS Post-stroke in Training/formation domain.

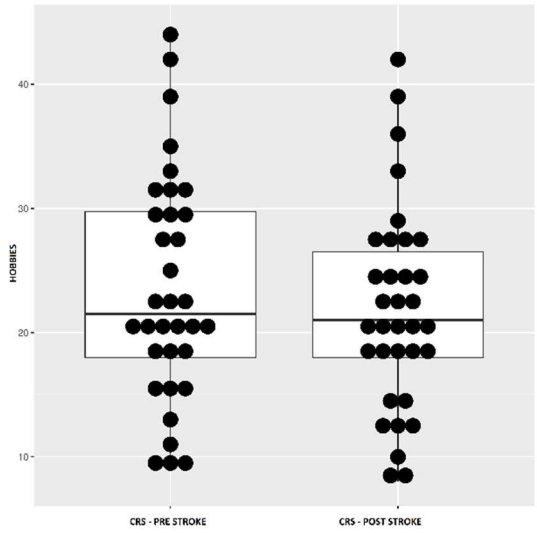


Fig. 4. Mean differences between scores in CRS Pre-stroke and scores in CRS Post-stroke in Hobbies domain.

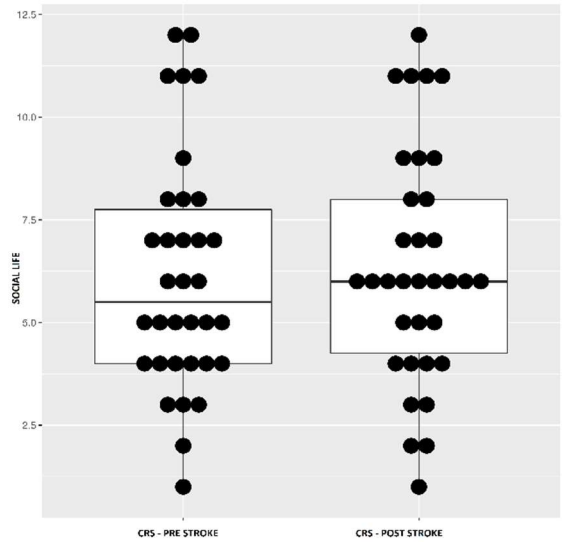


Fig. 5. Mean differences between scores in CRS Pre-stroke and scores in CRS Post-stroke in Social Life domain.

Table 2. Differences between CRS and demographics (Wilcoxon p values)

CRS	Age at stroke onset	Gender	Type of stroke
ADLs	0.74	0.65	0.60
Training/Formation	0.33	0.70	0.31
Hobbies	0.40	0.57	0.84
Social Life	0.94	0.80	0.97

Study 2. CR (Pre-CR and static proxies) and change in cognitive factors between admission-discharge stage and discharge-chronic stage of stroke

Scores in the four domains of *CRS pre-stroke* did not show significant correlations with the difference between the 3 cognitive factors at discharge-admission and chronic-discharge (see Appendices Table B).

We did not find mean differences in the change between cognitive factors based on demographics (gender, age at stroke onset and type of stroke) (see Appendices Table C) nor based on static proxies of cognitive reserve (occupation and years of education) (see Appendices Table D).

Study 3. Post-CR and cognitive functions and performance in daily life in chronic stage

We studied the relationship between CRS-post stroke and cognitive factors in chronic stage. Self-rating measures were studied too. Scores in each of the four domains of CRS-post stroke did not show significant correlations with cognitive factors of chronic stage (see Appendices Table E)

Scores in training/formation of CRS-post stroke showed significant correlation with PCRS (r= 0.469; p=0.029), RSAB (r= - 0.6; p=0.004), BRIEF-Metacognition (r= - 0.468; p=0.029). Sub-scores in Hobbies CRS-post stroke showed significant correlations with RSAB (r= - 0.471; p=0.029) (see Figures 6, 7, 8 and 9).

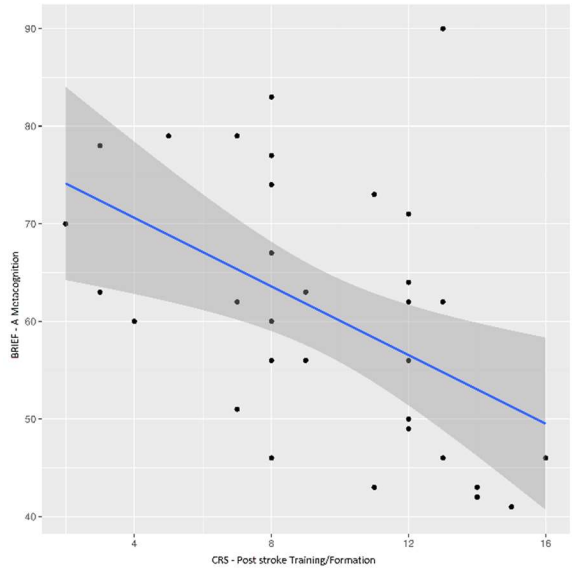


Fig. 6. Correlation between scores in Behavior Rating Inventory of Executive Function – Adult version Metacognition index and scores in CRS-Post stroke Training/Formation domain.

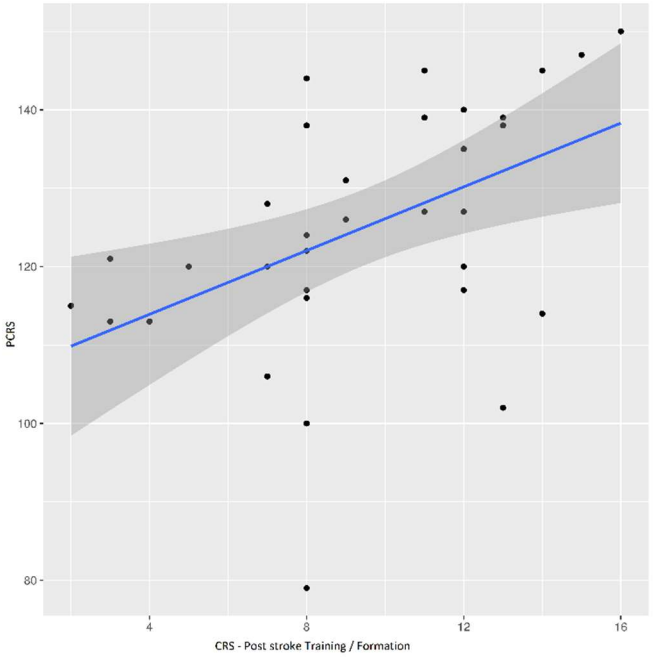


Fig. 7. Correlation between scores in Patient Competency Rating Scale and scores in CRS-Post stroke Training/Formation domain.

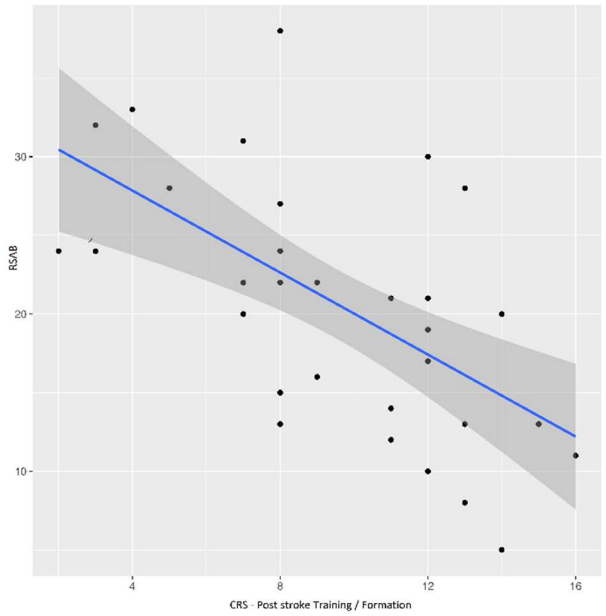


Fig. 8. Correlation between scores in Rating Scale for Attentional Behavior and scores in CRS-Post stroke Training/Formation domain.

