Effekte eines postoperativen kognitiven Trainings auf postoperative kognitive Defizite nach herzchirurgischen Operationen

Kumulative Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

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vorgelegt von

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Inhaltsverzeichnis

Zusammenfassung

Hintergrund

Herzchirurgische Operationen gelten als Risikofaktor für postoperative kognitive Defizite (POCD), die die gesundheitsbezogene Lebensqualität beeinträchtigen und die Mortalität erhöhen können. Das Ziel dieser Studie war es, ein kognitives Training zu entwickeln und die Auswirkungen dieser Intervention auf POCD, subjektiv eingeschätzte kognitive Beeinträchtigungen im Alltag und die gesundheitsbezogene Lebensqualität bei älteren Patienten nach herzchirurgischen Eingriffen zu untersuchen.

Methoden

In dieser multizentrischen, randomisierten, kontrollierten und ergebnisverblindeten Studie wurden ältere Patienten untersucht, die sich einer elektiven Herzklappenoperation mit extrakorporaler Zirkulation unterzogen hatten. Die Rekrutierung erfolgte in den Abteilungen für Herzchirurgie der Kerckhoff-Klinik in Bad Nauheim und der Universitätsklinik in Gießen. Die Patienten wurden entweder einer Papier- und Bleistift-basierten kognitiven Trainingsgruppe oder einer "Treatment as Usual"-Gruppe zugewiesen. Das kognitive Training begann eine Woche nach der Operation und dauerte etwa drei Wochen bis zur Entlassung aus der Rehabilitation. Um POCD zu untersuchen, wurden neuropsychologische Parameter vor der Operation, bei der Entlassung aus der Rehabilitation (primäres Ergebnis) sowie drei und zwölf Monate nach der Entlassung (sekundäres Ergebnis) getestet. Zusätzlich wurden die gesundheitsbezogene Lebensqualität (SF-36) und die subjektiv eingeschätzten kognitiven Beeinträchtigungen im Alltag (CFQ) vor der Operation sowie drei und zwölf Monate nach dem kognitiven Training erhoben (sekundäres Ergebnis).

Hauptergebnisse

Die Häufigkeit von POCD bei Entlassung aus der Rehabilitation (Trainingsgruppe, n=37; Kontrollgruppe, n=44) betrug 50% in der Kontrollgruppe und 19% in der Trainingsgruppe ($\chi^2[1]=8.45$, p=0.004; OR=4.29, 95% CI [1.56-11.80]). Drei Monate nach dem kognitiven Training (Trainingsgruppe, n=33; Kontrollgruppe, n=34) betrug die POCD-Häufigkeit 29% in der Kontrollgruppe und 6% in der Trainingsgruppe ($\chi^2[1]=6.21$, p=0.013; OR=6.46, 95% CI [1.29-32.28]). Zwölf Monate nach dem kognitiven Training (Trainingsgruppe, n=19; Kontrollgruppe, n=27) zeigte sich eine POCD-Häufigkeit von 22% in der Kontrollgruppe und 11% in der Trainingsgruppe ($\chi^2[1]=1.06$, p=0.440; OR=2.43, 95% CI [0.43-13.61]).

Weiterhin zeigten sich, unter Berücksichtigung der Baseline-Daten, in der Trainingsgruppe verglichen mit der Kontrollgruppe drei Monate nach dem Training verbesserte Werte in der gesundheitsbezogenen Lebensqualität, insbesondere in den Bereichen Rolleneinschränkungen durch

emotionale Probleme (U=-2.649, p=0.008, η^2=0.121), Energie und Müdigkeit (F[2.55]=5.72, p=0.020, η^2=0,062), soziale Funktionsfähigkeit (U=-2.137, p=0.033, η^2=0.076), Durchschnitt aller SF-36-Faktoren (U=-2.374, p=0.018, η^2=0.094), Veränderung des Gesundheitszustandes vom letzten Jahr zum aktuellen Zeitpunkt (U=-2.378, p=0.017, η^2=0.094), und Durchschnitt aller psychologischen Faktoren (U=-2.470, p=0.013, η^2=0.102). Zwölf Monate post-training (Training: n=30, Kontrolle: n=28) zeigten sich in der Trainingsgruppe verbesserte Werte in den Bereichen Rolleneinschränkungen aufgrund körperlicher Gesundheit (U=-2.447, p=0.015, η^2=0.109), Rolleneinschränkungen durch emotionale Probleme (U=-2.245, p=0.025, η^2=0.092), Schmerzen (U=-1.979, p=0.049, η^2=0.068), Durchschnitt aller SF-36-Faktoren (U=-3.237, p<0.001, η^2=0.181), Veränderung des Gesundheitszustandes vom letzten Jahr zum aktuellen Zeitpunkt (U=-2.091, p=0.037, η^2=0.075), Durchschnitt aller physiologischen Faktoren (U=-2.803, p=0.005, η2=0.138), und Durchschnitt aller psychologischen Faktoren (U=-2.350, p=0.018, η^2=0.095).

Es zeigten sich zwischen den Gruppen keine statistisch signifikanten Unterschiede (p<0.05) in den von den Patienten selbst berichteten kognitiven Beeinträchtigungen im Alltag.

Schlussfolgerung

Das von unserer Arbeitsgruppe vorgestellte kognitive Training kann eine Methode zur Prävention von POCD und zur Verbesserung der gesundheitsbezogenen Lebensqualität nach einer Herzoperation sein.

Abstract

Background

Cardiac surgical operations are considered a risk factor for postoperative cognitive deficits (POCD), which can impair health-related quality of life and increase mortality. The aim of this study was to develop a cognitive training, investigate this intervention's effects on POCD, and subjectively assess cognitive impairments in everyday life and health-related quality of life in older patients after cardiac surgical procedures.

Methods

In this multicenter, randomized, controlled, and outcome-blinded study, older patients who underwent elective heart valve surgery with extracorporeal circulation were examined. Recruitment took place in the departments of cardiovascular surgery at the Kerckhoff Clinic in Bad Nauheim and the University Clinic in Giessen. Patients were assigned to either a paper-and-pencil-based cognitive training group or a treatment-as-usual group. The cognitive training began one week after the surgery and lasted about three weeks, until discharge from rehabilitation. To investigate POCD, neuropsychological parameters were tested preoperatively, at discharge from rehabilitation (primary

outcome), and three and twelve months after discharge (secondary outcome). Additionally, health-related quality of life (SF-36) and subjectively assessed cognitive impairments in everyday life (CFQ) were assessed preoperatively and three and twelve months after cognitive training (secondary outcome).

Main results

The frequency of POCD at discharge from rehabilitation (training group, n=37; control group, n=44) was 50% in the control group and 19% in the training group (χ^2[1]=8.45, p=0.004; OR=4.29, 95% CI [1.56-11.80]). Three months after cognitive training (training group, n=33; control group, n=34), the POCD frequency was 29% in the control group and 6% in the training group (χ^2[1]=6.21, p=0.013; OR=6.46, 95% CI [1.29-32.28]). Twelve months after cognitive training (training group, n=19; control group, n=27), POCD frequency was 22% in the control group and 11% in the training group (χ^2[1]=1.06, p=0.440; OR=2.43, 95% CI [0.43-13.61]).

Additionally, considering baseline data, three months after training, compared to the control group, the training group showed improved values in health-related quality of life, especially in the domains of role limitations due to emotional problems (U=-2.649, p=0.008, η2=0.121), energy and fatigue (F[2.55]=5.72, p=0. 020, η2=0.062), social functioning (U=-2.137, p=0.033, η2=0.076), average of all SF-36 factors (U=-2.374, p=0.018, η2=0.094), health change from the past year (U=-2.378, p=0.017, η2=0.094), and average of all psychological factors (U=-2.470, p=0.013, η2=0.102). Twelve months after training (training: n=30, control: n=28), the training group showed improved scores in role limitations due to physical health (U=-2.447, p=0.015, η2=0.109), limitations due to emotional problems (U=-2.245, p=0.025, η2=0.092) pain (U=-1.979, p=0.049, η2=0. 068), average of all SF-36 factors (U=-3.237, p<0.001, η2=0.181), health change from the past year (U=-2.091, p=0.037, η2=0.075), average of all physiological factors (U=-2.803, p=0.005, η2= 0.138), and average of all psychological factors (U=-2.350, p=0.018, η2=0.095).

No statistically significant (p<0.05) differences were found in the self-reported cognitive impairments in daily life due to the training.

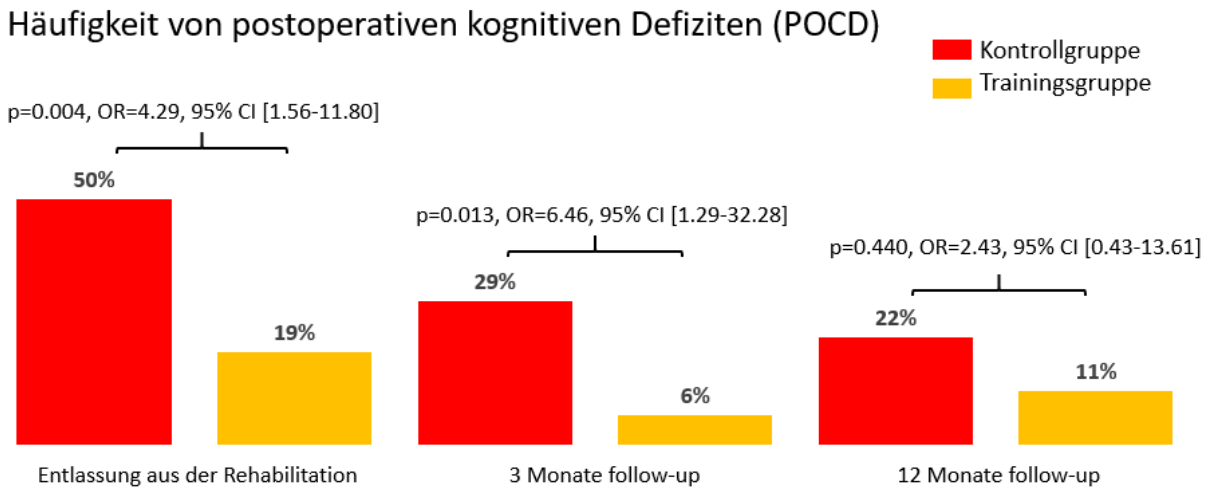
Conclusion

The cognitive training our working group presented can be a method for preventing POCD and improving health-related quality of life after heart surgery.

Registrierung der klinischen Studie

Deutsches Register für klinische Studien (DRKS00015512).

Graphischer Abstract



Graphischer Abstract: Häufigkeit von POCD zwischen den Gruppen und Messzeitpunkten. POCD = „postoperative kognitive Defizite".

Einleitung

Zu den neurologischen Komplikationen, die bei Herzchirurgie auftreten können, gehören Schlaganfälle (ischämisch und hämorrhagisch), Krampfanfälle, Delirium, das zerebrale Hyperperfusionssyndrom sowie postoperative kognitive Defizite (POCD) (1). Unter diesen scheint POCD die höchste Inzidenz aufzuweisen. Allerdings hängt die Häufigkeit stark von den Einschluss- und Ausschlusskriterien, dem Nachbeobachtungsintervall und den verwendeten Diagnosekriterien ab (2).

POCD kann definiert werden als ein Rückgang von mehr als einer Standardabweichung zwischen der präoperativen und postoperativen kognitiven Leistung eines Patienten in mindestens 20% aller gemessenen kognitiven Bereiche (z.B. verbales Gedächtnis, selektive Aufmerksamkeit oder Wortflüssigkeit) (3). Eine Meta-Analyse von Patienten mit koronarer Bypass-Operation (CABG) zeigte eine POCD-Häufigkeit von 28% zwischen dem ersten und vierten postoperativen Monat und 22% zwischen dem sechsten und zwölften postoperativen Monat (3). POCD kann weitere Folgen haben, wie z.B. eine verminderte Lebensqualität (4), eine erhöhte Sterblichkeit (5), erhöhte wirtschaftliche Kosten (5) und einen langfristigen kognitiven Abbau (6). Obwohl POCD häufig subklinisch auftritt und daher oft unerkannt bleibt, berichten sowohl Patienten als auch ihre Angehörigen über eine subjektive Abnahme der kognitiven Fähigkeiten im täglichen Leben bis zu mindestens 3 Monate nach der Herzoperation (7). Neben POCD kann auch eine postoperative kognitive Verbesserung (postoperative cognitive improvement, POCI) auftreten, deren Häufigkeit 3-6 mal geringer beziffert wird als die der POCD (8).

Mehrere Studien haben gezeigt, dass gesunde ältere Personen (9), Patienten mit leichter kognitiver Beeinträchtigung (10) sowie Schlaganfall- (11, 12) oder chirurgische Patienten nach Allgemeinanästhesie (13) ihre kognitiven Fähigkeiten durch kognitives Training verbessern können. Zusätzlich kann ein kognitives Training auch Depressionen reduzieren und die Alltagsfunktionen verbessern (14). Randomisierte kontrollierte Studien haben auch die Wirkung von kognitiven Trainings bei herzchirurgischen Patienten untersucht (15-17). Diese wurden durch computergestützte Trainingsverfahren durchgeführt und haben unterschiedliche Ergebnisse gezeigt.

Das Ziel dieser prospektiven, randomisierten und kontrollierten Studie war es, die Auswirkungen eines frühen postoperativen Papier- und Bleistift-basierten kognitiven Trainingsprogramms auf die kognitiven Funktionen und die gesundheitsbezogene Lebensqualität von Patienten zu untersuchen, die sich einer Herzoperation mit extrakorporaler Zirkulation unterziehen.

Auflistung der Manuskripte

Manuskripte publiziert

Manuskript 1:

Butz M, El Shazly J, Sammer G, Tschernatsch M, Kastaun S, Yenigün M, Braun T, Kaps M, Böning A, Puvogel U, Bachmann G, Mengden T, Schönburg M, Gerriets T, Juenemann M. Decreasing postoperative cognitive deficits after heart surgery: protocol for a randomized controlled trial on cognitive training. Trials. 2019 Dec 16;20(1):733. doi: 10.1186/s13063-019-3799-0. PubMed PMID: 31842959; PubMed Central PMCID: PMC6916013.

Zusammenfassung:

Die Studie wurde als multizentrische, randomisierte und kontrollierte Intervention konzipiert. Ältere Patienten mit elektiver Herzklappenoperation unter dem Einsatz der extrakorporalen Zirkulation wurden eingeschlossen. Die Rekrutierung erfolgte in den Abteilungen für Herzchirurgie der Kerckhoff-Klinik in Bad Nauheim und der Universitätsklinik in Gießen. Die Patienten wurden entweder einer Papier- und Bleistift-basierten kognitiven Trainingsgruppe oder einer "Treatment as Usual"-Gruppe zugewiesen. Das kognitive Training begann eine Woche nach der Operation und dauerte etwa drei Wochen bis zur Entlassung aus der Rehabilitation. Um POCD zu untersuchen, wurden neuropsychologische Parameter vor der Operation, bei der Entlassung aus der Rehabilitation (primäres Ergebnis) sowie drei und zwölf Monate nach der Entlassung (sekundäres Ergebnis) getestet. Zusätzlich wurden die gesundheitsbezogene Lebensqualität (SF-36) und die subjektiv eingeschätzten kognitiven Beeinträchtigungen im Alltag (CFQ) vor der Operation sowie drei und zwölf Monate nach dem kognitiven Training erhoben (sekundäres Ergebnis).

Im Rahmen der Studie wurde, aufgrund einer gründlichen Literaturrecherche über die Umsetzbarkeit und Wirksamkeit von kognitiven Trainings, ein Trainingskonzept entwickelt, das an die kognitiven Anforderungen unseres Patientenkollektivs angepasst wurde. Als Ergebnis konstruierten wir ein Papier- und Bleistift-basiertes Trainingsprogramm, das mehrere kognitive Funktionen trainiert, die vor allem im Alltag für die Aufrechterhaltung sozialer Funktionen und der Erwerbsfähigkeit notwendig sind (z.B. Wortflüssigkeit und Arbeitsgedächtnis). Eine Trainingseinheit dauert ca. 40 Minuten und sollte gemäß Plan an 6 Tagen pro Woche für 3 Wochen durchgeführt werden. Das tägliche Trainingsprogramm besteht aus 8 verschiedenen Aufgaben, die die Verarbeitung von Wörtern, Kategorien, Bildern, Kopfrechnen und Planung ansprechen. An jedem Trainingstag werden neue Wörter, Kategorien, Bilder, Kopfrechnungen und Planungsaufgaben präsentiert. Um die Bearbeitungszeit zu kontrollieren, müssen die Patienten ihre Arbeit pro Aufgabe mit Hilfe einer Digitaluhr begrenzen. Zu Beginn des Trainingsprogramms gibt ein psychologischer Trainingsleiter in einer 1-zu-1-Trainingseinheit explizite Anweisungen und steht bei Fragen zu den Übungen zur Verfügung. Wenn in den folgenden Trainingstagen keine weitere Hilfe benötigt wird, werden dem Patienten für die folgenden 6 Tage Trainingsmaterialien zur Verfügung gestellt, damit der Patient das Training selbstständig in seinem Stationszimmer absolvieren kann. Zu jeder Aufgabe gibt es genaue schriftliche Anweisungen, die als Hilfestellung bei der Ausführung dienen können. Wenn ein Patient Fragen zum Training hat, kann er sich an den Trainingsleiter zu vereinbarten Besprechungszeiten telefonisch oder persönlich im Büro wenden. Nach jedem 6. Tag wird die Arbeitsleistung der Patienten durch den Trainingsleiter überprüft und neues Trainingsmaterial zur Verfügung gestellt.

Manuskript 2:

Butz M, Gerriets T, Sammer G, El-Shazly J, Tschernatsch M, Huttner HB, Braun T, Boening A, Mengden T, Choi YH, Schoenburg M, Juenemann M. Effects of postoperative cognitive training on neurocognitive decline after heart surgery: A randomized clinical trial. Eur J Cardiothorac Surg. 2022 Apr 12:ezac251. doi: 10.1093/ejcts/ezac251. Epub ahead of print. PMID: 35415742.

Hauptergebnisse:

Bei Entlassung aus der Rehabilitationsklinik (Training: n=37, Kontrolle: n=44) betrug die POCD-Häufigkeit 50% (n=22) in der Kontrollgruppe und 19% (n=7) in der Trainingsgruppe ($\chi^2[1]=8,45$, p=0,004; OR=4,29, 95% CI [1,56-11,80]). Die POCI-Häufigkeit betrug 22% (n=8) in der Trainingsgruppe und 18% (n=8) in der Kontrollgruppe ($\chi^2[1]=0,15$, p=0,699; OR=0,81, 95% CI [0,27-2,41]).

Darüber hinaus zeigte das kognitive Training spezifische Effekte auf neuropsychologische Parameter. Zum Zeitpunkt der Entlassung aus der Rehabilitation zeigte die Trainingsgruppe im Vergleich zur Kontrollgruppe Verbesserungen in den Domänen selektive Aufmerksamkeit, gemessen mit dem „Trail-Making-Test-A“ (TMT-A) ($F[2.78]=5.66$, p=0.020, $\eta^2=0.04$), und der phonematischen Wortflüssigkeit,

ermittelt mit dem Regensburger-Wortflüssigkeitstest (RWT) (F[2.78]=6.18, p=0.015, η^2=0.06), während sich die Patienten der TAU-Gruppe in diesen Domänen verschlechterten.

Beim 3-Monats-Follow-up (Training: n=33, Kontrolle: n=34) betrug die POCD-Häufigkeit 29 % (n=10) in der Kontrollgruppe und 6 % (n=2) in der Trainingsgruppe (χ^2[1]=6,21, p=0,013; OR=6,46, 95% CI [1,29-32,28]). Die POCI-Häufigkeit betrug 36% (n=12) in der Trainingsgruppe und 15% (n=5) in der Kontrollgruppe (χ^2[1]=4,15, p=0,042; OR=0,30, 95% CI [0,09-0,99]). Weiterhin zeigten sich 3 Monate post-training spezifische Effekte zugunsten der Trainingsgruppe (Baseline korrigiert) in den Bereichen visuelle Wiedererkennungsfähigkeit, gemessen mit dem Syndrom-Kurz-Test (SKT) (U=-2,22, p=0,027, η^2=0.07), verbaler freier Abruf (kurze Verzögerung, ca. 1 Minute) gemessen mit dem „Verbalen Merk- und Lernfähigkeitstest“ (VLMT) (F[2,64]=4,21, p=0,044, η^2=0,04), verbale Arbeitsgedächtnisspanne, getestet mit dem „Letter-Number-Span-Test“ (LNS) (F[2,64]=6,77, p=0,011, η^2=0.070), kognitive Inhibitionsgeschwindigkeit, gemessen mit dem SKT (F[2.64]=4.02, p=0.049, η^2=0.02), und phonematische Wortflüssigkeit, getestet mit dem RWT (F[2.64]=6.99, p=0.010, η^2=0.07).

Manuskript 3:

Butz M, Gerriets T, Sammer G, El-Shazly J, Tschernatsch M, Schramm P, Doeppner TR, Braun T, Boening A, Mengden T, Choi YH, Schoenburg M, Juenemann M. The impact of postoperative cognitive training on health-related quality of life and cognitive failures in daily living after heart valve surgery: A randomized clinical trial. Brain Behav. 2023 Feb 13:e2915. doi: 10.1002/brb3.2915. Epub ahead of print. PMID: 36785920.

Hauptergebnisse:

Drei Monate nach der Entlassung aus der Rehabilitation wies die Trainingsgruppe (n=31) im Vergleich zur Kontrollgruppe (n=29) unter Berücksichtigung der präoperativen Ausgangsdaten einige Verbesserungen der gesundheitsbezogenen Lebensqualität auf. Diese Verbesserungen zeigten sich in den Bereichen Rolleneinschränkungen durch emotionale Probleme (U=-2.649, p=0.008, η^2=0.121), Energie und Müdigkeit (F[2.55]=5.72, p=0.020, η^2=0.062), soziale Funktionsfähigkeit (U=-2.137, p=0.033, η^2=0. 076), Durchschnitt aller SF-36-Faktoren (U=-2,374, p=0,018, η^2=0,094), Veränderung des Gesundheitszustandes vom letzten Jahr zum jetzigen Zeitpunkt (U=-2,378, p=0,017, η^2=0,094) und im Durchschnitt aller psychologischen Faktoren (U=-2,470, p=0,013, η^2=0,102). Es zeigten sich keine statistisch signifikanten Unterschiede in den von den Patienten selbst berichteten kognitiven Störungen im täglichen Leben.

Manuskript 4:

Butz M, Meyer R, Gerriets T, Sammer G, Doerr J, El-Shazly J, Doeppner T, Choi YH, Schoenburg M, Juenemann M. Increasing preoperative cognitive reserve to prevent postoperative delirium and

postoperative cognitive decline in cardiac surgical patients (INCORE): Study protocol for a randomized clinical trial on cognitive training. Front Neurol. 2022 Dec 12;13:1040733. doi:10.3389/fneur.2022.1040733. PMID: 36578306; PMCID: PMC9791586.

Zusammenfassung:

Die Validierung unseres Papier- und Bleistift-basierten kognitiven Trainingsprogramms, das postoperativ bei herzchirurgischen Patienten evaluiert wurde, wird nun in einem präoperativen Studienansatz umgesetzt. Im laufenden Forschungsvorhaben handelt es sich um eine monozentrische, 2-Arm randomisierte kontrollierte Interventionsstudie mit 100 Patienten, die sich einer elektiven herzchirurgischen Operation im Rahmen der extrakorporalen Zirkulation unterziehen (ClinicalTrials.gov ID: NCT04493996, prospektive Registrierung). Die Patienten werden entweder einer Trainingsgruppe oder einer "Treatment as Usual"-Gruppe zugeordnet. Die Intervention besteht aus einem standardisierten Papier- und Bleistift-basierten kognitiven Training, das ca. 40 Minuten pro Tag über einen präoperativen Zeitraum von ca. 2-3 Wochen zu Hause durchgeführt werden soll. Die Kontrollgruppe erhält weder ein kognitives Training noch eine Placebo-Intervention. Eine detaillierte Untersuchung der psychologischen Funktionen wird zu Beginn und am Ende des Trainings, während des Aufenthaltes in der Akutklinik, bei Entlassung aus der Akutklinik sowie 3 Monate nach der Operation durchgeführt. Das primäre Ziel dieser Studie besteht darin, den Interventionseffekt eines präoperativen kognitiven Trainings auf die Inzidenz von postoperativen Delirium während des Aufenthalts in der Akutklinik sowie die Inzidenz von POCD bei Entlassung aus der Akutklinik und 3 Monate nach der Operation zu untersuchen. Sekundäre Ziele sind der Trainingseffekt auf objektive kognitive Funktionen vor der Operation, subjektive kognitive Funktionen 3 Monate nach der Operation sowie der Trainingseffekt auf den Verlauf von Angst, Depression und gesundheitsbezogener Lebensqualität.

Manuskripte eingereicht

Manuskript 1:

Butz M, Gerriets T, Sammer G, El-Shazly J, Tschernatsch M, Braun T, Meyer R, Schramm P, Doeppner TR, Boening A, Mengden T, Choi YH, Schoenburg M, Juenemann M. Twelve-month follow-up effects of cognitive training after heart surgery on neurocognitive decline, health-related quality of life and cognitive failures in daily living. A randomized clinical trial. (Eingereicht am 11.04.23 beim Journal of the Neurological Sciences).

Hauptergebnisse:

Zwölf Monate nach dem kognitiven Training (Trainingsgruppe, n=19; Kontrollgruppe, n=27) zeigte sich

eine POCD-Häufigkeit von 22% (n=6) in der Kontrollgruppe und 11% (n=2) in der Trainingsgruppe (χ^2[1]=1.06, p=0.440; OR=2.43, 95% CI [0.43-13.61]). Die POCI-Häufigkeit zeigte sich in der Trainingsgruppe bei 47,4% (n=9) und 29,6% (n=8) in der Kontrollgruppe (χ^2[1]=1.51, p=0.352; OR=0.47, 95% CI [0.14-1.59]). Bezogen auf die neuropsychologischen Parameter (Baseline korrigiert) zeigte sich die visuelle Wiedererkennung gemessen mit dem SKT (U=-2.137, p=0.034, η^2=0.099) in der Trainingsgruppe verbessert. Bei der Nachuntersuchung zeigten sich keine statistisch signifikanten Trainings-Effekte hinsichtlich Depression und Angst.

Zwölf Monate nach der Entlassung aus der Rehabilitation wies die Trainingsgruppe (n=30) im Vergleich zur Kontrollgruppe (n=28) unter Berücksichtigung der präoperativen Ausgangsdaten einige Verbesserungen der gesundheitsbezogenen Lebensqualität auf. Diese Verbesserungen zeigten sich in den Bereichen Rolleneinschränkungen aufgrund körperlicher Gesundheit (U=-2.447, p=0.015, η^2=0.109), Einschränkungen durch emotionale Probleme (U=-2.245, p=0.025, η^2=0.092), Schmerzen (U=-1.979, p=0.049, η^2=0.068), Durchschnitt aller SF-36-Faktoren (U=-3.237, p<0.001, η^2=0.181), Veränderung des Gesundheitszustandes vom letzten Jahr zum aktuellen Zeitpunkt (U=-2.091, p=0.037, η^2=0.075), Durchschnitt aller physiologischen Faktoren (U=-2.803, p=0.005, η^2= 0.138) und Durchschnitt aller psychologischen Faktoren (U=-2.350, p=0.018, η^2=0.095). Es zeigten sich keine relevanten Interaktionseffekte zwischen der Kontrollgruppe und der Trainingsgruppe in den von den Patienten selbst berichteten subjektiv eingeschätzten kognitiven Störungen im täglichen Leben.

Diskussion

Wir entschieden uns für Papier-und-Bleistift basierte Trainingsaufgaben, da POCD nach kardiochirurgischen Eingriffen hauptsächlich ältere Menschen betrifft. In vielen Studien zur Wirkung von kognitivem Training wurden computergestützte Trainingsaufgaben verwendet (10), die den Vorteil bieten, Daten schnell und automatisiert zu erfassen. Allerdings stellen sie auch heute noch für ältere Menschen oft ein ungewohntes Medium dar, was bei der hier untersuchten älteren Population zu Irritation, Berührungsängsten und/oder Frustration führen könnte und somit einen potentiellen Bias darstellt.

Unser Trainingsprogramm konnte in der Rehabilitationsphase bei ca. 80% der Patienten in der Trainingsgruppe gut und vollständig durchgeführt werden. Etwa 20 % der Patienten konnten das Training aus gesundheitlichen Gründen oder wegen kognitiver Überforderung hinsichtlich der Übungen nicht beginnen oder fortsetzen. Darüber hinaus zeigte das kognitive Training einen bedeutsamen Unterschied zwischen den Gruppen mit einer POCD-Häufigkeit bei Entlassung aus der Rehabilitation von 50% in der Kontrollgruppe versus 19% in der Trainingsgruppe. Im Detail zeigte das Training zum Zeitpunkt der Entlassung aus der Rehabilitationsklinik signifikante Verbesserungen in

verschiedenen neuropsychologischen Parametern wie selektive Aufmerksamkeit und phonematische Wortflüssigkeit. Als relativen Langzeiteffekt blieb 3 Monate nach Entlassung die POCD-Häufigkeit in der Kontrollgruppe (29%) im Vergleich zur Trainingsgruppe (6%) höher. Im Speziellen zeigten sich auch in der 3-monatigen Nachuntersuchung Verbesserungen in den Bereichen der kognitiven Flexibilität, visuellen Wiedererkennungsfähigkeit, phonematischen Wortflüssigkeit, des verbalen Arbeitsgedächtnisses und verbalen kurzfristig-episodischen Gedächtnisses. Eine posthoc-explorative Analyse zeigte keinen wesentlichen Beitrag eines Delirs zu der Inzidenz von POCD und POCI bei allen postoperativen Auswertungen. Weiterhin zeigten sich 3 und 12 Monate nach dem Training positive Effekte in mehreren Bereichen der gesundheitsbezogenen Lebensqualität, wie Rolleneinschränkungen durch emotionale Probleme, Veränderung des Gesundheitszustandes vom letzten Jahr zum jetzigen Zeitpunkt und im Durchschnitt aller psychologischen Faktoren.

Derzeit haben drei Studien den Effekt eines kognitiven Trainings auf die postoperative Kognition nach Herzoperationen untersucht. In der Studie von O'Gara et al. (2020) (16) wurde ein computerbasiertes kognitives Training mindestens 10 Tage vor der Operation mit bis zu 4 Wochen postoperativ durchgeführt, was keinen signifikanten Effekt auf die Häufigkeit von POCD hatte. Diese Studie lässt sich nur eingeschränkt mit unserem Studiendesign vergleichen, da wir ein Papier- und Bleistift-basiertes Verfahren verwendeten und unser Training erst eine Woche nach der Operation begonnen hat. Weiterhin hat O'Gara et al. den Trainingseffekt zwischen der präoperativen und der postoperativen Trainingsphase nicht separat untersucht, was die Vergleichbarkeit mit unserer POCD-Inzidenz nicht ermöglicht. Das von de Tournay-Jette et al. (2012) (15) durchgeführte Training begann in der sechsten bis zehnten Woche postoperativ und zeigte positive Effekte auf unterschiedliche Kognitionen. Auch hier ist ein Vergleich mit unseren Daten begrenzt, da im Gegensatz zu unserer Studie die neuropsychologischen Ausgangsdaten einen Monat postoperativ erhoben wurden. Hiermit ist eine Bestimmung der POCD-Häufigkeit nicht möglich, da hierfür eine prä-postoperative Untersuchung Voraussetzung ist. Weiterhin begann ihr Training relativ spät (sechste bis zehnte Woche postoperativ) im Vergleich zu dem Training in unserer Studie (1 Woche postoperativ). Die Studie von Ajtahed et al. (2019) (17) zeigte in einem postoperativen Training Verbesserungen in Kognitionen und gesundheitsbezogener Lebensqualität. Auch hier ist die Vergleichbarkeit mit unserem Studiendesign eingeschränkt, da hier ein computerbasiertes Verfahren verwendet wurde, und die neuropsychologischen Ausgangsdaten, die für die Quantifizierung der POCD-Rate notwendig sind, postoperativ erhoben wurden.

