The use of eHealth in rehabilitation after stroke

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The effects of an 8-week computer-based brain training programme on cognitive functioning, QoL and self-efficacy after stroke

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Neuropsychological Rehabilitation 2016,26:5-6, 847-865.
Poster presentation: World Congress International Brain Injury Association, 20 March 2014, San Francisco, USA.

Abstract

Cognitive impairment after stroke has a direct impact on daily functioning and quality of life (QoL) of patients and is associated with higher mortality and healthcare costs. The aim of this study was to determine the effect of a computer-based brain training programme on cognitive functioning, QoL and self-efficacy compared to a control condition in stroke patients. Stroke patients with self-perceived cognitive impairment were randomly allocated to the intervention or control group. The intervention consisted of an 8-week brain training programme (Lumosity Inc.®). The control group received general information about the brain weekly. Assessments consisted of a set of neuropsychological tests and questionnaires. In addition, adherence with trained computer tasks was recorded. No effect of the training was found on cognitive functioning, QoL or self-efficacy when compared to the control condition, except for very limited effects on working memory and speed. This study found very limited effects on neuropsychological tests that were closely related to trained computer tasks, but no transfers to other tests or self-perceived cognitive failures, QoL or self-efficacy. These findings warrant the need for further research into the value of computer-based brain training to improve cognitive functioning in the chronic phase after stroke.

Introduction

The crude incidence of stroke in Western countries in the past decades is estimated to be 1.14 cases per 1000 persons per year for first ever strokes and 3.5 cases per 1000 persons per year for all strokes (Zhang et al., 2012). About 20–50% of the patients die within the first month (Truelsen et al., 2006). For the patients who survive, the disease impact is considerable, with the estimated proportions of patients with cognitive impairments being 50% directly after stroke (Douiri, Rudd, & Wolfe, 2013) and about 30% three years after a first stroke (Patel, Coshall, Rudd, & Wolfe, 2003). Cognitive impairment has a direct impact on daily functioning and quality of life (QoL) of patients and their relatives (Paker, Buğdaycı, Tekdöş, Kaya, & Dere, 2010). It is also associated with greater rates of institutionalisation (Pasquini, Leys, Rousseaux, Pasquier, & Henon, 2007), higher mortality (Tatemichi et al., 1994) and higher healthcare costs (Claesson, Lindén, Skoog, & Blomstrand, 2005).

Cognitive rehabilitation after stroke is usually based on specific learning strategies with differences between compensatory approaches: (1) focused on learning strategies to improve performance on cognitive tasks and restitution-based approaches, or (2) focused on training and stimulation of impaired cognitive functions for recovery. Among this last approach, computer-based cognitive rehabilitation (CBCR) has been shown to significantly improve performance on cognitive tasks assessing the specific domains trained within CBCR programmes (Lynch, 2002; Owen et al., 2010; Smith et al., 2009). CBCR interventions are based on principles that the impaired system(s) can be restored or at least improved by structured drills and practice using tasks that contain similar elements to the target skill (e.g., attention span, reaction time) (Lynch, 2002). A widely used CBCR intervention in stroke patients is CogMed®, a training targeting the cognitive domain of working memory (WM) by games aimed at remembering multiple stimuli at the same time, during short delays and in a unique order. Other examples of CBCR interventions are BrainGymmer® and Lumosity®, both designed to improve people's general cognitive performance with various games and mental exercises in multiple cognitive domains.

Regarding the effectiveness of CBCR interventions after stroke, several randomised controlled trials (RCTs) have been published in the last decade. Three RCTs specifically examined the effect of a computer-based attention (Barker-Collo et al., 2009) or WM training (Cogmed) (Åkerlund, Esbjörnsson, Sunnerhagen, & Björkdahl, 2013; Westerberg et al., 2007) as compared to standard care and no intervention. In Barker-Collo et al. (2009), 78 stroke patients received 30 hours of computerised attention training (intervention group) or standard care alone (control group) 6 months after stroke. Statistically significant effects were seen regarding a test combining visual and auditory attention scores, either separately or combined, but this was not reflected in statistically significant improvement on other attention measures, such as the Trail Making Task A and B, or in wider outcomes.

Westerberg et al. (2007) concluded that the treatment group improved significantly more than the passive control group on tests that measured WM and subjective cognitive failures. Effect sizes between groups were respectively 0.83 on the Span Board ($p = .05$), 1.58 on the Digit Span ($p < .01$), and 0.80 on the Cognitive Failures Questionnaire (CFQ) ($p < .01$). Åkerlund et al. (2013) also showed that results on the Digit span after WM training differed significantly compared to the results of usual rehabilitation at the same time, with greater improvement in the training group (Digit Span forward $p = .04$, Digit Span backward $p < .01$).

A review by Laver, George, Thomas, Deutsch, and Crotty (2015) pointed out that it is still unclear how effective virtual reality may be for cognitive rehabilitation after stroke. Akinwuntan et al. (2005) studied the effect on fitness to drive of a 5-week 15-hour simulator-based training (experimental group) compared to a driving-related cognitive tasks (control group) among 83 stroke patients. At 6–9 months post-stroke, significant differences between both groups were found in "road sign recognition" and "fitness to drive" in favour of the experimental subjects.

Overall the interpretation of the results of RCTs is hampered by relatively small sample sizes with 18, 47, and 78 participants in total (Åkerlund et al., 2013; BarkerCollo et al., 2009; Westerberg et al., 2007). Moreover, none of these trials included a training focused on multiple cognitive domains, although the literature suggests that targeting a variety of cognitive functions is needed to promote generalisation of abilities beyond the trained task and to achieve an outcome that also impacts on daily life (Buitenweg, Murre, & Ridderinkhof, 2012; Green & Bavelier, 2008; Sohlberg & Mateer, 2001). In addition, the effects on QoL have not been studied (Barker-Collo et al., 2009). Thus, there is a need for large studies focusing not only on WM and attention, but also on other cognitive domains and on QoL.