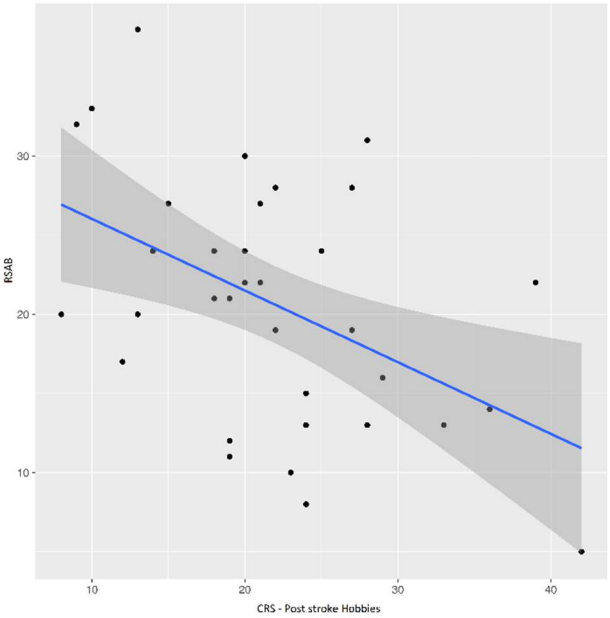
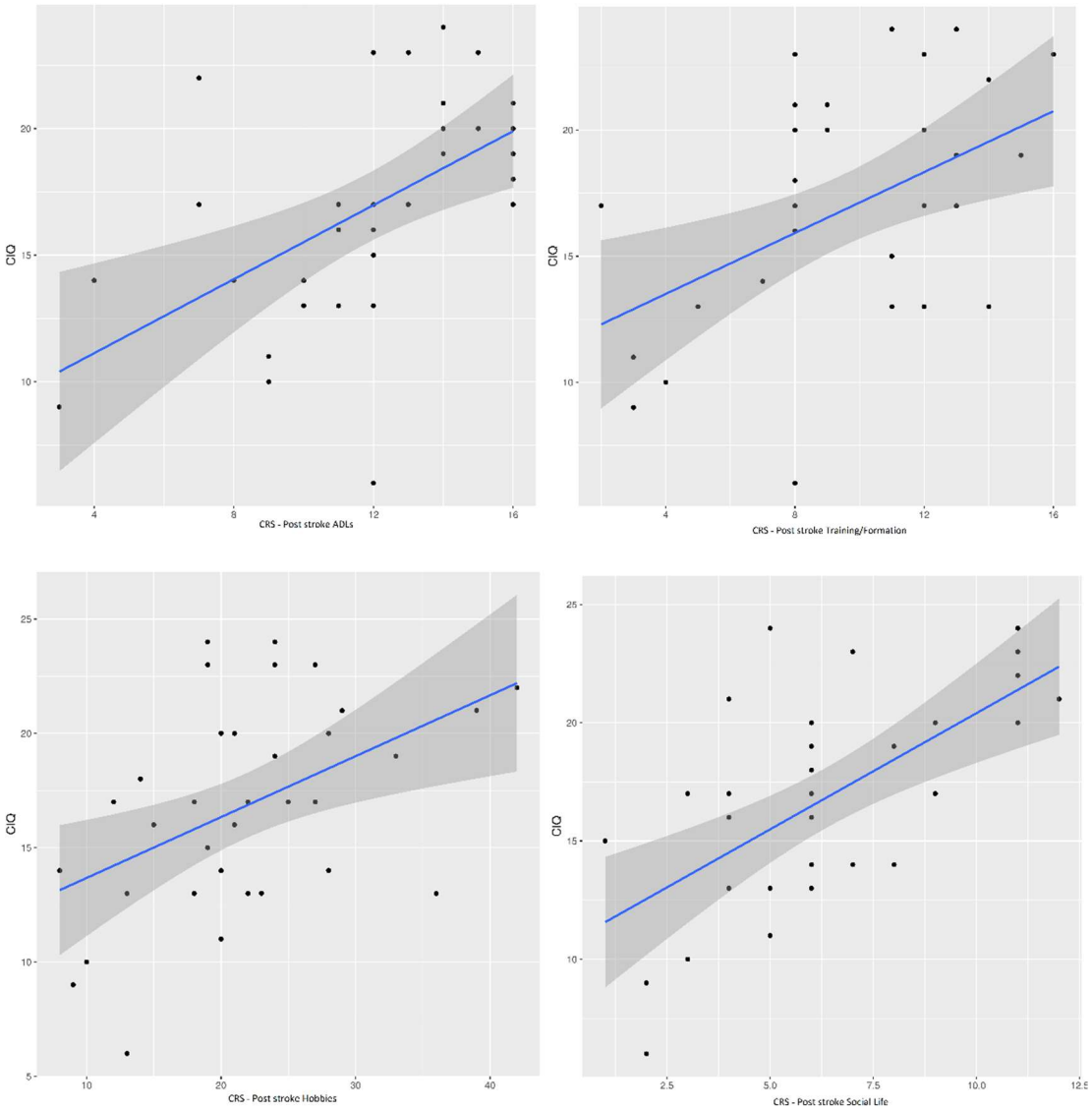


Fig 9. Correlation between scores in Rating Scale for Attentional Behavior and scores in CRS-Post stroke Hobbies domain.

CIQ showed significant correlations with CRS-Post stroke in the four domains: ADLs (r= 0.531; p=0.018), Training/formation (r= 0.475; p=0.029), Hobbies (r= 0.474 ; p=0.029) and Social Life (r= 0.611; p=0.004) (see Figures 10, 11, 12 and 13).



Figs. 10-13. Correlation between Community Integration Questionnaire total score and sub-scores in CRS-Post stroke ADLs domain (Fig 10), Training/Formation (Fig 11), Hobbies (Fig 12) and Social Life (Fig 13)..

No other significant correlations were found between the four domains of CRS-post stroke and self-rating measures (see Appendices Table F).

We also studied mean differences in cognitive factors according to occupation complexity and years of education. The results showed no significant differences in AT Chronic ("Occupation" p = 0,256; ε^2 = 0,180; "Years of education" p = 0,648; ε^2 = 0,076), M Chronic ("Occupation" p = 0,836 ; ε^2 = 0,015; "Years of education" p = 0,836; ε^2 = 0,039) and neither in EF Chronic ("Occupation" p = 0,253; ε^2 = 0,209; "Years of education" p = 0,253; ε^2 = 0,205).

Discussion

We retrospectively studied the relationship between different types of CR proxies and cognitive functions in different stages of post-stroke evolution. The results showed relationships between cognitive reserve and cognitive functioning in chronic stage of stroke. Specifically, we found a positive association between self-rating questionnaires of neuropsychological assessment in chronic stage and Post-CR. On the other hand, we did not find significant relationships between any type of CR proxy included in the study and change on any of 3 categories of cognitive factors we identified from our neuropsychological battery data, at any stage of stroke.