Unabhängig von der herzchirurgischen Population zeigen sich Trainingseffekte auf Kognitionen und gesundheitsbezogene Lebensqualität. Mehrere Studien zeigten, dass Patienten mit leichter kognitiver Beeinträchtigung (MCI) von einem computergestützten kognitiven Training profitieren können (10). Eine mögliche Erklärung für die Wirksamkeit von kognitiven Trainings könnte die

interventionsbedingte Veränderung der Neuroplastizität sein (d.h. die Fähigkeit des Gehirns, kognitive Funktionen und strukturelle neurophysiologische Parameter durch Stimulation zu verändern)(18). Als Reaktion auf ein kognitives Training zeigen ältere gesunde Erwachsene reproduzierbar günstige Veränderungen in der Struktur der grauen und weißen Substanz des Gehirns (19). Die funktionelle Plastizität hingegen zeigt bei älteren gesunden Erwachsenen ein gemischtes Muster aus erhöhter und reduzierter Aktivität in bestimmten Hirnregionen, während bei MCI-Patienten eine konsistente Aktivitätssteigerung als Folge des kognitiven Trainings festgestellt wurde (19). Zudem wurde nach einem kognitivem Training bei Schlaganfallpatienten eine erhöhte funktionelle „Resting State Connectivity“ zwischen dem Hippocampus und weiteren Hirnregionen festgestellt (11). Es gibt auch Hinweise darauf, dass ein kognitives Training mit einer Steigerung des Brain-Derived Neurotrophic Factor (BDNF) einhergeht (20, 21), der für die Neuroplastizität eine wichtige Rolle spielt.

Wir gehen davon aus, dass der Trainings-Effekt auf objektiv messbare kognitive Fähigkeiten auch auf psychologisch relevante Alltagssituationen und somit auf die gesundheitsbezogene Lebensqualität übertragbar ist. Beispielsweise könnte eine gesteigerte Kognition die Emotionsregulierung optimieren (22), was die Verbesserung im SF-36 Faktor "Rolleneinschränkungen durch emotionale Probleme" in unserer Trainingsgruppe erklären könnte. Exekutive Funktionen wie Willenskraft, Planung, zielgerichtetes Handeln, Leistungsüberwachung und Inhibition sind wichtig für die Initiierung oder Modifizierung körperlicher Aktivitäten (23). In diesem Zusammenhang hat sich gezeigt, dass ein erhöhtes Niveau an exekutiven Funktionen zu einer gesteigerten körperlichen Aktivität führen kann (23), was die verbesserte physische Komponente in unserer Trainingsgruppe erklären könnte. Untersuchungen bei gesunden älteren Menschen mit kontrollierten kognitiven Interventionen haben Verbesserungen in verschiedenen Parametern der Lebensqualität gezeigt (Rolleneinschränkungen durch emotionale Probleme, soziale Funktionsfähigkeit, Rolleneinschränkungen durch funktionelle Einschränkungen) (24). Auch bei älteren Erwachsenen mit subklinischer kognitiver Verschlechterung sind nach kognitivem Training Verbesserungen bei depressiven Symptomen beschrieben worden (25). Da die patientenorientierte subjektive Einschätzung der kognitiven Defizite im Alltag in unserer Studie keinen Unterschied zwischen den Gruppen gezeigt hat, gehen wir davon aus, dass der verwendete Fragebogen (Cognitive Failures Questionnaire, CFQ) nicht sensitiv genug ist, um die Verbesserungen in den Leistungstests durch das kognitive Training aufzuzeigen. Es gibt bereits Belege dafür, dass die subjektive Bewertung kognitiver Fähigkeiten oft nur geringfügig mit objektiven Tests der kognitiven Leistungsfähigkeit zusammenhängt (26, 27).

Der optimale Zeitpunkt für den Beginn eines postoperativen kognitiven Trainings ist gegenwärtig allerdings noch unklar. Kontrollierte Studien zur Neurorehabilitation von kognitiven Beeinträchtigungen nach Schlaganfall haben gezeigt, dass ein restitutives kognitives Training innerhalb von 2 Wochen (12) oder 7 Monaten (11) nach Schlaganfall positive Effekte auf verschiedene kognitive

Funktionen hat. Tiermodelle deuten auf eine zeitabhängige Erhöhung der Neuroplastizität (plastisches Fenster) nach ischämischem Schlaganfall hin, mit einem Höhepunkt bei 7-14 Tagen und einem Ende bei 30 Tagen. Aufgrund dieser Dynamik der Neuroplastizität, die für die kognitive Erholung wichtig ist, scheint eine frühe neuropsychologische Rehabilitation vorteilhafter zu sein als eine spätere Rehabilitation. Es ist jedoch zu beachten, dass die Übertragbarkeit dieser Befunde von der Laborsituation auf das Krankenbett schwierig ist und die Form und das Ausmaß des neuroplastischen Fensters beim Menschen weiter unklar bleibt (28).

Das Auftreten von POCD kann durch verschiedene perioperative Bedingungen erklärt werden, die Hirnschäden verursachen und fördern können und somit zu weiteren kognitiven Beeinträchtigungen führen. Zu diesen potentiellen pathophysiologischen Mechanismen gehören globale und regionale Hypoperfusion, ausgeprägte Temperaturschwankungen, Herzrhythmusstörungen, systemische Entzündungsreaktionen, Hämodilution, Anästhesie, zerebrale (Mikro- und Makro-) Embolisation mit anschließender Ischämie- und Reperfusionsschädigung sowie eine nachfolgende Blut-Hirn-Schranken-Dysfunktion (29-31). Insbesondere scheinen postoperative zerebrale subklinische Mikroinfarkte mit extrakorporaler Zirkulation häufiger aufzutreten als ohne extrakorporaler Zirkulation (32). Allerdings wird über die Auswirkung der extrakorporalen Zirkulation auf POCD kontrovers berichtet (33, 34). Um mehr Erkenntnisse in diesem Zusammenhang zu gewinnen, könnten experimentelle Studien durchgeführt werden, die untersuchen, wie die extrakorporale Zirkulation zu vermehrten Gasbläschen führt und wie diese zur zerebralen Mikroembolisation und POCD beitragen. Demnach konnte in kontrollierten Studien gezeigt werden, dass der intraoperative Einsatz eines dynamischen Gasbläschenfilters 3 Monate nach einer CABG-Operation (35) oder pulmonalen Endarteriektomie (36) zu besseren neuropsychologischen Leistungsfähigkeit führte.

Obwohl die Pathogenese von POCD noch kontrovers diskutiert wird, sind die Folgen der kognitiven Defizite gut beschrieben. Neben einer Verschlechterung der gesundheitsbezogenen Lebensqualität bis zu fünf Jahre nach der Operation (4), kann POCD zu einer verminderten Arbeits- und Erwerbsfähigkeit mit vorzeitigem Renteneintritt führen (5). Kognitive Fähigkeiten tragen wesentlich zur Persönlichkeit und Selbstwahrnehmung bei. Vor diesem Hintergrund können täglich wahrgenommene kognitive Defizite für die Betroffenen eine tiefgreifende und schwere Belastung darstellen. Für Patienten, Angehörige und das Gesundheitssystem ist es von besonderer Bedeutung, dass POCD in einer sehr vulnerablen Lebensphase auftritt, in der kognitive Defizite schnell zum Verlust der Selbstständigkeit und damit zu erhöhter Pflegebedürftigkeit führen können (37).

Die vorliegende Untersuchung weist einige Einschränkungen auf, die berücksichtigt werden sollten. Zunächst einmal haben wir nur Patienten untersucht, die unter Verwendung der extrakorporalen Zirkulation operiert wurden. Daher ist ein Vergleich mit Patienten ohne extrakorporale Zirkulation oder

einer gesunden Kontrollgruppe nicht möglich. Zweitens haben wir auf eine Placebo-Intervention für die Kontrollgruppe verzichtet, da die kognitiven Effekte von Placebo-Interventionen schwer zu erfassen sind. Eine weitere Einschränkung dieser Studie ist, dass wir nicht wissen, ob die Patienten zwischen dem Ende des kognitiven Trainings und der 3-monatigen Nachbeobachtung kognitiv fördernde Aktivitäten (Spiele spielen, Bücher lesen, soziales Engagement) (38) durchgeführt haben. Diese Freizeitaktivitäten könnten in der Trainingsgruppe insbesondere deswegen häufiger ausgeführt worden sein, weil die Patienten mit dem Kontakt zu dem kognitiven Training ein ausgeprägteres Bewusstsein hinsichtlich der Vorteile von kognitiven Alltagsaktivitäten bekommen haben könnten. Durch diese potentiell vermehrt ausgeführten kognitiven Aktivitäten wäre ein Einfluss auf die kognitive Plastizität mit wiederum positiven Effekt auf kognitive Leistungen möglich (38). Auch ist das Training für ältere Patienten entwickelt worden, weshalb es bei jüngeren Patienten möglicherweise aus Gründen der Unterforderung keine kognitiven Effekte zeigen könnte. Da wir eine gemischte Kohorte von Einzeloperationen wie Aortenklappenersatz (AKE) oder Mitralklappenrekonstruktion (MKR) und Kombinationseingriffen wie CABG + AKE untersucht haben, kann die Übertragbarkeit der Auswirkungen auf einzelne Patientenpopulationen, wie AKE ohne CABG oder CABG ohne AKE, nicht angemessen durchgeführt werden. Eine unerwartet hohe Zahl von Patienten (36%) wurde zwischen der präoperativen Untersuchung und dem Zeitpunkt der Aufnahme in die Rehabilitationsklinik ausgeschlossen, so dass unsere erwartete Dropout-Rate von 20 % zu niedrig angesetzt war. Aus organisatorischen Gründen konnten wir die erwarteten 91,2 Patienten bei der Entlassung nicht erreichen und mussten die Studie mit 81 Patienten beenden.

Da sich unser kognitives Training in der frühen Rehabilitationsphase als durchführbar und wirksam für den Erhalt oder die Verbesserung der Kognition und gesundheitsbezogener Lebensqualität gezeigt hat, kann diese Intervention eine vielversprechende Methode zum Schutz vor kognitivem Abbau nach einer Herzoperation darstellen. Da während der frühen Rehabilitation unklar ist, wer von langfristigen POCD betroffen sein wird, könnte unser Training für Patienten mit besonders erhöhtem Risiko nützlich sein. Darüber hinaus könnte es in die Behandlungsprogramme von Rehabilitationszentren für Patienten mit oder ohne Herzoperation, die von POCD betroffen sein könnten, integriert werden. Ökonomisch und organisatorisch ist die Implementierung des Trainings in die Behandlungsprogramme von Rehabilitationseinrichtungen ohne großen Aufwand möglich, da die kognitiven Übungen selbstständig durchführbar sind und keiner aufwändigen Betreuung bedürfen und Rehabilitationseinrichtungen in der Regel über Psychologen, Ergotherapeuten oder Pflegepersonal verfügen, die in die Organisation der Übungen, die Verteilung der Aufgaben oder die Klärung von Fragen eingebunden werden können. Neben dem Einsatz unseres Trainings im Rahmen von POCD, bietet es auch die Möglichkeit einer Evaluation bei Patienten mit kognitiven Beeinträchtigungen nach Schlaganfall oder im Verlauf einer Demenz. Außerdem wurde das kognitive Training so konzipiert, dass es in einem ambulanten Setting

durchgeführt werden kann, was für die Zeit nach der Rehabilitation oder vor einer Operation wichtig sein könnte. So könnten beispielsweise durch ein präoperatives, ambulantes kognitives Training (Prähabilitation) kognitive Reserven aufgebaut werden (39), die das Gehirn vor postoperativen neurokognitiven Störungen wie einem Delirium oder POCD schützen können.

Publikationsliste des Promovierenden mit Autorenbeteiligung

2023

Butz M, Gerriets T, Sammer G, El-Shazly J, Tschernatsch M, Schramm P, Doeppner TR, Braun T, Boening A, Mengden T, Choi YH, Schoenburg M, Juenemann M. The impact of postoperative cognitive training on health-related quality of life and cognitive failures in daily living after heart valve surgery: A randomized clinical trial. Brain Behav. 2023 Feb 13:e2915. doi: 10.1002/brb3.2915. Epub ahead of print. PMID: 36785920.

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<u>Vorträge und Posterpräsentationen mit Bezug zur Promotionsarbeit</u>

19.01.2023 Arbeitstagung Neurointensivmedizin, Berlin, Deutschland (Posterpräsentation)

Titel: Effekte eines postoperativen kognitiven Trainings auf die gesundheitsbezogene Lebensqualität nach herzchirurgischen Operationen: Eine randomisierte kontrollierte Studie (INCOGNITO-Trial)

21.01.2022 Arbeitstagung Neurointensivmedizin, Ludwigsburg, Deutschland (Vortrag)

Titel: Effekte eines postoperativen kognitiven Trainings auf postoperative kognitive Defizite nach herzchirurgischen Operationen: Eine randomisierte kontrollierte Studie (INCOGNITO-Trial)

7.-11.10.2020 World Congress for Neurorehabilitation, Lyon, Frankreich (Posterpräsentationen)

Titel: Postoperative cognitive training decreases neurocognitive decline after cardiac surgery: a randomized controlled trial.

Titel: Increasing preoperative cognitive reserve to prevent postoperative delirium and postoperative cognitive decline in cardiac surgical patients (INCORE). Protocol for a randomized controlled trial on cognitive training.

Eingeworbene Drittmittel

Als Hauptantragsteller

Retrospective analysis of blood biomarkers in cardiac surgery patients with postoperative neurocognitive disorders and sub-clinical brain infarcts (BICAPONI). Gefördert durch die William G. Kerckhoff-Stiftung in Höhe von 43.325 Euro.

Decreasing Preoperative Stress to Prevent Postoperative Delirium and Postoperative Cognitive Decline in Cardiac Surgical Patients. A randomized controlled trial on relaxation interventions via virtual reality and binaural beats (DESTRESS-SURG). Gefördert durch die Deutsche Stiftung für Herzforschung in Höhe von 65.106 Euro.

Increasing Preoperative Cognitive Reserve to Prevent Postoperative Cognitive Dysfunction in Cardiac Surgical Patients (INCORE). Gefördert durch die William G. Kerckhoff-Stiftung in Höhe von 45.084 Euro.

Als Mitantragsteller

Trainingsstudie zur Verbesserung postoperativer kognitiver Defizite nach Herzoperationen (INCOGNITO). Gefördert durch die Deutsche Stiftung für Herzforschung in Höhe von 30.300 Euro und durch die William G. Kerckhoff-Stiftung in Höhe von 36.000 Euro.

Cognitive Outcome After Surgical and Transcatheter Aortic Valve Replacement (COSTA). Gefördert durch die Deutsche Stiftung für Herzforschung in Höhe von 58.265 Euro.

Beantragte Drittmittel

Als Mitantragsteller

Prevention of Seizures after Cardiac Surgery to REduce Postoperative COGnitive Deficits, ReCog-Trial. Beantragt bei der Deutschen Forschungsgemeinschaft.

Verantwortlich für die Registrierung klinischer Studien

1. Decreasing Preoperative Stress to Prevent Postoperative Delirium and Postoperative Cognitive Decline in Cardiac Surgical Patients. A randomized controlled trial on relaxation interventions via virtual reality and binaural beats (DESTRESS-SURG). ClinicalTrials.gov Identifier: NCT05036538
2. Increasing Preoperative Cognitive Reserve to Prevent Postoperative Cognitive Dysfunction in Cardiac Surgical Patients. A randomized controlled trial on cognitive training (INCORE). ClinicalTrials.gov Identifier: NCT04493996

3. Cognitive Outcome After Surgical and Transcatheter Aortic Valve Replacement (COSTA). ClinicalTrials.gov Identifier: NCT04535076
4. Trainingsstudie zur Verbesserung postoperativer kognitiver Defizite nach Herzoperationen (INCOGNITO). DRKS-ID der Studie: DRKS00015512

Selbstständigkeitserklärung

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Bad Nauheim, 04.05.23 Dipl.-Psych. Marius Butz

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Trials

STUDY PROTOCOL Open Access

Decreasing postoperative cognitive deficits after heart surgery: protocol for a randomized controlled trial on cognitive training

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Abstract

Background: The occurrence of postoperative cognitive deficits, especially after heart surgery, has been demonstrated in several studies. These deficits can clearly be noticed by the patients and by their close relatives in daily life. Furthermore, postoperative cognitive deficits can decrease quality of life in social functioning and earning capacity. The aim of this study is to investigate whether early postoperative cognitive training can reduce subjective and objective postoperative cognitive deficits.

Methods: The proposed study is a multicenter, two-arm, randomized controlled trial involving 144 elderly patients undergoing elective heart-valve surgery with extracorporeal circulation. Patients will be assigned to either a training group or a control group. The intervention involves paper-and-pencil-based cognitive training, which is conducted for 36 min over a period of 18 days. The training starts about 1 week after surgery and is carried out during the hospitalized rehabilitation phase. The control group will not receive cognitive training or a placebo intervention. A detailed assessment of psychological functions and health-related quality of life prior to surgery at discharge from rehabilitation and 3 and 12 months after discharge will be performed. The primary outcome of this trial is the training effect on objective cognitive functions at discharge from rehabilitation. Secondary outcomes are the training effect on objective and subjective cognitive functions (3 and 12 months after discharge), depression, health-related quality of life, and the impact of perioperative cerebral ischemia on the training effect. Perioperative cerebral ischemia will be measured with postoperative magnetic resonance imaging including diffusion-weighted sequences.

Discussion: Should it be shown that our cognitive training can improve postoperative cognitive deficits and quality of life, one possibility could be to integrate this intervention into early rehabilitation. Furthermore, we hope that the investigation of perioperative ischemia by diffusion-weighted magnetic resonance imaging will improve our understanding of neurobiological factors influencing the course of postoperative cognitive plasticity.

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Keywords: Heart surgery, Postoperative cognitive deficits, Postoperative cerebral microinfarcts, Magnetic resonance imaging, Cognitive training

Background

Neurological complications of cardiac surgery include ischemic and hemorrhagic stroke, seizures, delirium, cerebral hyperperfusion syndrome, cranial and peripheral nerve injuries, and postoperative cognitive decline (POCD) [1]. Amongst these, POCD seems to have the highest incidence, but its frequency strongly depends on the inclusion/exclusion criteria, the follow-up interval and the diagnostic criteria used [2]. There is no uniform definition of POCD, but a widespread criterion for POCD is a decline of 1 standard deviation from preoperative to 3 months postoperative in at least two objectively measured cognitive functions such as verbal memory, attention, cognitive flexibility, language, or visuomotor abilities [2]. Three months after coronary artery bypass grafting (CABG) surgery, POCD occurs in 16% [3] to 23% [4] of patients, and POCD has even been reported in 31% of patients 3 years after undergoing CABG [4]. A longitudinal study assessing the incidence of POCD in CABG surgery reported early improvement in cognitive function within 6 months after surgery that was followed by a later decline and led to a 42% incidence of POCD after 5 years. In this study, early POCD could be identified as an important predictor of long-term cognitive decline [5]. Even though POCD often appears as subclinical, both patients and their relatives report a significant decrease in patients' cognitive abilities in daily living up to at least 3 months after heart surgery [6]. In addition to POCD, postoperative cognitive improvement (POCI) is also reported, but its frequency seems to be 3–6 times lower than POCD [7].

Several perioperative conditions are discussed as potential pathophysiological mechanisms causing and promoting cerebral injury, such as global and regional hypoperfusion, pronounced temperature, arrhythmia, systemic inflammatory response, hemodilution, anesthesia itself and, particularly, cerebral (micro and macro) embolization followed by ischemia/reperfusion injury and subsequent blood-brain barrier dysfunction [8, 9]. A meta-analysis of randomized controlled trials has shown higher incidence of POCD in CABG with extracorporeal circulation (cardiopulmonary bypass, on-pump) compared to off-pump CABG 3 months after surgery [10]. In this respect, cerebral micro-embolization has been reported to substantially contribute to perioperative neurological complications [11].

Although the pathophysiology of POCD is still the subject of controversial debate, consequences of cognitive deficits are well-described. Aside from a decline in health-related quality of life (HQL) up to 5 years after surgery [12], POCD can result in reduced working and earning capacity with premature retirement, and diminished social functioning resulting in increased social dependency [13]. Cognitive abilities substantially contribute to personality and self-perception; in this light, daily perceived POCD can impose a profound and heavy burden on those concerned. For patients, relatives, and the healthcare system, it is of particular significance that POCD occurs during a highly vulnerable period of life, where cognitive deficits can quickly lead to loss of independence and thus increased need of long-term care [14].

Several studies have shown that patients with mild cognitive impairment (MCI) can benefit from computerized cognitive training [15]. These effects are mainly attributed to cognitive and neurological plasticity (i.e., the ability of the brain to alternate cognitive functions and structural or functional neurophysiological parameters through stimulation). In response to cognitive training, older healthy adults reproducibly present with an increased pattern in the gray and white matter structure [16]. Functional plasticity, on the other hand, shows a mixed pattern of increased and decreased activity in specific brain regions in older healthy adults and consistent increased activity in individuals with MCI, as a result of cognitive training [16]. Furthermore, a functional magnetic resonance imaging (MRI) study reported increased resting-state functional connectivity between the hippocampus and certain brain regions after effective cognitive training in patients with stroke [17]. Cognitive training is also associated with improvements in depression and everyday functioning [18]. To date, only one prospective investigation has addressed the value of cognitive training in patients undergoing cardiac surgery [19]. The authors reported a beneficial effect of memory and attentional training in patients who underwent CABG compared to patients who underwent CABG and received no additional cognitive training.

The purpose and primary outcome of this prospective, randomized and controlled study is to evaluate the effectiveness of a paper-and-pencil-based cognitive training program on objectively measured cognitive functions for patients undergoing cardiac surgery with

extracorporeal circulation. The primary outcome will be evaluated directly after training at discharge from rehabilitation. The delivery of the cognitive training will start at the beginning of rehabilitation, which means approximately 1 week after surgery. Secondary outcomes are the training effect on cognitive functions, depression and health-related quality of life 3 and 12 months after discharge from rehabilitation, and the impact of perioperative cerebral ischemia on the training effect. Perioperative cerebral ischemia will be measured with postoperative diffusion-weighted magnetic resonance imaging (DW-MRI) during the first postoperative week. To our knowledge, this is the first study to explore the impact of cerebral ischemia on cognitive training for patients who have undergone cardiac surgery.

Methods

Study design and enrollment

This study is a multicenter, randomized controlled trial conducted at the department of cardiac surgery of the Kerckhoff Heart and Thorax Center in Bad Nauheim, Germany, and at the department of cardiovascular surgery of the University Hospital Giessen, Germany. It complies with the Declaration of Helsinki and has been approved by the ethics committee of the Justus Liebig University Giessen (ref. 28/14). The study coordinator receives information about planned elective cardiac surgery from the participating study centers, which he screens according to eligibility criteria. Potential patients will be contacted and informed verbally and in writing in detail about the purpose, procedure, and possible consequences of the study project. If the patient agrees to participate, a written informed consent form will be signed by the patient and the investigator prior to the patient's enrollment.

Our study team consists of members of the departments of neurology, neuropsychology, neuroradiology, heart surgery, and rehabilitation who are responsible for running the study, including preparing the protocol, monitoring the study and writing the study reports. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline (see Additional file 1).

Due to the planned small sample size, the expected lack of harm and the relatively short execution time of the cognitive training (3 weeks), the implementation of a data monitoring committee was not considered.

All patients will pass a detailed neuropsychological assessment the day before surgery, at discharge from rehabilitation, and at 3 and 12 months after discharge. At every time point, patients will complete a standardized questionnaire on depression and anxiety. Questions about cognitive failure in daily life and HQL will be assessed before heart surgery and at 3 and 12 months after discharge from rehabilitation. Before surgery, data documentation will include age, sex, education, body mass index, preexisting conditions, and medication. Documentation of perioperative date will be the type and amount of anesthesia administered, duration of anesthesia administration, type and amount of analgesia administered, duration of analgesia administration, duration of surgery, duration of extracorporeal circulation, cross-clamp time and perioperative complications. Post-surgery intensive care unit (ICU) days, total length of inpatient stay, postoperative complications and postoperative delirium will be recorded. At 6–10 days after surgery, MRI of the brain will be conducted to screen for cerebral ischemia, hemorrhage, or other acute pathologic conditions potentially confounding neuropsychological assessment and the effects of cognitive training. Following the inpatient stay in the acute hospital (approximately 7 days), patients will be directly transferred to the department of rehabilitation at the Kerckhoff Clinic in Bad Nauheim, Germany.

During their stay at the rehabilitation center, which usually lasts 3 weeks, all patients will receive standard cardiac rehabilitation including physical exercise, medical management and nutritional counseling. The cognitive training group will undergo an additional cognitive training program consisting of paper-and-pencil exercises. The study design is shown in Fig. 1. A detailed trial schedule in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guideline is shown in Table 1.

Inclusion and exclusion criteria

Patients receiving elective aortic or mitral valve replacement/reconstruction with or without CABG will be included in this study. All heart operations will be performed with standard extracorporeal circulation. Due to the use of a standardized psychological assessment, patients must be native German speakers. Exclusion criteria are history of stroke and preexisting psychiatric or neurological disorders. Patients whose health insurance does not grant the postoperative treatment in the department of rehabilitation at the Kerckhoff Clinic in Bad Nauheim (Germany) must also be excluded.

If patients no longer wish to participate in the cognitive training or neuropsychological examination due to a deteriorating state of health, lack of motivation, any other reason, or without reasons given, they may discontinue participation in the study. Furthermore, participants will be excluded from the study if they are transferred to another clinic during their stay in the rehabilitation center.

Medical and psychological interventions in the context of other studies that may exert effects on patients' cognition are prohibited. In general, concomitant care and interventions as part of the standard rehabilitation program are permitted.

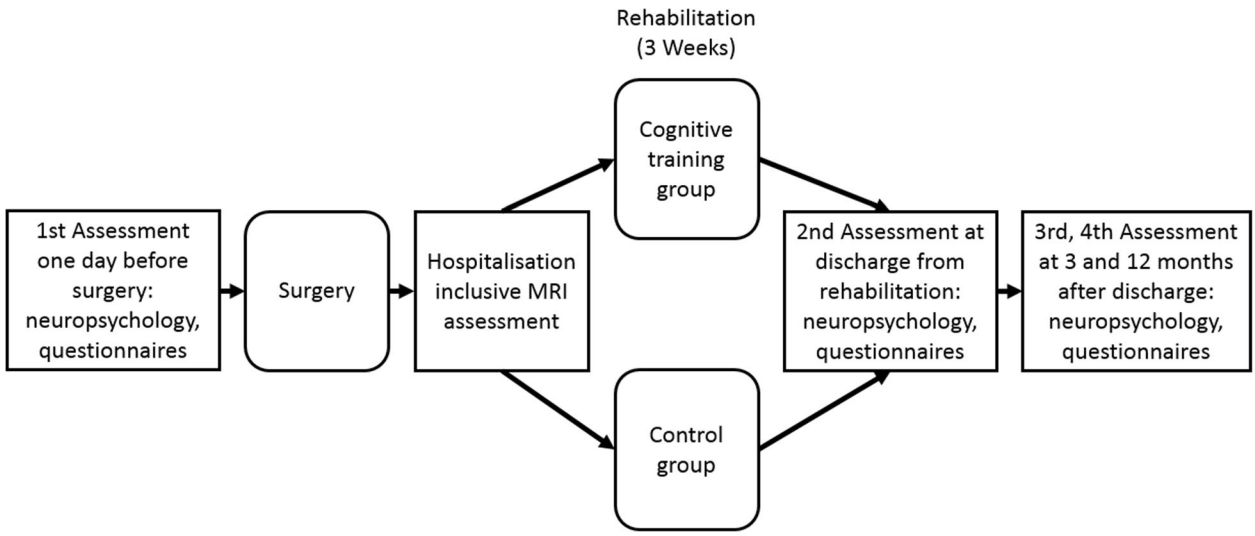

Fig. 1 Timeline of study-related events. The first assessment includes neuropsychological tests and questionnaires on the day before surgery. Within 6–10 days after surgery, magnetic resonance imaging (MRI) of the brain is scheduled. After the acute hospitalization, patients will be transferred to the center of rehabilitation and randomly assigned to the cognitive training group or the control group. A second neuropsychological assessment will be administered at discharge from rehabilitation. To determine the long-term effects of the cognitive training, a neuropsychological test and questionnaires will be administered at 3 and 12 months after discharge from rehabilitation

Randomization

After enrollment and a baseline assessment, patients will randomly be assigned by the study coordinator to the cognitive training group or the control group, which will not receive cognitive training. Patients will be randomized using a computer-generated randomization list with a 1:1 blocked allocation ratio. The randomization list will be sequentially numbered and will be generated by the study coordinator prior to the start of the study.

Blinding

Surgeons, radiologists and neuropsychologists who are involved in the outcome variables will be blinded to the randomization status. Cognitive testing and training will be carried out by two different, experienced neuropsychologists in order to maintain the blinding. During follow-up assessments, patients may tell the blinded neuropsychologist accidentally before the start of the neuropsychological test whether or not they have received previous cognitive training. In this case, however, the neuropsychological test will be performed and discussed in the study reports.

Neuropsychological assessment

A battery of cognitive tests will be performed by a neuropsychologist on the day before surgery, at discharge from rehabilitation, and at 3 and 12 months after discharge. When available, parallel test forms will be used at follow up to account for learning effects. The order in which the parallel test forms are presented will be counterbalanced so that each parallel test form occurs with the same frequency at each test time point.

The cognitive test battery assesses selective attention, verbal and visual memory with short-delay and long-delay episodic memory conditions, verbal working memory, cognitive flexibility, word fluency and symbol processing. Selective attention will be examined using the Trail Making Test A (TMT-A) [20] and the *Alterskonzentrationstest* (AKT) [21]. In the TMT-A, the patient has to link numbers in ascending order on a test sheet. The AKT consists of a matrix of similar visual stimuli, where a target stimulus has to be marked.

To assess verbal memory, the *Verbaler Lern- und Merkfähigkeitstest* (VLMT), a modified German version of the Rey Auditory Verbal Learning Test [22], will be applied. This test can be used to evaluate short-term memory, learning, episodic memory, and verbal discriminability. First, the patient has to concentrate on a word list that is read out loud by the investigator. The direct retrieval of the patient is scored as short-term memory performance. Second, the patient has to learn the word list in five learning trials. The sum of the recalled words represents a learning parameter. Third, a second word list with new words is presented verbally only once, to divert attention from the first word list. After this, the learned words of the first word list have to be recalled; this is used as a measurement of a short-delayed function of verbal episodic memory. A second verbal episodic memory measurement is performed 20 min later (long delay). Finally, the verbal recognition ability is proven by discriminating between already learned and

Table 1 Trial schedule of enrollment, interventions, and assessments

STUDY PERIOD							
	Enrolment	**Post-allocation**					**Close-out**
TIME POINT	$-t_1$	t_1	t_2	t_3	t_4	t_{3m}	t_{12m}
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
Heart surgery		X					
Cognitive training				←	→		
ASSESSMENTS:							
MRI			X				
TMT	X				X	X	X
AKT	X				X	X	X
VLMT	X				X	X	X
Block tapping	X				X	X	X
NVLT	X				X	X	X
SKT	X				X	X	X
RWT	X				X	X	X
SVT	X				X	X	X
HADS	X				X	X	X
s-CFQ	X					X	X
f-CFQ	X					X	X
SF36	X					X	X

MRI magnetic resonance imaging, *TMT* Trail Making Test, *AKT Alterskonzentrationstest*, *VLMT Verbaler Lern- und Merkfähigkeitstest*, *NVLT* Non-Verbal Learning Test, *SKT Syndrom-Kurztest*, *RWT Regensburger Wortflüssigkeits-Test*, *SVT Symbolverarbeitungstest*, *HADS* Hospital Anxiety and Depression Scale, *s-CFQ* Cognitive Failure Questionnaire for self-assessment, *f-CFQ* Cognitive Failure Questionnaire for foreign assessment, *SF36* Short Form-36

new words. Between the short-delayed verbal episodic memory trial and the long-delayed verbal episodic memory trial, nonverbal cognitive tests are performed to avoid the potential effect of interfering words not included in the learned wordlist.