The aim of this study was to determine the effect of a CBCR intervention on multiple aspects of cognitive functioning, QoL, and self-efficacy, and compare it to a control intervention in patients with self-perceived cognitive impairments 12–36 months after stroke. Additionally, within the intervention group the aim was to study adherence with the intervention. The hypothesis of the study was that a CBCR training targeting multiple cognitive domains leads to greater improvements on processing speed, flexibility and fluid intelligence in stroke patients than the provision of information through the internet (Rebok et al., 2014; Van der Oord, Ponsioen, Geurts, Ten Brink, & Prins, 2012).

Materials, methods and patient characteristics

Design

This study had a randomised, controlled design and tookplace in The Netherlands between January 2013 and September 2013 at the Rijnlands Rehabilitation Centre in Leiden and Sophia Rehabilitation in The Hague. The study was approved by the Medical Ethical Review Board of the Leiden University Medical Centre (P 12.190). All participants gave written informed consent prior to participation and were rewarded with a gift card of 50 euros for participating in the trial, with no difference between those who completed the games and those who did not. The CONSORT (Consolidated Standards of Reporting Trials) guidelines were used for adequate reporting of the study (Moher et al., 2010).

Recruitment and inclusion

Inclusion criteria for participation in the study were: age between 45 and 75 years, diagnosed with stroke 12–36 months ago, having self-perceived cognitive impairments (extracted from the checklist accompanying the recruitment letter), having access to the internet, being able to visit the rehabilitation centre, and having time to participate. Exclusion criteria were: antidepressant use, receiving actual treatment for cognitive impairments, severe aphasia, lack of computer skills, and not being proficient in Dutch. In addition, participants with psychological disorders in need of treatment, for example depression, and patients with physical disorders known to impact cognition were excluded.

Potentially eligible patients were identified by first searching the electronic patient registers of the rehabilitation centres for patients who were aged between 45 and 75 years and who had had a stroke 12–36 months ago. The chosen age range constitutes the largest proportion of patients admitted to rehabilitation and to prevent age-specific bias (e.g., stroke patient 18 years old versus 75 years old). Onset of stroke was "not more recently than 12 months" to minimise the influence of natural recovery and "not longer ago than 36 months" to prevent the risk of impaired learning due to age group specific comorbidities (e.g., Alzheimer's). Potential participants received a letter with information about the study, a checklist concerning the other four inclusion criteria (having self-perceived cognitive impairments, having access to internet, being able to visit the rehabilitation centre and having time to participate) and a form to indicate their willingness to participate in the study. All responding patients received a telephone call from one of the researchers (MW, IV, AK) to make sure they met the inclusion criteria and did not meet the exclusion criteria. Also they were asked to state their age (years), sex and educational level (categorised as low: lower technical and vocational training; medium: secondary technical and vocational training; and high: higher technical and vocational training and university) (Centraal Bureau voor de Statistiek [CBS], 2006).

Randomisation

Included patients were subsequently randomised by an administrative assistant who was not involved in the study. A blocked randomisation scheme (blocks of six), with stratification for age and education level (extracted from the recruitment form and checked by examining the electronic patient registers), made up by a random digit generator (Microsoft Excel 2010), was used to allocate the patients either to the intervention group or control group. Stratification for age and education level was based on findings in a study of Patel et al. (2003) who studied the relationship between different variables and cognitive functioning among 645 stroke patients. As the majority of patients was of the same ethnic origin, stratification for that variable was not performed. The variable "age" was divided into two categories (≤ 58 and > 58), since the median age was 58 years. The variable "education level" was divided into the categories "low", "moderate" and "high", by using a standardised classification system (CBS, 2006).

Blinding

The randomisation sequence was concealed (blinded) from research personnel, so that assessors were not aware of whether a subject was randomised to the intervention or control group.

Intervention and control conditions

The conditions compared in the study consisted of a CBCR training (intervention) versus weekly information about the brain (control). All participants received a user identification and password to log on to a website specifically designed for this study (www.spelenderwijsbeter.nl). After log-on, the website provided either access to the training or the information. All participants were given the contact details of a research assistant, whom they could contact by telephone in case of difficulties using the website or, in case of participants in the intervention group, with the training software.

Intervention

The training consisted of gaming at home during a period of 8 weeks, at least 5 days per week, approximately 15–20 minutes per day, resulting in a requested play time of 600 minutes. The training software was supplied by Lumosity Inc.®. This software was chosen because it targets more cognitive domains than other CBCR interventions (e.g., Cogmed), since effective training should include games in several cognitive areas, including flexibility (Buitenweg et al., 2012). Moreover, frequent switches prevent boredom and thereby therapy compliance is stimulated. The recently developed training software of BrainGymmer® was

not available when this study took place.

Sixteen games were used and five cognitive domains were targeted: attention, speed, memory, flexibility and problem solving. Three games were randomly assigned to the participant per session. The duration of each game was approximately five minutes. After finishing all sessions of a single game, a new game started after pressing the "next" button. When all three games were completed, participants received feedback that the session for that day was finished. Participants were able to play longer by selecting games from the menu themselves after finishing the training session.

With each game, all participants began at the same level of difficulty. The difficulty level was then raised or lowered depending on the performance in the previous round of the respective game. The software provided feedback about game scores. Furthermore, participants were instructed to complete an extra game session when they missed a session and/or were not able to play five days a week. After eight weeks, participants still had access to the games, but were instructed to temporarily quit playing.