While static CR proxies are resistant to change once a certain stage of life has passed (education during youth and occupation during adult life), the nature of the dynamic proxies makes it possible to start them and to quit at any stage of life. Stroke causes many changes in routine and frequent activities that used to be performed by patients before the stroke (Cott, Wiles & Devitt, 2007). Thus, it makes sense that stroke also affects the frequency of CR dynamic proxies, and because of this possibility we studied the differences between Pre-CR and Post-CR. We found that study participants had reduced their participation in some reserve-related activities, but they tended to maintain the same frequency in others. Our findings indicate that they lower their participation in ADLs, the management of personal, economic and domestic matters, and in training/formation, the

expansion of knowledge and new skills. In contrast, they tend to resume previously chosen hobbies, considered as leisure activities and physical activities, and social life. Other studies have explored the reengagement in daily life activities in chronic stage of stroke. Verberne et al. (2018) studied social participation of stroke patients and found that those more dependent on ADLs were more likely to have less participation in general 2 years after stroke. Singam, Ytterberg, Tham & von Koch (2015) found that participation in ADLs after stroke was linked to mobility, and participation in leisure activities was associated with both age at stroke onset and mobility. Jellema et al. (2017) carried out a systematic review of environmental factors that influence stroke patients' reengagement to "personally valued activities" and found that social support (availability of family and friends) was highly related. These studies highlight the need to design long-term rehabilitation programs to increase participation in life situations, and based on our results, cognitive reserve activities such as ADLs and training and formation should be especially addressed.

We have found relationships between Post-CR and self-reported cognitive functioning. Concretely, engagement in training and formation showed inverse relationship with self-rating scores in attentional complaints, but direct association with level of metacognition, the ability of planning and monitoring one´s thinking and actions and functional abilities in daily life. Also, frequency in Post-CR hobbies is inversely related to attentional complaints. However, it is still not clear the nature of this relationship. Scarmeas & Stern (2003) and Stern et al. (2018) have discussed before if the relationship between proxies of cognitive reserve and cognitive functioning is causal or reflective of reverse causation. Following their conclusions, those who initially have a good performance in attention and executive functions are more motivated towards participating in cognitively stimulating activities, since they are more effective and obtain a greater sense of achievement than those who have more cognitive difficulties. On the other hand, it is possible that

participating in this type of activity helps to stimulate or maintain cognitive functioning. Future research should be focused on exploring this question.

We have also explored static proxies, concretely, education and occupation. Our results showed that years of formal education was not significantly related to rate of change in attention, memory, and executive function as factors in our 3-factor model. Education has shown to be a predictor of cognitive performance and it is considered as having a protective role against brain damage (Steward et al., 2018). Kessels et al. (2017) found evidence of the relationship between education and grade performance on tests in stroke patients, but this relationship was mediated by the age, so the role of education by itself was not clear. On the other hand, Berggren, Nilsson & Lövdén (2018) pointed out that education has no relationship with the rate of cognitive decline in heathy elders. Lenehan, Summers, Saunders, Summers & Vickers (2014) concluded that education is directly related to level of performance on tests but there isn´t a relationship between education and age-related cognitive decline. Our results suggest that the same phenomenon happens in stroke-related cognitive change over time. The moment when the education is received (childhood and adolescence) "modulates" the way we learn to respond to test and exam situations, and therefore the way we respond to cognitive tests, but the rate of change in performance over time is independent. Education may protect against brain damage but does not influence the rate of cognitive recovery after stroke.

We also did not find significant relationships between complexity of occupation and any measure of neuropsychological assessments. In a review, Baldivia, Andrade & Bueno (2008) pointed out that the evidence of the relationship between occupation and cognition is limited. Perhaps occupation can be considered as informal education. Helmer et al. (2001) indicated that occupation is related to levels of education and literacy and hence is difficult to study as a separate variable. On the other hand, studies with the elderly

population found that occupation is related to better cognitive functioning (Adam, Bonsang, Grotz & Perelman, 2013; Schooler, Mulatu & Oates, 1999). We are inclined to think that every variable in lifestyle has some potential to influence cognitive functioning after stroke, and this might include occupation. In our study we used the classification of the National Institute of Qualifications of Spain to differentiate levels of work complexity. This classification is organized in levels of qualification, defined as professional skills that can be acquired through training or through work experience. There are other ways to assess complexity and involvement of cognitive functions of a profession as discussed by other authors (Finkel, Andel, Gatz & Pedersen, 2009; Schooler, Mulatu & Oates, 2004). In conclusion, most CR studies are focused on aging and dementia, while there is no evidence of the role of occupation in stroke recovery. Our study has been the first to address this issue, with results suggesting there is no relationship. Future research is necessary to further explore the possible role of occupation in stroke.

Lastly, we also analyzed social integration in our study. Other researchers have used CIQ to study populations with stroke (Dalemans, De Witte, Beurskens, Van Den Heuvel & Wade, 2010; Lee, Lee, Choi & Pyun, 2015). In our study, we found that total score of CIQ showed significant correlations with all domains of CRS. CIQ assesses community integration using three domains: competence in instrumental ADLs, social integration, and productive activities. The relationship with CRS could indicate that community integration could be another dimension of cognitive reserve or, on the other hand, that CIQ is assessing the same as CRS and hence, it could be used as a tool to assess dynamic proxies of CR in people who have suffered stroke. Given the importance of assessing CR, and that CIQ is a measurement tool designed specifically for people with brain injury

(Dijkers, 2000), we may propose that it is a good candidate proxy worthy of further study for its utility in assessing CR in this type of patients.

We see strengths but also important limitations in our research. First, we focused on a subpopulation of young to middle-age adults with moderate to severe stroke who are living at home (these might not be representative of an elderly population or those living in nursing homes and health centers). We did not include visuospatial modality of learning and working memory, and neither speed of processing, being this last one an important variable since it is related to functional outcome after stroke (Barker-Collo, Feigin, Parag, Lawes & Senior, 2010) and many neuropsychological measures of attention and executive functioning involve time-sensitive tasks. Another limitation of the study is that part of our results is based on self-rating scales, which cannot exclude the possibility of response bias. Moreover, we did not study or account for the effect of "self-awareness" or the capacity of the person to inform accurately regarding their own performance, which may tend to be altered after stroke. Another limitation was sample size, which could impact the sensitivity and/or resolving power of CFA analysis, mean differences, and correlations. Finally, we did not include neuroimaging, so we could not control brain lesion characteristics besides the type of stroke.

Conclusions

Activities related to ADLs and learning tend to be more abandoned after a stroke, while there is a reengagement in previously practiced hobbies and social life. On the other hand, none of the static CR proxies included in the study were related to cognitive performance in either post-acute or chronic stages of stroke. However, dynamic proxies of CR such as training activities and hobbies are related to the perception that patients had about their functional abilities, attention performance, and metacognition in daily life.

Our results suggest that dynamic proxies are related to cognitive performance in daily life in chronic stroke. We propose that dynamic proxies of CR should be included in neuropsychological assessments in stroke patients and also in the design of programs for long-term rehabilitation. Also, more research of CR in stroke is needed to better understand the implications of static proxies in cognitive recovery.

Acknowledgements

Authors declare no conflict of interests.

The authors are grateful to Admissions Department and Documentation Area (O. Araujo) of Institut Guttmann, and to Dr. Schrum and C. Molina-Mendiola for providing writing assistance and general support.