Visual memory will be examined using the Block-Tapping Test [23], the Non-Verbal Learning Test (NVLT) [24] and the pictorial memory subtest of the German *Syndrom-Kurztest* (SKT) [25]. In the Block-Tapping Test, the patient has to tap blocks on a board with his or her hand in a given order forward and backward. The NVLT is a test to evaluate the visual recognition of repeated abstract symbols within a variety of 60 cards. The pictorial memory subtest of the German SKT will be administered to the patient to evaluate short-term episodic memory and recognition of 12 visual pictures, which are presented in one learning trial. With the Letter Number Test, a subtest of the MATRIX test

battery, the verbal working memory is tested through the mental reorganization of numbers and letters [26]. Cognitive flexibility will be assessed by the Trail Making Test B (TMT-B) [20], where numbers and letters have to be alternately linked, and by another subtest of the SKT (SKT 7) [25], where the patient has to name interfering letters (e.g., "A" instead of "B," and vice versa).

Furthermore, semantic and phonetic verbal fluency will be tested using the "Regensburger Wortflüssigkeits-Test" (RWT) [27]. In this test, in 1 min, the patient has to name words from a specific category to test semantic fluency and words with a specific initial letter to test phonetic fluency. At the end of the test battery, the *Symbolverarbeitungstest* (SVT) will be performed to test the processing of symbolic pictures [28].

Questionnaires

Study patients will complete a validated German version of the Cognitive Failures Questionnaire for self-assessment (s-CFQ) [29]. Close relatives of the patients will answer a cognitive questionnaire to evaluate foreign assessment (f-CFQ) [30]. The questionnaires will examine the frequency of failures in daily living related to memory, attention, action, and perception. Because memory impairment is an important element that affects everyday functioning, the s-CFQ was modified with additional questions related to memory failures, taken from the validated German version of the Memory Complaint Questionnaire [31]. Depression and anxiety will be scored using the validated German version of the Hospital Anxiety and Depression Scale (HADS) [32]. HQL will be assessed using the Short Form-36 (SF36) questionnaire [33]. The SF36 covers eight health-related factors including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The HADS will be used at every neuropsychological test time point; the s-CFQ, f-CFQ and SF36 will be completed at baseline and 3 and 12 months after discharge from rehabilitation.

Magnetic resonance imaging

Cranial MRI will be performed 6–10 days after surgery using a 3-T scanner (Skyra; Siemens, Erlangen, Germany). The protocol of imaging will include a T2-weighted turbo spin-echo sequence (slice thickness = 3 mm, field of view (FOV) = 220 × 220 mm, matrix = 512 × 391, repetition time (TR) = 7490 ms, echo time (TE) = 100 ms), a T2-weighted turbo spin-echo sequence for dark fluid (slice thickness = 3 mm, FOV = 220 × 220 mm, matrix = 320 × 224, TR = 7000 ms, TE = 81 ms), a T1-weighted FLASH sequence (slice thickness = 3 mm, FOV = 220 × 220 mm, matrix = 320 × 320, TR = 250 ms, TE = 2.49 ms) and a diffusion-weighted echo-planar imaging sequence (slice thickness = 3 mm, FOV = 220 × 220 mm, matrix = 160 × 160, TR = 7720 ms, TE = 64 ms, slice gradients of b values = 0 and 1000 s/mm^2). The postoperative diffusion-weighted sequence will be used by two blinded, experienced observers for registration and planimetric evaluation of acute ischemic lesions.

Primary outcome measure

The primary outcome measure will be the training effect on all objectively measured neuropsychological functions at discharge from rehabilitation.

Secondary outcome measure

As a secondary outcome, we will evaluate the training effect of all objectively measured neuropsychological functions at 3 and 12 months after discharge from rehabilitation. Second, we will evaluate the training effect on the subjective self-assessment and external assessment by relatives of cognitive failures at 3 and 12 months after discharge from rehabilitation. Third, we will evaluate the training effect on HRQ at 3 and 12 months after discharge from rehabilitation. Fourth, we want to investigate the extent to which the cognitive training has an impact on depression at all follow-up time points. Last, we will examine the impact of perioperative cerebral ischemia on the neuropsychological measured training effect at all follow-up time points. Perioperative cerebral ischemia will be measured with postoperative DW-MRI during the first postoperative week. The number and size of ischemic lesions are determined and will be used as a control variable for the analysis of the training effect.

Cognitive training

There is currently only one study in which effective cognitive training was performed in patients undergoing cardiac surgery [19]. This study used a combination of computer-based training (with a focus on selective attention) and memory strategy training (method of loci). We decided against this training concept because we think that our elderly patients are not familiar with the use of computers, and we will therefore use a purely paper-and-pencil approach. Second, memory strategies seem to be less effective than cognitive exercises such as computerized or paper-and-pencil procedures [34]. To our knowledge, there is no specific cognitive domain that clearly emerges over time in the context of POCD, such as memory or attention. Therefore, we decided to train several cognitive functions that are used especially in everyday life to maintain social functions and earning capacity. These include word fluency, working memory, attention, and the ability to plan.

For the preparation of our training program we first conducted a literature search on German-language-validated

paper-and-pencil-based cognitive exercise methods. The literature is very scarce. In a controlled study design, a training program by Müller et al. (2004) [35] showed cognitive improvements in patients with executive dysfunction [36]. Their program included training in word fluency, cognitive flexibility, working memory, and planning ability. However, we found the cognitive training of Müller et al. (2004) [35] in some parts to be too unentertaining for our patients, whereby we took over only a few training tasks and combined them with new tasks designed by our group to achieve better acceptance.

Cognitive training in the intervention group will include paper-and-pencil-based exercises practicing multi-domain cognitive executive functions such as word fluency, verbal and visual working memory, selective visual attention, and planning. One training session will last approximately 40 min and will be performed 6 days a week for 3 weeks.

The daily training program consists of eight different types of standardized tasks addressing the processing of words, categories, images, head calculation, and planning. New words, categories, images, head calculations, and planning tasks will be presented on each training day. Each task takes between 2 and 10 min; to manage the working time, the patients must limit their work using a digital clock. At the beginning of the training program, a trained investigator will give explicit instructions in a one-to-one training session and will be nearby to help with any questions about the exercises. If no further help is needed in the following training days, the patient will be provided with training material for the following 6 days so that patients can complete the training independently in their ward rooms. Each task contains precise written instructions that can be used to assist in its execution. If a patient has questions about the training, he or she can contact the trainer. After every 6th day, the extent to which the tasks have been completed is checked by the training investigator and new training material will be provided. Patients are told that their exercise solutions are not evaluated or corrected. Therefore, it does not matter whether the solutions are right or wrong. An important concern for the patients is that they concentrate on the tasks and cognitively exert themselves. In this way, we can avoid possible performance pressure and also avoid patients exchanging the right approaches among themselves. The different types of tasks are presented in the following standardized order.

Phonetic word fluency

The patient is given three letters on a sheet of paper. Within 2 min, he or she has to note as many words as possible that begin with these letters. This task is mainly intended to train word fluency and was adapted from Müller et al. (2004) [35].

Categorical word fluency

In this task, the patient is given three different categorical terms on a sheet of paper. Within 2 min, as many words as possible that can be assigned to these categories must be found and noted. This task is mainly intended to train word fluency and was adapted from Müller et al. (2004) [35].

Comic strips

Patients receive 4–5 popular German comics from German illustrators such as Wilhelm Busch, Erich Ochser or Hans Jürgen Press, with 3–16 pictures of a story in mixed order. Within 5 min, the pictures have to be arranged mentally in a meaningful order. The new invented order should be documented by numbering the pictures with a pencil. This task is mainly intended to train working memory and was created by our group.

Mental arithmetic

The patient is asked to complete several calculation tasks on a sheet of paper. The result of the first arithmetic problem, which includes addition, subtraction and multiplication of numbers, must be memorized. In the second step, another calculation task must be solved, and the result must also be memorized. In the last step, the last result should be subtracted from the first result, and the final result should be written down. The time limit for this exercise is 5 min. This task is mainly intended to train working memory and was adapted from Müller et al. (2004) [35].

Synonymic fluency

The next worksheet contains three different terms. For each term, patients must find words with similar meanings (synonyms). For example, if the term is *wallet*, then other words would be *portmonee* or *money purse*. The time limit is 2 min. This task is mainly intended to train word fluency and was created by our group.

Fill in the blank text

In the next training task, short stories are presented. These are generally known stories by Wilhelm Busch, the Brothers Grimm, Hans Christian Andersen or fables from antiquity, German studies, Buddhism, and Japan. The stories have gaps that have to be filled in with a self-chosen, meaningful word. The time limit for this exercise is 5 min. This task is mainly intended to train word fluency and working memory and was constructed by our group.

Where is Waldo

An illustration of Martin Handford's "Where is Waldo?" is presented on a DIN A3 sheet of paper. The picture contains dozens or more people doing a variety of things

in a particular place. The patient has to find some specific signs or objects listed on a sheet of paper by marking them with a pen on the DIN A3 sheet within 5 min. This task is mainly intended to train selective attention and working memory and was created by our group.

Planning

In the last task, the patient must read a text in which an imaginary person has to perform transactions or organize appointments. The patient's task is to solve the problems by writing down a concrete solution. The time limit for this task is 10 min. The task is mainly intended to train planning ability and working memory and was adapted from Müller et al. (2013) [37].

Planned statistical analyses

The effect of cognitive training will be analyzed by repeated measures (mixed between-within) analysis of variance (ANOVA) with groups (control group/intervention group) as the between-subject factor and assessment time (baseline and all follow-up assessments) as the within-subject factor for all cognitive tests and questionnaires, respectively. Assumptions for repeated measures ANOVA will be tested using the Levene test for variance-homogeneity and Mauchly's test for sphericity. If sphericity is violated, alpha levels will be adjusted using the Greenhouse-Geisser correction. Normal distribution will be tested using the Shapiro-Wilk test. To control for the possibility of confounder variables that could affect the results, we will conduct additional repeated measures analysis of covariance (ANCOVA), which includes covariates such as preoperative cognitive values, age, sex, education, psychiatric scores (depression/anxiety), and perioperative variables such as duration of extracorporeal circulation, administration of anesthesia, and number and size of ischemic lesions.

Post hoc explorative between-subject comparisons will be analyzed using the t test for independent samples. In this case, we will compare the intervention group with the control group by calculating a change score in cognitive values (post-training score minus pre-training score). The change in cognitive values is the dependent variable, and the treatment group (cognitive training group/control group) is the independent variable.

Within-subject comparisons will be analyzed using the paired t test. When the assumptions for parametric tests (normal distribution, variance-homogeneity between two groups) are not given, the variables will be analyzed using non-parametric variance techniques. In this case, between-group differences will be calculated using the Mann-Whitney U test, using change scores in cognitive values (post-training score minus pre-training score) and the Wilcoxon signed-rank test for within-group comparisons. Nominal variables will be analyzed by Pearson's chi-squared test. Depending on the parametric level of the data, correlation with continuous variables will be calculated using Pearson product-moment correlation, Spearman rank correlation, or Kendall tau correlation. Effect size of the cognitive training will be calculated by the difference in the pretest-posttest measure between the intervention and control group, weighted by the pooled standard deviation of the pretest measurement, because this is the recommended choice for a pretest-posttest controlled design [38]. The criterion for statistical significance will be set at $p < 0.05$. In the case of multiple tests, we will control p values using the false discovery rate (FDR) correction method [39]. Since we expect dropout of some patients on follow-up assessments, all patients will be included in the intention-to-treat analysis, where missing data will be imputed by a multiple imputation method. To evaluate the impact of missing data, a complete case analysis will also be performed, followed by best-worst and worst-best case sensitivity analyses.

Another approach to identifying a training effect on cognition will be to compare the frequencies of POCD and POCI between the groups using Pearson's chi-squared test. POCD will be defined as a decline from pre to post assessment of 1 standard deviation in at least two neuropsychological parameters as this is a widely used method [2]. Similarly, POCI will be defined as an improvement from pre to post assessment of 1 standard deviation in at least two neuropsychological parameters.

Interim analyses will be carried out during the study period to identify adverse events, an overwhelming effect, or the futility of the experimental arm. In this case, the study could be terminated prior to its completion. The decision will be made by the study team.

Power and sample size estimation

Cognitive training for patients undergoing heart surgery administered by de Tournay-Jette et al. (2012) [19] revealed medium-to-large effect sizes ($\eta^2 = 0.10–0.23$). We have decided to use the smaller effect size ($\eta^2 = 0.10$) for calculation so as not to underestimate the required sample size. Using this effect size, 37 patients per group are needed to obtain statistical power of 80% at a significance level of $p = 0.05$ (two-tailed). Based on previous cardiosurgical studies, we estimate a dropout rate of 20% between each of the four assessment time points. Thus, the number of study patients recruited at baseline assessment was fixed at 72 patients per group. For sample size and statistical power calculations, we used G*Power-3 analysis software.

Data management

All personal information about enrolled patients will be subject to medical confidentiality. Paper-based assessment

forms will be used to record the outcome variables. The data will be manually entered in an electronic database, which is password-protected and will be checked for quality and accuracy. All assessment forms, signed informed consent forms, and the randomization list will be stored in a locked cabinet.

Dissemination policy

Our goal is to make the study results available to the general public, healthcare providers, and scientists by publishing them in the public press, at scientific congresses, and as original articles in peer-reviewed journals. The results will be reported regardless of the amount and direction of the effect.

Discussion

The aim of this study is to evaluate a paper-and-pencil-based cognitive training program for patients undergoing heart surgery with extracorporeal circulation. POCD shows the highest incidence of neurological complications that can occur in the context of surgery, especially cardiac surgery [1]. Adverse effects of POCD on daily living abilities can be noticed by patients themselves and their relatives in both the short and long term [6]. The etiology remains controversial but can be considered a multifactorial event in which extracorporeal circulation plays a crucial role [8].

Here, we present cognitive training that integrates well with standard rehabilitation, takes place as early as possible, and aims to reduce the occurrence and persistence of cognitive deficits in the short and long term. It is also of interest whether patients with perioperative ischemic stroke benefit from this intervention to varying degrees or in different forms.

We intentionally opted for technically simple paper-and-pencil-based training tasks because POCD after cardiosurgical procedures mainly affects elderly people. Many studies on the effect of cognitive training have used computer-based training tasks [15], which provide the advantage of generating and capturing data simply, quickly and very precisely. However, even today, they often represent an unfamiliar medium for older people, which could lead to irritation, fear of contact, and/or frustration in the older population studied here and thus constitute a potential bias. A placebo intervention for the control group is intentionally omitted because cognitive effects of placebo interventions on cognitive performance are difficult to control. In order to credibly suggest to patients that the placebo intervention could have an influence on their memory and thus also to achieve a willingness to participate, the structure of the placebo intervention will have to be closely related to cognitive training (e.g., relaxation exercises, crossword puzzles, conversation therapy, computer games, etc.) and thus also achieve cognitive training effects.

The only prospective investigation of patients undergoing cardiac surgery to date reported a beneficial effect of memory and attentional training in patients who underwent CABG [19], but no information was given on the use of extracorporeal circulation in this collective. In this study, training took place between the 6th and the 10th week following surgery. However, it is still not clear when the optimal time point for cognitive training should be set and for how long the intervention should be carried out. It seems possible that the rehabilitation of postoperatively impaired cognitive function will be more improved by an earlier intervention starting in the range of a week compared to one month after surgery. Controlled studies on neurorehabilitation of post-stroke cognitive impairment have shown beneficial effects for several cognitive functions when restitutive cognitive training begins within 2 weeks [40] or about 7 months [17] after stroke onset. Animal models suggest a time-dependent increase in neuroplasticity (plastic window) after ischemic injury, with a peak at 7–14 days and near completion at 30 days. Nevertheless, it should be noted that the assignability of these findings from bench to bedside is difficult, and the shape and extent of the neuroplastic window in humans remains unclear [41].

In our study, the detection of acute, perioperative cerebral ischemia is performed by MRI with DWI. With the use of DWI, a preoperative baseline assessment is not necessary because in this sequence, acute ischemic tissue is presented as a bright area that typically occurs 2–3 h after the onset of damage and usually subsides within 2–3 weeks [42]. These acute cerebral ischemic lesions can be detected by DW-MRI in 14–61% of the patients after cardiac surgery [11, 43]. The significance of those acute MRI lesions, especially with regard to manifestation of POCD, remains unclear [42]. To our knowledge, there are no studies controlling for the potentially confounding effect of peri-interventionally endured cerebral ischemia detected during the first postoperative week. In this context, it seems of particular interest whether patients with acute cerebral ischemia benefit from cognitive training to any other degree or in any other form.

So far, increased efforts have been made to prevent POCD, addressing anesthesia, cardiotechnology, and cardiac surgery [9], with limited but measurable success; these procedural preventive measures alone can reduce the incidence of POCD in the magnitude of 30% [44]. In contrast to procedural prevention strategies, the concept of cognitive training allows the

patient to act independently, responsibly and actively. This can perhaps exert a positive effect on the recovery process through the experienced self-efficacy that seems to contribute to better recovery after heart surgery in terms of patients' worries, energetic mood, reading, ambulating, and fitness [45]. With the knowledge that cognitive deficits can be actively addressed afterward, the fear of surgery can possibly be reduced; finally, one must not forget the drastic experience of a potentially life-threatening cardiac disease. Preoperative anxiety has been shown to be a predictor of major morbidity and mortality in patients who have undergone heart surgery [46].

The present investigation certainly contains some limitations. First of all, participation in the study is tied to the performance of a heart operation using a heart-lung machine. A comparison with patients undergoing off-pump cardiac surgery is therefore not possible. Given the lack of knowledge about the optimal starting time or duration of training, the intervention may be too early or the duration of approximately 3 weeks too short. It could also be discussed as to whether an additional follow-up investigation after several years would provide further valuable information on the long-term course of POCD and the training effects. For the aforementioned reasons, no placebo intervention is planned in the present study; this may formally affect the quality of the study and the transferability of the results. Finally, our cognitive training consists of a combination of validated [36] and unvalidated tasks. Since our self-created tasks are not validated, we do not know whether they might potentially contribute to an alteration in cognition.

The results of our study could have potentially important implications for the prevention and treatment of POCD. In particular, if our cognitive training is feasible and effective in maintaining or improving cognition and quality of life, it could be integrated into the treatment programs of rehabilitation centers that treat patients after heart surgery. Economically and organizationally, this is possible without much effort because the cognitive exercises are independently workable and need no great control, and rehabilitative centers usually have psychologists who could be involved in the organization of the exercises, distribution of tasks, or clarification of questions. Furthermore, the cognitive training is designed in such a way that it could also be carried out in an ambulant setting.

Trial status

The study is currently enrolling patients. Recruitment started on 13 July 2016. Recruitment is expected to be completed in February 2020. Protocol version: 1.4 (10-08-2019).

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3799-0.

Additional file 1. SPIRIT 2013 Checklist: recommended items to address in a clinical trial protocol and related documents.

Abbreviations

AKT: Alterskonzentrationstest; ANCOVA: Analysis of covariance; ANOVA: Analysis of variance; CABG: Coronary artery bypass grafting; DW-MRI: Diffusion-weighted magnetic resonance imaging; FA: Fractional anisotropy; f-CFQ: Cognitive Failure Questionnaire for foreign assessment; FDR: False discovery rate; FOV: Field of view; HADS: Hospital Anxiety and Depression Scale; HQL: Health-related quality of life; ICU: Intensive care unit; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; NVLT: Non-Verbal Learning Test; POCD: Postoperative cognitive decline; POCI: Postoperative cognitive improvement; RWT: Regensburger Wortflüssigkeits-Test; s-CFQ: Cognitive Failure Questionnaire for self-assessment; SKT: Syndrom-Kurztest; SVT: Symbolverarbeitungstest; TE: Echo time; TMT: Trail Making Test; TR: Repetition time; VLMT: Verbaler Lern- und Merkfähigkeitstest

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None.

Authors' contributions

MB: conception and design (study protocol, neuropsychological assessment, cognitive training), patient recruitment, collection of neuropsychological and medical data, data analysis, data interpretation, manuscript writing, and critical revision. JES: conception and design (study protocol, neuropsychological assessment, cognitive training), patient recruitment, collection of neuropsychological and medical data, data analysis, data interpretation, and critical revision. GS: conception and design (study protocol, neuropsychological assessment, cognitive training), data analysis, data interpretation, and critical revision. MT: critical revision. SK: conception and design (study protocol) and critical revision. MY: critical revision. TB: critical revision. MK: critical revision. AB: responsible for surgical process and critical revision. UP: collection of medical data and critical revision. GB: conception and design (study protocol), collection of MRI data, and critical revision. TM: conception and design (study protocol), responsible for medical rehabilitation, and critical revision. MS: conception and design (study protocol), responsible for surgical process and critical revision. TG: conception and design (study protocol), data interpretation, and critical revision. MJ: conception and design (study protocol), data interpretation, manuscript writing, and critical revision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Central ethical approval has been confirmed from the Justus Liebig University Giessen (ref approval no. 28/14) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained. All amendments to the protocol will be submitted to the ethics committee of the Justus Liebig University Giessen. Each patient will give written informed consent. The written informed consent form is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Effects of postoperative cognitive training on neurocognitive decline after heart surgery: a randomized clinical trial

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Key question

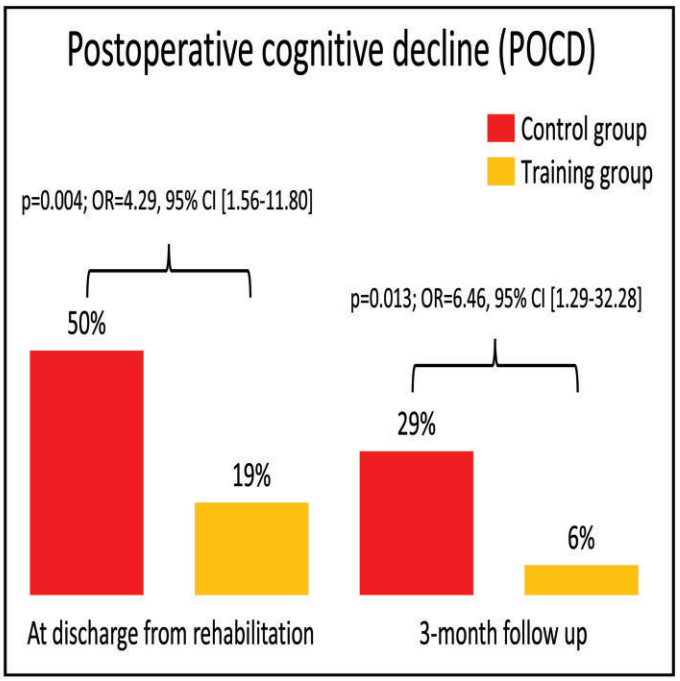
What is the effect of postoperative cognitive training on postoperative cognitive decline (POCD) after cardiac surgery?

Key finding(s)

POCD differed between groups at end of (control=50%, training=19%) and 3 months after the intervention (control=29%, training=6%).

Take-home message

A three-week randomized controlled cognitive training after cardiac surgery could be useful for the prevention of POCD.



Abstract

OBJECTIVES: Following cardiac surgery, postoperative cognitive decline (POCD) is a common complication that can impair the quality of life and increase mortality. The aim of this study was to investigate whether early postoperative cognitive training can decrease POCD after cardiac surgery.

METHODS: The study was a multi-centred, two-arm, randomized (1:1 ratio), controlled trial involving older patients undergoing elective heart valve surgery with extracorporeal circulation. Recruitment took place at the Department of Cardiac Surgery of the Kerckhoff-Clinic in Bad Nauheim (Germany) and the University-Hospital in Giessen (Germany). The patients were randomized to either a paper-and-pencil-based cognitive training group or a standard rehabilitation care control group. The cognitive training started 1 week after surgery and lasted about 3 weeks until discharge from rehabilitation. To detect POCD, neuropsychological functions were assessed prior to surgery, upon discharge from rehabilitation (primary outcome), and 3 months after discharge (secondary outcome). Data were primarily analysed in a per-protocol fashion.

RESULTS: The frequency of POCD at discharge from rehabilitation (training group, $n = 37$; control group, $n = 44$) was 50% in the control group and 19% in the training group ($\chi^2[1] = 8.45$, $P = 0.004$; odds ratio = 4.29, 95% confidence interval [1.56–11.80]). Three months after the cognitive training (training group, $n = 33$; control group, $n = 34$), POCD frequency was 29% in the control group and 6% in the training group ($\chi^2[1] = 6.21$, $P = 0.013$; odds ratio = 6.46, 95% confidence interval [1.29–32.28]).

CONCLUSIONS: Since our cognitive training showed beneficial effects, it could be a promising method to prevent POCD.

Keywords: Postoperative cognitive decline • Cardiac surgery • Cognitive training

ABBREVIATIONS

ANCOVA	Analysis of covariance
CABG	Coronary artery bypass grafting
CI	Confidence interval
HADS-D	Hospital Anxiety and Depression Scale
OR	Odds ratio
POCD	Postoperative cognitive decline
POCI	Postoperative cognitive improvement
SD	Standard deviation
ITT	Intention to treat

INTRODUCTION

Several neurocognitive complications have been described after cardiac surgery, including delirium [1], postoperative cognitive decline (POCD) [2] and dementia [3]. POCD can be defined as a decline of 1 standard deviation (SD) between a participant's pre-operative and postoperative cognitive performance, in at least 20% of all objectively measured cognitive domains (e.g. verbal memory, selective attention, word fluency or executive functions) [4]. A meta-analysis of coronary artery bypass grafting (CABG) patients that applied this definition showed a POCD prevalence of 28% between the first and fourth postoperative months and 22% between the sixth and 12th postoperative months [4]. POCD has further consequences such as reduced quality of life [5], increased mortality [6], increased economic costs [6] and long-term cognitive decline [2]. Although POCD often occurs subclinically and therefore often remains undetected, both patients and their relatives report a subjective decrease in the patients' cognitive abilities in daily life up to at least 3 months after cardiac surgery [7]. Besides POCD, postoperative cognitive improvement (POCI) can also be found after major surgery, with a frequency of 3–6 times lower than that of POCD [8]. Taken together, POCD seems to be a clinically relevant intervention target. Several studies have shown that healthy older individuals [9], cardiac surgery patients [10] or patients with mild cognitive impairment [11] can improve their cognitive functions through cognitive training. The aim of this prospective, randomized controlled trial was to investigate the effects of an early postoperative paper-and-pencil-based cognitive training programme in patients undergoing cardiac surgery with extracorporeal circulation.

PATIENTS AND METHODS

Ethical statement

The study, including obtaining informed consent, has been approved by the Ethics Committee of the Justus-Liebig University, Giessen (27 February 2014, Ref.: 28/14), and complies with the Declaration of Helsinki. Written informed consent of the patient was obtained prior to the enrolment.

Study design

This study was designed as a multi-centred, parallel group, 1:1 randomized and controlled trial, and it was conducted at the following locations: the Department of Cardiac Surgery of the Kerckhoff Heart and Thorax Center in Bad Nauheim, Germany; the Department of Cardiovascular Surgery at the University Hospital in Giessen, Germany; and the Department of Rehabilitation at the Kerckhoff Clinic in Bad Nauheim, Germany. Full details of the study protocol have been published elsewhere in advance [12]. With regard to the study protocol, no changes occurred in terms of eligibility criteria, interventions, examinations, data collection, methods of analysis and outcomes.

Patients

Patients scheduled for elective aortic or mitral valve replacement/reconstruction with or without CABG were included in this study. Cardiac surgery was performed with standard extracorporeal circulation. A sufficiently good knowledge of the German language was necessary as cognitive training and neuropsychological tests are language dependent. Exclusion criteria were history of stroke and pre-existing psychiatric or neurological disorders (e.g., dementia) that may impair the neuropsychological evaluation. Furthermore, patients were excluded when their health insurance did not cover postoperative rehabilitation at the Kerckhoff Clinic. The 2 participating study centres provided information on scheduled elective cardiac procedures to the study coordinators, who screened them according to eligibility criteria. Potential participants were contacted and informed in detail about the purpose and procedure of the study project.

Randomization and blinding

After recruitment and the first preoperative neuropsychological examination, the study coordinators allocated patients to the cognitive training group or the control group. The randomization was implemented using a computer-generated randomization list with a 1:1 blocked allocation ratio. The block sizes varied randomly. The randomization list was generated, sequentially numbered and concealed by a study coordinator prior to starting the study. The study coordinators informed the psychological training supervisor on which patients should be trained. The surgeons, neurologists and neuropsychologists involved in the assessment of outcome variables were blinded with respect to the randomization status.

Study procedures

At baseline, the documented data included age, sex, school and occupational education, body mass index, pre-existing conditions and the severity partition for left ventricular ejection fraction [13]. Duration of surgery, extracorporeal circulation, cross-clamp time and invasive ventilation time were recorded perioperatively. After surgery, postoperative complications and postoperative delirium were documented. Following the acute hospitalization, patients were directly transferred to the Department of Rehabilitation at the Kerckhoff Clinic in Bad Nauheim, Germany.

After admission to the rehabilitation centre, the control group and the cognitive training group received inpatient cardiac rehabilitation therapies that were individualized and based on the International Classification of Functioning. Essential elements of the therapeutic treatments were endurance, strength training, respiratory gymnastics and educative lectures. On average, the patients received about 12–14 therapeutic units per week. In addition, patients of the training group underwent cognitive training. The detailed description of the development and concept of the cognitive training was previously published elsewhere [12]. In brief, our cognitive training included standardized paper-and-pencil-based exercises practicing multidomain cognitive functions, which are especially important for everyday life, social functions and earning capacity. These include word fluency, working memory, attention and the ability to plan. Daily training sessions last 36 min. These should be done 6 days a week for a period of 3 weeks. The control group did not receive a placebo intervention because placebos (e.g. reading a newspaper) could have effects on cognitive performance. Two trained neuropsychologists applied a battery of validated cognitive tests 1–2 days before surgery, upon discharge from rehabilitation, and 3 months after discharge from rehabilitation. When available, parallel test forms were used at follow-up assessments to minimize learning effects.

Outcomes

The primary outcome was the training effect on each neuropsychological function at discharge from rehabilitation. As another primary outcome, we used each neuropsychological function to hereby determine the diagnoses of POCD/POCI for the time of discharge from rehabilitation. The secondary outcomes were the training effect on POCD/POCI and on each neuropsychological function at 3 months after discharge and the training effect on depression and anxiety.

POCD was defined as a decline and POCI as an improvement from pre- to postassessment of at least 1 SD in at least 20% of all neuropsychological subdomains [4]. To measure the difference of 1 SD between pre- and postassessment, we used *Z*-scores, which were calculated by the difference of the individual raw values from the mean value of the total baseline data divided by the SD of the total baseline data. The neuropsychological subdomains were defined according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* [14], as described in Supplementary Material, Table S1. As we have measured several neuropsychological parameters that can be contextually grouped into cognitive subdomains, we have summarized them by a mean value. A detailed description of the neuropsychological test battery was published elsewhere [12]. Patients assessed their recent (prior week) depressive and anxiety symptoms using the validated German version of the Hospital Anxiety and Depression Scale (HADS-D) [15].

Statistical analyses

Cognitive training for heart surgery patients conducted by de Tournay-Jetté *et al.* [10] showed training related medium to large effect sizes (η^2 = 0.10–0.23) in neuropsychological tests related to inhibition or verbal free recall (short delay). To avoid underestimating the needed sample size, we used the smaller effect size (η^2 = 0.10) for sample size calculation. Using this effect size, a total sample size of 73 patients were needed to obtain a statistical power of 80% at a significance level of $P = 0.05$ (two-tailed) in the context of an analyses of covariance (ANCOVA). We applied a dropout rate of 20% for each individual measurement time point. Accordingly, we expected a 20% dropout rate from baseline (114 patients) to discharge from rehabilitation (91.2 patients) and then a 20% dropout rate from discharge to 3-month follow-up (72.96 patients). Thus, the number of patients recruited at baseline assessment was fixed at 114 patients for the total sample size. For sample size and statistical power calculations, we used the analysis software G*Power (version 3.1.9.2).