Control

The participants in the control group received weekly information about stroke after log-on at the website of the study. The information provision was not interactive, it provided unidirectional explanations about brain differences between men and woman, the influence of stress on brain function and possible difficulties with living with a damaged brain. Each week, during a period of 8 weeks, new information (text or a video clip) was added to the website. The information was accessible for the participants during the period of 8 weeks. The total duration of the control intervention was on average 70 minutes per person.

Assessments

All assessments were done before the intervention (t0), and 8 and 16 weeks thereafter (t1 and t2). At all time points, the assessments consisted of a set of electronic questionnaires and computer-based performance tests. With respect to the questionnaires, participants received an e-mail with a digital link to the questionnaires one week before each planned assessment, with the request to complete it at home. All computerised performance tests, which took approximately one hour to complete, were conducted in the rehabilitation centre. Tests were administered in a fixed order and every patient received the same instructions. Assistance during testing was provided by the principal investigator (MB) and two students and consisted of logging the participant on to the computer, setting up the tests, providing support in case of technical problems, explaining the test procedure if necessary and saving test results.

Sociodemographic and disease characteristics

Characteristics recorded at baseline by means of a questionnaire were: living situation (alone/together), daily functioning (dependent/independent), and participation in paid work (yes/no). In addition, the affected hemisphere (left/right/other), type of stroke (infarction/haemorrhage), time between stroke and enrolment, and time spent in rehabilitation centre (in months) were recorded from the medical records. The group of responders was compared to the group of non-responders regarding their age and gender using the Mann Whitney U test, the Chi-square test.

Adherence

Data about participants' total play time (in days and minutes) were provided by the software of the training programme.

Primary outcome measures

The primary outcome measures included five neuropsychological tests and the Cognitive Failures Questionnaire (CFQ). Secondary outcomes included a measure of QoL and of self-efficacy. As patients in the intervention group were discouraged from playing the games after 8 weeks, and under the assumption that a present effect would diminish afterwards, time point 1 was chosen as the primary endpoint for both primary and secondary outcome measures.

Attention and flexibility

The Trail Making Test (TMT; Reitan & Wolfson, 1985) was used to assess attention and flexibility. It consists of two parts (TMT-A and TMT-B): In TMT-A the participants were asked to draw lines sequentially connecting 25 encircled numbers distributed on the screen. In TMT-B task requirements were similar, however the participants must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). The scores represent the amount of time required to complete task A and B (attention) and the mean difference between time A and B (flexibility) (Strauss, Sherman, & Spreen, 2006). Lower scores for attention and higher scores for flexibility indicate better functioning. In addition, the number of correct connections made by the patients was scored. Both tests were proven to be valid indicators of organic brain damage (Lezak, Howieson, & Loring, 2004).

Working memory

The Block Span Task (Corsi, 1972) and Digit Span Task (Wechsler, 1945) were used to assess working memory with two subtests: blocks/digits forward (sequential order) and blocks/

digits backward (reversed order). The scores consist of the highest number of blocks/digits a participant can correctly reproduce, so that higher scores indicate better functioning. A number of studies have published data on the Block Span Task in stroke patients and concluded that it can be used effectively to assess visuospatial short-term memory in patients with brain damage (Chechlacz, Rotshtein, & Humphreys, 2014; De Renzi, Faglioni, & Previdi, 1977; Kessels, Van Zandvoort, Postma, Kappelle, & De Haan, 2000).

Speed and flexibility

With the Eriksen Flanker Task (Eriksen & Schultz, 1979) participants are instructed to respond as quickly as possible to a central target stimulus, which was flanked by either four congruent (e.g., ←←←←←) or four incongruent (e.g., ←←→←←) stimuli (Eriksen, 1995). The score of the test is the reaction time in milliseconds (speed) and the mean difference between reaction time incongruent and congruent (resistance to interference, flexibility) (Levin & Cross, 2004). Better functioning is indicated by lower scores for speed and higher scores for flexibility.

Fluid intelligence

The Raven Standard Progressive Matrices (SPM; Raven, 1958) is a multiple-choice test consisting of incomplete figures, in which participants are asked to choose the correct missing part depicted in one of the six alternatives. Three versions of equal difficulty with 20 items each were derived from the original 60-item version to assess fluid intelligence at the three time points in a counterbalanced order. The score of the test is the number of correct items translated in IQ scores. Higher scores indicate better functioning. Internal consistency coefficients tend to cluster around .90 for adults (Llabre, 1984) and retest reliability correlations are in the range of .70 and .90 (Llabre, 1984).

Cognitive Failures Questionnaire (CFQ)

The CFQ (Broadbent, Cooper, FitzGerald, & Parkes, 1982) in a Dutch version (Merckelbach, Muris, Nijman, & de Jong, 1995) was used to measure self-perceived cognitive failure. The CFQ includes 25 questions, for example: "Do you fail to notice signposts on the road?". The 5-point scale ranges from 0 (never) to 4 (very often). The total score ranges from 0 to 100, with higher scores indicating less cognitive failure. Broadbent et al. (1982) reported that the questionnaire has high test-retest correlation and high internal consistency. This was confirmed in a Dutch study by Merckelbach et al. (1995), in which the test-retest reliability (.83) and internal validity (Cronbach's $\alpha = .81$) were high. The questionnaire was also completed by the spouse or a person related to the participant.

Secondary outcome measures

Stroke Specific Quality of Life Scale (SS-QoL-12)

A Dutch and short version of the SS-QoL was used to measure health-related QoL (HRQoL) (Post et al., 2011). The self-rating 5-point scale consisted of 12 items. The total score ranges from 12 to 60, with higher scores indicating better function (Williams, Weinberger, Harris, Clark, & Biller, 1999). The questionnaire has been validated in patients with haemorrhage and ischaemic stroke (Post et al., 2011).