This work was supported by BIOCAT La Fundació BioRegió de Catalunya – Registry Number: COM15–1-0004 and Fundació Bancària “la Caixa” - Obra Social “la Caixa” Project number: LCF/PR/PR16/11110004

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Capítulo V:

Discusión

5.1 Discusión general

En este estudio hemos explorado si los pacientes de ictus en fase crónica, de una media de 2 años de evolución, podían beneficiarse de realizar un tratamiento personalizado de telerehabilitación cognitiva domiciliaria (CCT-C). Se realizó un estudio retrospectivo para analizar las diferencias entre las puntuaciones al alta del hospital de neurorrehabilitación y en el reclutamiento, que mostró que no había diferencias, por lo que el rendimiento cognitivo "pre-estudio" era estable. La segunda parte del estudio fue prospectiva, y seguimos a los participantes a lo largo de un año, durante los cuales realizaron dos tratamientos CCT domiciliarios, uno personalizado (CCT-C) y otro no personalizado (CCT-non-C) y un seguimiento a largo plazo. En la comparación pre y post tratamientos observamos beneficio en las pruebas cognitivas de ambos grupos después de realizar los dos tratamientos. Además, observamos evolución positiva en las escalas funcionales en el Grupo A después de realizar el tratamiento personalizado (CCT-C), y evolución positiva en los test en ambos grupos después de la CCT-non-C. También, analizamos la influencia de las actividades cognitivamente estimulantes, estudiadas como variables de reserva cognitiva, en el rendimiento cognitivo post ictus en fase crónica. En este caso se realizó un estudio observacional retrospectivo. Los resultados obtenidos indican que los pacientes de ictus en fase crónica tienden a abandonar las actividades cognitivamente estimulantes relacionadas con las actividades de la vida diaria (gestión de asuntos personales, económicos y domésticos) y con la formación/actualización (ampliación de conocimiento y aprendizaje de nuevas habilidades), mientras que recuperan la frecuencia de actividades relacionadas con los hobbies (actividades de ocio y tiempo libre, actividad física) y con la vida social.

En cuanto a los hallazgos sobre el beneficio de la CCT en pacientes crónicos, hemos hallado resultados similares a los expuestos en la literatura. En los estudios de Westerberg

et al (2007) y de Johansson & Tornmalm (2010), los autores hallaron mejoras tanto en test y una disminución de quejas cognitivas en las actividades de la vida diaria. No obstante, estos autores hallaron mejoras en la memoria de trabajo, mientras que en nuestro caso ha sido en test de memoria verbal. Así mismo, Lebowitz, Dams-O'Connor & Cantor (2012) hallaron efectos positivos de la CCT en test y cuestionarios, pero en su caso era una muestra de pacientes de traumatismo craneoencefálico. En la revisión sistemática de Poulin et al (2012), los autores concluyen que la mejora observada después de la aplicación de un tratamiento CCT en pacientes crónicos está causada por una mejora de las habilidades cognitivas derivada del fenómeno de restitución. Otros autores han arrojado luz sobre diferentes factores que podrían potenciar este fenómeno. Por ejemplo, el hecho de participar en un estudio ayuda a los pacientes a desarrollar conciencia de déficit y conocer mayor sus limitaciones (Buitenberg, Murre & Ridderinkhof, 2012). En el estudio de Spikman et al (2010), los autores señalaron que el feedback inmediato que proporcionan los ejercicios de la CCT causa sensación de autoeficacia en el usuario, y esto se refleja en las mejoras derivadas del tratamiento. Recientemente, la revisión sistemática de Cicerone et al (2019) ha señalado que la CCT ha de ser supervisada y domiciliaria para poder generar beneficio. Dado que en nuestro estudio los dos grupos obtuvieron beneficio de ambos tratamientos, nuestra explicación se centra en las características comunes de ambos tipos de CCT testadas en este estudio. Los dos tratamientos eran domiciliarios, proporcionaban feedback sobre la ejecución al participante y también eran supervisados, con un terapeuta implicado en el proceso de tratamiento, que supervisaba que los participantes realizaran los tratamientos con el régimen establecido, fomentando la adherencia y resolviendo dudas siempre que los participantes lo necesitaban. De hecho, los participantes del estudio mostraron gran adherencia a ambos tipos de CCT (el Grupo A completó una media de 26 sesiones de la CCT-C y 24 de CCT-non-C, mientras que el Grupo B completó una media de 25 en CCT

y 19 en CCT-non-C). Además, ambos tipos de tratamiento se plantearon como una actividad rutinaria, que debía incluirse en el día a día y ser ejecutada de forma periódica, y como resultado el participante terminaba integrando en su día a día una actividad estimulante. Por lo tanto, como han descrito otros autores (van de Ven et al, 2017), nuestra tarea placebo ha funcionado como un tratamiento real. Futuras líneas de investigación deberían centrarse en determinar la magnitud de beneficio que cada característica de la CCT aporta al tratamiento rehabilitador.

También observamos que el grupo que realizó primero el CCT-C fue el que mejor evolución mostró en cuanto a las medidas subjetivas de atención, memoria y funciones ejecutivas. La diferencia entre ambos grupos fue el orden en el que recibieron los tratamientos. Esto sugiere que recibir primero la CCT-C potencia los resultados de subsiguientes tratamientos CCT, personalizados o no personalizados. Otros autores han señalado que el hecho de entrenar varios dominios cognitivos, como nuestro programa CCT-C, es necesario para promover la generalización de las mejoras cognitivas y trasladar esta mejora a la vida diaria (Green & Bavelier, 2008; Sohlberg & Mateer, 2001). El Grupo A inició antes que el Grupo B el tratamiento personalizado y multidominio, lo cual pudo permitir que mostrara mayores mejoras funcionales.

Además, ambos grupos mostraron mejoras en pruebas de rendimiento óptimo. Todos nuestros participantes eran antiguos pacientes de Institut Guttmann que, durante la hospitalización y el régimen ambulatorio en fase post-aguda, habían recibido tratamiento CCT-C de manera intensiva. Por lo tanto, habría que considerar la posibilidad de que el tratamiento CCT-C en fase post-aguda haya potenciado el beneficio de posteriores tratamientos CCT aplicados en la fase crónica.

En cuanto al análisis intragrupo, las diferencias observadas se dieron en ambos grupos después de ambos tratamientos. Nosotros administramos cada tipo de CCT durante un

período de 6 semanas, 5 sesiones semanales y 30 horas en total, mientras que el tiempo total invertido en ambos tratamientos incluyendo el tiempo de descanso ascendía a 6 meses. En Lampit, Hallock & Valenzuela (2014), se indica como dosis recomendable de CCT no más de 3 sesiones por semana, pero estos estudios se basan en población de adultos sin daño cerebral. Los autores que han estudiado el efecto dosis en población con deterioro cognitivo leve indican que el tiempo de exposición al tratamiento no media en la eficacia de este (Coyle, Traynor & Solowij, 2015). En contraste con estos estudios, nuestros resultados indican que la cantidad de tiempo de tratamiento que necesitan los pacientes de ictus en fase crónica sería superior al indicado en otras poblaciones, y que el tiempo de tratamiento puede ser una variable mediadora en el beneficio cognitivo.

También, se investigaron otras variables ajenas al CCT que pudieran influenciar el rendimiento cognitivo de los participantes, es decir, si las actividades o rutinas de los participantes del estudio podían tener relación con el resultado de las evaluaciones neuropsicológicas. Para ello, realizamos el estudio retrospectivo de reserva cognitiva, que mostró correlación entre la frecuencia de ejecución de actividades cognitivamente estimulantes y la disminución de quejas del funcionamiento cognitivo en la fase crónica. Mientras que los indicadores estáticos de reserva cognitiva son más resistentes al cambio a lo largo de la vida (nivel educativo en la juventud, ocupación en la edad adulta), la naturaleza de los indicadores dinámicos hace que sean más variables a lo largo de las diferentes etapas de la vida. El ictus causa muchos cambios en las rutinas y en las actividades que solían realizar los pacientes antes del ictus (Cott, Wiles & Devitt, 2007). Por lo tanto, tiene sentido deducir que también cause cambios en las actividades cognitivamente estimulantes, en los indicadores dinámicos. En nuestro estudio hemos podido confirmar que los pacientes de ictus en fase crónica tienden a abandonar algunas actividades mientras que recuperan otras. Esta "recuperación" se ha estudiado como "*reengagement*" en la literatura científica (Jellema et al, 2017; Singam, Ytterberg, Tham

& von Koch, 2015; Verbene et al, 2018). En general, los estudios resaltan la necesidad de diseñar programas de rehabilitación a largo plazo que promuevan la participación del paciente en su entorno. En base a nuestros resultados, los programas de rehabilitación a largo plazo para pacientes de ictus deberían incluir las actividades cognitivamente estimulantes identificadas como indicadores dinámicos de reserva cognitiva, y en especial potenciar las *AVDs* y la formación/actualización.