To reveal the training effect on cognition, frequencies of dichotomous (yes/no) POCD and POCI variables were compared with Pearson's χ^2 test between the groups. The effect size of the difference in POCD/POCI frequencies between the groups is given by odds ratio (OR) with a 95% confidence interval (CI). To determine the effects of cognitive training on each neuropsychological parameter and on depression and anxiety, ANCOVAs were conducted with postoperative test value as the dependent variable, groups (control group or training group) as the fixed factor and preoperative test value as the covariate. Assumptions for ANCOVAs were tested using the Levene test for variance homogeneity of the dependent variable, QQ and distribution plots of the dependent variable for normality, and a statistically significant correlation between dependent variable and covariate (preoperative test value) calculated with Pearson's product-moment correlation. The effect sizes of the ANCOVA results are given in η^2. When assumptions for ANCOVA were violated, difference values between pre- and posttests were calculated, followed by the Mann–Whitney *U*-test for between-subject effects. To control for the possibility of confounder variables that could affect the results, we conducted the correlation analysis between demographic variables, perioperative details and neuropsychometrical changes between pre- and postoperative testing. In case of significant contributions of these variables, they were

Table 1: Baseline demographics and characteristics

	Training ($n = 47$)	Control ($n = 47$)
Demographics		
Age (years)	71.2 (4.7)	73.0 (4.9)
Sex		
Women	8 (17%)	13 (28%)
Men	39 (83%)	34 (72%)
Education (years)	13.5 (3.0)	13.4 (3.0)
Medical history		
Body mass index (kg/m^2)	27.7 (3.8)	26.6 (3.8)
Arterial hypertension	31 (66%)	31 (66%)
Diabetes mellitus	10 (21%)	5 (11%)
Renal insufficiency	4 (9%)	7 (15%)
Dyslipidaemia	39 (83%)	37 (79%)
LV EF (mildly abnormal)	5 (11%)	6 (13%)
LV EF (moderately abnormal)	3 (6%)	1 (2%)
Heart failure	10 (21%)	9 (19%)
Type of surgery		
AVR	23 (50%)	22 (47%)
AVR + CABG	18 (38%)	19 (40%)
MVR	4 (9%)	1 (2%)
MVR + CABG	0 (0%)	3 (6%)
AVR + MVR	2 (4%)	2 (4%)
Perioperative details		
Duration of surgery (min)	190.3 (38.1)	200.6 (58.9)
Duration of extracorporeal circulation (min)	96.5 (26.5)	105.2 (37.5)
Cross-clamp time (min)	69.1 (19.9)	74.7 (26.7)
Ventilation time invasive (min)	616.2 (331.3)	588.1 (213.6)
Postoperative complications		
Delirium	2 (4%)	4 (9%)
Arrhythmia	18 (38%)	21 (45%)
Atrial fibrillation	18 (38%)	17 (36%)
Renal insufficiency	6 (13%)	6 (13%)
Acute blood loss anemia	10 (21%)	12 (26%)
Transient ischaemic attack	1 (2%)	0 (0%)
Dysathria/aphasia	0 (0%)	1 (2%)
Medical details at admission to rehabilitation		
Blood pressure (systolic; mmHg)	128.1 (12.7)	127.7 (18.4)
Blood pressure (diastolic; mmHg)	74.5 (11.1)	71.4 (10.6)

Data are mean (SD) or number of subjects (%). Renal insufficiency was defined by a creatinine value above the in-house norms (men: >1.2 mg/dl, women: >0.9 mg/dl).

AVR: aortic valve replacement; CABG: coronary artery bypass grafting; LF EV: left ventricular ejection fraction; MVR: mitral valve replacement/reconstruction; SD: standard deviation.

implemented in addition to the preoperative cognitive values as further covariates to the ANCOVA. The criterion for statistical significance was set at $P < 0.05$ (two-sided). Our data set was evaluated using a per-protocol analysis. In a secondary approach, we used an intention-to-treat (ITT) analysis with the following specifications. For each single neuropsychological parameter with missing data at follow-up assessments, due to patient dropout (see reasons in the flowchart), we used a multiple imputation process in SPSS (version 22). The method of imputation was the fully conditional specification method, which is an iterative Markov chain Monte Carlo method. We set the number of iterations to 10. Within a linear regression model, we used group, age, education and the neuropsychological values from baseline, discharge from rehabilitation and 3-month follow-up as predictors. We set the number of imputations to 29 because about 29% of the data were missing at 3-month follow-up. We used the average of the 29 imputations for each neuropsychological parameter to replace the missing data. All analyses were performed using the statistical software SPSS (version 22) and JASP (version 0.12.2). The implementation of a data monitoring committee was not considered.

Study population

Between 13 July 2016 and 8 January 2020, a total of 130 patients were enrolled, randomized and tested preoperatively. The last patient was tested on 27 February 2020 for the 3-month follow-up. After randomization of the 130 patients, 36 patients (training group, $n = 18$; control group, $n = 18$) were lost to follow-up before the training or control intervention had started. Thus, 94 patients (training group, $n = 47$; control group, $n = 47$) were considered for the baseline sample, which has no between-group differences in baseline characteristics (see Table 1), or baseline neuropsychological tests. Furthermore, 13 patients (training group, $n = 10$; control group, $n = 3$) were lost to follow-up until discharge from rehabilitation, resulting in 81 patients (training group, $n = 37$; control group, $n = 44$), with another 15 patients (training group, $n = 5$; control group, $n = 10$) lost to follow-up at the 3-month follow-up, resulting in 67 patients (training group, $n = 33$; control group, $n = 34$). Reasons for losing patients to follow-up are shown in Fig. 1. The training intervention lasted 14.9 (SD 2.5) days and did not cause adverse events.

RESULTS

Per-protocol analysis

Primary outcome measures. At the time of discharge from rehabilitation, the training group ($n = 37$) showed an improvement compared to the control group ($n = 44$) in domains of selective attention measured with the Trail Making Test-A (TMT-A) ($F[2.78] = 5.66$, $P = 0.020$, $\eta^2 = 0.04$), and phonetic word fluency revealed with the Regensburger Word Fluency Test (RWT) ($F[2.78] = 6.18$, $P = 0.015$, $\eta^2 = 0.06$), whereas patients in the control group deteriorated in these domains. The significant interaction effects are shown in Supplementary Material, Fig. S1. A full description of the results of all neuropsychological test parameters is given in Supplementary Material, Table S2. Potentially confounding continuous demographic variables or intraoperative details made no significant contribution to the results, which were implemented as covariates in an adjusted ANCOVA.

Furthermore, at discharge from the rehabilitation clinic, POCD frequency was 50% ($n = 22$) in the control group and 19% ($n = 7$) in the training group, with a significant group difference ($\chi^2[1] = 8.45$, $P = 0.004$; OR = 4.29, 95% CI [1.56–11.80]). POCI frequency was 22% ($n = 8$) in the training group and 18% ($n = 8$) in the control group, with no significant group difference ($\chi^2[1] = 0.15$, $P = 0.699$; OR = 0.81, 95% CI [0.27–2.41]).

Secondary outcome measures. The specific effects on neuropsychological parameters are given as follows. Analysis of 67 patients (training group, $n = 33$; control group, $n = 34$) at 3 months after discharge from rehabilitation showed a statistically significant beneficial effect for the training group compared to the control group in domains of visual recognition memory revealed with the Short Performance Test ("Syndrom-Kurztest", SKT) ($U = -2.22$, $P = 0.027$, $\eta^2 = 0.07$), verbal free recall (short

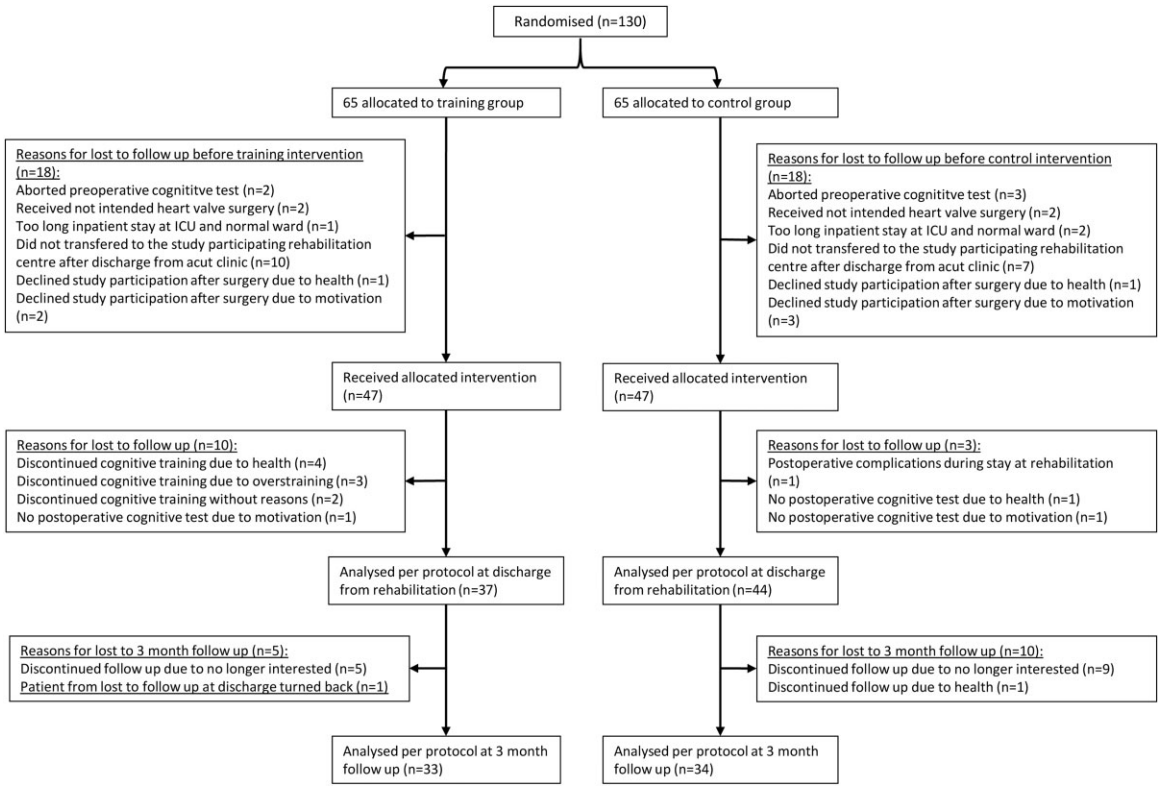


Figure 1: Consolidated Standards of Reporting Trials flowchart illustrating all steps in the study from randomisation to follow-up and analysis. ICU: intensive care unit.

delay) measured with the Auditory Verbal Learning and Memory Test ("Verbaler Lern- und Merkfähigkeitstest", VLMT) (F[2.64] = 4.21, P = 0.044, η^2 = 0.04), verbal working memory span tested with the Letter Number Span Test (LNS) (F[2.64] = 6.77, P = 0.011, η^2 = 0.07), cognitive inhibition speed measured with the SKT (F[2.64] = 4.02, P = 0.049, η^2 = 0.02) and phonetic word fluency tested with the RWT (F[2.64] = 6.99, P = 0.010, η^2 = 0.07). The significant interaction effects are shown in Supplementary Material, Fig. S2. A full description of the results of all neuropsychological test parameters is given in Supplementary Material, Table S3. In the adjusted ANCOVA with potentially confounding continuous demographic variables, only education as an additional covariate contributed significantly to cognitive inhibition speed revealed with the SKT (F[3.63] = 4.25, P = 0.043, η^2 = 0.02). In the adjusted ANCOVA with potentially confounding continuous demographic variables or intraoperative details, only education as an additional covariate contributed significantly to cognitive inhibition speed revealed with the SKT (F[3.63] = 4.25, P = 0.043, η^2 = 0.02).

At 3-month follow-up, POCD frequency was 29% (n = 10) in the control group and 6% (n = 2) in the training group, which differs significantly between the groups (χ^2[1] = 6.21, P = 0.013; OR = 6.46, 95% CI [1.29–32.28]). POCI frequency was 36% (n = 12) in the training group and 15% (n = 5) in the control group, with significant group difference (χ^2[1] = 4.15, P = 0.042; OR = 0.30, 95% CI [0.09–0.99]).

From baseline to discharge from rehabilitation, no group difference (training group, n = 36; control group, n = 40) in depression or anxiety was detected using the HADS-D. At 3-month follow-up, a marginal improvement in depression was shown in the training group (n = 33) compared with the control group (n = 33) measured with the HADS-D (U = -1.86, P = 0.063, η^2 = 0.05).

Subgroup analyses. Our sample showed an unequal distribution of delirious patients between the groups at discharge from the rehabilitation and at 3-month follow-up (control group n = 4; training group n = 0). As delirium is considered as a risk factor for the development of POCD [16] and we do not want to overestimate our described training's effect on POCD, we calculated a *post hoc* explorative analysis in which we excluded all delirious patients. In this adjusted analysis, excluding all delirious patients, the training effect on POCD/POCI at the time of discharge from the rehabilitation clinic was nearly the same as that with delirious patients (POCD: 50% [n = 20] in the control group, 19% [n = 7] in the training group; χ^2[1] = 8.16, P = 0.004; OR = 4.29, 95% CI [1.53–12.01]/POCI: 22% [n = 8] in the training group, 18% [n = 7] in the control; χ^2(1) = 0.21, P = 0.648; OR = 0.77, 95% CI [0.25–2.38]). Even 3 months after the cognitive intervention, the training effect on POCD/POCI seemed to remain, independent of delirium (POCD: 30% [n = 9] in the control group, 6% [n = 2] in the training group; χ^2[1] = 6.25, P = 0.012; OR = 6.64, 95% CI [1.30–33.88]/POCI: 36% [n = 12] in the training group, 13% [n = 4] in the control; χ^2[1] = 4.40, P = 0.036; OR = 0.27, 95% CI [0.08–0.96]).

Intention-to-treat analysis

A full description of the ITT analysis is given in Supplementary Material, File 1S.

DISCUSSION

The cognitive training demonstrated a statistically significant difference between the groups in POCD frequency at discharge. The frequency in the control group was 50% (23% in ITT analysis),

whereas it was 19% (6% in ITT analysis) in the training group. As a long-term effect, at 3 months after discharge, the control group's POCD frequency remained significantly higher, at 29% (30% in ITT analysis), than that of the training group, which was 6% (13% in ITT analysis). Besides the lower incidence of cognitive decline in the training group, a significantly higher POCI was observed 3 months after discharge from rehabilitation for the training group with 36%, compared to 15% in the control group. Furthermore, our training programme could be performed well in the early rehabilitation phase in ∼80% of the patients randomized to the training group. About 20% of the patients were not able to start or continue the training due to health reasons or overstraining from the exercises.

For the per-protocol approach, a *post hoc* power analysis of the difference in POCD incidence between the groups showed a sufficiently high power of 0.83 at the time of discharge from rehabilitation and a power of 0.7 at the 3-month follow-up, which is slightly underpowered but in our opinion clinically relevant. Within the ITT analysis, the *post hoc* power of the training's effect on POCD was 0.64 at the time of discharge and 0.53 at the 3-month follow-up, which is clearly underpowered. However, it should be noted that the powers of some single neuropsychological parameters were sufficiently high [at discharge: phonetic word fluency = 0.85; at 3-month follow-up: phonetic word fluency = 0.92, verbal free recall (short delay) = 0.83, verbal working memory = 0.81].

At this time, 2 studies have investigated the effect of computer-based cognitive training on postoperative cognition after cardiac surgery. In the study conducted by O'Gara *et al.* [17] the training was performed at least 10 days before surgery up to 4 weeks postoperatively, which had no significant effect on the frequency of POCD. However, this study cannot be compared with our study design, because we used a paper-and-pencil procedure, which started 1 week after surgery. A paper-and-pencil procedure might be more feasible and effective than computer-based training for older patients. However, this question cannot be answered because O'Gara *et al.* did not investigate the training effect between the preoperative and postoperative training phases separately. The training carried out by de Tournay-Jetté *et al.* [10] in 2012 began in the sixth to tenth weeks postoperatively and showed a positive effect on cognition. Again, comparison with our data is difficult because, contrary to our study, the baseline neuropsychological data used for their training effect were collected 1 month postoperatively. Furthermore, their training started relatively late (sixth to tenth weeks postoperatively) compared with the training in our study (1 week postoperatively). The optimal time for postoperative cognitive training to begin is still not clear. For example, animal studies suggest a time-dependent increase in neuroplasticity (plastic window) after ischaemic injury, with a peak at 7–14 days and near completion at 30 days [18]. With this dynamic of neuroplasticity, which is important for cognitive recovery, early neuropsychological rehabilitation seems to be more beneficial than later rehabilitation.

A possible explanation for the effectiveness of our training could be the intervention-related alteration in neuroplasticity. For example, various studies have shown that cognitive training can increase patterns in the brain structure in healthy subjects [19] and in patients with memory impairments [20].

There are a few limitations to consider. First, we only examined patients who had been operated on with the use of extracorporeal circulation. Therefore, comparison with patients without extracorporeal circulation or a healthy control cohort is not possible. A second major limitation of this study is that we do not know whether the patients performed cognitively enhancing activities (playing games, reading books, social engagement) [21] between the end of cognitive training and the 3-month follow-up. Third, the training was designed for older patients, so it might be too easy for younger patients and therefore not achieve any cognitive effect. As we studied a mixed cohort of single surgeries such as AVR or MVR and combination surgeries such as CABG + AVR, transmissibility of the effects on single patient populations, such as AVR without CABG or CABG without AVR, cannot be adequately performed. The training results regarding POCD incidence display relatively wide confidence intervals, probably due to the small sample size. To better quantify the confidence intervals, the data would need to be replicated in a larger sample. An unexpectedly high number of patients (36%) were excluded between the time of recruitment and preoperative testing and the time of admission to the rehabilitation clinic; thus, our anticipated dropout rate of 20% was an underestimation. For organizational reasons, we were unable to reach the expected 91.2 patients at discharge and had to end the study with 81 patients.

As our cognitive training in the early rehabilitation phase has shown to be feasible and effective at maintaining or improving cognition, this intervention could be a promising method to protect against cognitive decline after cardiac surgery. Although the beneficial effect at the short-term follow-up seems promising, the results at a 1-year follow-up would also be of great interest.

Economically and organizationally, the integration of the training into the treatment programmes of rehabilitation centres is possible without much effort, because the cognitive exercises are independently workable and need no elaborate supervision, and rehabilitative centres usually have psychologists or occupational therapists who can be involved in the organization of the exercises, distribution of tasks or clarification of questions. Furthermore, the paper-and-pencil-based process is inexpensive, so we assume that the benefit outweighs the cost. As it is unclear during the early rehabilitation who will be affected by long-term POCD, our training could be useful for patients at particularly increased risk.

Furthermore, it could be integrated in preoperative as well as peri- and postrehabilitative treatment settings or in the context of cognitive impairment after stroke and in the progression of dementia. Postoperative care of patients in rehabilitative clinics generally has a positive effect on the overall outcome. With cognitive training, in addition to standardized rehabilitation, a further benefit can be achieved with regard to cognition. Comparison to cognitive training that can be performed independently by the patients in a postoperative in-home rehabilitation setting would be interesting and should be considered in further research. Preoperative cognitive training (prehabilitation) in particular could build up cognitive reserves [22], which could potentially protect the brain against postoperative neurocognitive dysfunctions such as delirium or POCD.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

Data Availability Statement

De-identified participants' data analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

Marius Butz: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Tibo Gerriets:** Conceptualization; Funding acquisition; Project administration; Writing—review & editing. **Gebhard Sammer:** Conceptualization; Methodology; Supervision; Validation; Writing—review & editing. **Jasmin El-Shazly:** Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Writing—review & editing. **Marlene Tschernatsch:** Writing—review & editing. **Hagen B. Huttner:** Writing—review & editing. **Tobias Braun:** Writing—review & editing. **Andreas Boening:** Resources; Writing—review & editing. **Thomas Mengden:** Conceptualization; Resources; Writing—review & editing. **Yeong-Hoon Choi:** Writing—review & editing. **Markus Schoenburg:** Conceptualization; Funding acquisition; Project administration; Writing—review & editing. **Martin Juenemann:** Conceptualization; Funding acquisition; Project administration; Supervision; Writing—review & editing.

Reviewer information

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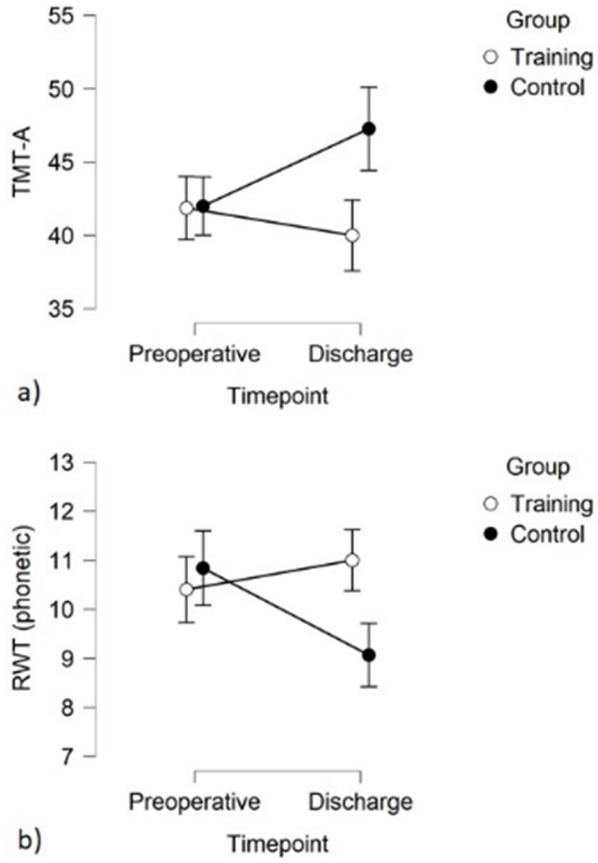
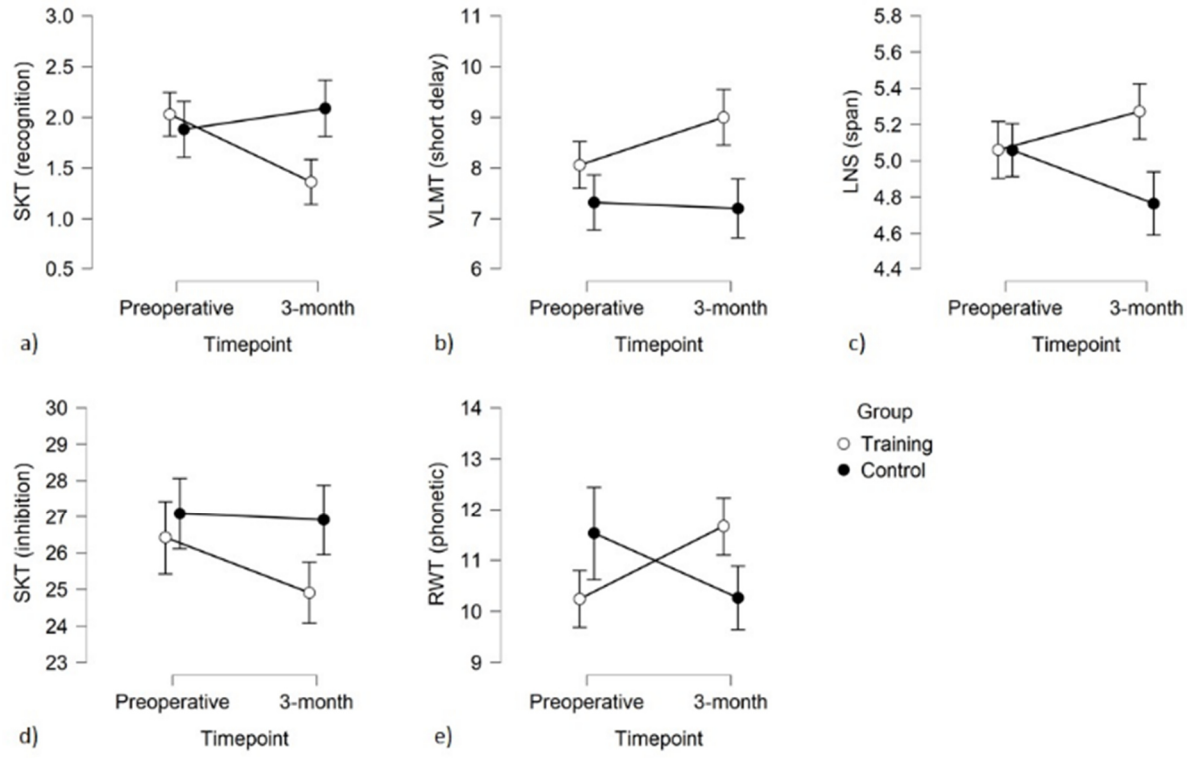


Supplementary Figure S1: Significant interaction effects of neuropsychological parameters between training group and control group. Shown are the mean values including SE bars for preoperative testing and discharge from the rehabilitation clinic for a) Trail Making Test-A (TMT-A) given in seconds (p=0.020) and b) "Regensburger Wortflüssigkeits-Test" (RWT-phonetic) given as number of correct items (p=0.015).



Supplementary Figure S2: Significant interaction effects of neuropsychological parameters between training group and control group. Shown are the mean values including SE bars for preoperative testing and at 3 months after discharge for a) “Syndrom-Kurztest” (SKT-recognition) given as numbers of false items (p=0.027), b) “Verbaler Lern- und Merkfähigkeitstest” (VLMT-short delay) given as number of correct items (p=0.044), c) Letter Number Span (LNS) given as span (p=0.011), d) SKT-inhibition given in seconds (p=0.049), and e) “Regensburger Wortflüssigkeits-Test” (RWT-phonetic) given as number of correct items (p=0.010).

Supplementary File 1

Intention to treat analysis

Primary Outcome Measures

At the time of discharge from rehabilitation, the ANCOVA with imputed data (training group, n=47; control group, n=47) revealed an improvement in the training group compared to the control group in domains of selective attention measured with the TMT-A ($F[2.91]=6.49$, $p=0.012$, $\eta2=0.04$), and phonetic word fluency revealed with the RWT ($F[2.91]=8.84$, $p=0.004$, $\eta2=0.07$), whereas patients in the control group deteriorated in these domains. Results of all neuropsychological test parameters are given in Supplementary Table 4. Potentially confounding variables made no significant contribution to the results, which were implemented as covariates in an adjusted ANCOVA.

At discharge from the rehabilitation clinic, POCD frequency was 23% (n=11) in the control group and 6% (n=3) in the training group, with a significant group difference ($\chi^2[1]=5.37$, $p=0.020$; OR=4.48, 95% CI [1.16-17.29]). POCI frequency was 19% (n=9) in the training group and 9% (n=4) in the control group, with no significant difference ($\chi^2[1]=2.23$, $p=0.135$; OR=0.39, 95% CI [0.11-1.38]).

Secondary Outcome Measures

At 3-month follow-up, the ANCOVA with imputed data (training group, n=47; control group, n=47) showed a statistically significant beneficial effect for the training group compared to the control group in visual free recall ($F[2.91]=7.11$, $p=0.009$, $\eta2=0.05$) tested with the SKT, visual recognition memory revealed with the SKT ($U=-2.63$, $p=0.009$, $\eta2=0.07$) and the NVLT ($F[2.91]=4.99$, $p=0.028$, $\eta2=0.04$), verbal free recall (short delay) ($F[2.91]=8.38$, $p=0.005$, $\eta2=0.04$) and verbal free recall (long delay) ($F[2.91]=6.67$, $p=0.011$, $\eta2=0.04$) measured with

the VLMT, verbal working memory span tested with the LNS ($F[2.91]=8.00$, $p=0.006$, $\eta 2=0.05$), cognitive inhibition speed measured with the SKT ($F[2.91]=6.69$, $p=0.011$, $\eta 2=0.02$), and phonetic word fluency tested with the RWT ($F[2.91]=11.08$, $p=0.001$, $\eta 2=0.07$). Results of all neuropsychological test parameters are given in Supplementary Table 4. Potentially confounding variables made no significant contribution to the results, which were implemented as covariates in an adjusted ANCOVA.

At 3-month follow-up, POCD frequency was 30% (n=14) in the control group and 13% (n=6) in the training group, with significant difference ($\chi^2[1]=4.07$, $p=0.044$; OR=2.89, 95% CI [1.00-8.37]). POCI frequency was 17% (n=8) in the training group and 6% (n=3) in the control group, with no significant difference ($\chi^2[1]=2.58$, $p=0.109$; OR=0.33, 95% CI [0.08-1.34]).

From baseline to discharge and to the 3-month follow-up, we detected no group differences in depression or anxiety using the HADS-D.

Supplementary Table 1: Definition of neuropsychological parameters and cognitive subdomains.

Cognitive domain (*DSM-5*)	**Cognitive subdomains (*DSM-5*)**	**Neuropsychological parameter**	**Task (scale of measurement)**
Learning and memory	Visual Immediate memory span	SKT	Recalling objects immediately (number of false items)
		BTT	Tapping blocks in a given order (span forward)
	Visual free recall	SKT	Recalling objects after delay (number of false items)
	Visual recognition memory	SKT	Recognising between learned and new objects (number of false items)
		NVLT	Recognising repeated abstract figures (number of correct items)
	Verbal Immediate memory span	VLMT	Recalling items on a word list (number of correct items· first trial)
	Verbal free recall	VLMT	Recalling items on a word list (summarised number of correct items· learning trials)

		VLMT	Recalling items on a word list (number of correct items· short delay)
		VLMT	Recalling items on a word list (number of correct items· long delay)
	Verbal recognition memory	VLMT	Recognising between learned and new words (number of correct items)
Complex attention	Selective attention	TMT-A (speed)	Linking numbers in ascending order (seconds)
		AKT (speed)	Marking target stimuli (seconds)
		AKT (accuracy)	Marking target stimuli (number of correct items)
Executive functions	Verbal working memory	LNS	Mental reorganisation of letters and numbers (span)
	Visual working memory	BTT	Tapping blocks in a given order (span backward)
	Cognitive flexibility	TMT-B (speed)	Linking numbers and letters in alternate order (seconds)
	Inhibition	SKT	Naming interfering letter· e.g.· “S” instead of “T” (seconds)
	Decision making	SVT	Selecting target symbol from several symbols (number of correct items)

Language	Word fluency	RWT (phonetic)	Naming words with a specific initial letter (number of correct items)
		RWT (semantic)	Naming words from a specific category (number of correct items)

SKT=Syndrom-Kurztest (Short Performance Test). BTT=Block-Tapping Test. NVLT=Non-Verbal Learning Test. VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test). TMT=Trail Making Test. AKT=Alterskonzentrationstest (Geriatric Concentration Test). LNS=Letter Number Span. SVT=Symbolverarbeitungstest (Symbol Processing Task). RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test).