General Self-Efficacy Scale (GSES)

A Dutch version of the GSES, a 10-item self-rating scale (Schwarzer & Jerusalem, 1995), was used to assess participants' belief in the ability to respond to and cope with novel or difficult situations and unexpected setbacks or obstacles. The scale ranged from 1 (not at all true) to 4 (exactly true), resulting in a sum score ranging from 10 to 40, with higher scores indicating greater self-efficacy.

Data analysis

The target sample size was based on the ability to detect a difference of 25% in the proportion of patients (35% in the intervention group and 10% in the control group) showing a 25% improvement of the Raven SPM. Although larger than the effects seen in previous similar studies (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Karbach & Kray, 2009; Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002; Schmiedek, Lövdén, & Lindenberger, 2010; Shipstead, Redick, & Engle, 2012; Van Muijden, Band, & Hommel, 2012), this difference was considered to be clinically relevant. Based on a power of .80 to detect a significant difference (2-sided $p = .05$), 43 patients would be required for each study group. To compensate for an expected dropout rate of 15%, we planned to enrol at least 50 patients in each study group.

Adherence of participants in the intervention group was analysed using descriptive statistics and presented as the mean with the range or numbers and percentages. Change scores of endpoint measures over time between t0 and t1 and t1 and t2 in both the intervention and control groups were computed with the 95% confidence interval and analysed by means of paired t-tests or Wilcoxon Signed Rank test, where appropriate. Differences in the change scores between the groups were analysed by independent t-tests or Mann-Whitney U tests, where appropriate.

In addition, a linear mixed model with patient number as a random factor and group and measurement moments interaction as fixed factors were used to determine effects over the total period (t0–t1–t2). Corrections were made for differences in type of stroke

between the intervention and control group. Moreover, Spearman correlation coefficients were calculated to determine correlations between subjective cognitive impairment (CFQ) at baseline and change scores on neuropsychological tests between t0 and t1 and between play time on WM games and change scores on neuropsychological tests between t0 and t1.

All effectiveness analyses were based on intention to treat, meaning all available data were used. Per protocol analysis was performed, including the participants from the intervention group who played at least 600 minutes. For all analyses, the level of statistical significance was set at .05. All analyses were done with the software SPSS version 21.

Results

According to the registers, 889 patients who were aged between 45 and 75 years and had had a stroke between 12–36 months ago, were identified and invited to participate (Figure 1). Of these, 146 patients (64 in Leiden, 82 in The Hague) indicated they fulfilled the inclusion criteria and were interested in the study, of whom 142 were screened for eligibility (4 could not be reached). From these 142 patients, 27 were excluded because they either did not fulfil one or more inclusion criteria or met one or more of the exclusion criteria, so that 115 patients were included and randomised. Directly after randomisation, five patients refused further participation. Eventually, 110 patients were present at the first assessment day and included in the analysis (53 intervention and 57 control). Of these, 107 participants (97%) completed the study, 50/53 (94%) in the treatment group and 57/57 (100%) in the control group.

Demographic characteristics

The demographic and clinical characteristics of the 110 study participants are shown in Table 1. Participants' characteristics were similar in the intervention and control groups at baseline. However, in the intervention group significantly more patients had had a haemorrhage (21/53; 40%) compared to the control group (13/57; 23%) ($p = .02$).

No significant differences were found between age and gender for the group of 146 responders (median age 59, range 46–74; male n = 69, 63%) compared to the group of 743 non-responders (median age 61, range 45–75; male n = 459, 59%), $p = .62$ for age and $p = .66$ for gender, respectively.

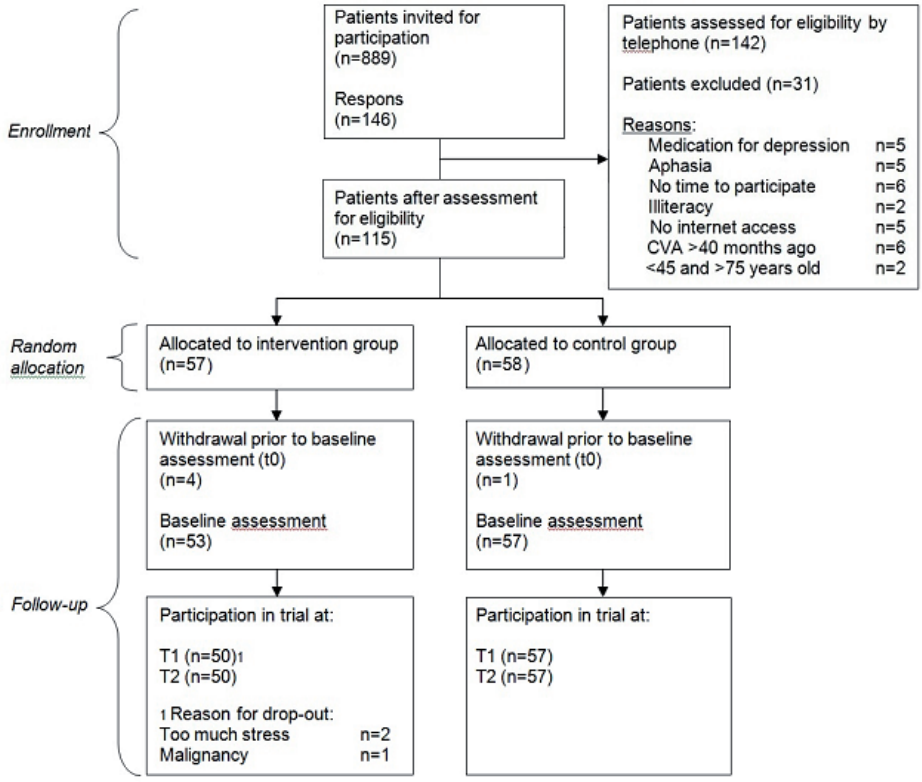

Figure 1. Trial profile.