En general, este estudio aporta evidencia del beneficio de la CCT en el rendimiento cognitivo y funcional de los pacientes de ictus con déficit cognitivo en fase crónica, además de indicar qué tipo de actividades cognitivamente estimulantes se asocian más con el rendimiento cognitivo post-ictus y cuáles han de ser especialmente potenciadas en los programas de rehabilitación en pacientes de ictus en fase crónica. Nuestros resultados indican una relación entre la CCT-C y las actividades cognitivamente estimulantes, ya que ambas se relacionan con una disminución de quejas subjetivas. Por lo tanto, la ejecución de un tratamiento domiciliario CCT-C, como la plataforma de telerehabilitación GNPT®, se puede considerar como una actividad relacionada con la reserva cognitiva.

En definitiva, esta tesis doctoral aporta evidencia científica a favor de (I) los pacientes crónicos con déficit cognitivo asociado a un ictus cambian su nivel de rendimiento cognitivo y funcional después de haber trabajado con una plataforma de telerehabilitación cognitiva domiciliaria y supervisada, (II) los pacientes crónicos con déficit cognitivo asociado a un ictus cambian la frecuencia de ejecución de actividades relacionadas con la reserva cognitiva, y (III) al estar dichas actividades relacionadas con un mejor funcionamiento cognitivo, deben ser integradas en los procesos de evaluación y rehabilitación de los pacientes crónicos.

5. 2 Limitaciones

En primer lugar, nuestro estudio carece de un grupo control pasivo, el cual hubiera sido necesario para poder discriminar nuestras observaciones de las que derivarían del propio gradiente temporal. Si bien, al utilizar los datos obtenidos entre el alta hospitalaria y el inicio del reclutamiento hemos podido controlar los resultados de la fase de tratamiento con la fase de no tratamiento. Por otro lado, la metodología del "Estudio 1" sigue un diseño cruzado, con un periodo de lavado cuyo objetivo era crear un desvanecimiento de los efectos de cada tratamiento antes de iniciar la Fase II. Sin embargo, un diseño cruzado no es el adecuado si se espera observar un mantenimiento de resultados después de aplicar un determinado tratamiento, ya que los beneficios de la primera fase se mezclan con los de la segunda. Habría sido más adecuado realizar un diseño no cruzado de tres brazos: un grupo experimental, un grupo control activo (que utilizara la tarea sham) y un grupo control pasivo. Por otro lado, la metodología basada en medidas repetidas aumenta la probabilidad del efecto de aprendizaje. También, hay que tener en cuenta que el uso de escalas autoinformadas, aumenta el riesgo de utilizar información sesgada por el paciente. También se identifica un alto riesgo de sesgo de muestra, ya que todos los pacientes del estudio fueron diagnosticados de ictus moderado-grave, lo cual hace que los resultados obtenidos no puedan ser generalizables a toda la población de ictus, como el ictus leve, y se restringe además a pacientes que actualmente viven en sus casas.

5.1 Líneas futuras

A raíz de los resultados de esta tesis se proponen las siguientes líneas:

- El estudio de las variables de los tratamientos CCT que consiguen generar un beneficio en los pacientes crónicos. En el "Estudio 1" se quiso aislar la variable

"personalización" mediante la creación de una plataforma "sham" que no fuera personalizada. Sin embargo, no se controló hasta qué punto se diferenciaban ambos tratamientos en cuanto a los dominios cognitivos que estimulaban: la plataforma CCT-C es una plataforma multidominio, mientras que *ictus.online* fue concebido con el objetivo de no estimular ningún dominio concreto. Por lo tanto, es posible que lo que hayamos comparado finalmente sea una plataforma multidominio versus una unidominio.

- Investigar el peso de la variable "supervisión" en la aplicación de un tratamiento de telerehabilitación cognitiva domiciliaria.
- Realizar un diseño experimental que aborde la hipótesis expuesta en la discusión sobre la exposición a la CCT-C en fase post-aguda y su posible efecto a la hora de potenciar el beneficio de futuras terapias en fase crónica. Para ello, se debería reclutar un grupo de pacientes de ictus en fase crónica que no haya recibido CCT-C en fase post-aguda y comprobar qué efecto tiene la CCT (CCT-C y CCT-non-C) en fase crónica.
- Estudiar el "efecto de grupo" en la aplicación de la terapia rehabilitadora, el efecto terapéutico que se da al estar rodeado de otras personas con problemas similares (Cochrane, 2016). Futuros estudios podrían incluir en su diseño un grupo de pacientes que realizara el tratamiento en solitario, como los de nuestro estudio, y otro grupo que lo realizara de forma grupal.
- Ampliar el conocimiento sobre los tiempos o "dosis" de CCT que han de prescribirse para los pacientes de ictus con déficit cognitivo en fase crónica de evolución.
- Dado que las tecnologías de la CCT permiten el registro y el almacenamiento de todos los datos derivados del trabajo del paciente con las tareas (tasas de acierto, tiempo de trabajo), se propone relacionar estas variables con las variables

demográficas de los pacientes y con las puntuaciones de las evaluaciones neuropsicológicas. De este modo se podría obtener un "perfil de paciente" que obtiene mayor beneficio del trabajo con la CCT.

- En relación con el punto anterior, estudiar la relación entre la calidad de ejecución de las tareas de telerehabilitación cognitiva domiciliaria supervisada y personalizada y las puntuaciones reportadas en los cuestionarios de reserva cognitiva.
- Estudiar la relación de causalidad en las correlaciones observadas entre los indicadores de reserva cognitiva post ictus (Post-CR) y el rendimiento reportado en las escalas de funcionamiento cognitivo.

Capítulo VI: Conclusiones

Conclusiones generales

1 Los pacientes crónicos con déficit cognitivo derivado de un ictus mejoran su rendimiento cognitivo y funcional después de realizar un tratamiento de telerehabilitación cognitiva domiciliaria y supervisada. Se observa beneficio después de un tratamiento personalizado y también después de un tratamiento no personalizado.

2 Los beneficios obtenidos después de realizar los tratamientos de telerehabilitación cognitiva domiciliaria y supervisada se mantienen a largo plazo.

3 Los pacientes crónicos con déficit cognitivo derivado de un ictus reducen significativamente la ejecución de rutinas relacionadas con actividades de la vida diaria y las actividades de formación. No obstante, recuperan la frecuencia en actividades relacionadas con hobbies y vida social.

4 La frecuencia con la que los pacientes crónicos con déficit cognitivo derivado de un ictus realizan rutinas cognitivamente estimulantes está positivamente relacionada con el funcionamiento cognitivo en la vida diaria.

5 Realizar un tratamiento de telerehabilitación cognitiva domiciliaria, supervisada y personalizada puede considerarse un indicador dinámico de reserva cognitiva en pacientes crónicos con déficit cognitivo derivado de un ictus.

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Apéndices

APÉNDICE A. Materiales suplementarios

A.1 Material suplementario Artículo 1

A.2 Material suplementario Estudio 1

A.3 Material suplementario Estudio 2 (Published paper)

APÉNDICE B.