Supplementary Table 2: Neuropsychological test results per group and assessment time (Baseline to discharge from rehabilitation)

	Baseline (n=81)				Discharge (n=81)					
	Training (n=37)		Control (n=44)		Training (n=37)		Control (n=44)			
Test parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	η2
SKT visual immediate memory span	5.5	1.6	6.1	1.5	5.7	1.4	5.8	1.3	0.853	0.00
SKT inhibition (speed)	26.9	5.7	27.5	5.5	26.3	5.3	27.9	6.4	0.228	0.01
TMT-A selective attention (speed)	41.9	13.1	42.0	13.2	40.0	14.7	47.3	18.9	0.020	0.04
TMT-B cognitive flexibility (speed)	94.2	33.4	106.8	39.4	94.0	40.2	110.9	49.2	0.491	0.00
SKT visual free recall	6.6	1.5	6.9	2.0	6.9	1.8	7.3	1.9	0.477	0.38
SKT visual recognition memory*	1.9	1.2	1.8	1.6	1.7	1.6	2.2	1.6	0.110	0.03
RWT word fluency (semantic)	20.6	6.1	20.5	5.8	18.4	5.6	17.4	5.6	0.419	0.01
RWT word fluency (phonetic)	10.4	4.1	10.8	5.0	11.0	3.8	9.1	4.3	0.015	0.06
VLMT verbal immediate memory span	5.4	1.9	4.9	1.5	5.3	1.5	4.9	1.5	0.332	0.01
VLMT verbal free recall (learning process)	42.0	10.3	39.2	10.2	41.6	10.3	39.1	10.0	0.691	0.00
VLMT verbal free recall (short delay)	7.9	2.7	7.2	3.5	7.8	3.4	6.8	3.4	0.341	0.01
NVLT visual recognition memory*	13.0	3.0	12.3	3.0	12.2	2.9	10.6	4.2	0.291	0.00
AKT selective attention (speed)	33.9	6.6	33.6	7.8	35.4	7.3	35.8	9.5	0.720	0.00
AKT selective attention (accuracy) *	54.2	1.1	54.1	1.4	54.2	0.9	53.5	3.2	0.253	0.02
LNS verbal working memory span	5.0	0.9	4.9	1.0	5.1	0.9	5.0	0.9	0.632	0.00

BTT visual immediate memory span (forward)	5.1	0.9	5.1	0.9	5.3	1.0	5.3	0.8	0.856	0.00
BTT visual working memory span (backward)	4.5	0.9	4.6	1.2	4.7	1.0	4.5	1.2	0.429	0.01
VLMT verbal free recall (long delay)	7.4	3.5	7.1	3.4	7.0	3.8	5.9	3.9	0.177	0.01
VLMT verbal recognition memory (accuracy) *	8.7	4.3	8.1	5.2	8.1	4.5	5.6	6.6	0.121	0.00
SVT decision making*	15.8	1.8	15.8	1.7	16.3	1.3	15.6	2.0	0.227	0.00

All test parameters were calculated with the ANCOVA, except those marked with an asterisk (*). Data are means (SD). p=value. η2=effect size. SKT=Syndrom-Kurztest (Short Performance Test). TMT=Trail Making Test. RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test). VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test). NVLT=Non-Verbal Learning Test. AKT=Alterskonzentrationstest (Geriatric Concentration Test). LNS=Letter Number Span. BTT=Block Tapping Test. SVT=Symbolverarbeitungstest (Symbol Processing Task).

Supplementary Table 3: Neuropsychological test results per group and assessment time point (Baseline to 3-month follow-up)

	Baseline (n=67)				3 months follow up (n=67)					
	Training (n=33)		Control (n=34)		Training (n=33)		Control (n=34)			
Test parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	η2
SKT visual immediate memory span	5.6	1.5	6.2	1.4	5.1	1.6	5.8	1.6	0.231	0.02
SKT inhibition (speed)	26.4	5.7	27.1	5.7	24.9	4.8	26.9	5.6	0.049	0.02
TMT-A selective attention (speed)	40.8	12.0	42.5	13.6	38.4	9.5	41.2	13.4	0.417	0.01
TMT-B cognitive flexibility (speed)	89.9	31.2	104.0	41.2	86.9	32.7	105.4	49.1	0.391	0.00
SKT visual free recall	6.6	1.6	6.9	1.9	6.3	1.4	7.1	2.0	0.075	0.04
SKT visual recognition memory *	2.0	1.2	1.9	1.6	1.4	1.3	2.1	1.6	0.027	0.07
RWT word fluency (semantic) *	21.2	6.1	20.3	5.8	20.6	5.6	19.6	7.1	0.950	0.00
RWT word fluency (phonetic)	10.2	3.2	11.5	5.3	11.7	3.3	10.3	3.6	0.010	0.07
VLMT verbal immediate memory span	5.3	2.0	5.1	1.4	5.5	1.9	5.4	1.8	0.975	0.00
VLMT verbal free recall (learning process)	42.8	10.3	39.5	9.8	45.2	11.2	41.1	10.5	0.407	0.01
VLMT verbal free recall (short delay)	8.1	2.6	7.3	3.2	9.0	3.2	7.2	3.4	0.044	0.04
NVLT visual recognition memory	13.0	2.9	12.4	2.5	13.1	2.5	11.9	2.6	0.100	0.04
AKT selective attention (speed)	33.3	6.5	33.8	7.7	33.1	8.5	35.1	8.0	0.325	0.01
AKT selective attention (accuracy) *	54.2	1.1	54.1	1.3	54.4	0.8	53.9	1.3	0.457	0.01

LNS verbal working memory span	5.1	0.9	5.1	0.9	5.3	0.9	4.8	1.0	0.011	0.07
BTT visual immediate memory span (forward)	5.1	0.9	5.1	0.9	5.3	0.8	5.3	0.9	0.892	0.00
BTT visual working memory span (backward)	4.6	1.0	4.6	1.3	4.6	1.1	4.6	1.2	0.962	0.00
VLMT verbal free recall (long delay)	7.6	3.5	7.0	3.2	8.1	3.3	6.4	3.5	0.055	0.04
VLMT verbal recognition memory (accuracy) *	8.6	4.4	8.2	4.8	9.2	4.1	8.4	4.6	0.561	0.01
SVT decision making*	15.7	1.9	16.0	1.2	16.6	1.3	16.2	1.7	0.152	0.03

All test parameters were calculated with the ANCOVA, except those marked with an asterisk (*). Data are means (SD). p=value. η2=effect size. SKT=Syndrom-Kurztest (Short Performance Test). TMT=Trail Making Test. RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test). VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test). NVLT=Non-Verbal Learning Test. AKT=Alterskonzentrationstest (Geriatric Concentration Test). LNS=Letter Number Span. BTT=Block Tapping Test. SVT=Symbolverarbeitungstest (Symbol Processing Task).

Supplementary Table 4: Neuropsychological test results per group and assessment time (Intention to treat analysis)

	Baseline (n=94)				Discharge (n=94)						3 months follow up (n=94)					
	Training (n=47)		Control (n=47)		Training (n=47)		Control (n=47)				Training (n=47)		Control (n=47)			
Test parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	η2	Mean	SD	Mean	SD	p	η2
SKT visual immediate memory span	5.7	1.6	6.1	1.4	5.7	1.3	5.8	1.3	0.996	<0.001	5.2	1.4	5.8	1.4	0.115	0.02
SKT inhibition (speed)	28.5	6.9	27.4	5.4	27.6	5.9	27.8	6.2	0.149	0.01	26.5	5.3	27.1	5.1	0.011	0.02
TMT-A selective attention (speed)	42.6	13.5	41.4	13.0	41.3	14.3	47.0	18.3	0.012	0.04	39.8	9.2	41.2	12.2	0.316	0.01
TMT-B cognitive flexibility (speed)	103.0	44.8	105.6	38.4	102.1	45.4	109.8	47.8	0.286	0.00	99.7	43.6	107.9	44.6	0.122	0.00
SKT visual free recall	6.9	1.5	6.8	2.0	7.1	1.6	7.3	1.8	0.463	0.00	6.4	1.3	7.1	1.7	0.009	0.05
SKT visual recognition memory*§	1.8	1.3	1.7	1.6	1.8	1.4	2.2	1.6	0.428	0.01	1.5	1.1	2.1	1.4	0.009	0.07
RWT word fluency (semantic)	19.9	6.3	20.9	5.9	18.1	5.0	17.5	5.4	0.424	0.01	20.2	4.9	19.9	6.1	0.517	0.00
RWT word fluency (phonetic)	9.5	4.4	11.1	5.1	10.8	3.4	9.2	4.2	0.004	0.07	11.3	3.0	10.2	3.3	0.001	0.07
VLMT verbal immediate memory span	4.9	2.1	4.9	1.5	5.2	1.4	4.9	1.4	0.239	0.01	5.2	1.6	5.3	1.6	0.719	0.00
VLMT verbal free recall (learning process)	40.6	10.8	39.2	9.9	40.6	10.0	39.2	9.7	0.728	0.00	43.5	10.5	40.6	10.0	0.201	0.01
VLMT verbal free recall (short delay)	7.7	2.7	7.1	3.5	7.7	3.1	6.7	3.3	0.262	0.01	8.8	2.8	7.1	3.2	0.005	0.04
NVLT visual recognition memory*	13.0	2.9	12.2	3.1	12.1	2.6	10.6	4.1	0.067	0.04	13.0	2.2	11.8	2.4	0.028	0.04
AKT selective attention (speed)	34.6	7.7	33.6	7.9	36.0	7.0	35.8	9.2	0.758	0.00	33.8	7.9	35.0	7.4	0.135	0.01
AKT selective attention (accuracy)*§	54.0	1.1	54.1	1.3	53.9	1.1	53.5	3.1	0.890	0.00	54.2	0.7	53.8	1.1	0.065	0.04
LNS verbal working memory span	4.9	1.0	4.9	1.0	5.1	0.9	5.0	0.9	0.633	0.00	5.1	0.8	4.7	0.9	0.006	0.05
BTT visual immediate memory span (forward)	5.1	0.9	5.1	0.9	5.3	0.9	5.3	0.7	0.925	0.00	5.3	0.7	5.3	0.7	0.927	0.00
BTT visual working memory span (backward)*	4.5	0.9	4.6	1.2	4.7	0.9	4.5	1.2	0.300	0.01	4.6	0.9	4.6	1.0	0.811	0.00
VLMT verbal free recall (long delay)	7.2	3.4	7.0	3.4	6.9	3.5	5.9	3.8	0.130	0.01	7.8	2.9	6.4	3.1	0.011	0.04
VLMT verbal recognition memory (accuracy)*	8.1	4.4	7.9	5.3	7.6	4.3	5.6	6.5	0.110	0.03	8.7	3.7	8.2	4.2	0.494	0.00
SVT decision making*§	15.6	1.9	15.8	1.7	16.1	1.2	15.6	1.9	0.506	0.01	16.4	1.2	16.1	1.5	0.299	0.01
HADS-D anxiety*§	6.1	3.7	5.7	3.2	4.3	2.8	3.8	3.2	0.927	0.00	4.1	2.5	4.3	3.2	0.393	0.01
HADS-D depression*§	4.0	3.2	3.8	2.4	3.2	2.7	3.1	2.7	0.772	0.00	3.0	2.8	3.4	2.6	0.158	0.02

All test parameters were calculated with the ANCOVA, except those marked with * and §, which were calculated with the Mann-Whitney U-test at discharge from rehabilitation (*) and at 3-month follow-up (§). Data are means (SD). p=value. η2=effect size. SKT=Syndrom-Kurztest (Short Performance Test). TMT=Trail Making Test. RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test). VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test). NVLT=Non-Verbal Learning Test. AKT=Alterskonzentrationstest (Geriatric Concentration Test). LNS=Letter Number Span. BTT=Block Tapping Test. SVT=Symbolverarbeitungstest (Symbol Processing Task). HADS-D=Hospital Anxiety and Depression Scale.

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ORIGINAL ARTICLE

The impact of postoperative cognitive training on health-related quality of life and cognitive failures in daily living after heart valve surgery: A randomized clinical trial

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Abstract

Background: Heart surgery is a risk factor for objectively and subjectively assessable postoperative cognitive decline (POCD), which is relevant for everyday life. The aim of this study was to investigate whether early postoperative cognitive training has an impact on health-related quality of life and cognitive failures in daily living after cardiac surgery.

Methods: The study was a two-arm, randomized, controlled, outcome-blinded trial involving older patients undergoing elective heart valve surgery with extracorporeal circulation (ECC). Recruitment took place at the Departments of Cardiac Surgery of the Kerckhoff Clinic in Bad Nauheim (Germany) and the University Hospital in Giessen (Germany). The patients were randomized (1:1 ratio) to either a paper-and-pencil–based cognitive training group or a control group. We applied the Short Form Health Survey (SF-36) and the Cognitive Failures Questionnaire (CFQ) prior to surgery and 3 months after the cognitive training. Data were analyzed in a per-protocol fashion.

Results: Three months after discharge from rehabilitation, the training group ($n = 31$) showed improvement in health-related quality of life compared to the control group ($n = 29$), especially in role limitations due to emotional problems ($U = -2.649$, $p = .008$,

$\eta^2 = 0.121$), energy and fatigue ($F[2.55] = 5.72$, $p = .020$, $\eta^2 = 0.062$), social functioning ($U = -2.137$, $p = .033$, $\eta^2 = 0.076$), the average of all SF-36 factors ($U = -2.374$, $p = .018$, $\eta^2 = 0.094$), health change from the past year to the present time ($U = -2.378$, $p = .017$, $\eta^2 = 0.094$), and the mental component summary ($U = -2.470$, $p = .013$, $\eta^2 = 0.102$).

Conclusion: As our cognitive training has shown beneficial effects, this intervention could be a promising method to enhance health-related quality of life after cardiac surgery.

KEYWORDS
cardiac surgery, cognitive failures, cognitive training, health-related quality of life, valve replacement

1 | INTRODUCTION

Neurocognitive complications have been described following cardiac surgery. These include delirium (Kotfis et al., 2018) and postoperative cognitive decline (POCD) (Greaves et al., 2019), which both potentially lead to reduced quality of life (Newman et al., 2001) or increased mortality (Steinmetz et al., 2009). POCD often appears to be subclinical and therefore remains unrecognized. Nevertheless, patients and their relatives report a decrease in cognitive abilities in daily living up to at least 3 months after cardiac surgery (Kastaun et al., 2016). Taken together, subjectively assessed POCD and health-related quality of life represent a clinically relevant intervention target. The pathogenesis of POCD involves several preoperative risk factors, such as depression (Kadoi et al., 2011; Tully et al., 2009), anxiety (Andrew et al., 2000; Tully et al., 2009) or mild cognitive impairment (Bekker et al., 2010). Furthermore, perioperative mechanisms are thought to cause and promote POCD. These include anesthesia, particularly cerebral (micro- and macro-)embolization, and neuroinflammation (Berger et al., 2018). In addition, preoperative administration of dexamethasone ameliorates the inflammatory response provoked by surgery, which is related to a reduction in the incidence of POCD (Glumac et al., 2017). As we have recently demonstrated in a prospective, randomized controlled interventional study, early postoperative paper-and-pencil–based cognitive training can reduce the incidence of objectively measurable POCD (Butz et al., 2022). To further elucidate the clinical relevance of our cognitive training, this report evaluates the training-induced effects on health-related quality of life and cognitive failure in daily living after cardiac surgery. Our hypothesis is that "there is a difference between the control group and the training group in relation to health-related quality of life and cognitive failures in daily living."

2 | METHODS

2.1 | trial design and enrolment

This study was a bicentered, two-arm, 1:1 randomized, controlled trial, conducted at following locations: The Department of Cardiac Surgery of the Kerckhoff Heart and Thorax Centre in Bad Nauheim, Germany; the Department of Cardiovascular Surgery at the University Hospital in Giessen, Germany; and the Department of Rehabilitation at the Kerckhoff Clinic in Bad Nauheim, Germany. The study, including informed consent, has been approved by the Ethics Committee of the Justus-Liebig University Giessen (Ref.: 28/14), complies with the Declaration of Helsinki, and is registered with the German Clinical Trials Register (ID: DRKS00015512). The study protocol was published in advance (Butz et al., 2019).

The study coordinator screened the patient information on elective cardiac surgery for eligibility criteria. Potential participants received detailed information about the study project. Written informed consent was signed if the patient agreed.

Age, sex, education, body mass index, preexisting conditions, and the severity partition for left ventricular ejection fraction (Lang et al., 2015) were documented at baseline. Perioperatively, duration of surgery and extracorporeal circulation (ECC), cross-clamp time, and invasive ventilation time were recorded. Postoperative complications, including delirium, were documented. After acute hospitalization, patients were directly transferred to the Department of Rehabilitation at the Kerckhoff Clinic in Bad Nauheim, Germany, where both groups received inpatient cardiac rehabilitation therapies that were individualized and based on the International Classification of Functioning. Key features of the therapeutic treatments were endurance and strength training, respiratory gymnastics, and educational lectures. Patients received 12–14 therapy sessions per week. In addition, patients of the training group underwent a multidomain cognitive intervention consisting of paper-and-pencil exercises that started about 1 week after surgery and lasted about 15 days until discharge from the rehabilitation clinic. A detailed description of the development and concept of the cognitive training (Butz et al., 2019) and its beneficial effects on cognition (Butz et al., 2022) have been published in advance.

2.2 | Inclusion and exclusion criteria

Inclusion criteria included elective aortic or mitral valve replacement/reconstruction with or without coronary artery bypass crafting

under ECC and sufficient knowledge of German. Exclusion criteria comprised history of stroke, psychiatric or neurological diseases, and health insurance that did not support postoperative rehabilitation at the Kerckhoff Clinic.

2.3 | Randomization

A computer-generated list with a 1:1 blocked allocation ratio was used for randomization. The randomization has randomly varied block sizes, and the study coordinator generated, sequentially numbered, and concealed it prior to the start of the study. After preoperative neuropsychological assessment, the study coordinator assigned the patients to the cognitive training group or the control group.

2.4 | Blinding

Surgeons, neurologists, and neuropsychologists involved in the outcome variables were blinded for randomization status.

2.5 | Outcome measures

The results of the primary outcome of the study have been published in advance (Butz et al., 2022). Secondary outcomes published in the present paper are the effect of cognitive training on health-related quality of life and subjectively assessed cognitive failure in daily living at 3 months after the cognitive training.

2.6 | Questionnaires

To reveal cognitive failures in daily living, we used the Cognitive Failures Questionnaire (CFQ), which is the most widely used instrument to assess self-reported cognitive failures (Carrigan & Barkus, 2016). Study patients completed a validated German 25-item version of the Cognitive Failures Questionnaire for self-assessment (s-CFQ) (Klumb, 1995). The patients' close relatives responded to an 8-item Cognitive Failures Questionnaire to evaluate foreign assessment (f-CFQ) (Broadbent et al., 1982). Both have to be answered on a 5-point scale from "never" to "very often." The questionnaires examine the frequency of failures in daily living related to memory, attention, action, and perception. Because memory impairment is an important element that can affect every day functioning, the s-CFQ was supplemented by 4 additional questions related to memory failures, taken from the validated German version of the Memory Complaint Questionnaire (MCQ) (Heß, 2005). We calculated various models to assess self-reported cognitive failures. First, we averaged all items to a one-factor value. Since several cognitive functions are integrated into the averaged one-factor value and we did not overlook training effects on specific cognitive factors (e.g., distractibility, memory for names, misdirected actions), we analyzed several CFQ factor models that have already been described (Larson et al., 1997; Pollina et al., 1992; Rast et al., 2009; Wallace et al., 2002). According to the CFQ factor models, we calculated a single factor of the 4 memory questions taken from the MCQ.

We assessed health-related quality of life using the 36-Item Short Form Health Survey (SF-36, Version 1.0) (Bullinger & Kirchberger, 1998). The SF-36 includes 36 items covering 8 health-related factors, including physical functioning (10 items), role limitations due to physical health (4 items), role limitations due to emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), social functioning (2 items), pain (2 items), and general health (5 items). Furthermore, we determined a total score across all 8 factors, as well as a 2-factor model, indicating the physical component summary (physical functioning, role limitations due to physical health, pain, general health) and mental component summary (role limitations due to emotional problems, energy/fatigue, emotional well-being, and social functioning). The answers provided by the patients within the factors refer to the last 4 weeks, except for the factor physical functions and the first question of the factor general health, which refer to the present state of health. Furthermore, it also contains a single item (item 2, health change), which gives an indication of the extent to which the present health has changed in relation to the past year. The SF-36 was scored using the RAND scoring method (Hays et al., 1993). Each item in the questionnaire was assigned a score from 0 to 100, with a higher score indicating a better health state.

For all questionnaires, the CFQ, the MCQ, and the SF-36 handling with missing data were as follows. If the patients answered at least 50% of all items per factor, per time point, the mean score of this factor was calculated to determine the values of the factors. Items that were left blank (missing data) were not considered. Therefore, the factor values represent the average for all items of a factor that the respondent responded to.

Since worries about one's cognition could have an impact on self-reported cognitive failures in a way that depressed people answering themselves more conservative (Könen & Karbach, 2020; Wilhelm et al., 2010), we considered depression values as a control variable taken from the validated German version of the Hospital Anxiety and Depression Scale (HADS-D) (Herrmann-Lingen et al., 2011).

2.7 | Statistical analyses

We carried out a sample size calculation for the primary outcome of our study (cognitive training–related effect on objectively assessed cognition), which was published in advance (Butz et al., 2022). Therefore, we did not perform any sample size calculation for this report, which refers to the secondary outcomes of our trial, and we analyzed the data exploratively.

To determine the effect of cognitive training on cognitive failure in daily living and health-related quality of life, we conducted analyses of covariance (ANCOVAs) with the postoperative questionnaire value as the dependent variable, groups (control group/training group) as the fixed factor, and the preoperative questionnaire value as the covariate. We tested assumptions for ANCOVAs using the Levene test

(homogeneity of variance between groups) for the dependent variable and a statistically significant correlation between the dependent variable and covariate (preoperative test value) calculated using the Pearson product-moment correlation. As a further assumption, we checked the distribution and Q-Q plots for normality. When assumptions for ANCOVA were violated, we calculated difference values between pre- and posttests, followed by the Mann–Whitney *U*-test for between-subject effects. To control for the possibility of confounder variables that could affect the results, we conducted correlation analysis between potentially confounding variables (e.g., continuous demographic variables, perioperative details, changes in anxiety and depression) and changes between pre- and postoperative SF-36 and CFQ assessment. In the case of these variables' significant contributions, we implemented them additionally to the preoperative values as further covariates to the ANCOVA. We checked all data entries for inconsistent values.

Subjective-POCD was defined as a decline and subjective-POCI as an improvement from pre- to postassessment of at least 1 SD (Kastaun et al., 2016) in all considered CFQ models. To measure the difference of 1 SD between pre- and postassessment, we used Z-scores, which were calculated by the difference of the individual raw values from the mean value of the total baseline data divided by the SD of the total baseline data. To reveal the training effect on cognition, frequencies of dichotomous (yes/no) subjective-POCD and subjective-POCI variables were compared with Pearson's χ^2 test between the groups.

We give the effect size as η^2 and set the criterion for statistical significance at $p < .05$. We evaluated our data set with a per-protocol analysis, and we performed all analyses using the statistical software SPSS (version 22) and JASP (version 0.12.2).

3 | RESULTS

Between July 13, 2016 and January 8, 2020, a total of 130 patients were enrolled, randomized, and tested preoperatively. The last patient was tested on February 27, 2020 for the 3-month follow-up. The recruitment has concluded.

After randomization of 130 patients, 36 (training group $n = 18$, control group $n = 18$) were lost to follow-up before the training or control intervention had begun. Thus, 94 patients (training group $n = 47$, control group $n = 47$) were considered for the baseline sample. Table 1 lists the baseline characteristics. No statistical significant group differences have been shown in the baseline data. Thirteen patients (training group $n = 10$, control group $n = 3$) were lost to follow-up, whereas 81 patients (training group $n = 37$, control group $n = 44$) remained at discharge from rehabilitation. Thus, about 80% of the patients completed the training. Another 21 patients (training group $n = 6$, control group $n = 15$) were lost to the 3-month follow-up, resulting in 60 patients (training group $n = 31$, control group $n = 29$) for analysis. Five patients (training group $n = 2$, control group $n = 3$) did not answer enough questions within the questionnaires to complete the missing data, resulting in different sample sizes in the statistical tests (see Table 2). Figure 1 outlines the reasons that patients were lost to follow-up. The train-

TABLE 1 Baseline demographics and characteristics of the intention to treat the population.

	Training ($n = 47$)	Control ($n = 47$)
Demographics		
Age (years)	71.2 (4.7)	73.0 (4.9)
Sex		
Women	8 (17%)	13 (28%)
Men	39 (83%)	34 (72%)
Education (years)	13.5 (3.0)	13.4 (3.0)
Medical history		
Body mass index (kg/m^2)	27.7 (3.8)	26.6 (3.8)
Arterial hypertension	31 (66%)	31 (66%)
Diabetes mellitus	10 (21%)	5 (11%)
Renal insufficiency	4 (9%)	7 (15%)
Dyslipidemia	39 (83%)	37 (79%)
LV EF (mildly abnormal)	5 (11%)	6 (13%)
LV EF (moderately abnormal)	3 (6%)	1 (2%)
Heart failure	10 (21.3%)	9 (19.1%)
Type of surgery		
AVR	23 (50%)	22 (47%)
AVR+CABG	18 (38%)	19 (40%)
MVR	4 (9%)	1 (2%)
MVR+CABG	0 (0%)	3 (6%)
AVR+MVR	2 (4%)	2 (4%)
Perioperative details		
Duration of surgery (minutes)	190.3 (38.1)	200.6 (58.9)
Duration of extracorporeal circulation (minutes)	96.5 (26.5)	105.2 (37.5)
Cross-clamp time (minutes)	69.1 (19.9)	74.7 (26.7)
Ventilation time invasive (minutes)	616.2 (331.3)	588.1 (213.6)
Postoperative complications		
Delirium	2 (4%)	4 (9%)
Arrhythmia	18 (38%)	21 (45%)
Atrial fibrillation	18 (38%)	17 (36%)
Renal insufficiency	6 (13%)	6 (13%)
Acute blood loss anemia	10 (21%)	12 (26%)
Transient ischemic attack	1 (2%)	0 (0%)
Dysathria/aphasia	0 (0%)	1 (2%)
Medical details at admission to rehabilitation		
Blood pressure (systolic; mmHG)	128.1 (12.7)	127.7 (18.4)
Blood pressure (diastolic; mmHG)	74.5 (11.1)	71.4 (10.6)

Note: Data include means (SD) or number of subjects (%). LF EV = left ventricular ejection fraction, defined according to Lang et al. (2015). AVR = aortic valve replacement. CABG = coronary artery bypass grafting. MVR = mitral valve replacement/reconstruction. Renal insufficiency was defined by a creatinine value above the in-house norms (men: > 1.2 mg/dL, women: > 0.9 mg/dL).

TABLE 2 SF-36 results per group and assessment time for the per-protocol analysis.

SF-36 Factor	Timepoint	Group	Mean	SD	*n*	*p* Value	η^2
Physical functioning	Baseline	Control	64.563	22.055	28		
		Training	63.553	24.420	31		
	3-month follow-up	Control	76.190	22.394	28		
		Training	80.932	14.156	31		
						.568	0.006
Role limitations due to physical health	Baseline	Control	48.077	42.381	26		
		Training	43.011	41.337	31		
	3-month follow-up	Control	60.577	42.528	26		
		Training	71.774	35.790	31		
						.126	0.041
Role limitations due to emotional problems	Baseline	Control	85.057	31.605	29		
		Training	72.414	37.869	29		
	3-month follow-up	Control	66.667	43.644	29		
		Training	91.954	21.185	29		
						.008	0.121
Energy/fatigue*	Baseline	Control	51.296	16.675	27		
		Training	48.548	16.842	31		
	3-month follow-up	Control	56.975	21.593	27		
		Training	64.570	15.623	31		
						.020	0.062
Emotional well-being	Baseline	Control	73.778	14.606	27		
		Training	72.710	18.927	31		
	3-month follow-up	Control	76.556	17.579	27		
		Training	81.290	12.623	31		
						.462	0.009
Social functioning	Baseline	Control	79.741	21.499	29		
		Training	81.855	16.085	31		
	3-month follow-up	Control	78.448	25.638	29		
		Training	89.516	17.410	31		
						.033	0.076
Pain	Baseline	Control	83.276	19.017	29		
		Training	79.274	26.459	31		
	3-month follow-up	Control	81.810	22.018	29		
		Training	86.129	19.936	31		
						.336	0.016
General health*	Baseline	Control	59.226	13.174	28		
		Training	57.056	15.175	31		
	3-month follow-up	Control	59.152	14.900	28		
		Training	64.516	18.989	31		
						.067	0.04
Average of all factors	Baseline	Control	67.648	13.699	29		
		Training	64.611	16.514	31		
	3-month follow-up	Control	69.515	20.672	29		
		Training	78.497	14.049	31		
						.018	0.094

(Continues)

TABLE 2 (Continued)

SF-36 Factor	Timepoint	Group	Mean	SD	*n*	*p* Value	η^2
Health change (Item 2)	Baseline	Control	32.759	21.238	29		
		Training	22.581	14.937	31		
	3-month follow-up	Control	61.207	28.020	29		
		Training	71.774	27.189	31		
						.017	0.094
Physical component summary	Baseline	Control	63.020	18.257	29		
		Training	60.724	19.413	31		
	3-month follow-up	Control	69.547	20.666	29		
		Training	75.838	18.003	31		
						.173	0.031
Mental component summary	Baseline	Control	72.517	16.029	29		
		Training	68.647	17.245	31		
	3-month follow-up	Control	69.273	23.630	29		
		Training	81.156	11.352	31		
						.013	0.102

Note: All test parameters were calculated with difference values between pre- and posttests, followed by Mann–Whitney *U*-test for between-subject effects, except those marked with an asterisk (*), which were calculated by ANCOVA. Data include means (SD). *n* = number of cases. η^2 = effect size

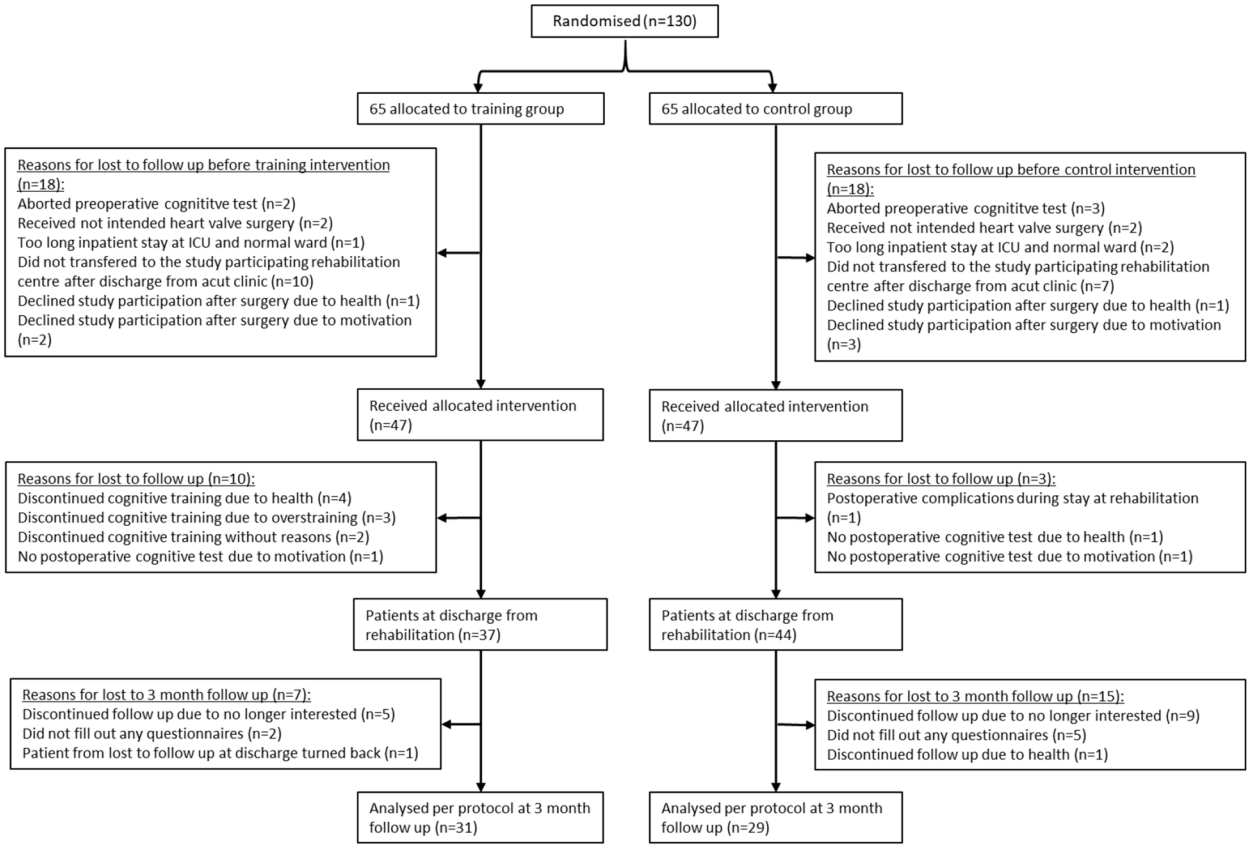

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart illustrating all steps in the study from randomization to follow-up and analysis. ICU = intensive care unit.

ing intervention lasted 14.86 (SD = 2.507) days and did not cause any adverse events.