Adherence to the intervention

Seven out of 53 patients in the intervention group failed to play games due to technical problems with their computer (n = 3), lack of motivation (n = 2) or not feeling well (n = 2). The number of days and total play time of the remaining 46 patients who actually played are shown in Table 2. The median number of days these patients played was 45 (range = 4–63) and the median total time played in minutes was 562 (range = 63–1264).

Two patients logged on only once and three patients between three and five times, so their play time was very limited. Reasons for not playing, according to the participants' personal coaches were: having difficulties playing the games due to health status, not sufficiently motivated, or technical problems with the computer. A group of seven patients played more than the 600 minutes requested. Two patients (4%) in the intervention group completed 2–3 training sessions during the follow-up period (8–16 weeks) despite explicit discouragement to do so.

Table 1. Baseline demographic and clinical characteristics of the 110 stroke patients.

	Intervention group (*n* = 53)	Control group (*n* = 57)
Age in years; median (range)	59 (46–74)	59 (46–73)
Sex, male n (%)	34 (64)	35 (61)
Type of stroke Infarction n (%)	29 (55)	44 (77)
Haemorrhage n (%)	21 (40)	13 (23)
Unknown [a] n (%)	3 (5)	0 (0)
Location of stroke		
Hemisphere left n (%)	23 (43)	28 (49)
Hemisphere right n (%)	26 (49)	26 (47)
Basal ganglia n (%)	3 (6)	0 (0)
Unknown [a] n (%)	1 (2)	2 (4)
Time from stroke onset to randomisation in months; mean ± SD	26 ± 9.1	25 ± 7.4
Time spent in rehabilitation centre in months; mean ± SD	6 ± 3.6	5 ± 3.4
Educational status [b]		
Low n (%)	17 (32)	20 (35)
Intermediate n (%)	18 (34)	18 (32)
High n (%)	18 (34)	19 (33)
Living alone n (%)	13 (25)	15 (25)
Independent in daily functioning n (%)	52 (98)	54 (95)
Participation in paid work n (%)	14 (26)	20 (32)
Subjective cognitive failure (CFQ); median (IQR)	63 (19)	64 (21)

[a] No data were available for medical status.
[b] Low: lower technical and vocational training; medium: secondary technical and vocational training; and high: higher technical and vocational training and university.

Primary outcome measures

Intention-to-treat analysis

Baseline and follow-up scores of primary outcomes are shown in Table 3(a). At baseline, no significant differences were found between the groups. A significant difference between the groups of changes between t0 and t1 was found regarding the number of correct items in favour of the intervention group on the Block Span Forward Test ($p = .02$) and the reaction time incongruent on the Eriksen Flanker Test ($p < .01$). No differences in improvement were seen between the two groups on other outcome measures.

Within both groups significant improvements were found between t0 and t1 regarding the cognitive domain attention for the parameters Time B and Items Correct B, but not for

Time A and Items Correct A. Moreover, participants in the intervention group improved between t0 and t1 within the cognitive domain flexibility (TMT-A/TMT-B), reaction time congruent (Eriksen Flanker Task) and fluid intelligence (Raven SPM, Peck score), whereas no significant changes were seen within the control group. In addition, there were no statistically significant differences between the groups taking into account all time points (T0-T1-T2) (mixed model analysis of variance).

The following correlations were found between baseline scores of subjective cognitive impairment (CFQ) and mean differences between t0 and t1 on the neuropsychological tests: TMT A Spearman, r = .180 (p = .07), and TMT B, r = .308 (p < .01), Block Span forward, r = –.181 (p = .06), and backward, r = –.079 (p = .42), Digit Span forward, r = –.184 (p = .06), and backward, r = –.295 (p < .01), Flanker incongruent, r = .168 (p = .09), and congruent, r = .158 (p = .11), and the Raven SPM, r = –.158 (p = .15). No significant correlations were found between play time on WM games and change scores on neuropsychological tests between t0 and t1.

Table 2. Total days and minutes played during the 8-week training period in the intervention group (46 out of 53 patients).

Characteristics	**Median (IQR)** [a]	
Participants who played	46	
Total time played (days)	45	(4–63)
Total time played (minutes)	528	(63–1264)
Total time played per cognitive domain (minutes):		
Attention	60	(3–408)
Speed	53	(3–139)
Memory	232	(26–646)
Flexibility	111	(6–349)
Problem solving	81	(1–265)

[a] IQR's are expressed as the net result of 75th percentile minus 25th percentile.

Table 3a. Baseline, follow-up and change scores for attention, flexibility, memory, speed, fluid intelligence and cognitive failure in the intervention versus the control group.