B.1 Resumen de la Comunicación Oral presentada en el II Congreso Iberoamericano de Neuropsicología en Almería, Mayo 2018

A1: Material suplementario Artículo 1

A1.1: Standard Protocol Items: Recommendations for Interventional Trials

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____7_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___12-13_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____16-17____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____17_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

A1.2: CONSORT 2010 Checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14-16
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6-7
	11b	If relevant, description of the similarity of interventions	12
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	16-17
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	16-17
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18-19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

A.2: Material suplementario Estudio 1

A2.1 Tablas incluidas como Apéndice del Estudio 1

Table A1. Within differences in Phase I

	Group A (n=13)			Group B (n=17)		
	t1	t2	*p*	t1	t2	*p*
Digit Forwards	5.31 (1.44)	5.69 (1.03)	0.26	5.24 (1.35)	5.47 (1.07)	0.19
Digit Backwards	4.23 (1.09)	4.31 (1.18)	0.65	4.00 (1.22)	3.76 (1.15)	0.87
TMTA	51.9 (36.4)	51.7 (58.7)	0.45	49.6 (26.3)	47.2 (33.7)	0.19
TMTB	104 (58.5)	110 (53.7)	0.60	101 (47.9)	107 (60.7)	0.69
Stroop	1.27 (8.81)	1.70 (3.95)	0.83	-2.07 (7.32)	-1.24 (5.62)	0.72
Symbol Digit	56.6 (19.5)	59.8 (21.3)	0.58	47.3 (15.9)	49.1 (15.8)	0.50
Letter-Number Seq	8.54 (2.44)	8.92 (2.78)	0.60	8.25 (3.00)	9.25 (2.72)	0.33
RAVLT Learning	47.0 (8.55)	44.4 (7.37)	0.39	42.4 (11.6)	41.7 (9.16)	0.75
RAVLT Long Term	10.1 (2.81)	9.85 (2.88)	0.85	7.82 (3.80)	8.94 (2.84)	0.60
RAVLT Recognition	12.8 (2.70)	12.1 (3.82)	0.33	9.35 (4.42)	10.3 (4.44)	0.79
PMR	46.1 (12.3)	46.8 (17.8)	0.83	34.4 (13.2)	36.9 (16.0)	0.79
CPTHitR	49.6 (9.06)	47.0 (7.29)	0.47	61.2 (16.5)	63.2 (21.3)	0.77
CPT-Omissions	50.5 (12.2)	48.8 (8.18)	0.84	57.8 (26.4)	63.2 (32.7)	0.87
CPT-Comissions	52.0 (15.5)	49.6 (12.3)	0.76	50.7 (10.3)	49.4 (11.4)	0.60

(*) Significance $p < 0.05$
Values expressed in mean (sd)

Table A2. Within differences through Phase I

	Group A (n=13)			Group B (n=17)		
Questionnaires	t1	t2	*p*	t1	t2	*p*
PCRSp Total	124 (20.1)	124 (22.6)	0.83	126 (18.1)	125 (14.2)	0.87
RSABp Total	20.2 (11.0)	17.0 (11.6)	0.41	21.5 (7.23)	21.4 (7.37)	0.95
PRMQp Total	32.5 (12.2)	28.2 (12.1)	0.19	31.9 (9.07)	31.4 (7.19)	0.83
BRIEFAp Total	110 (25.1)	107 (22.2)	0.62	111 (25.4)	116 (20.9)	0.53

(*) Significance $p < 0.05$

Values expressed in mean (sd)

Table A3. Long-term within group differences after Phase I

	Group A			Group B		
Test	t1	t3	*p*	t1	t3	*p*
Digit Forwards	5.31 (1.44)	5.62 (0.87)	0.31	5.24 (1.35)	5.65 (1.50)	0.42
Digit Backwards	4.23 (1.09)	4.54 (0.88)	0.39	4.00 (1.22)	3.76 (1.25)	0.57
TMTA	51.9 (36.4)	54.1 (58.9)	0.60	49.6 (26.3)	53.8 (39.0)	0.67
TMTB	104 (58.5)	99.9 (45.0)	0.71	101 (47.9)	115 (55.8)	0.75
Stroop	1.27 (8.81)	-0.45 (8.25)	0.69	-2.07 (7.32)	-0.50 (7.11)	0.66
Symbol Digit	56.6 (19.5)	60.0 (20.3)	0.62	47.3 (15.9)	48.6 (14.7)	0.69
Letter-Number Seq	8.54 (2.44)	8.77 (3.35)	0.95	8.25 (3.00)	8.56 (2.83)	0.87
RAVLT Learning	47.0 (8.55)	50.3 (10.1)	0.41	42.4 (11.6)	47.0 (11.8)	0.14
RAVLT Long Term	10.1 (2.81)	10.7 (3.30)	0.60	7.82 (3.80)	9.18 (3.15)	0.31
RAVLT Recognition	12.8 (2.70)	12.6 (2.96)	1.00	9.35 (4.42)	10.9 (3.22)	0.33
PMR	46.1 (12.3)	47.9 (15.9)	0.60	34.4 (13.2)	38.5 (14.4)	0.45
CPTHitR	49.6 (9.06)	46.9 (7.78)	0.40	61.2 (16.5)	62.9 (19.6)	0.88
CPT-Omissions	50.5 (12.2)	58.5 (38.6)	0.97	57.8 (26.4)	60.4 (31.0)	0.58
CPT-Comissions	52.0 (15.5)	51.9 (9.26)	0.59	50.7 (10.3)	47.6 (9.53)	0.52

(*) Significance $p < 0.05$
Values expressed in mean (sd)

Table A4. Long-term within group differences after Phase I

	Group A			Group B		
Questionnaires	t1	t3	*p*	t1	t3	*p*
PCRSp Total	124 (20.1)	128 (19.1)	0.48	126 (18.1)	128 (14.1)	0.77
RSABp Total	20.2 (11.0)	16.0 (10.4)	0.30	21.5 (7.23)	20.5 (7.03)	0.60
PRMQp Total	32.5 (12.2)	26.9 (11.7)	0.13	31.9 (9.07)	30.9 (7.96)	0.71
BRIEFAp Total	110 (25.1)	106 (21.8)	0.66	111 (25.4)	113 (17.4)	0.53

(*) Significance $p < 0.05$
Values expressed in mean (sd)

Table A5 Within differences after wash-out

	Group A			Group B		
Test	t2	t3	*p*	t2	t3	*p*
Digit Forwards	5.69 (1.03)	5.62 (0.87)	0.95	5.47 (1.07)	5.65 (1.50)	0.97
Digit Backwards	4.31 (1.18)	4.54 (0.88)	0.69	3.76 (1.15)	3.76 (1.25)	0.88
TMTA	51.7 (58.7)	54.1 (58.9)	0.79	47.2 (33.7)	53.8 (39.0)	0.55
TMTB	110 (53.7)	99.9 (45.0)	0.66	107 (60.7)	115 (55.8)	0.76
Stroop	1.70 (3.95)	-0.45 (8.25)	0.13	-1.24 (5.62)	-0.50 (7.11)	0.74
Symbol Digit	59.8 (21.3)	60.0 (20.3)	0.97	49.1 (15.8)	48.6 (14.7)	0.97
Letter-Number Seq	8.92 (2.78)	8.77 (3.35)	0.69	9.25 (2.72)	8.56 (2.83)	0.43
RAVLT Learning	44.4 (7.37)	50.3 (10.1)	0.07	41.7 (9.16)	47.0 (11.8)	0.19
RAVLT Long Term	9.85 (2.88)	10.7 (3.30)	0.43	8.94 (2.84)	9.18 (3.15)	0.86
RAVLT Recognition	12.1 (3.82)	12.6 (2.96)	0.56	10.3 (4.44)	10.9 (3.22)	0.91
PMR	46.8 (17.8)	47.9 (15.9)	0.91	36.9 (16.0)	38.5 (14.4)	0.76
CPTHitR	47.0 (7.29)	46.9 (7.78)	0.94	63.2 (21.3)	62.9 (19.6)	0.93
CPT-Omissions	48.8 (8.18)	58.5 (38.6)	0.93	63.2 (32.7)	60.4 (31.0)	0.53
CPT-Comissions	49.6 (12.3)	51.9 (9.26)	0.54	49.4 (11.4)	47.6 (9.53)	0.72