Three months after discharge from rehabilitation, some improvements in health-related quality of life were evident for the training group compared to the control group. These improvements have been seen in role limitations due to emotional problems ($U = -2.649$, $p = .008$, $\eta^2 = 0.121$), energy and fatigue ($F[2.55] = 5.72$, $p = .020$, $\eta^2 = 0.062$), social functioning ($U = -2.137$, $p = .033$, $\eta^2 = 0.076$), the average of all SF-36 factors ($U = -2.374$, $p = .018$, $\eta^2 = 0.094$), health change from the past year to the present time ($U = -2.378$, $p = .017$, $\eta^2 = 0.094$), and the mental component summary ($U = -2.470$, $p = .013$, $\eta^2 = 0.102$). Figure 2 shows the interaction effects. Table 2 provides a full description of the results of all SF-36 factors.

In the adjusted ANCOVA with potentially confounding variables, cross-clamp time ($F[3.54] = 6$, $p = .018$, $\eta^2 = 0.058$) and changes in depression over time ($F[3.54] = 4.19$, $p = .046$, $\eta^2 = 0.046$) contributed significantly to the SF-36 factor energy/fatigue.

There were no statistically significant or clinically relevant interaction effects between the control group and the training group in all considered s-CFQ models, f-CFQ, and MCQ.

4 | DISCUSSION

Our key findings were beneficial effects 3 months after discharge from rehabilitation in several health-related quality-of-life domains. These have been found in role limitations due to emotional problems, energy and fatigue, social functioning, the average of all SF-36 factors, health change from the past year to the present time, and the mental component summary. The treatment success of cardiac surgery is potentially based on the objective clinical or physiological status. The subjective patient-centered changes (physical and psychological) seem to be important as well and may especially contribute to the treated patient's quality of life (Koch et al, 2008). Therefore, we used the SF-36 questionnaire to assess postoperative patient's physical and mental processes in the context of a cognitive training program.

A computerized approach has shown enhancements for health-related quality of life after postoperative cognitive training, which is in line with our results (Ajtahed et al., 2019). In addition, healthy older people showed various improvements in quality-of-life parameters (e.g., role limitations due to emotional problems, social functioning, role limitations due to functional limitations) after a controlled cognitive intervention with positive posttraining effects at a 3-month follow-up (Shati et al., 2021). Cognitive training–related improvements of depressive symptoms also exist in older adults with subclinical cognitive decline (Gooding et al., 2016). Reduced postoperative health-related quality of life can increase mortality after cardiac surgery (Steinmetz et al., 2009), making the beneficial effects of cognitive training particularly important.

Cognitive abilities were evaluated as an additional outcome in this study because they contribute substantially to independence, personality, and self-image for elderly patients, and also represent another important factor of health-related quality of life. In the present investigation, the subjective assessment of cognitive failures in everyday living has not shown a difference between the groups. Therefore, we assumed that the CFQ-questionnaire might not be sensitive enough to reveal alterations from the cognitive training. There is evidence that subjective assessments of cognitive ratings are unrelated to objective testing of cognitive performance (Brück et al., 2019; Carrigan & Barkus, 2016). Studies have discussed whether ICU survivors or elderly people, who may be more likely to be affected by cognitive impairment, inadequately estimate their own cognitive performance. This could lead to a lack of correlation with objective tests (Brück et al., 2019). In addition, it is possible that people underestimate cognitive deficits in the daily life of relatives who has survived a potentially life-threatening disease or medically necessary surgery.

Nevertheless, we have shown that cognitive training is associated with psychometrically confirmed improvements in postoperative cognition (Butz et al., 2022). We assume that this effect can be transferred to psychologically relevant everyday situations and, therefore, increase health-related quality of life.

A few limitations should be mentioned. First, a comparison with patients without the use of an ECC or a healthy control cohort does not seem possible, as we only examined patients who had been operated with ECC. Related to the results reported here and a previously published article concerning the objectively determined frequency of POCD (Butz et al., 2022), another limitation of our study emerges. We did not evaluate the incidence of "postoperative mild and major neurocognitive disorders" as defined by Evered et al. (2018), which is recommended for the research of POCD. This was not possible because some of the following research criteria were not implemented in our study protocol: the questions about postoperative alterations in activity of daily living (ADL) and the patientt's subjective decrease of postoperative cognition, specifically referring to heart surgery. Furthermore, the use of a healthy control group to calculate a reliable change index (controls for time and practice effects), which is also recommended to calculate POCD (Rasmussen et al., 2001), was not involved in our study. Furthermore, we did not evaluate if and how the patients practiced some cognitive-enhancing activities (e.g., playing games, reading books, pronounced social activities) between the end of cognitive training and the 3-month follow-up, which could have also had an impact on cognitive plasticity (Xu et al., 2019). Since patients in the cognitive training group learned specifically what type of training material could be used for cognitive improvement, they would be more likely to come up with the idea of using similar material in the postrehabilitation period than the control group, who were only made aware of the potential of cognitive-enhancing training through the consent form and information sheet. Compared to the control group, the training group showed shorter duration of surgery, extracorporeal circulation, and cross-clamp time. As duration of surgery and anesthesia are reported to be risk factors for POCD (Vu & Smith, 2022), this could also affect health-related quality of life (HQL), as an association between POCD and HQL has been found (Phillips-Bute et al., 2006). However, the duration of surgery, extracorporeal circulation, and cross-clamp time seems unassociated with HQL (Sanders et al., 2022). In addition, no significant group differences were shown for

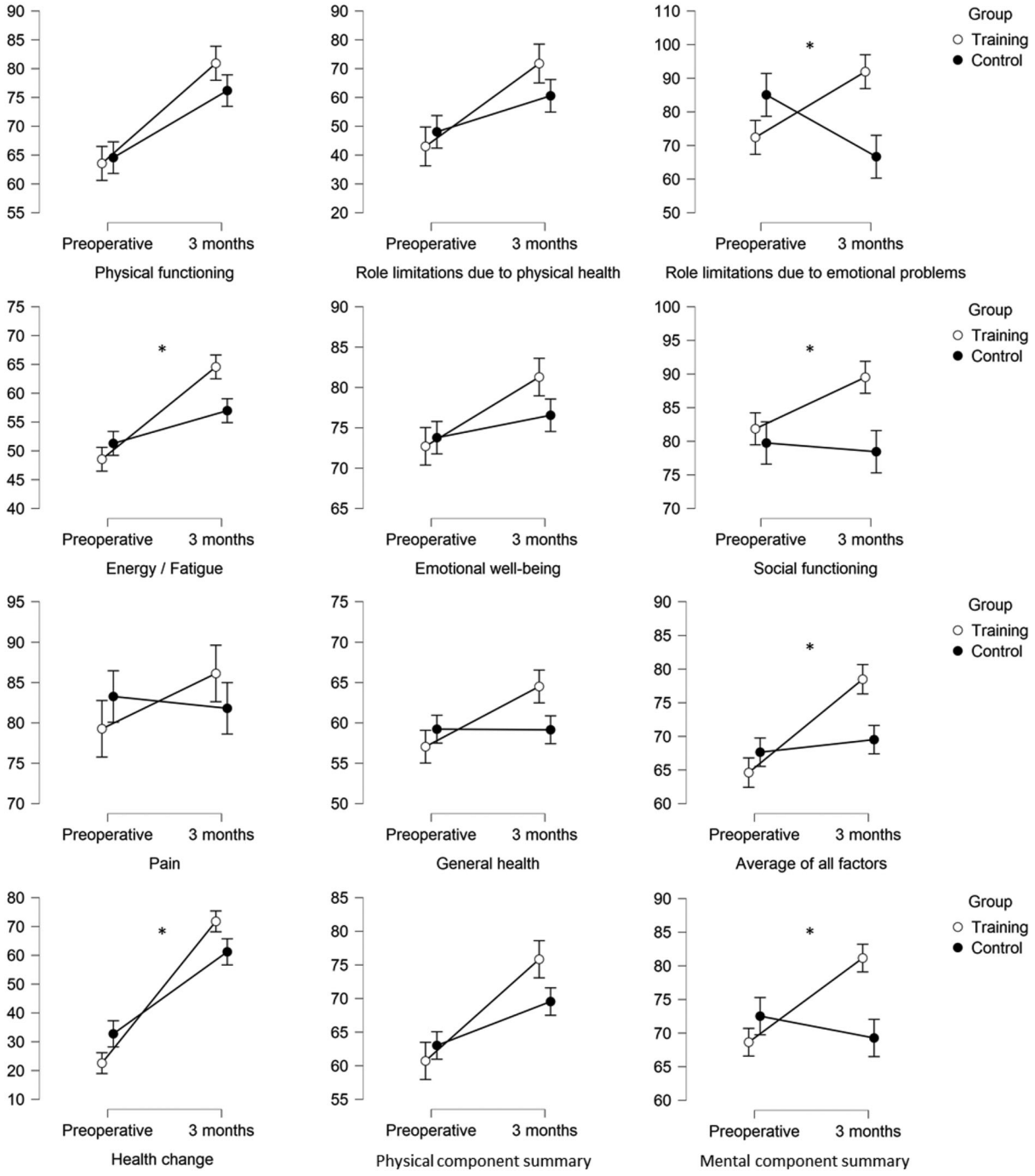

FIGURE 2 Interaction effects of all SF-36 factors between the training group and control group. Shown are the mean values (higher scores indicating a better health state), including SE bars for preoperative testing and 3 months after discharge from the rehabilitation clinic. Statistical significant interaction effects with a p value of <.05 are marked with an asterisk (*).

these factors in our sample, and a post hoc ANCOVA with these factors as control variables showed no changes in between-group effects from statistically significant to nonsignificant results. We counted the incidence of POD using medical records. As we did not perform a standardized daily assessment of POD in the ICU and normal ward, the frequency of POD cases in our sample may be underreported. Because health insurance for patients transferred from the acute clinic to the rehabilitation center only covers patients of retirement age, the results of cognitive training are limited to this particular cohort.

Since our training concept was able to decrease POCD or maintain and improve health-related quality of life after cardiac surgery, it could also be useful for noncardiac surgery patients potentially affected by POCD. In general, it may also be beneficial for patients suffering cognitive impairment after stroke or in the context of dementia. In addition, our concept is designed to be continued in an ambulatory setting after

clinical implementation (e.g., in a home-based environment) or performed in a home-based setting prior to surgery that has the potential to impair cognition. Preoperative cognitive training might build up a so-called cognitive reserve, which could provide prophylactic protection of the brain (Saleh et al., 2015).

AUTHOR CONTRIBUTIONS

Marius Butz: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; writing-original draft. Tibo Gerriets: Conceptualization; funding acquisition; methodology; project administration; supervision; writing–review & editing. Gebhard Sammer: Conceptualization; methodology; project administration; supervision; validation; writing–review & editing. Jasmin El-Shazly: Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; validation; writing–review & editing. Marlene Tschernatsch: Writing–review & editing. Patrick Schramm: Writing–review & editing. Thorsten R. Doeppner: Writing–review & editing. Tobias Braun: Writing–review & editing. Andreas Boening: Resources; writing–review & editing. Thomas Mengden: Conceptualization; resources; writing–review & editing. Yeong-Hoon Choi: Writing–review & editing. Markus Schoenburg: Conceptualization; funding acquisition; methodology; project administration; resources; supervision; writing–review & editing. Martin Juenemann: Conceptualization; funding acquisition; methodology; project administration; supervision; writing–review & editing.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

Deidentified participants' data analyzed during the current study are available from the corresponding author on reasonable request.

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PEER REVIEW

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Increasing preoperative cognitive reserve to prevent postoperative delirium and postoperative cognitive decline in cardiac surgical patients (INCORE): Study protocol for a randomized clinical trial on cognitive training

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Introduction: Postoperative delirium (POD) and postoperative cognitive decline (POCD) can be observed after cardiosurgical interventions. Taken together, these postoperative neurocognitive disorders (PNCDs) contribute to increased morbidity and mortality. Preoperative risk factors of PNCD, such as decreased neuropsychometric performance or decreased cognitive daily activities, can be interpreted as reduced cognitive reserve. This study aims to build up cognitive reserves to protect against the development of PNCD through preoperative, home-based, cognitive training.

Methods: The planned research project is a monocentric, two-arm randomized controlled intervention study involving 100 patients undergoing elective cardiac surgery with extracorporeal circulation. Patients will be assigned to a training group or control group. The intervention involves a standardized, paper-and-pencil-based cognitive training that will be performed by the patients at home for ~40 min per day over a preoperative period of 2–3 weeks. The control group will receive neither cognitive training nor a placebo intervention. A detailed assessment of psychological functions will be performed ~2–3 weeks before the start of training, at the end of the training, during hospitalization, at discharge from the acute clinic, and 3 months after surgery. The primary objective of this study is to investigate the interventional effect of preoperative cognitive training on the incidence of

POD during the stay in the acute clinic, the incidence of POCD at the time of discharge from the acute clinic, and 3 months after surgery. Secondary objectives are to determine the training effect on objective cognitive functions before the surgery and subjective cognitive functions, as well as health-related quality of life 3 months after surgery.

Discussion: Should it become evident that the use of our cognitive training can both reduce the incidence of POCD and POD and improve health-related quality of life, this intervention may be integrated into a standardized prehabilitation program.

KEYWORDS

cardiac surgery, postoperative delirium, postoperative cognitive decline, prehabilitation, cognitive reserve, cognitive training

Introduction

Neuropsychological complications following cardiac surgery include postoperative delirium (POD), postoperative cognitive decline (POCD) (1), and dementia (2). Depending on age and evaluation methods, the frequency of POD after cardiac surgery varies between 14 and 50% (3). The prevalence of POCD is reported to be in the range of 28% between the first and fourth postoperative month and 22% between the sixth and 12th postoperative month (4). Postoperative cognitive improvement (POCI) can also be measured after surgeries but occurs about three to six times less frequently than POCD (5). POCD is more noticeable in objective psychometric assessments and often appears subclinically; nevertheless, patients and their relatives have reported a subjective decrease in patients' cognitive abilities in daily living after heart surgery (6). POD and POCD are related to a reduced quality of life, long-term cognitive decline, increased economic costs, and higher mortality (3).

Preoperative psychological risk factors for the development of POCD include depression (7, 8) and reduced neuropsychometric functions (9). Preexisting cognitive impairment may also contribute to the development of dementia (10). In addition, depression (11), preoperatively reduced objective cognitive functions (11), or reduced cognitive everyday activities such as reading, writing, solving crosswords, and playing computer games (12) could be linked to the development of POD. Furthermore, in a rat model, it was shown that a preoperative enrichment of activity opportunities can lower the rate of POCD (13). In summary, diminished neuropsychometric functions or reduced cognitive everyday activities can be declared as a lower cognitive reserve. In the classical sense, the term "cognitive reserve" refers to the adaptability of cognitive processes, which can help to explain the sensitivity of cognitive abilities or everyday functions in the context of physiological aging and pathological neurodegeneration of the brain. The cognitive reserve can be influenced, among other things, by general cognitive ability in early life (intelligence), education, occupation, physical activity, leisure activities, or social engagement (14). For example, it has been shown that increased cognitive or social leisure activities performed within a wide life span (childhood to adulthood) can reduce the risk of developing dementia (15, 16). Increasing the cognitive reserve through focused cognitive training may, therefore, be a potential intervention target to prevent postoperative neurocognitive dysfunctions.

The primary objective of this study is to investigate the interventional effect of preoperative cognitive training on the incidence of POD during the stay in the acute clinic, the incidence of POCD at the time of discharge from the acute clinic, and 3 months after surgery. Secondary objectives are to determine the training effect on objective cognitive functions before the surgery and subjective cognitive functions, as well as health-related quality of life 3 months after surgery.

Abbreviations: ANCOVA, Analysis of covariance; BVMT-R, Brief Visuospatial Memory Test-Revised; CAM, Confusion Assessment Method; CAS, Cognitive Activity Scale; f-CFQ, Cognitive Failure Questionnaire for foreign assessment; FDR, False discovery rate; HADS, Hospital Depression and Anxiety Scale; ICDSC, Intensive Care Delirium Screening Checklist; LEQ-D, Lifetime of Experiences Questionnaire; LNS, Letter Number Test; MOCA, Montreal Cognitive Assessment; POCD, Postoperative cognitive decline; POD, Postoperative delirium; POCI, Postoperative cognitive improvement; RWT, Regensburger Wortflüssigkeits-Test; s-CFQ, Cognitive Failure Questionnaire for self-assessment; SF-36, 36-Item Short Form Health Survey; SKT, Syndrom-Kurztest Test; TMT, Trail Making Test; VLMT, Verbaler Lern- und Merkfähigkeitstest.

Methods and analysis

General conditions

The planned research project is a monocentric, randomized controlled study conducted by the Heart and Brain Research Group—a cooperation project between the Department of Cardiac Surgery of the Kerckhoff Heart and Thoracic Center in Bad Nauheim and the Department of Neurology of the University Hospital Giessen. Our working group consists of members of the Departments of Neurology, Neuropsychology, Radiology, and Cardiac Surgery who are responsible for the study procedure, including preparing the protocol, monitoring the study, and writing the study reports. This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (17). The data monitoring committee was not believed to be necessary, as no adverse effects of cognitive training are expected.

Trial registration

The study is prospectively registered with ClinicalTrials.gov (Identifier: NCT04493996. First posted: July 31, 2020. First patient enrolled: August 14, 2020).

Dissemination policy

Our aim is to make the study results available to the public, healthcare providers, and scientists by publication in the public press, at scientific congresses, and as original articles in peer-reviewed journals. The results will be reported regardless of the size and direction of the effect.

Recruitment

A study coordinator will receive information from the Department of Cardiac Surgery of the Kerckhoff Heart and Thoracic Center in Bad Nauheim about planned elective cardiac surgeries. After screening inclusion and exclusion criteria, patients will be informed in detail about the purpose and procedure of the study project.

Inclusion criteria

- Elective cardiac surgery (on pump)
    - Coronary artery bypass surgery (CABG)
    - Aortic valve replacement (AVR)
    - Mitral valve replacement/reconstruction (MVR)
    - Combination surgery (CABG+AVR, CABG+MVR, AVR+MVR, CABG+AVR+MVR)
- Age > 18 years
- Good knowledge of the German language (cognitive training and neuropsychological tests are language-dependent).

Exclusion criteria

- Preexisting psychiatric disorders (depression and dementia) with acute clinical symptoms can impair psychological performance.
- Preexisting neurological disorders (stroke, Parkinson's disease, and multiple sclerosis) with acute clinical symptoms can impair psychological performance.

Randomization

Randomization will be implemented using a computer-generated randomization list (www.randomization.com) with a 1:1 blocked allocation ratio and block sizes of 10. The randomization list will be generated, sequentially numbered, and concealed before the start of the study by the randomization list holder, who is located in the department of Neurology at the University Hospital Giessen and Marburg. After recruitment and the first preoperative neuropsychological examination, a study coordinator will allocate patients to the cognitive training or control group. A study coordinator will inform the psychological training supervisor about which patients should be trained.

Blinding

Neuropsychologists and nursing staff who will be involved in the assessment of outcome variables will be blinded for randomization status. The training sessions will be conducted by a psychological training supervisor who is not involved in the evaluation of outcome parameters to ensure blinding. The holder of the randomization list is not involved in the supervision of the training or the evaluation of all examinations on neuropsychometrical functions and delirium. In addition, the randomization list and its holder are located in the department of Neurology at the University Hospital in Giessen where the psychological evaluations, the intervention, and the surgery do not take place. Furthermore, when we inform patients by mail about which randomization group they are assigned to, we instruct them for all subsequent assessments not to inform the investigators about their randomization status.

Study process

After we obtain written consent from the patients, a detailed neuropsychometric assessment will be carried out 2–3 weeks preoperatively, and the patients will provide other information *via* questionnaires. These questionnaires, which must be completed by the patients themselves, refer to depression, anxiety, health-related quality of life, cognitive and social activities in everyday life, and questions on cognitive failures in everyday life. In addition, close relatives will also assess cognitive failures in the patients' everyday life in a separate questionnaire. Following neuropsychological assessment, randomization into a cognitive training group or control group will be performed. Patients in the training group will receive a package with the training material by mail. Those in the control group will receive a letter stating that they will not be involved in a training program. The control group will receive neither cognitive training nor placebo intervention. A second detailed neuropsychometric status assessment will be performed when patients are admitted to the acute clinic, which usually is scheduled 1 day before surgery. In addition, patients will complete questionnaires on depression, anxiety, and recent cognitive and social activities. At the time of discharge from the acute clinic, a short cognitive screening test (MOCA) will be carried out. Three months after surgery, all patients will be included in a final examination, which will take place at the Kerckhoff Clinic in Bad Nauheim, Germany, or at the patients' homes if required. This examination will include a further detailed neuropsychometric assessment, as well as questionnaires on depression, anxiety, health-related quality of life, questions on cognitive failures in everyday life, and recent cognitive and social everyday activities.

Baseline demographics and characteristics will include age, gender, years of educational and occupational background, body mass index, preexisting medical conditions (arterial hypertension, diabetes mellitus, dyslipidemia, and severity partition for left ventricular ejection fraction [defined by Lang et al. (18)]), heart failure, renal insufficiency (defined by a creatinine value above the in-house norms (men: >1.2 mg/dl, women: >0.9 mg/dl)), preoperative medication, type of surgery (CABG, AVR, MVR, and combination surgery), anesthesia and analgesics administered (type, amount, and duration), duration of the operation, duration of extracorporeal circulation, cross-clamp time, lowest body temperature, invasive ventilation time, peri- and postoperative complications (delirium, arrhythmia, atrial fibrillation, renal insufficiency, acute blood loss anemia, transient ischemic attack, stroke, dysarthria, aphasia, and death), days on the intensive care unit, and the total length of stay on the normal ward. We plan no systematic and standardized pre- or postoperative neuroradiological imaging.

The study process is shown in Figure 1. A detailed trial schedule according to the SPIRIT guidelines for study protocols is shown in Table 1 (17).

Primary outcomes

1. Number of participants with POCD at 3 months after surgery.
2. Number of participants with POCD at the time of discharge from the acute clinic.
3. Number of participants with POD during the stay in the intensive care unit.
4. Number of participants with POD during the stay in the normal ward.

Secondary outcomes

1. Change from baseline cognitive failures in everyday life (CFQ) at 3 months after surgery.
2. Change from baseline health-related quality of life (SF-36) at 3 months after surgery.
3. Changes from baseline neuropsychological parameters at the end of cognitive training.
4. Number of participants with POCI at 3 months after surgery.
5. Number of participants with POCI at the time of discharge from the acute clinic.

Planned statistical analyses

Postoperative cognitive decline is defined as a decline and POCI as an improvement from pre- to post-assessment of at least 1 SD in at least 20% of all neuropsychological subdomains (4). The difference of 1 SD between pre- and post-assessment will be measured using Z-scores, defined by the difference in individual raw values from the mean value of the total baseline data divided by the SD of the total baseline data. We will use the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (19) to define neuropsychological subdomains, as shown in Table 2. As some neuropsychological parameters can be contextually grouped into cognitive subdomains (see Table 2), we will summarize them by the mean value. POCD/POCI at the time of discharge from the acute clinic is defined as a decrease or increase between pre-examination and post-examination of 1 SD within the total score of the MOCA screening test. POD is defined as the occurrence of at least one delirious episode during the stay in the intensive care unit or normal ward. POCD/POCI and POD will be compared with Pearson's chi-square test (or Fischer's exact test). The effect size will be reported by odds ratio (OR) with a 95% confidence interval (CI).

Analyses of covariance (ANCOVAs) will be conducted to determine the effects of cognitive training on each neuropsychological parameter, CFQ, SF-36, and HADS-D. In the ANCOVA, the postoperative test value will be the dependent

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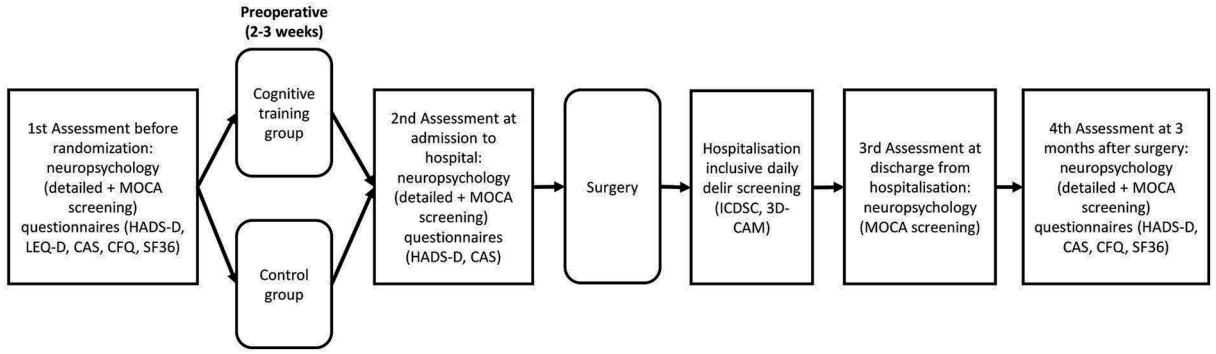

FIGURE 1
Timeline of the study-related events. The first examination includes neuropsychological tests and questionnaires before randomization and training. After the preoperative training period, neuropsychological tests and questionnaires will be administered a second time on admission to the acute clinic. After the surgery, daily delirium screenings will be performed and, on discharge from the acute clinic, neuropsychological screening will be carried out. To determine the long-term effects of cognitive training, neuropsychological tests and questionnaires will be carried out 3 months after surgery. MOCA, Montreal Cognitive Assessment; HADS, Hospital Depression and Anxiety Scale; LEQ-D, Lifetime of Experiences Questionnaire; CAS, Cognitive Activity Scale; CFQ, Cognitive Failure Questionnaire; SF-36, 36-Item Short Form Health Survey; ICDSC; Intensive Care Delirium Screening Checklist; CAM, Confusion Assessment Method.

TABLE 1 Study plan for recruitment, interventions, and investigations.

Time point	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8
Recruitment									
Inclusion criteria	X								
Informed consent	X								
Randomization		X							
Interventions									
Surgery					X				
Cognitive training			X						
Assessments									
MOCA	X			X				X	X
BVMT-R	X			X					X
VLMT	X			X					X
TMT	X			X					X
LNS	X			X					X
SKT-7	X			X					X
RWT	X			X					X
CFQ	X								X
LEQ-D	X								
CAS	X			X					X
HADS	X			X					X
SF36	X								X
ICDSC						X			
3-CAM							X		

MOCA, Montreal Cognitive Assessment; BVMT-R, Brief Visuospatial Memory Test-Revised; VLMT, Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test); TMT, Trail Making Test; LNS, Letter Number Span; SKT, Syndrom-Kurztest Test (Short Performance Test); RWT, Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test); CFQ, Cognitive Failure Questionnaire; LEQ-D, Lifetime of Experiences Questionnaire; CAS, Cognitive Activity Scale; HADS, Hospital Depression and Anxiety Scale; SF-36, 36-Item Short Form Health Survey; ICDSC, Intensive Care Delirium Screening Checklist; CAM, Confusion Assessment Method.

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TABLE 2 Definition of neuropsychological parameters and cognitive subdomains.

Cognitive domain (DSM-5)	Cognitive subdomains (DSM-5)	Neuropsychological parameter	Task (scale of measurement)
Learning and memory	Visual immediate memory span	BVMT-R	Recalling objects immediately (number of correct items)
	Visual free recall	BVMT-R	Recalling objects after delay (number of correct items)
	Visual recognition memory	BVMT-R	Recognizing between learned and new objects (number of correct items)
	Verbal immediate memory span	VLMT	Recalling items of word list (number of correct items, first trial)
	Verbal free recall	VLMT	Recalling items of word list (summarized number of correct items, learning trials)
		VLMT	Recalling items of word list (number of correct items, short delay)
		VLMT	Recalling items of word list (number of correct items, long delay)
	Verbal recognition memory	VLMT	Recognizing between learned and new words (number of correct items)
Complex attention	Selective attention	TMT-A (speed)	Linking numbers in ascending order (seconds)
Executive functions	Verbal working memory	LNS	Mentally reorganization of letters and numbers (span)
	Cognitive flexibility	TMT-B (speed)	Linking numbers and letters in alternately order (seconds)
	Inhibition	SKT-7	Naming interfering letter, e.g., "S" instead of "T" (seconds)
Language	Word fluency	RWT (phonetic)	Naming words with specific initial letter (number of correct items)
		RWT (semantic)	Naming words from a specific category (number of correct items)
Perceptual motor	Visuo-construction	MOCA (3-D figure)	Drawing a 3-D figure (number of correct items)

BVMT-R, Brief Visuospatial Memory Test-Revised; VLMT, Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test); TMT, Trail Making Test; LNS, Letter Number Span; SKT, Syndrom-Kurztest Test (Short Performance Test); RWT, Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test); MOCA, Montreal Cognitive Assessment.

variable, groups will be the fixed factor, and the preoperative test value will be the covariate. Confounder variables that could affect the results will be implemented in addition to the preoperative cognitive values as further covariates to the ANCOVA. Confounder variables are defined as whether a correlation analysis among demographic variables, perioperative details, and neuropsychometrical changes between pre- and postoperative testing is significant.

Assumptions for ANCOVAs will be tested using a visual inspection of QQ and distribution plots of the dependent variable for normality, the Levene test for variance-homogeneity of the dependent variable, and a statistically significant correlation between the dependent variable and covariate (preoperative test value) calculated with Pearson's product–moment correlation. When assumptions for the ANCOVA are violated, difference values between pre- and post-tests will be calculated, followed by Mann–Whitney U-tests for between-subject effects. The effect sizes of continuous results will be given in $\eta 2$.

If peri- and postoperative complications such as delirium, stroke, cardiovascular events, or other complications occur which could affect neuropsychological performance, and if these factors are unbalanced between the groups, we will calculate a subgroup analysis without those patients to reveal a more stringent outcome effect. In addition, we will perform subgroup analyses for each of the individual surgery cohorts, including AVR, MVR, CABG, and combination surgeries (AVR+MVR, CABG+AVR, CABG+MVR, and CABG+AVR+MVR) if the sample size of these subgroups allows for statistical analysis. Perioperative medical conditions or drug factors may have an impact on cognitive function. With the randomization principle, we expect these to be equally distributed between the groups. Otherwise, if the groups differ with respect to these factors, these can be accounted for in a subgroup analysis.

All analyses will be performed using the statistical software SPSS (version 22) and JASP (version 0.12.2).

Furthermore, interim analyses will be carried out during the investigation period to identify adverse events, overwhelming

effects, or futility of the intervention arm. In this case, the study could be terminated before its planned completion. The decision will be made by the members of the study team.

Power and sample size estimation

Because there are currently no effect sizes for extensive paper-and-pencil-based preoperative cognitive training in cardiac surgical patients using extracorporeal circulation, and because their influence on the incidence of POD and POCD is unclear, we have estimated sample size based on the effect sizes of general cognitive training in older healthy individuals, which ranges between $d = 0.4$ and $d = 0.9$ (20, 21). To not underestimate or overestimate the required sample size, we use an average value of $d = 0.65$. To find an effect size of $d = 0.65$ at a test power of 0.8 (alpha = 0.05) within an ANCOVA, a sample size of 77 subjects is required. With an estimated dropout rate of 23% in the preoperative test phase, the total sample size will be 100 subjects. The sample size per group is thus 50 patients. We used the analysis software G*Power-3 to calculate the sample sizes and the statistical power (22). We want to note that the power analysis refers to our secondary outcome "Changes from baseline neuropsychological parameters at the end of cognitive training." Accordingly, the primary outcomes regarding the incidence of POD and POCD will be calculated exploratively.

Metric assessments

Cognitive tests will be performed by a neuropsychologist 2–3 weeks before surgery, at admission to the acute clinic, during postoperative stays in intensive care and the normal ward, at discharge from the cardiac surgery clinic, and 3 months after surgery. Parallel test forms will be used in the follow-up examinations to account for individual learning effects. Parallel test forms will be counterbalanced for each test time point.

Objective cognition

The cognitive test battery measures verbal and visual memory with immediate-, free recall-, and recognition conditions, selective attention, verbal working memory, cognitive flexibility, inhibition, word fluency, and visuoconstruction.

With the German-validated version of the Montreal Cognitive Assessment (MOCA) (23), cognitive functions such as visuoconstructive ability, object naming, verbal memory, working memory, attention, phonematic word fluency, abstraction, cognitive flexibility, and orientation are assessed within the framework of a 10-min screening procedure (23).