		T0		T0-T1			T1-T2		
				Within group	Between groups		Within group	Between groups	
		Median (IQR)[a]		Mean difference (95% CI)[b]	*p*-value[c]		Mean difference (95% CI)[b]	*p*-value[c]	
Working memory									
Items forward (Block Span Task)	I:	3	(2)	0.7	(0.3,1.1)	**0.02**	-0.1	(-0.4,0.3)	0.59
(0-9 items)	C:	4	(2)	-0.1	(-0.6,0.4)		0.2	(-0.2,0.6)	
Items backward (Block Span Task)	I:	3	(2)	0.3	(-0.2,0.8)	0.45	-0.2	(-0.7,0.2)	0.56
(0-8 items)	C:	3	(4)	0.1	(-0.3,0.6)		-0.1	(-0.6,0.4)	
Items forward (Digit Span Task)	I:	5	(2)	0.1	(-0.6,0.5)	0.23	0.4	(-0.1,0.8)	0.43
(0-9 items)	C:	5	(3)	0.5	(-0.0,0.1)		0.0	(-0.3,0.3)	
Items backward (Digit Span Task)	I:	4	(2)	0.1	(-0.5,0.8)	0.28	0.1	(-0.5,0.7)	0.25
(0-8 items)	C:	3	(3)	0.6	(0.1,1.1)		-0.2	(-0.7,0.2)	
Attention									
Time A (TMT-A)	I:	78	(49)	-7	(-21.6,7.8)	0.54	-5	(-17.2,8.1)	0.87
(0-2880s)	C:	74	(42)	-19	(-39.8,1.9)		8	(-12.3,27.7)	
Time B (TMT-B)	I:	169	(142)	-73	(-134.1,-11.5)	0.10	-11	(-27.5,4.9)	0.40
(0-2880s)	C:	144	(202)	-58	(-102.3,-12.8)		25	(-18.6,68.0)	
Items correct A (TMT-A)	I:	24	(0)	0.6	(-0.3,1.5)	0.85	0.1	(-0.7,0.9)	0.11
(0-24)	C:	24	(0)	0.7	(-0.4,1.8)		-0.3	(-0.7,0.1)	
Items correct B (TMT-B)	I:	17	(13)	2.5	(0.7,4.2)	0.38	1.1	(-0.3,2.6)	0.30
(0-24)	C:	20	(15)	1.6	(0.2,2.9)		-0.2	(-1.4,1.1)	
Speed (Flanker Task)									
Reaction time congruent	I:	770	(258)	-51	(-97.1,-5.4)	0.08	-16	(-38.8,6.6)	0.48
(0-2000 milliseconds)	C:	816	(285)	-4	(-57.9,50.7)		-42	(-86.0,2.5)	
Reaction time incongruent	I:	797	(268)	-63	(-118.9,-7.4)	**0.00**	-14	(-38.2,9.3)	0.08
(0-2000 milliseconds)	C:	833	(342)	9	(-49.5,67.1)		-46	(-91.1,-0.9)	
Flexibility									
Difference time A/time B	I:	-80	(125)	66	(6.5,124.7)	0.18	7	(-13.0,26.9)	0.56
(TMT-A/TMT-B)	C:	-61	(145)	34	(-15.7,84.5)		-17	(-65.9,31.8)	
Difference reaction time congruent/	I:	-31	(39)	10	(-9.4,29.0)	0.62	1	(-9.0,11.5)	0.56
incongruent (Flanker Task)	C:	-33	(62)	-12	(-39.8,15.0)		4	(-11.9,20.5)	
Fluid intelligence (Raven SPM)									
Peck-score	I:	110	(19)	6	(1.3,9.8)	0.47	-3	(-7.4:1.0)	0.34
(0-150)	C:	111	(17)	3	(-1.4,7.3)		-1	(-5.7:3.1)	
Cognitive failure (CFQ)									
Total score (participant)	I:	63	(19)	-0.5	(-3.9,2.9)	0.14	-0.9	(-5.5,3.8)	0.87
(0-100)	C:	64	(21)	1.4	(-1.0,3.6)		-1.6	(-4.9,1.7)	
Total score (relatives)	I:	63	(35)	-0.2	(-4.4,3.9)	0.75	1.5	(-2.8,5.8)	0.81
(0-100)	C:	59	(19)	3.2	(-2.0,8.5)		-0.05	(-5.6,5.5)	

[a] IQRs are expressed as the net result of 75th percentile minus 25th percentile. All analyses were done with adjustment for significant differences in baseline characteristics between patients.
[b] Values are the difference in mean change values between groups (treatment effect with 95% confidence interval).
[c] *p*-values were analysed using Mann-Whitney U test or mixed model analyses where appropriate.

Table 3b. Baseline and follow-up scores of variables attention, flexibility, working memory, and speed with significance between groups per protocol (n = 19).

		T0		T0-T1			T1-T2		
				Within group		Between groups	Within group		Between groups
		Median (IQR)[a]		Mean difference (95% CI)[b]		*p*-value[c]	Mean difference (95% CI)[b]		*p*-value[c]
Working memory									
Items forward (Block Span Task)	I:	4	(3)	0.9	(0.4,1.8)	.09	-0.3	(-0.4,0.3)	.66
(0-9 items)	C:	4	(2)	-0.1	(-0.6,0.4)		0.2	(-0.2,0.6)	
Items backward (Block Span Task)	I:	3	(2)	0.4	(-0.2,0.7)	.42	-0.2	(-0.8,0.2)	.35
(0-8 items)	C:	3	(4)	0.1	(-0.3,0.6)		-0.1	(-0.6,0.4)	
Items forward (Digit Span Task)	I:	5	(2)	0.1	(-0.8,0.5)	.50	0.4	(-0.1,0.7)	.21
(0-9 items)	C:	5	(3)	0.5	(-0.0,0.1)		0.0	(-0.3,0.3)	
Items backward (Digit Span Task)	I:	4	(3)	0.1	(-0.5,0.7)	.40	0.2	(-0.6,0.7)	.88
(0-8 items)	C:	3	(3)	0.6	(0.1,1.1)		-0.2	(-0.7,0.2)	
Attention									
Time A (TMT-A)	I:	76	(45)	-27	(-45,2,-3.8)	.69	-9	(-14.1,10.1)	.93
(0-2880s)	C:	74	(42)	-19	(-39.8,1.9)		8	(-11.5,34.7)	
Time B (TMT-B)	I:	169	(143)	-81	(-160.0,-3.0)	.04	-12	(-14.9,3.7)	.30
(0-2880s)	C:	144	(202)	-58	(-102.3,-12.8)		25	(-18.6,68.0)	
Items correct A (TMT-A)	I:	24	(0)	0.6	(-0.3,1.5)	.35	0.1	(-0.9,1.1)	.20
(0-24)	C:	24	(0)	0.7	(-0.4,1.8)		-0.3	(-0.7,0.1)	
Items correct B (TMT-B)	I:	17	(15)	2.5	(0.7,4.2)	.45	1.4	(-0.3,2.6)	.12
(0-24)	C:	20	(15)	1.6	(0.2,2.9)		-0.2	(-1.4,1.1)	
Speed (Flanker Task)									
Reaction time congruent	I:	696	(244)	-59	(-110.1,-13.2)	.09	-22	(-40.2,7.8)	.48
(0-2000 milliseconds)	C:	816	(285)	-4	(-57.9,50.7)		-42	(-86.0,2.5)	
Reaction time incongruent	I:	719	(266)	-71	(-125.0,-5.4)	.07	-19	(-36.6,12.3)	.08
(0-2000 milliseconds)	C:	833	(342)	9	(-49.5,67.1)		-46	(-91.1,-0.9)	
Flexibility									
Difference time A/time B	I:	-91	(119)	71	(12.2,136.9)	**.00**	-14	(-3.6,32,8)	.56
(TMT-A/TMT-B)	C:	-61	(145)	34	(-15.7,84.5)		-17	(-65.9,31.8)	
Difference reaction time congruent	I:	-26	(32)	15	(-5.4,32.2)	.62	4	(-11.5,9.9)	.56
/incongruent (Flanker Task)	C:	-33	(62)	-12	(-39.8,15.0)		4	(-11.9,20.5)	
Fluid intelligence (Raven SPM)									
Peck-score	I:	107	(21)	7	(1.0,9.3)	.47	-3	(-7.4:1.0)	.34
(0-150)	C:	111	(17)	3	(-1.4,7.3)		-1	(-5.7:3.1)	
Cognitive failure (CFQ)									
Total score (participant)	I:	63	(19)	-0.4	(-4.0,3.19)	.14	-0.5	(-3.6,2.3)	.87
(0-100)	C:	64	(21)	1.4	(-1.2,3.4)		-1.6	(-4.9,1.7)	
Total score (relatives)	I:	63	(35)	-0.2	(-4.2,3.2)	.75	0.5	(-2.8,3.6)	.81
(0-100)	C:	59	(19)	3.2	(-2.0,8.5)		-0.05	(-5.6,5.5)	