(*) Significance $p < 0.05$
Values expressed in mean (sd)

Table A6. Within differences after wash-out

	Group A			Group B		
Questionnaires	t2	t3	*p*	t2	t3	*p*
PCRSp Total	124 (22.6)	128 (19.1)	0.68	125 (14.2)	128 (14.1)	0.49
RSABp Total	17.0 (11.6)	16.0 (10.4)	0.93	21.4 (7.37)	20.5 (7.03)	0.69
PRMQp Total	28.2 (12.1)	26.9 (11.7)	0.66	31.4 (7.19)	30.9 (7.96)	1.00
BRIEFAp Total	107 (22.2)	106 (21.8)	0.93	116 (20.9)	113 (17.4)	0.71

(*) Significance $p < 0.05$

Values expressed in mean (sd)

Table A7. Between groups differences after Phase I (t2)

	Group A N=13	Group B N=17	*p*	*d*
Digit Forward	5.69 (1.03)	5.47 (1.07)	0.569	0,21
Digit Backwards	4.31 (1.18)	3.76 (1.15)	0.196	0,48
TMTA	51.7 (58.7)	47.2 (33.7)	0.571	0,10
TMTB	110 (53.7)	107 (60.7)	0.661	0,06
Stroop (Inhibition)	1.70 (3.95)	-1.24 (5.62)	0.172	0,60
Digit Symbol	59.8 (21.3)	49.1 (15.8)	0.101	0,61
Letter-Number Seq.	8.54 (2.44)	8.25 (3.00)	0.877	0,12
RAVLT Learning	8.92 (2.78)	9.25 (2.72)	0.356	0,32
RAVLT Long Term	9.85 (2.88)	8.94 (2.84)	0.388	0,32
RAVLT Recognition	12.1 (3.82)	10.3 (4.44)	0.374	0,44
PMR	46.8 (17.8)	36.9 (16.0)	0.137	0,61
CPT Hit Response	47.0 (7.29)	63.2 (21.3)	0.015*	0,96
CPT Omissions	48.8 (8.18)	63.2 (32.7)	0.368	0,57
CPT Commissions	49.6 (12.3)	49.4 (11.4)	0.833	0,01

(*) Significance $p < 0.05$

Values expressed in mean (sd)

A.3: Apéndices Estudio 2 (Published paper)

A3.1 Material suplementario Estudio 2

Table A. Descriptive statistics of the tests included in the CFA

	Admission				Discharge				Chronic			
Tests	Mean	sd	min	max	Mean	sd	min	max	Mean	sd	min	max
Digit Forward	6	1	3	8	6	1	4	8	5	1	3	8
TMT A	63	39	17	199	61	45	17	207	51	29	14	137
RAVLT Learning	38	9	22	55	46	10	26	69	44	10	28	66
RAVLT Long Term	7	3	0	15	9	4	0	15	9	3	2	14
RAVLT Recognition	10	5	0	15	13	3	6	15	11	4	0	15
Digit Backwards	4	1	2	6	4	1	2	6	4	1	2	7
L-N Sequencing	8	3	4	15	9	3	3	15	8	3	3	15
PMR	33	14	11	59	40	14	15	65	4	1	2	7

Table B. Correlation between evolution in cognitive factors and CRS-Pre stroke

CRS-Pre-stroke	Cognitive factors	Time Frame	r	min	max	*p*
ADLs	AT	Admission Discharge	0,260	-0,085	0,550	0,495
	M		0,218	-0,130	0,518	0,495
	EF		0,231	-0,528	0,117	0,495
	AT	Discharge Chronic	0,185	-0,492	0,163	0,803
	M		0,118	-0,229	0,439	0,803
	EF		0,041	-0,301	0,374	0,818
Training/formation	AT	Admission Discharge	0,196	-0,153	0,501	0,495
	M		0,116	-0,231	0,437	0,685
	EF		0,209	-0,511	0,139	0,495
	AT	Discharge Chronic	0,161	-0,474	0,187	0,803
	M		0,325	-0,015	0,598	0,729
	EF		0,223	-0,125	0,521	0,803
Hobbies	AT	Admission Discharge	0,187	-0,161	0,494	0,495
	M		0,204	-0,144	0,507	0,495
	EF		0,046	-0,379	0,296	0,954
	AT	Discharge Chronic	0,064	-0,394	0,280	0,803
	M		0,124	-0,224	0,443	0,803
	EF		0,083	-0,262	0,410	0,803
Social Life	AT	Admission Discharge	0,007	-0,332	0,344	0,970
	M		0,015	-0,325	0,351	0,970
	EF		0,138	-0,210	0,455	0,654
	AT	Discharge Chronic	0,120	-0,227	0,440	0,803
	M		0,060	-0,390	0,284	0,803
	EF		0,073	-0,402	0,272	0,803

Admission Discharge: Grade difference on Cognitive Factors between Admission and Discharge; Discharge Chronic: Grade difference on Cognitive Factors between Discharge and Chronic.

Table C. Demographics and difference between cognitive factors

Time frame	Cognitive factors	Demographics	ε^2	*p*
Admission vs. Discharge	AT	Age at stroke	0,018	0,959
		Type of stroke	0,183	0,853
		Gender	0,808	0,496
	M	Age at stroke	0,073	0,853
		Type of stroke	0,362	0,853
		Gender	0,589	0,853
	EF	Age at stroke	0,040	0,853
		Type of stroke	0,159	0,853
		Gender	0,083	0,853
Discharge vs. Chronic	AT	Age at stroke	0,195	0,866
		Type of stroke	0,454	0,566
		Gender	0,108	0,831
	M	Age at stroke	0,398	0,566
		Type of stroke	0,092	0,866
		Gender	0,087	0,866
	EF	Age at stroke	0,281	0,566
		Type of stroke	0,370	0,566
		Gender	0,205	0,866

Admission vs. Discharge: Grade difference on Cognitive Factors between Admission and Discharge; Discharge vs. Chronic: Grade difference on Cognitive Factors between Discharge and chronic stage of stroke.

Table D. Difference between cognitive factors and cognitive reserve static proxies

Time frame	Cognitive factors	Static proxies	ε^2	*p*
Admission vs Discharge	AT	Occupation	0,019	0,853
		Studies	0,072	0,853
	M	Occupation	0,049	0,853
		Studies	0,044	0,853
	EF	Occupation	0,074	0,853
		Studies	0,046	0,853
Discharge vs Chronic	AT	Occupation	0,121	0,566
		Studies	0,036	0,831
	M	Occupation	0,096	0,566
		Studies	0,079	0,566
	EF	Occupation	0,009	0,866
		Studies	0,073	0,566

Admission vs. Discharge: Grade difference on Cognitive Factors between Admission and Discharge; Discharge vs. Chronic: Grade difference on Cognitive Factors between Discharge and chronic stage of stroke.