Verbal memory will be assessed using the Verbaler Lern- und Merkfähigkeitstest (VLMT), a modified German version of the Rey Auditory Verbal Learning Test (24). This test can be used to evaluate immediate-, free recall-, and recognition conditions. Between the short-delayed and longer-delayed verbal episodic memory recall, non-verbal cognitive tests are performed to avoid possible effects of interfering words not included in the learned word list.

With the Letter–Number Test (LNS), the verbal working memory will be tested. The patient is supposed to rearrange a mixed sequence of letters and numbers through mental reorganization in such a way that first all numbers and then all letters are to be named in ascending order (25).

Visual memory will be examined with the Brief Visuospatial Memory Test-Revised (BVMT-R) (26). In the BVMT-R, the patient is shown six geometric figures for 10 s on a DIN A4 sheet of paper, which are to be drawn directly afterward. This procedure is repeated with the same figures in a total of three learning trials. The figures are to be freely replicated in a time-delayed episode with the following recognition help.

Selective attention will be examined using the Trail Making Test A (TMT-A), for which three validated parallel test versions are available (27). In the TMT-A, the patient has to connect numbers in ascending order on a test sheet as fast as possible.

Cognitive flexibility will be measured by the Trail Making Test B (TMT-B) (27) and cognitive inhibition by a subtest of the Syndrom-Kurz Test (SKT-7) (28). With the TMT-B, the patient's task is to connect numbers and letters alternately in ascending order. In the SKT-7, the patient has to rename a series of letters (e.g., "S" instead of "T," and vice versa).

The semantic-categorical word fluency is tested with the Regensburger Wortflüssigkeits-Test (RWT) (29). In this test, the patient has to name in 1 min as many words as possible from a certain category.

Subjective cognition

Study patients will be asked to complete a validated German 25-item version of the Cognitive Failures Questionnaire for Self-Assessment (s-CFQ) (30). Because memory disorders play an important role in the everyday functions of patients, the s-CFQ was modified with four additional questions related to memory failures, taken from the validated German version of the Memory Complaint Questionnaire (31). Close relatives of the patients will also be asked to answer an eight-item cognitive questionnaire for external assessment (f-CFQ) with regard to the patients (32). All have to be answered on a 5-point scale from "never" to "very often." The purpose of these questionnaires is to investigate the frequency of failure in daily living in terms of memory, attention, action, and perception in the past 3 months.

Cognitive reserve/cognitive everyday activities

The Lifetime of Experiences Questionnaire (LEQ-D), which has been translated and validated into German, is intended to

determine the cognitive reserve in 34 items for three areas of life: education, occupation attainment, and lifestyle activities (33). These relate to early-, midlife-, and late-life reserve measures. Because the LEQ-D records the cognitive everyday activities unspecifically for the time immediately before surgery, the cognitive activity scale (CAS) according to Tow et al. (12) will also be used. This scale covers 12 cognitive activities, such as reading the newspaper, solving crosswords, writing, or group meetings, related to the previous week.

Delirium

Postoperative delirium will be examined during the stay in the intensive care unit with the German-validated Intensive Care Delirium Screening Checklist (ICDSC) (34). To be able to record the status of POD with high sensitivity and specificity, even during the stay in the normal ward, a newly developed version of the Confusion Assessment Method (3D-CAM) validated in German will also be used (35). Both tests record the clinical symptoms of consciousness, attention, orientation, hallucinations, psychomotor retardation or agitation, speech, and changing symptoms by observing behavior and asking concrete questions to the patient. The ICDSC also documents disturbances in the sleep–wake rhythm.

Depression and anxiety

Patients assessed their recent (prior week) depressive and anxiety symptoms using the validated German version of the Hospital Anxiety and Depression Scale (HADS-D) (36). Each scale contains seven questions to be answered by the patients.

Health-related quality of life

Health-related quality of life will be assessed with the 36-Item Short Form Health Survey (SF-36, Version 1.0) (37). The SF-36 includes 36 items covering eight health-related factors, including physical functioning (10 items), role limitations due to physical health (four items), role limitations due to emotional problems (three items), energy/fatigue (four items), emotional wellbeing (five items), social functioning (two items), pain (two items), and general health (five items). Furthermore, we will determine a total score across all eight factors, as well as a two-factor model, indicating the physical state of health (physical functioning, role limitations due to physical health, pain, and general health) and psychological state of health (role limitations due to emotional problems, energy/fatigue, emotional wellbeing, and social functioning). The answers provided by the patients within the factors refer to the last 4 weeks, except for the factor physical functions and the first question of the factor general health, which refer to the present state of health. Furthermore, it also contains a single item (item 2, health change), which indicates the extent to which the present health has changed in relation to the past year. The SF-36 will be scored using the RAND scoring method (38). Each item in the questionnaire is assigned a score from 0 to 100, with a higher score indicating a better health state.

For the CFQ, MCQ, and SF-36, missing data will be handled as follows. If the patients answered at least 50% of all items per factor and time point, the mean score of this factor will be calculated to determine the values of the factors. Items left blank (missing data) will not be considered. Therefore, the factor values will represent the average for all items of a factor that the respondent responded to.

Data management

All personal data about recruited patients will be subject to medical confidentiality. Paper-based assessment forms will be used to record all variables. The data will be entered into an electronic database, which will be password-protected and double-checked for accuracy. All signed informed consent forms, assessment forms, and the randomization list will be stored in locked cabinets. Each patient will receive a sequential number recorded on the paper-based assessment forms and in the electronic database. Personal data such as first name, last name, and address will not be included in the paper-based assessment forms or the electronic database.

Cognitive training

We have validated a postoperative paper-and-pencil-based cognitive training program for older cardiac-surgery patients with the effect of reduced POCD at discharge from rehabilitation (after 3 weeks of training) and at a 3-month follow-up (39). In the INCORE study, we will use this training program for the preoperative setting. Here, we will provide information about the concept of our training.

We derived the design of our cognitive training program using the German language-validated, paper-and-pencil-based intervention by Müller et al. (40). This program is intended to train working memory, cognitive flexibility, word fluency, and planning skills. To achieve better patient acceptance, we only adopted exercises that we found most useful and combined them with new tasks developed by our group. Furthermore, we initially constructed our training to address several cognitive functions that are particularly important in everyday life to maintain social functions and earning capacity. These include word fluency, working memory, attention, and the ability to plan. One training unit will last approximately 40 min and will be conducted for 2–3 weeks, about 6 days a week. The daily training program consists of eight different types of standardized tasks related to the processing of words, categories, images, mental arithmetic, and planning. On each training day, new

words, categories, images, head calculations, and planning tasks will be presented. Each task takes between 2 and 10 min to complete. To manage their working time, the patients must use a digital clock. If the patient has any questions about the tasks, they can contact the training supervisor by telephone. In addition, the training supervisor will call the patient once a week to monitor cooperation. Each task contains precise written instructions that may be helpful in the execution. Patients will also be told that their exercise solutions will not be corrected. Therefore, it does not matter whether the solutions are right or wrong. In this way, we can avoid any possible pressure to perform and patients looking for the right solutions at home. The different types of tasks are presented in the following standardized order.

Phonetic word fluency

The patient receives three letters on a sheet of paper. The task is to note as many words as possible that begin with these letters within 2 min. This task is mainly used to train word fluency and was adapted from the work of Müller et al. (40).

Categorical word fluency

In this task, the patient receives three different categorical terms on a sheet of paper. The task is to find and note as many words as possible within 2 min that can be assigned to these categories. This task serves mainly to train word fluency and was adapted from the work of Müller et al. (40).

Picture stories

The patients receive four to five popular German picture stories by German illustrators such as Wilhelm Busch, Erich Ochser, or Hans Juergen Press, with 3–16 pictures of a story in mixed order. Within 5 min, the pictures have to be arranged mentally in a meaningful order. The newly invented order is to be documented by numbering the pictures with a pen. This task is mainly intended to train working memory and was created by our group.

Mental arithmetic

The patient is asked to perform several calculation tasks on one sheet of paper. The result of a first arithmetic problem involving the addition, subtraction, and multiplication of numbers must be memorized. The second step is to solve another arithmetic problem and memorize the result. In the last step, the last result should be subtracted from the first result, and the final result should be written down. The time limit for this exercise is 5 min. This task is mainly intended to train working memory and was adapted from the work of Mueller et al. (40).

Synonymic fluency

The next worksheet contains three different terms. For each term, patients must find words with similar meanings (synonyms). For example, if the term is wallet, then other words with similar meanings would be portemonnaie or money purse. The time limit is 2 min. This task is mainly intended to train word fluency and was created by our group.

Gap text

In the next training task, short stories will be presented. These are generally known stories by Wilhelm Busch, the Brothers Grimm, or Hans Christian Andersen or ancient German, Buddhist, and Japanese fables. The stories have gaps that are to be filled in with a self-chosen, meaningful word. The time limit for this exercise is 5 min. This task is mainly intended to train word fluency and working memory and was developed by our group.

Where is Waldo

An illustration of Martin Handford's "Where is Waldo?" is shown on a DIN A3 sheet. The picture contains dozens or more people doing a variety of things in a particular place. The task is to find specific people or objects listed on a sheet of paper by marking them with a pen on the illustration within 5 min. This task is mainly intended to train selective attention and working memory and was created by our group.

Organizing and planning

In the last task, the patient must read a text in which an imaginary person must perform certain actions or organize appointments. The patient's task is to solve the problems and write down the solutions on a sheet of paper. The time limit for this task is 10 min. The task primarily serves to train planning ability and working memory and was adapted from the work of Müller et al. (41).

To control the quality of the cognitive training, we will assess the number of tasks completed by the patients and report it as a percentage.

Discussion

This research project offers our patients preoperative cognitive training based on paper-and-pencil aiming to prevent POD and POCD.

Investigations have already been conducted to treat the preoperative physical condition of cardiosurgical patients to improve postoperative outcomes, which is defined by the term prehabilitation (42). Initial efforts have also been made with regard to preoperative cognitive training. Saleh et al. showed a lower incidence of POCD 1 week after gastrointestinal tumor

resection with a controlled 3 x 1-h preoperative memory strategy training (loci method) (43). Several studies have investigated the effect of perioperative computer-based cognitive training on postoperative cognition after cardiac surgery. In the study conducted by O'Gara et al. (44), the training was performed at least 10 days before surgery up to 4 weeks postoperatively, which had no significant effect on the frequency of POD or POCD. Humeidan et al. found a reduced incidence of POD with preoperative computer-based cognitive training (median 4.6 h) (45). Vlisides et al. showed that participation in preoperative computer-based cognitive training was difficult for older adults who underwent surgery (46). Mainly because of the feeling of overwhelming demands and technical problems with the 7-day computer exercises, 48% of the patients discontinued the training.

The difference in our study concept compared with the above-mentioned studies is that we use paper-and-pencil-based instead of computer-based cognitive training, which is probably more feasible and effective for older patients. Furthermore, our program will take place in the preoperative phase, which will help to address differences between preoperative and [as we have conducted in the past; (39)] postoperative training. As we saw in the postoperative setting, this cognitive training appears to be adequately feasible regardless of educational status. Therefore, we did not set a limit for a required educational status in the inclusion criteria.

Cognitive training allows patients to be independent, responsible, and active. With the knowledge that cognitive deficits can be actively prevented, anxiety regarding a severe operation can be reduced. This has particular clinical relevance, as preoperative anxiety is considered a risk factor for increased morbidity and mortality in cardiac surgery patients (47).

Morphological alterations have also been found in response to cognitive training in healthy adults with reproducible increased patterns in the structure of gray and white matter (48) and patients with memory impairments, with increased volume of gray matter in certain brain regions (49). These effects are mainly attributed to cognitive and neuronal plasticity.

The limitations of this study are as follows. The study only includes patients undergoing cardiac surgery with ECC. A comparison with patients undergoing off-pump cardiac surgery, non-cardiac surgery, or non-surgery (healthy controls) is, therefore, not intended. A placebo intervention for the control group is intentionally avoided because the cognitive effects of placebo interventions on cognitive performance are hardly controllable. To convincingly communicate to patients that the placebo intervention could have an influence on their memory and thus also achieve a willingness to participate, the structure of the placebo intervention would have to be closely related to cognitive training (e.g., crossword puzzles, conversation therapy, computer games, cognitive information, etc.) and would thus also achieve cognitive training effects. This could formally affect the quality of the study and the transferability of the results. As we do not know whether paper-and-pencil-based preoperative cognitive training can reduce the incidence of POD and POCD, we do not see any ethical problems if the control group does not receive cognitive training. Finally, in principle, it may be that cognitive intervention proves useless and that patients' preoperative time would be better spent on other validated and clinically relevant interventions. Furthermore, according to our study design, it is not possible to put the patients of the control group on a waiting list, as they would have already been operated on. If a subgroup analysis for each cardiac surgery method (CABG, AVR, MVR, and combination surgeries such as AVR + MVR, CABG + AVR, CABG + MVR, and CABG + AVR + MVR) is statistically inadequate due to the small sample size, we cannot adequately perform generalization of the training effect on a single surgery cohort.

In addition to altering preoperative cognitive performance to potentially counteract POD and POCD, other risk factors regarding POD such as poor sleep burden (50) and heart rate response/recovery to exercise (51) can also be modified in the preoperative setting and may be linked to preoperative risk factors such as depression and reduced cognitive functions.

Should it become evident that the use of our cognitive training can both reduce the incidence of POCD and POD and improve health-related quality of life, one possibility could be to integrate this intervention into a standardized prehabilitation program. It can also be evaluated in other patient populations affected by postoperative neurocognitive dysfunctions.

Trial status

The study is currently enrolling patients. This study is registered with ClinicalTrials.gov (Identifier: NCT04493996. First posted: July 31, 2020. The first patient was enrolled on August 14, 2020). Recruitment is expected to be completed in November 2023. Protocol version: 1.0 (17-01-2022).

Ethics statement

The studies involving human participants were reviewed and approved by by the Ethics Committee of the Justus Liebig University Giessen (Ref.: 48/20). Written informed consent will be obtained from the patients to participate in this study. All changes to the study protocol will be submitted to the Ethics Committee.

Author contributions

MB: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, and writing the original draft. RM:

data curation, investigation, project administration, and review and editing. TG: methodology, funding acquisition, project administration, and review and editing. GS: methodology, supervision, and review and editing. JD: data curation, project administration, and review and editing. JE-S: methodology, reviewing, and editing. TD: reviewing and editing. Y-HC: project administration, resources, and reviewing and editing. MS and MJ: methodology, funding acquisition, project administration, resources, and reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Journal of the Neurological Sciences

Twelve-month follow-up effects of cognitive training after heart valve surgery on cognitive functions and health-related quality of life. A randomized clinical trial.

--Manuscript Draft--

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Abstract:	Objectives Postoperative cognitive decline (POCD) or decreased health-related quality of life (HQL) have been reported after cardiac surgery. A previous investigation showed beneficial effects of postoperative cognitive training on POCD and HQL 3 months after heart surgery. Here, we present the 12-month follow-up results. Methods This bi-centric, 1:1 randomized and treatment-as-usual controlled trial included elderly patients scheduled for elective heart valve surgery. The training consisted of paper-and-pencil-based exercises practicing multiple cognitive functions for about 36 minutes/day 6 days/week over a period of 3 weeks. Neuropsychological tests and questionnaires assessing HQL (SF-36) and cognitive failures in daily living (CFQ) were performed pre-surgery and 12 months after training. Results Twelve months post-training, the training group (n=30) showed improvements in HQL compared to the control group (n=28), especially in role limitations due to physical health (U=-2.447, p=0.015, η2=0.109), role limitations due to emotional problems (U=-2.245, p=0.025, η2=0.092), pain (U=-1.979, p=0.049, η2=0.068), average of all SF-36 factors (U=-3.237, p<0.001, η2=0.181), health change from the past year to the present time (U=-2.091, p=0.037, η2=0.075), physical component summary (U=-2.803, p=0.005, η2= 0.138), and mental component summary (U=-2.350, p=0.018, η2=0.095). Furthermore, the training group (n=19) showed an improvement compared to the control group (n=27) in visual recognition memory (U=-2.137, p=0.034, η2=0.099). POCD frequency was 22% (n=6) in the control group and 11% (n=2) in the training group (χ^2[1]=1.06, p=0.440; OR=2.43, 95% CI [0.43-13.61]).

	Conclusion In conclusion, postoperative cognitive training shows enhancing effects on HQL in cardiac surgery patients after 12 months.
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Cover Letter

Dear Mr. John D. England and Richard M. Paddison:

Please find enclosed the manuscript “Twelve-month follow-up effects of cognitive training after heart valve surgery on cognitive functions and health-related quality of life. A randomized clinical trial.” to be submitted as a Clinical Research Paper in the *Journal of the Neurological Sciences*. Our study revealed beneficial effects on postoperative cognition and health related quality of life through a randomized controlled three-week paper-and-pencil-based cognitive training program in patients undergoing elective heart valve surgery involving extracorporeal circulation.

In particular, by publishing our study in the *Journal of the Neurological Sciences*, we hope to reach a large readership within the neurological research community, members of which could make valuable contributions to the neurorehabilitation of patients with acute or progredient cognitive impairment by applying our method.

All authors have reviewed the manuscript and approved it for submission, and we confirm that it has not been published (in whole or in part) or simultaneously submitted elsewhere. No previous publications overlap with the current work except for a study protocol (inclusive statistical plan) published in *Trials*, which was also cited in the manuscript.

I guarantee, that I will take full responsibility for the data, analyses and interpretation, and the research conduct. I have full access to the data, and I have the right to publish any and all data separately and apart from any sponsor. The authors declare they have no competing interests.

We hope that the editorial board and the reviewers will agree on the interest of this study.

Best regards,

Marius Butz

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Highlights

Paper-and-pencil-based cognitive training can be implemented after cardiac surgery

Cognitive training has beneficial effects on health-related quality of life

Cognitive training has preliminary effects on cognition at 12-month follow-up

Twelve-month follow-up effects of cognitive training after heart valve surgery on cognitive functions and health-related quality of life. A randomized clinical trial.

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Abstract

Objectives

Postoperative cognitive decline (POCD) or decreased health-related quality of life (HQL) have been reported after cardiac surgery. A previous investigation showed beneficial effects of postoperative cognitive training on POCD and HQL 3 months after heart surgery. Here, we present the 12-month follow-up results.

Methods

This bi-centric, 1:1 randomized and treatment-as-usual controlled trial included elderly patients scheduled for elective heart valve surgery. The training consisted of paper-and-pencil-based exercises practicing multiple cognitive functions for about 36 minutes/day 6 days/week over a period of 3 weeks. Neuropsychological tests and questionnaires assessing HQL (SF-36) and cognitive failures in daily living (CFQ) were performed pre-surgery and 12 months after training.

Results

Twelve months post-training, the training group (n=30) showed improvements in HQL compared to the control group (n=28), especially in role limitations due to physical health (U=-2.447, p=0.015, η2=0.109), role limitations due to emotional problems (U=-2.245, p=0.025, η2=0.092), pain (U=-1.979, p=0.049, η2=0.068), average of all SF-36 factors (U=-3.237, p<0.001, η2=0.181), health change from the past year to the present time (U=-2.091, p=0.037, η2=0.075), physical component summary (U=-2.803, p=0.005, η2= 0.138), and mental component summary (U=-2.350, p=0.018, η2=0.095). Furthermore, the training group (n=19) showed an improvement compared to the control group (n=27) in visual recognition memory (U=-2.137, p=0.034, η2=0.099). POCD frequency was 22% (n=6) in the control group and 11% (n=2) in the training group (χ^2[1]=1.06, p=0.440; OR=2.43, 95% CI [0.43-13.61]).

Conclusion

In conclusion, postoperative cognitive training shows enhancing effects on HQL in cardiac surgery patients after 12 months.

Keywords

Cardiac surgery, Valve replacement, Cognitive training, Postoperative cognitive decline, Health-related quality of life, Cognitive failures in daily living

1. Introduction

Postoperative cognitive decline (POCD) after cardiac surgery has a detrimental impact on HQL [1]. POCD is commonly defined as a decrease in cognitive functions such as memory, attention, and speech from a pre- to post-operative neuropsychological assessment. It has a prevalence of about 22% between the 6th and 12th postoperative month in patients with coronary artery bypass grafting (CABG) [2]. Since POCD is often examined psychometrically with objective test procedures, patients' subjective perceptions in the postoperative course are also important for the estimation of clinical relevance. In this context, subjectively assessed cognitive failures in daily life were reported by the patients themselves as well as by their relatives [3, 4].

Risk factors involved in the development of POCD have been described for the preoperative (age, diabetes, depression, cognitive impairment), intraoperative (intubation time, duration of surgery), and postoperative (cardiac arrhythmias, delirium) periods [5, 6]. In particular, POCD in the early postoperative phase is associated with long-term cognitive decline [7]. As cognitive functions can potentially be improved by cognitive training [8], we implemented a treatment-as-usual, controlled, paper-and-pencil-based cognitive training program in the early postoperative period for cardiac surgery patients [9]. As a result, we were able to show improved effects on POCD [10] and HQL [11] at 3 months post-training. Here, we report the training effects on POCD, HQL and CFQ at a 12-month follow-up assessment.

2. Methods

2.1 General conditions

This bi-centric, 1:1 randomized and treatment-as-usual controlled trial included elderly patients scheduled for elective aortic or mitral valve replacements/reconstructions with or without CABG. Recruitment took place at the Departments of Cardiac Surgery of the Kerckhoff-Clinic in Bad Nauheim and the University-Hospital in Giessen. Following acute hospitalisation, patients were transferred directly to a rehabilitation centre and received the interventions. The training consisted of paper-and-pencil-based exercises practicing multiple cognitive functions for about 36 minutes/day 6 days/week over a period of 3 weeks. Neuropsychological tests and questionnaires assessing HQL (SF-36) and cognitive failures in daily living (CFQ) were performed prior to surgery and 12 months after training. Full details on the study procedure, neuropsychological tests, questionnaires, and cognitive training have been published in advance [9]. The study, including informed consent, has been approved by the Ethics Committee of the Justus Liebig University Giessen (Ref.: 28/14), complies with the Declaration of Helsinki, and is registered with the German Clinical Trials Register (ID: DRKS00015512). The patients provided informed written consent.

2.2 Outcomes

The results of the primary outcome of the study have been published in advance [10]. Secondary outcomes shown in the present paper are the effect of cognitive training on POCD, HQL, CFQ, depression and anxiety at 12 months after the cognitive training. Since postoperative cognitive improvement (POCI) can likewise occur after cardiac surgery [12] and there is a risk of overestimating the incidence of POCD in this context, POCI was also used as an outcome.

2.3 Inclusion and exclusion criteria

Inclusion criteria included elective aortic or mitral valve replacement/reconstruction with or without CABG under extracorporeal circulation and sufficient knowledge of German. Exclusion

criteria comprised history of stroke, psychiatric or neurological diseases, and health insurance that did not support postoperative rehabilitation at the Kerckhoff-Clinic.

2.4 Randomization and blinding

After performing preoperative neuropsychological examinations on the patients, the study coordinators allocated them to the cognitive training group or the treatment-as-usual group. A computer-generated randomization list with a 1:1 blocked (sizes varied randomly) allocation ratio was generated, sequentially numbered, and concealed by a study coordinator prior to the first enrolment. Neurologists, neuropsychologists, and surgeons were blinded with respect to the patients' randomization status.

2.5 Definitions of POCD / POCI

POCD was defined as a decline and POCI as an enhancement of at least 1 SD in at least 20% of all neuropsychological subdomains from pre- to post-tests [2]. The difference in SD between the pre- and post-tests was calculated using Z-scores (difference between the individual raw values and the mean value of the total baseline data divided by the SD of the total baseline data). The neuropsychological subdomains were defined according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) [13], as specified in Supplementary Table 1. As we measured several neuropsychological parameters that can be contextually grouped into cognitive subdomains, we summarised them using a mean value. A detailed description of the neuropsychological tests was published in the study protocol [9].

2.6 Questionnaires

HQL was assessed using the 36-Item Short Form Health Survey (SF-36, Version 1.0) [14], which covers eight factors, including physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. We also determined an average of all eight factors and calculated a two-factor model indicating the physical component and mental component

summaries. Additionally, the extent to which health had changed in relation to the past year was evaluated with a single item. The SF-36 was scored using the RAND scoring method [15].

The validated German version of the Cognitive Failures Questionnaire for self-assessment (s-CFQ, 25-item) [16] was used to evaluate cognitive failures in daily living. The patients' close relatives responded to the Cognitive Failures Questionnaire to provide external assessment (f-CFQ, 8-item) [17]. Furthermore, the validated German version of the Memory Complaint Questionnaire (MCQ, 4-item) [18] was applied to reveal more information on the cognitive domain of memory. Additionally, we calculated further CFQ factor models that have already been described [19-22].

To reveal psychopathological symptoms, we used the validated German version of the Hospital Anxiety and Depression Scale (HADS-D) [23].

2.7 Statistical analyses

We carried out a sample-size calculation for the primary outcome of our study (cognitive training-related effect on objectively assessed cognition), which was published in advance [10]. Therefore, we did not perform a sample-size calculation for this report, which refers to the secondary outcomes of our trial, and we analyzed the data exploratively.

To analyse the training's effect on cognition, the frequencies of POCD and POCI were compared with Pearson's χ^2 tests between the groups. The effect size was determined by calculating the odds ratio (OR) with a 95% confidence interval (CI). To calculate the training's effects on each neuropsychological parameter, SF-36, CFQ and HADS, ANCOVAs were conducted with the postoperative test values as the dependent variable, groups as the fixed factor, and preoperative test values as the covariate. Confounding variables were used as additional covariates in the ANCOVAs. The assumptions for the ANCOVAs were assessed using the Levene test to determine variance-homogeneity of the dependent variable, visual inspections of QQ and distribution plots of the dependent variable were used to determine normality, and a statistically significant correlation between the dependent variable and

covariate (preoperative test value) was calculated with Pearson's product-moment correlation. When the assumptions for an ANCOVA were violated, the difference values between the pre- and post-tests were calculated in a Mann-Whitney U-test for between-subjects effects. The effect sizes of the ANCOVAs and U-tests are given in η^2. The criterion for statistical significance was set at $p<0.05$ (two-sided). Post hoc power (1-ß) was also calculated. Our data set was evaluated using a per-protocol analysis. All statistical analyses were performed with SPSS (version 22), JASP (version 0.17.1) and G*Power (3.1.9.2).

3. Results

Between July 13, 2016 and January 8, 2020, 130 patients were enrolled, randomized, and tested preoperatively. The last patient was tested on March 9, 2021, for the 12-month follow-up. After randomization of the 130 patients, 36 patients (training group, n=18; control group, n=18) were lost to follow-up before the training or control intervention started. Thus, 94 patients (training group, n=47; control group, n=47) were considered for the baseline sample, which had no between-groups differences in baseline characteristics (see Table 1) or baseline neuropsychological tests. All patients were of white/Caucasian ethnicity. The reasons for losing patients to follow-up are shown in Figure 1. The training lasted 14.9 (SD=2.5) days and did not cause adverse events.

At 12 months follow-up, the training group (n=19) showed an improvement compared to the control group (n=27) in visual recognition memory (U=-2.137, p=0.034, η2=0.099, 1-ß=0.56). See Supplementary Table 2 for details.

POCD frequency was 22% (n=6) in the control group and 11% (n=2) in the training group ($\chi^2[1]=1.06$, p=0.440; OR=2.43, 95% CI [0.43-13.61]). POCI frequency was 47.4% (n=9) in the training group and 29.6% (n=8) in the control group ($\chi^2[1]=1.51$, p=0.352; OR=0.47, 95% CI [0.14-1.59]). No training effects on depression or anxiety were observed.

As our sample showed an unequal distribution of delirious patients at the 12-month follow-up (control group n=3; training group n=0), and delirium is discussed as a risk factor for POCD [24], we calculated a post hoc explorative analysis without the delirious patients. In this case, the training effect on the POCD/POCI at the 12-month follow-up was about the same as that with the delirious patients (POCD: control group 20.8% [n=5], training group 10.5% [n=2], $\chi^2[1]=0.827$, p=0.437, OR=2.24, 95% CI [0.38-13.07]. POCI: training group 47.4% [n=9], control group 29.2% [n=7], $\chi^2[1]=1.50$, p=0.341, OR=0.46, 95% CI [0.13-1.61]).

Twelve months after discharge from rehabilitation, the training group (n=30) showed improvement in HQL compared to the control group (n=28), especially in role limitations due to physical health (U=-2.447, p=0.015, η2=0.109, 1-ß=0.7), role limitations due to emotional problems (U=-2.245, p=0.025, η2=0.092, 1-ß=0.62), pain (U=-1.979, p=0.049, η2=0.068, 1-ß=0.51), the average of all SF-36 factors (U=-3.237, p<0.001, η2=0.181, 1-ß=0.93), health change from the past year to the present time (U=-2.091, p=0.037, η2=0.075, 1-ß=0.55), physical component summary (U=-2.803, p=0.005, η2=0.138, 1-ß=0.83), and mental component summary (U=-2.350, p=0.018, η2=0.095, 1-ß=0.66). See figure 2 and Supplementary Table 3 for details. No statistically significant differences were found in the patients' self-reported cognitive impairments in daily life. When close relatives assessed patients' cognitive abilities in daily living, the control group (n=20) showed a better outcome compared to the training group (n=24) (F[2.41]=5.417, p=0.025, η2=0.052, 1-ß=0.25).

In an adjusted ANCOVA, no potentially confounding variables made a significant contribution to the results.

	Training (n=47)	Control (n=47)
Demographics		
Age (years)	71.2 (4.7)	73.0 (4.9)
Sex		
Women	8 (17%)	13 (28%)
Men	39 (83%)	34 (72%)
Education (years)	13.5 (3.0)	13.4 (3.0)
Medical history		

Body-mass index (kg/m²)	27.7 (3.8)	26.6 (3.8)
Arterial hypertension	31 (66%)	31 (66%)
Diabetes mellitus	10 (21%)	5 (11%)
Renal insufficiency	4 (9%)	7 (15%)
Dyslipidemia	39 (83%)	37 (79%)
LV EF (mildly abnormal)	5 (11%)	6 (13%)
LV EF (moderately abnormal)	3 (6%)	1 (2%)
Heart failure	10 (21.3%)	9 (19.1%)
Type of surgery		
AVR	23 (50%)	22 (47%)
AVR+CABG	18 (38%)	19 (40%)
MVR	4 (9%)	1 (2%)
MVR+CABG	0 (0%)	3 (6%)
AVR+MVR	2 (4%)	2 (4%)
Perioperative details		
Duration of surgery (minutes)	190.3 (38.1)	200.6 (58.9)
Duration of extracorporeal circulation (minutes)	96.5 (26.5)	105.2 (37.5)
Cross-clamp time (minutes)	69.1 (19.9)	74.7 (26.7)
Ventilation time invasive (minutes)	616.2 (331.3)	588.1 (213.6)
Postoperative complications		
Delirium	2 (4%)	4 (9%)
Arrhythmia	18 (38%)	21 (45%)
Atrial fibrillation	18 (38%)	17 (36%)
Renal insufficiency	6 (13%)	6 (13%)
Acute blood loss anemia	10 (21%)	12 (26%)
Transient ischemic attack	1 (2%)	0 (0%)
Dysathria/Aphasia	0 (0%)	1 (2%)
Medical details at admission to rehabilitation		
Blood pressure (systolic; mmHG)	128.1 (12.7)	127.7 (18.4)
Blood pressure (diastolic; mmHG)	74.5 (11.1)	71.4 (10.6)

Table 1: Baseline demographics and characteristics of the intention to treat the population. Data include means (SD) or number of subjects (%). LF EV=left ventricular ejection fraction [25]. AVR=aortic valve replacement. CABG=coronary artery bypass grafting. MVR=mitral valve replacement/reconstruction. Renal insufficiency was defined by a creatinine value above the in-house norms (men: > 1.2 mg/dl, women: > 0.9 mg/dl).