[a] IQRs are expressed as the net result of 75th percentile minus 25th percentile. All analyses were done with adjustment for significant differences in baseline characteristics between patients.
[b] Values are the difference in mean change values between groups (treatment effect with 95% confidence interval).
[c] *p*-values were analysed using Mann-Whitney U test or mixed model analyses where appropriate.

Per protocol analysis

Comparisons of change scores between the intervention and control group (n = 57), while including only the 19 patients who played at least 600 minutes in the intervention group are shown at Table 3(b). A significant difference between groups was found at 8 weeks regarding attention (TMT-B, Time B, p = .04) and flexibility (TMT-A/TMT-B, Difference time A and time B, p < .01), both in favour of the intervention group. In the intention-to-treat (ITT) analysis no significant differences were found between groups regarding the TMT. However, effects found in the ITT analysis between groups did not remain significant in the per protocol analysis when compared to the control group regarding Block Span items correct forward (p = .07) and reaction time incongruent on the Flanker Task (p = .09).

When compared to ITT analysis, the magnitude of improvements in the per-protocol analysis increased within the intervention group between t0 and t1 regarding speed (Eriksen Flanker Task, reaction time congruent; reaction time incongruent), working memory (Block Span backward), flexibility (difference time A/time B; difference reaction time congruent/incongruent), fluid intelligence (Raven SPM) and subjective cognitive failure (CFQ).

Secondary outcome measures

Baseline and follow-up scores of secondary outcomes are shown in Table 4. At baseline, no significant differences were found between both groups and no differences were seen in change scores between the two groups. In addition, there were no statistically significant difference between the groups taking into account all time points (T0-T1-T2) (mixed model analysis of variance).

Table 4. Baseline and follow-up scores of QoL and self-efficacy with significance in the intervention versus the control group.

		T0 Median (IQR)[a]	T0–T1 Mean difference (95% CI)[b]	*p*-value[c]	T1–T2 Mean difference (95% CI)[b]	*p*-value[c]
QoL[d]	I:	3.9 (1.5)	0.0 (−0.2,0.2)	.76	0.1 (−0.1,0.3)	.45
Total score (0–5)	C:	3.8 (1.3)	0.0 (−0.1,0.2)		0.0 (−0.1,0.1)	
Self-efficacy[e]	I:	31 (10)	1.0 (0.3,2.2)	.15	0.52 (−0.6,1.6)	.86
Total score (0–40)	C:	30 (8)	−0.6 (−1.8,0.6)		0.29 (−1.1,1.7)	

[a] IQR's are expressed as the net result of 75th percentile minus 25th percentile. All analyses were done with adjustment for significant differences in baseline characteristics between patients.
[b] Values are the difference in mean change values between groups (treatment effect with 95% confidence interval).
[c] *p*-values were analysed using Mann-Whitney U test or mixed model analyses where appropriate.
[d] Measured with the Stroke Specific Quality of Life Questionnaire (SSQoL).
[e] Measured with the General Self-efficacy Scale (GSES).

Discussion

In this randomised study an 8-week computer-based brain training programme was compared with providing information to patients with cognitive complaints after stroke. In general only performances on cognitive function tests that were similar to the games included in the intervention improved in the CBCR training group compared to the control group. However, no near transfer effect was found to tasks such as the Digit Span Task or Trail Making Task.