Table E. Correlation between chronic cognitive factors and CRS post stroke

CRS post stroke	Cognitive factors	r	min	max	p
ADLs	AT Chronic	-0,330	-0,601	0,009	0,169
	M Chronic	0,226	-0,121	0,524	0,297
	EF Chronic	0,401	0,072	0,651	0,075
Training/formation	AT Chronic	-0,206	-0,509	0,142	0,323
	M Chronic	0,266	-0,079	0,554	0,250
	EF Chronic	0,410	0,083	0,657	0,075
Hobbies	AT Chronic	-0,073	-0,401	0,272	0,681
	M Chronic	0,445	0,126	0,681	0,075
	EF Chronic	0,291	-0,053	0,573	0,229
Social Life	AT Chronic	0,073	-0,272	0,401	0,681
	M Chronic	0,255	-0,091	0,546	0,250
	EF Chronic	0,106	-0,240	0,429	0,659

Table F. Correlation between questionnaires and CRS post stroke

CRS post stroke	Self-rating measures	r	conf_min	conf_max	p
ADLs	PCRS	0,214	-0,134	0,515	0,394
	CIQ	0,531	0,235	0,737	0,018 *
	RSAB	-0,249	-0,542	0,097	0,339
	PRMQ Prospective	0,234	-0,113	0,530	0,350
	PRMQ Retrospective	-0,161	-0,473	0,187	0,589
	PRMQ Total	0,016	-0,324	0,353	0,971
	BRIEF Regulation	0,031	-0,310	0,366	0,971
	BRIEF Metacognition	-0,023	-0,358	0,318	0,971
	BRIEF Total	0,001	-0,337	0,339	0,995
Training/Formation	PCRS	0,469	0,156	0,697	0,029 *
	CIQ	0,475	0,164	0,701	0,029 *
	RSAB	-0,600	-0,780	-0,328	0,004 *
	PRMQ Prospective	-0,120	-0,441	0,227	0,730
	PRMQ Retrospective	-0,350	-0,615	-0,014	0,155
	PRMQ Total	-0,265	-0,554	0,080	0,339
	BRIEF Regulation	-0,303	-0,582	0,039	0,276
	BRIEF Metacognition	-0,468	-0,696	-0,155	0,029 *
	BRIEF Total	-0,414	-0,660	-0,088	0,066
Hobbies	PCRS	0,274	-0,070	0,561	0,339
	CIQ	0,474	0,162	0,700	0,029 *
	RSAB	-0,471	-0,698	-0,158	0,029 *
	PRMQ Prospective	0,181	-0,167	0,489	0,517
	PRMQ Retrospective	-0,019	-0,355	0,321	0,971
	PRMQ Total	0,097	-0,250	0,421	0,833
	BRIEF Regulation	-0,041	-0,374	0,302	0,952
	BRIEF Metacognition	-0,040	-0,373	0,302	0,952
	BRIEF Total	-0,042	-0,375	0,300	0,952
Social Life	PCRS	0,295	-0,048	0,575	0,286
	CIQ	0,611	0,344	0,787	0,004 *
	RSAB	-0,403	-0,652	-0,075	0,073
	PRMQ Prospective	0,245	-0,101	0,539	0,339
	PRMQ Retrospective	-0,004	-0,341	0,335	0,995
	PRMQ Total	0,157	-0,191	0,470	0,589
	BRIEF Regulation	-0,249	-0,542	0,097	0,339
	BRIEF Metacognition	-0,249	-0,542	0,097	0,339
	BRIEF Total	-0,261	-0,551	0,085	0,339

A3. 2 Abstract y link de acceso a Estudio 2 (Artículo 2)

Journal of the International Neuropsychological Society (2019), 1–12

doi:10.1017/S1355617719000638

A Positive Relationship between Cognitive Reserve and Cognitive Function after Stroke: Dynamic Proxies Correlate Better than Static Proxies

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(Received February 1, 2019; Final revision May 7, 2019; Accepted May 17, 2019)

Abstract

Objectives: How brain damage after stroke is related to specific clinical manifestation and recovery is incompletely understood. We studied cognitive reserve (CR) in stroke patients by two types of measurements: (i) objectively verifiable static proxies (i.e., education, occupational attainment), and (ii) subjective, dynamic proxies based on patient testimony in response to a questionnaire. We hypothesized that one or both of these types of CR measurements might correlate positively with patient cognitive performance during the post-acute and chronic phases of recovery.
Method: Thirty-four stroke patients underwent neuropsychological assessment at 2, 6 and 24 months after stroke onset. In chronic stage at 24+ months, self-rating assessments of cognitive performance in daily life and social integration were obtained. CR before and after stroke was estimated using static proxies and dynamic proxies were obtained using the Cognitive Reserve Scale (*CRS-Pre-stroke, CRS-Post-stroke*). **Results:** CRS-Pre-stroke and CRS-Post-stroke showed significant mean differences. Dynamic proxies showed positive correlation with self-assessment of attention, metacognition, and functional ability in chronic stage. In contrast, significant correlations between static proxies and cognitive recovery were not found. **Conclusions:** Dynamic proxies of CR were positively correlated with patients' perception of their functional abilities in daily life. To best guide cognitive prognosis and treatment, we propose that dynamic proxies of CR should be included in neuropsychological assessments of patients with brain damage.

Keywords: Brain injury, Daily living, Self-assessment, Prognosis, Cognition, Neuropsychological tests

Link de acceso al artículo:

https://www.cambridge.org/core/journals/journal-of-the-international-neuropsychological-society/article/positive-relationship-between-cognitive-reserve-and-cognitive-function-after-stroke-dynamic-proxies-correlate-better-than-static-proxies/BA44E1FFE49189CE238B72D5B32BCE60

Apéndice B. Resumen de la Comunicación Oral presentada en el II Congreso Iberoamericano de Neuropsicología en Almería, Mayo 2018

Pòster o Comunicació Oral	Comunicación Oral: "Perfil de afectación de la reserva cognitiva en personas que han sufrido un ictus".

Societat Organitzadora	Sociedad Andaluza de Neuropsicología		
Tipus i Nom d'esdeveniment	II Congreso Iberoamericano de Neuropsicología y XIV Congreso de la Sociedad Andaluza de Neuropsicología		
Idioma	Castellano	**Lloc**	Almería (España)
Data	3 – 5 Mayo 2018	**Data límit Inscripció**	15 – 4 -2018

Nom projecte relacionat	Rehabilitación cognitiva domiciliaria en pacientes crónicos con alteraciones cognitivas asociadas a un ictus.	**Codi**	IG- 2016251

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Abstract o Resumen:

- **Objetivo**: Estudiar la repercusión de un ictus sobre actividades que promueven reserva cognitiva. Se considera la influencia de variables demográficas (género, edad, años de educación) y tipo de ictus (hemorrágico o isquémico).
- **Método**: 37 sujetos (15 mujeres) de entre 28 y 64 años ($\bar{x}$= 49,8; $\underline{\sigma}$=8,1), diagnosticados de ictus hemorrágico (n=16) o isquémico (n=21), con un tiempo de evolución tras la lesión superior a 12 meses ($\bar{x}$= 24; $\underline{\sigma}$=6) han sido reclutados. Todos residen en su domicilio. Se ha administrado la Escala de Reserva Cognitiva (ERC); la cual abarca cuatro dominios: Actividades de la Vida Diaria (AVDs), Formación e Información, Hobbies y Vida Social. En el estudio se registra la frecuencia de realización de actividades de cada dominio en dos periodos temporales: (1) antes del ictus y (2) en el momento actual (post-ictus). Se aplica prueba no paramétrica (test de Wilcoxon, p <0,05).
- **Resultados**: Se obtienen diferencias estadísticamente significativas entre las puntuaciones (1) y (2) en los dominios AVDs (p= 0,001) y Formación e Información (p= 0,004); independientemente de la etiología del ictus, la edad, el género y los años de educación. No se obtienen diferencias significativas en los otros dominios.
- **Conclusiones**: Existe un descenso en la frecuencia de ejecución de actividades relacionadas con la reserva cognitiva tras sufrir un ictus, en concreto en autonomía funcional (AVDs) y en ampliación de conocimientos (Formación/Información). No se observan cambios a nivel de las actividades de ocio y vida social. Estos aspectos deberían tenerse en cuenta y ser integrados en el proceso rehabilitador.