The effects found in our study on the WM tests; effect size 0.23 regarding the Span board and 0.11 regarding the Digit Span between groups, were smaller than other studies using CBCR training primarily focused on one cognitive function among stroke patients. Westerberg et al. (2007), who compared a computerised 5-week WM training (Cogmed) on various WM tasks with a passive control group, reported significant improvements in favour of the intervention group on the WM tests; effect size Span Board 0.83 and effect size Digit Span 1.58. Åkerlund et al. (2013) also found a significant difference on the Digit Span Task in favour of the group who received WM training in the sub-acute phase compared to usual rehabilitation. Smith et al. (2009) evaluated the effect of a 40-hour CBCR training targeting speed and information processing among healthy adults and found an effect size of 0.26 between groups on the Digit Span Backward in favour of the intervention group. Based on these results it can be concluded that the effects of the CBCR training were limited in this group of patients.

Moreover, other CBCR studies found improvements of daily functioning after training. Westerberg et al. (2007) reported a significant change on the CFQ ($p < .01$) and Åkerlund et al. (2013) found less depressive symptoms after WM training between groups ($p = .03$), in both studies in favour of the intervention group. In the current study, no far transfer effects were shown, i.e., no significant difference was found on cognitive functioning by means of the CFQ, QoL scale or self-efficacy scale. Although results of the studies cannot be easily compared to the current study, since the total training period was lower in our study, they indicate that interventions primarily focused on one cognitive function instead of multiple cognitive domains might be more effective for stroke patients. However, in line with the results in our study, Barker-Collo et al. (2009) found very limited effects on tests that were related to the trained tasks and no result in a near or far transfer.

There are a number of potential explanations for the observed lack of effect. Apart from the intervention not being effective, it remains unclear to what extent responsiveness of the outcome measures also played a role, although the neuropsychological tests have proven ability to measure changes over time in studies among stroke patients (Åkerlund et al., 2013; Barker-Collo et al., 2009; Broadway & Engle, 2010; Chechlacz et al., 2014; Kessels et al., 2000; Nys et al., 2006; Sanchez-Cubillo et al., 2009; Spikman, 2001; Westerberg et al., 2007).

Second, it is questionable whether the dose of the training was enough to achieve responses (dose-response relation). Seven out of the 53 people in the intervention group did not follow the training and only 19 out of the 53 patients, who actually played, completed the training (playing > 600 minutes). This was why a per protocol analysis was done. Indeed, within the intervention group the magnitude of change was larger in the per protocol analysis than with the ITT analysis. However, the difference with the control condition did not reach statistical significance, most likely due to a lack of power because of the limited sample size.

Of note was the finding that some significant improvements were also seen in the control group (time B and items correct B). This might be explained by a learning effect on the neuropsychological tests, since patients became more familiar with using the computer while testing more frequently. For instance, the TMT requires skills moving the mouse on the screen to connect items. By using strategies, for example, using the non-affected hand, scores can increase. Although the primary focus of our study was to investigate an intervention based on restitution approaches, it cannot be ruled out that patients developed strategies that had positive effects on the outcomes. Unfortunately, the average time spent on the control intervention was not available at the level of the individual patient.

Overall, significant differences between both groups were found on 2 out of the 17 outcome measures used in the study. Since multiple outcomes are used, appearances of significant differences can occur from chance alone. However, no corrections for multiple testing were performed for the reason that as the number of tests increases, the p-value that has to be exceeded to achieve statistical significance decreases markedly, lowering the statistical power (Armstrong, 2014; Nakagawa, 2004).

The observation that only 19/53 completed the intervention as it was intended indicates that the feasibility of a programme in the present form is limited. Non-users were also found in other CBCR studies among stroke patients (Connor & Standen, 2012; Cruz et al., 2013), where it was suggested that CBCR training is not well used by all patients, probably due to high demands of training and the motivation needed to complete the training. On the other hand, the fact that 46 out of 53 patients (partly) followed the training (93%), indicates that there is a need among some stroke patients for online training in the chronic phase after stroke. More research is needed to determine patient characteristics that can impair or improve compliance and which stroke patients can benefit the most from CBCR or cognitive rehabilitation in general.

A limitation of the study is that participants were selected on the basis of subjective cognitive impairment and that scores on the CFQ showed that the level of impairment varied widely among patients. Selection bias could have occurred when included patients had lower ability to improve because they were objectively not impaired. Moreover, patients with aphasia or patients unable to use a computer were excluded. This implies that the

patients who were selected were in better health.

A second limitation is that all patients (age: 45–75 years, CVA: 12–36 months ago) were invited by letter to participate in the trial by their treating physician, but were only asked to return the letter if they were willing to participate. Therefore, it is not clear why non-responders did not wish to participate.

In addition, the sample size was based on the assumption that the intervention would lead to a relatively large difference in neuropsychological function as compared to the control group. This assumption was probably too optimistic, leading us to the conclusion that in future research even larger studies are needed to detect changes over time and/or differences between groups. With more knowledge about the clinical relevance of improvements becoming available in stroke research, future sample size calculations will be better underpinned, using empirical data.

A strength of the study is that it was one of the first to examine the effect of CBCR on multiple cognitive functions and also to assess the transferability to QoL and self-efficacy after stroke. Additionally, it is one of the few RCT CBCR studies with a large sample and follow-up that has investigated long-term effects. Furthermore, only three participants did not complete the follow-up assessments, so the drop-out rate was relatively low.

Overall, the results of this study and similar research imply that CBCR interventions targeting one cognitive domain are more effective for stroke patients in terms of near and far transfer effects compared to those targeting multiple cognitive domains. In order to improve daily activities of stroke patients, computer tasks need to be closely related to the impaired task itself. Thus, CBCR training needs to be tailored and adapted to each patient's individual profile. It would appear important to support stroke patients with CBCR training, since training is not well used by all patients. It is possible patients benefit more when they learn how to use strategies in their training and when motivated by clinicians (Lynch, 2002). Further research is needed to determine if CBCR training can improve cognitive functioning in chronic stroke patients. Brain mapping techniques, such as functional magnetic resonance imaging, might be helpful in identifying effects on brain plasticity (Carter et al., 2010).

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