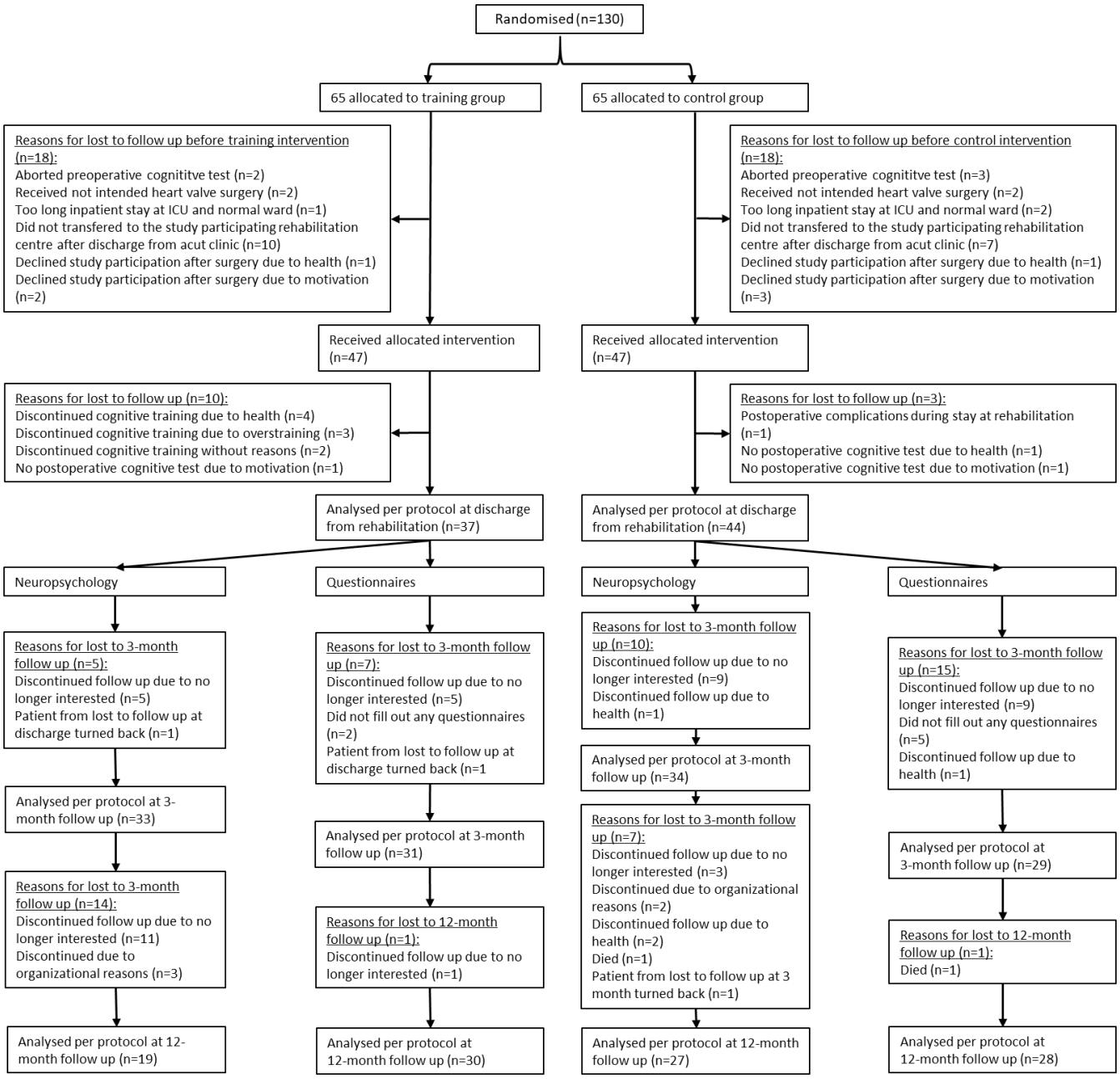
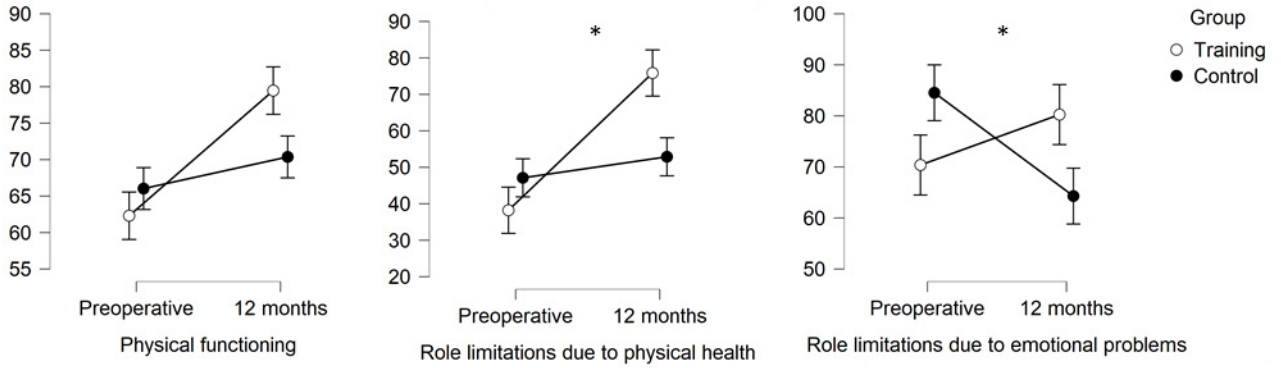
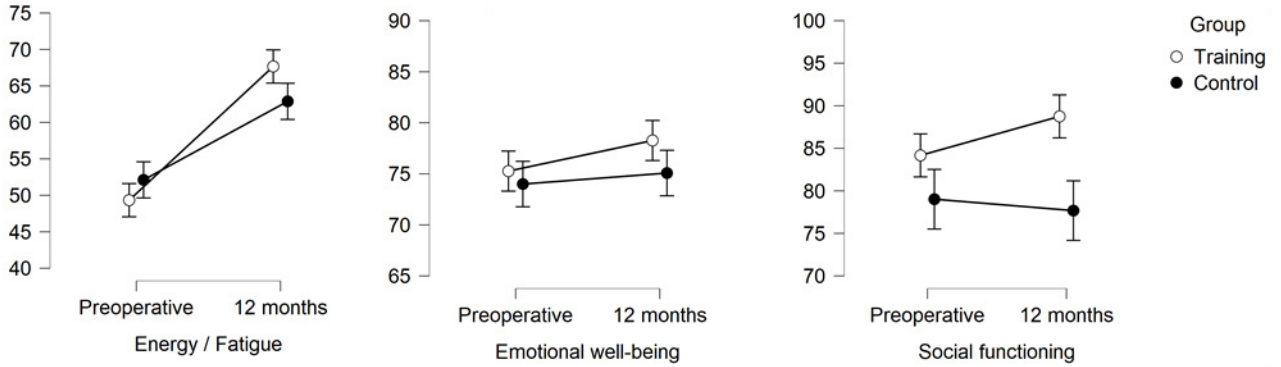
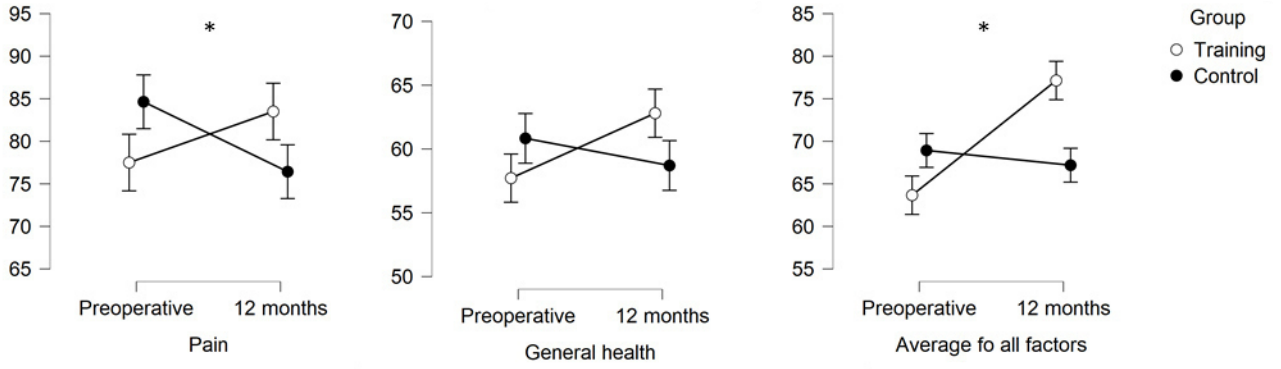


Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flowchart illustrating all steps in the study from randomization to follow-up and analysis. ICU=intensive care unit.


Group
Training
Control
Preoperative
12 months
Physical functioning
Role limitations due to physical health
Role limitations due to emotional problems


Group
Training
Control
Preoperative
12 months
Energy / Fatigue
Emotional well-being
Social functioning


Group
Training
Control
Preoperative
12 months
Pain
General health
Average fo all factors

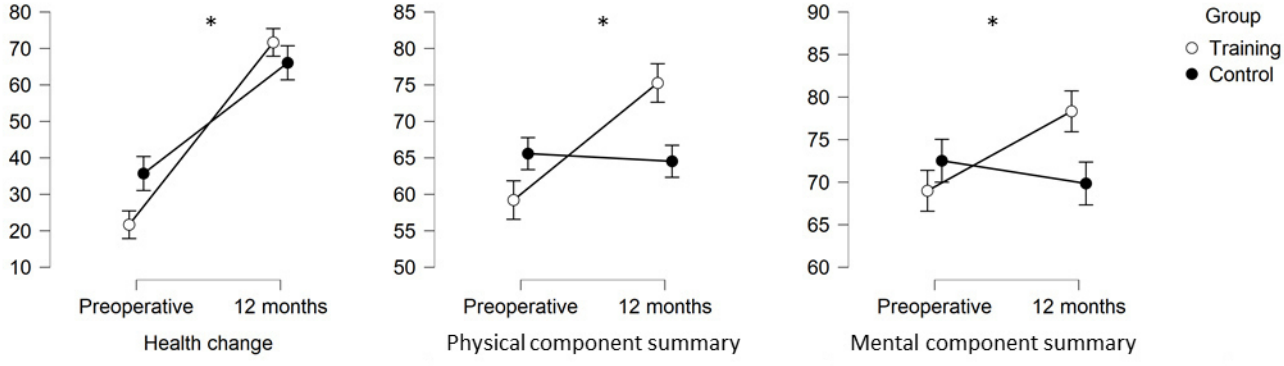

Group
Training
Control
Preoperative
12 months
Health change
Physical component summary
Mental component summary

Figure 2: Interaction effects of all SF-36 factors between the training group and control group. Shown are the mean values (higher scores indicating a better health state), including SE bars for preoperative testing and 12 months after discharge from the rehabilitation clinic. Statistical significant interaction effects with a p-value of < 0.05 are marked with an asterisk (*).

4. Discussion

At the 12-month follow-up assessment, patients in the cognitive training group showed better scores in visual recognition memory. The frequency of POCD and POCI differed numerically between the groups, suggesting a beneficial effect, but the difference did not reach statistical significance. The cognitive training group achieved higher values in several HQL factors, especially in the average of all HQL factors, with a high post hoc power of 0.93. POCD incidence in our control group was higher than in the training group at the time of discharge from the rehabilitation clinic (50% vs. 19%, p=0.004) and 3 months after completion of the training (29% vs. 6%, p=0.013) [10]. However, this benefit seemed less pronounced after 12 months (22% vs. 11%, p=0.44). On one hand, the training effect in our study might have seemed lower after 12 months due to the reduction of the sample size during follow-up or because the training effect was lost over time. However, this question cannot be answered clearly, because there seem to be no 12-month follow-up data from cognitive training programs in cardiac surgery patients or older surgical patients after general anaesthesia [26]. In older adults comparable in age and duration of training with our study group, inhomogeneous effects have been seen 1 year after cognitive training [27, 28]. Nevertheless, postoperative cognitive training in cardiac surgical patients exerted promising effects at least 6 months post-training in cognitive function and HQL [29, 30].

Neuroplasticity (changes in brain structure) could be an explanation for the effectiveness of the cognitive training on cognitive functions [8]. The improvement of objectively assessed cognitive abilities (i.e., working memory or executive functions) through our training may explain enhanced HQL [10]. For example, improved working memory could foster more

adequate emotion regulation [31], which might explain the enhancement in role limitations due to emotional problems in the training group. Executive functions such as volition, planning, goal-directed action, performance monitoring, and inhibition are important for initiating or modifying physical activities [32, 33]. In this context, it has been shown that elevated levels of executive functions lead to increased physical activity [32], which could account for the heightened physical component of our training group. Patients' self-rated cognitive failures in daily living did not reveal a difference between the groups. As we assumed, enhanced objective cognition in our training group at 3 months post-training [10] could lead to increased HQL. The lack of an association with patients' subjective and objective assessed cognition might indicate that these two perspectives seem to be unrelated [34, 35]. Unexpectedly, close relatives' assessments regarding patients' cognition were better in the control group. However, a post hoc power analysis revealed a clearly underpowered result (1-ß=0.25), so we do not consider this difference meaningful.

Findings might be limited by the lack of a healthy control group (to control for time and practice effects), no evaluation of cognition-enhancing activities (playing games, social engagement) during follow-up (for the purpose of control analysis) [36], and the small group size. We performed a sample-size estimation using our primary outcome (neuropsychological effect at discharge from rehabilitation). Therefore, the 12-month follow-up analysis did not consider sample-size calculation. Furthermore, we did not perform a neuropsychological examination after surgery or before the start of the training intervention. This could have shown whether the two groups were homogeneous in terms of neuropsychological conditions. Such a postoperative cognitive examination could have been performed, for example, about 1 week postoperatively, when the patients were admitted to the rehabilitation clinic. However, an extensive and detailed test with a duration of about 90 minutes, as we used, would have been too overwhelming for patients, who were likely still affected by the side effects of anaesthesia and surgery. An alternative to detailed testing would have been a screening procedure such as the MOCA test [37], which only takes about 10 minutes to perform. Postoperative delirium was not systematically assessed. The frequency was taken from medical records and may

therefore be underrepresented, since the hypoactive deliriant type often remains unrecognized due to its intrinsic symptomatology [38].

As our training concept was at least able to maintain and improve HQL 12 months after cardiac surgery, it could be integrated in postoperative rehabilitative programs, especially focusing on high-risk patients. Booster sessions should be considered to achieve benevolent effects on cognitive functions up to or beyond 12 months [39]. Furthermore, since our training worked well for about 80% of the patients in the early postoperative rehabilitative phase, it could also be implemented in a preoperative setting. Investigations in the preoperative period have already been done related to physical condition, with the aim to improve postoperative outcomes in cardiosurgical patients (prehabilitation) [40]. Increasing preoperative cognitive reserves with the help of cognitive interventions to protect against potentially postoperative neurocognitive disorders such as delirium or impairments in memory and attention could also be useful [41, 42].

5. Conclusion

In conclusion, postoperative cognitive training suggests enhancing effects, especially in HQL, for cardiac surgery patients after 12 months.

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Declarations of interest

None

Data Availability

De-identified participants' data analyzed during the current study are available from the corresponding author on reasonable request.

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Supplementary Table 1: Definition of neuropsychological parameters and cognitive subdomains.

Cognitive domain (*DSM-5*)	**Cognitive subdomains (*DSM-5*)**	**Neuropsychological parameter**	**Task (scale of measurement)**
Learning and memory	Visual Immediate memory span	SKT	Recalling objects immediately (number of false items)
		BTT	Tapping blocks in a given order (span forward)
	Visual free recall	SKT	Recalling objects after delay (number of false items)
	Visual recognition memory	SKT	Recognising between learned and new objects (number of false items)
		NVLT	Recognising repeated abstract figures (number of correct items)

	Verbal Immediate memory span	VLMT	Recalling items on a word list (number of correct items· first trial)
	Verbal free recall	VLMT	Recalling items on a word list (summarised number of correct items· learning trials)
		VLMT	Recalling items on a word list (number of correct items· short delay)
		VLMT	Recalling items on a word list (number of correct items· long delay)
	Verbal recognition memory	VLMT	Recognising between learned and new words (number of correct items)
Complex attention	Selective attention	TMT-A (speed)	Linking numbers in ascending order (seconds)
		AKT (speed)	Marking target stimuli (seconds)
		AKT (accuracy)	Marking target stimuli (number of correct items)
Executive functions	Verbal working memory	LNS	Mental reorganisation of letters and numbers (span)
	Visual working memory	BTT	Tapping blocks in a given order (span backward)
	Cognitive flexibility	TMT-B (speed)	Linking numbers and letters in alternate order (seconds)

	Inhibition	SKT	Naming interfering letter· e.g.· “S” instead of “T” (seconds)
	Decision making	SVT	Selecting target symbol from several symbols (number of correct items)
Language	Word fluency	RWT (phonetic)	Naming words with a specific initial letter (number of correct items)
		RWT (semantic)	Naming words from a specific category (number of correct items)

SKT=Syndrom-Kurztest (Short Performance Test). BTT=Block-Tapping Test. NVLT=Non-Verbal Learning Test. VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test). TMT=Trail Making Test. AKT=Alterskonzentrationstest (Geriatric Concentration Test). LNS=Letter Number Span. SVT=Symbolverarbeitungstest (Symbol Processing Task). RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test).

Supplementary Table 2: Neuropsychological test results per group and assessment time

	Baseline (n=46)				12-month follow up (n=46)					
	Training (n=19)		Control (n=27)		Training (n=19)		Control (n=27)			
Test parameter	x̄	s	x̄	s	x̄	s	x̄	s	p	η2
SKT visual immediate memory span	5.6	1.5	6.0	1.3	5.1	1.5	5.7	1.3	0.225	0.03
SKT inhibition (speed)	25.3	6.0	26.9	5.7	23.6	4.8	27.1	5.4	0.144	0.05
TMT-A selective attention (speed)	37.3	10.5	41.4	11.4	37.6	15.0	40.8	10.5	0.679	0.00
TMT-B cognitive flexibility (speed)	88.9	37.0	97.7	25.8	87.7	36.0	99.7	29.5	0.43	0.01

SKT visual free recall	6.5	1.6	6.7	1.9	6.2	1.8	7.0	1.8	0.18	0.03
SKT visual recognition memory*	2.1	1.5	1.7	1.6	1.5	1.1	2.2	1.7	0.034	0.10
RWT word fluency (semantic)	22.4	6.2	21.2	5.5	21.2	6.0	20.7	5.1	0.618	0.00
RWT word fluency (phonetic)	10.5	3.0	11.9	5.3	12.0	4.0	12.3	5.3	0.388	0.01
VLMT verbal immediate memory span	5.4	2.0	4.9	1.5	6.2	1.6	5.1	2.1	0.12	0.04
VLMT verbal free recall (learning process)	43.0	9.8	39.4	10.9	46.4	9.7	42.6	10.9	0.633	0.00
VLMT verbal free recall (short delay)	8.3	2.6	7.5	3.2	9.1	3.5	8.7	3.7	0.718	0.00
NVLT visual recognition memory*	12.9	2.9	12.5	2.8	12.2	2.6	11.8	4.1	0.728	0.00
AKT selective attention (speed)	32.6	7.0	33.9	8.9	32.2	8.1	33.9	8.3	0.658	0.00
AKT selective attention (accuracy) *	54.2	1.3	54.1	1.4	54.3	1.0	54.1	1.3	0.846	0.00
LNS verbal working memory span	5.2	0.9	5.1	0.8	5.3	0.7	5.1	0.9	0.496	0.01
BTT visual immediate memory span (forward)	4.9	0.8	5.1	0.8	5.4	0.8	5.2	0.8	0.234	0.03
BTT visual working memory span (backward)	4.5	1.0	4.6	1.2	4.9	1.0	4.6	1.0	0.123	0.05
VLMT verbal free recall (long delay)	7.5	3.5	7.1	3.2	7.8	3.7	8.1	3.7	0.439	0.01
VLMT verbal recognition memory (accuracy) *	8.3	5.0	8.3	4.7	8.3	4.8	8.4	5.6	0.695	0.00
SVT decision making*	15.9	1.9	16.0	1.3	16.6	1.0	15.8	1.5	0.288	0.03

All test parameters were calculated with the ANCOVA, except those marked with an asterisk (*). Data are means (SD). p=value. η2=effect size. SKT=Syndrom-Kurztest (Short Performance Test). TMT=Trail Making Test. RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test). VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory

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Supplementary Table 3: SF-36 results per group and assessment time for the per-protocol analysis

SF-36 Faktor	Timepoint	Group	Mean	SD	n	p	η2
Physical functioning	Baseline	Control	66.029	21.312	27		
		Training	62.304	25.296	29		
	12-month follow-up	Control	70.370	21.791	27		
		Training	79.464	25.569	29		
						0.242	0.025
Role limitations due to physical health	Baseline	Control	47.115	43.201	26		
		Training	38.218	40.368	29		
	12-month follow-up	Control	52.885	40.204	26		
		Training	75.862	36.279	29		
						0.015	0.109
Role limitations due to emotional problems	Baseline	Control	84.524	32.052	28		
		Training	70.370	38.490	27		
	12-month follow-up	Control	64.286	42.483	28		
		Training	80.247	37.278	27		
						0.025	0.092
Energy / Fatigue*	Baseline	Control	52.115	17.842	26		
		Training	49.333	16.802	30		
	12-month follow-up	Control	62.885	17.786	26		
		Training	67.667	17.847	30		
						0.148	0.03

Emotional well-being	Baseline	Control	74.000	14.935	26		
		Training	75.267	17.759	30		
	12-month follow-up	Control	75.077	13.917	26		
		Training	78.267	14.694	30		
						0.967	0
Social functioning	Baseline	Control	79.018	22.062	28		
		Training	84.167	16.059	30		
	12-month follow-up	Control	77.679	25.765	28		
		Training	88.750	16.199	30		
						0.113	0.044
Pain	Baseline	Control	84.643	18.767	28		
		Training	77.500	27.606	30		
	12-month follow-up	Control	76.429	27.007	28		
		Training	83.500	24.217	30		
						0.049	0.068
General health*	Baseline	Control	60.833	14.855	28		
		Training	57.716	15.353	29		
	12-month follow-up	Control	58.705	18.414	28		
		Training	62.802	19.295	29		
						0.087	0.031
Average of all factors	Baseline	Control	68.926	14.707	28		
		Training	63.664	16.819	30		
	12-month follow-up	Control	67.190	17.038	28		
		Training	77.145	18.898	30		
						<0.001	0.181
Health change (Item 2)	Baseline	Control	35.714	24.934	28		
		Training	21.667	14.284	30		
	12-month follow-up	Control	66.071	24.734	28		

		Training	71.667	25.200	30		
						0.037	0.075
Physical component summary	Baseline	Control	65.583	18.882	28		
		Training	59.215	20.113	29		
	12-month follow-up	Control	64.531	19.040	28		
		Training	75.265	21.685	29		
						0.005	0.138
Mental component summary	Baseline	Control	72.518	16.410	28		
		Training	68.989	17.117	30		
	12-month follow-up	Control	69.848	20.157	28		
		Training	78.329	18.918	30		
						0.018	0.095

All test parameters were calculated with difference values between pre- and post-tests, followed by Mann–Whitney U-test for between-subject effects, except those marked with an asterisk (*), which were calculated by ANCOVA. Data include means (SD). n=number of cases. p=p-value. η2=effect size.

	Training (n=47)	Control (n=47)
Demographics		
Age (years)	71.2 (4.7)	73.0 (4.9)
Sex		
Women	8 (17%)	13 (28%)
Men	39 (83%)	34 (72%)
Education (years)	13.5 (3.0)	13.4 (3.0)
Medical history		
Body-mass index (kg/m²)	27.7 (3.8)	26.6 (3.8)
Arterial hypertension	31 (66%)	31 (66%)
Diabetes mellitus	10 (21%)	5 (11%)
Renal insufficiency	4 (9%)	7 (15%)
Dyslipidemia	39 (83%)	37 (79%)
LV EF (mildly abnormal)	5 (11%)	6 (13%)
LV EF (moderately abnormal)	3 (6%)	1 (2%)
Heart failure	10 (21.3%)	9 (19.1%)
Type of surgery		
AVR	23 (50%)	22 (47%)
AVR+CABG	18 (38%)	19 (40%)
MVR	4 (9%)	1 (2%)
MVR+CABG	0 (0%)	3 (6%)
AVR+MVR	2 (4%)	2 (4%)
Perioperative details		
Duration of surgery (minutes)	190.3 (38.1)	200.6 (58.9)
Duration of extracorporeal circulation (minutes)	96.5 (26.5)	105.2 (37.5)
Cross-clamp time (minutes)	69.1 (19.9)	74.7 (26.7)
Ventilation time invasive (minutes)	616.2 (331.3)	588.1 (213.6)
Postoperative complications		
Delirium	2 (4%)	4 (9%)
Arrhythmia	18 (38%)	21 (45%)
Atrial fibrillation	18 (38%)	17 (36%)
Renal insufficiency	6 (13%)	6 (13%)
Acute blood loss anemia	10 (21%)	12 (26%)
Transient ischemic attack	1 (2%)	0 (0%)
Dysathria/Aphasia	0 (0%)	1 (2%)
Medical details at admission to rehabilitation		
Blood pressure (systolic; mmHG)	128.1 (12.7)	127.7 (18.4)
Blood pressure (diastolic; mmHG)	74.5 (11.1)	71.4 (10.6)

Table 1: Baseline demographics and characteristics of the intention to treat the population.

Data include means (SD) or number of subjects (%). LF EV=left ventricular ejection fraction

[25]. AVR=aortic valve replacement. CABG=coronary artery bypass grafting. MVR=mitral valve replacement/reconstruction. Renal insufficiency was defined by a creatinine value above the in-house norms (men: > 1.2 mg/dl, women: > 0.9 mg/dl).

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		VLMT	Recalling items on a word list (number of correct items· short delay)
		VLMT	Recalling items on a word list (number of correct items· long delay)

	Verbal recognition memory	VLMT	Recognising between learned and new words (number of correct items)
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Supplementary Table 2: Neuropsychological test results per group and assessment time

	Baseline (n=46)				12-month follow up (n=46)					
	Training (n=19)		Control (n=27)		Training (n=19)		Control (n=27)			
Test parameter	x̄	s	x̄	s	x̄	s	x̄	s	p	η2
SKT visual immediate memory span	5.6	1.5	6.0	1.3	5.1	1.5	5.7	1.3	0.225	0.03
SKT inhibition (speed)	25.3	6.0	26.9	5.7	23.6	4.8	27.1	5.4	0.144	0.05
TMT-A selective attention (speed)	37.3	10.5	41.4	11.4	37.6	15.0	40.8	10.5	0.679	0.00
TMT-B cognitive flexibility (speed)	88.9	37.0	97.7	25.8	87.7	36.0	99.7	29.5	0.43	0.01
SKT visual free recall	6.5	1.6	6.7	1.9	6.2	1.8	7.0	1.8	0.18	0.03
SKT visual recognition memory*	2.1	1.5	1.7	1.6	1.5	1.1	2.2	1.7	0.034	0.10
RWT word fluency (semantic)	22.4	6.2	21.2	5.5	21.2	6.0	20.7	5.1	0.618	0.00
RWT word fluency (phonetic)	10.5	3.0	11.9	5.3	12.0	4.0	12.3	5.3	0.388	0.01
VLMT verbal immediate memory span	5.4	2.0	4.9	1.5	6.2	1.6	5.1	2.1	0.12	0.04
VLMT verbal free recall (learning process)	43.0	9.8	39.4	10.9	46.4	9.7	42.6	10.9	0.633	0.00
VLMT verbal free recall (short delay)	8.3	2.6	7.5	3.2	9.1	3.5	8.7	3.7	0.718	0.00
NVLT visual recognition memory*	12.9	2.9	12.5	2.8	12.2	2.6	11.8	4.1	0.728	0.00
AKT selective attention (speed)	32.6	7.0	33.9	8.9	32.2	8.1	33.9	8.3	0.658	0.00
AKT selective attention (accuracy) *	54.2	1.3	54.1	1.4	54.3	1.0	54.1	1.3	0.846	0.00
LNS verbal working memory span	5.2	0.9	5.1	0.8	5.3	0.7	5.1	0.9	0.496	0.01

BTT visual immediate memory span (forward)	4.9	0.8	5.1	0.8	5.4	0.8	5.2	0.8	0.234	0.03
BTT visual working memory span (backward)	4.5	1.0	4.6	1.2	4.9	1.0	4.6	1.0	0.123	0.05
VLMT verbal free recall (long delay)	7.5	3.5	7.1	3.2	7.8	3.7	8.1	3.7	0.439	0.01
VLMT verbal recognition memory (accuracy)*	8.3	5.0	8.3	4.7	8.3	4.8	8.4	5.6	0.695	0.00
SVT decision making*	15.9	1.9	16.0	1.3	16.6	1.0	15.8	1.5	0.288	0.03

All test parameters were calculated with the ANCOVA, except those marked with an asterisk (*). Data are means (SD). p=value. η2=effect size. SKT=Syndrom-Kurztest (Short Performance Test). TMT=Trail Making Test. RWT=Regensburger Wortflüssigkeits-Test (Regensburger Word Fluency Test). VLMT=Verbaler Lern- und Merkfähigkeitstest (Auditory Verbal Learning and Memory Test). NVLT=Non-Verbal Learning Test. AKT=Alterskonzentrationstest (Geriatric Concentration Test). LNS=Letter Number Span. BTT=Block Tapping Test. SVT=Symbolverarbeitungstest (Symbol Processing Task).

Supplementary Table 3: SF-36 results per group and assessment time for the per-protocol analysis

SF-36 Faktor	Timepoint	Group	Mean	SD	n	p	η2
Physical functioning	Baseline	Control	66.029	21.312	27		
		Training	62.304	25.296	29		
	12-month follow-up	Control	70.370	21.791	27		
		Training	79.464	25.569	29		
						0.242	0.025
Role limitations due to physical health	Baseline	Control	47.115	43.201	26		
		Training	38.218	40.368	29		
	12-month follow-up	Control	52.885	40.204	26		
		Training	75.862	36.279	29		
						0.015	0.109
Role limitations due to emotional problems	Baseline	Control	84.524	32.052	28		
		Training	70.370	38.490	27		
	12-month follow-up	Control	64.286	42.483	28		
		Training	80.247	37.278	27		
						0.025	0.092
Energy / Fatigue*	Baseline	Control	52.115	17.842	26		
		Training	49.333	16.802	30		
	12-month follow-up	Control	62.885	17.786	26		
		Training	67.667	17.847	30		
						0.148	0.03
Emotional well-being	Baseline	Control	74.000	14.935	26		
		Training	75.267	17.759	30		
	12-month follow-up	Control	75.077	13.917	26		
		Training	78.267	14.694	30		
						0.967	0

Social functioning	Baseline	Control	79.018	22.062	28		
		Training	84.167	16.059	30		
	12-month follow-up	Control	77.679	25.765	28		
		Training	88.750	16.199	30		
						0.113	0.044
Pain	Baseline	Control	84.643	18.767	28		
		Training	77.500	27.606	30		
	12-month follow-up	Control	76.429	27.007	28		
		Training	83.500	24.217	30		
						0.049	0.068
General health*	Baseline	Control	60.833	14.855	28		
		Training	57.716	15.353	29		
	12-month follow-up	Control	58.705	18.414	28		
		Training	62.802	19.295	29		
						0.087	0.031
Average of all factors	Baseline	Control	68.926	14.707	28		
		Training	63.664	16.819	30		
	12-month follow-up	Control	67.190	17.038	28		
		Training	77.145	18.898	30		
						<0.001	0.181
Health change (Item 2)	Baseline	Control	35.714	24.934	28		
		Training	21.667	14.284	30		
	12-month follow-up	Control	66.071	24.734	28		
		Training	71.667	25.200	30		
						0.037	0.075
Physical component summary	Baseline	Control	65.583	18.882	28		
		Training	59.215	20.113	29		
	12-month follow-up	Control	64.531	19.040	28		
		Training	75.265	21.685	29		

						0.005	0.138
Mental component summary	Baseline	Control	72.518	16.410	28		
		Training	68.989	17.117	30		
	12-month follow-up	Control	69.848	20.157	28		
		Training	78.329	18.918	30		
						0.018	0.095

All test parameters were calculated with difference values between pre- and post-tests, followed by Mann–Whitney U-test for between-subject effects, except those marked with an asterisk (*), which were calculated by ANCOVA. Data include means (SD). n=number of cases. p=p-value. η2=effect size.

Figure 1

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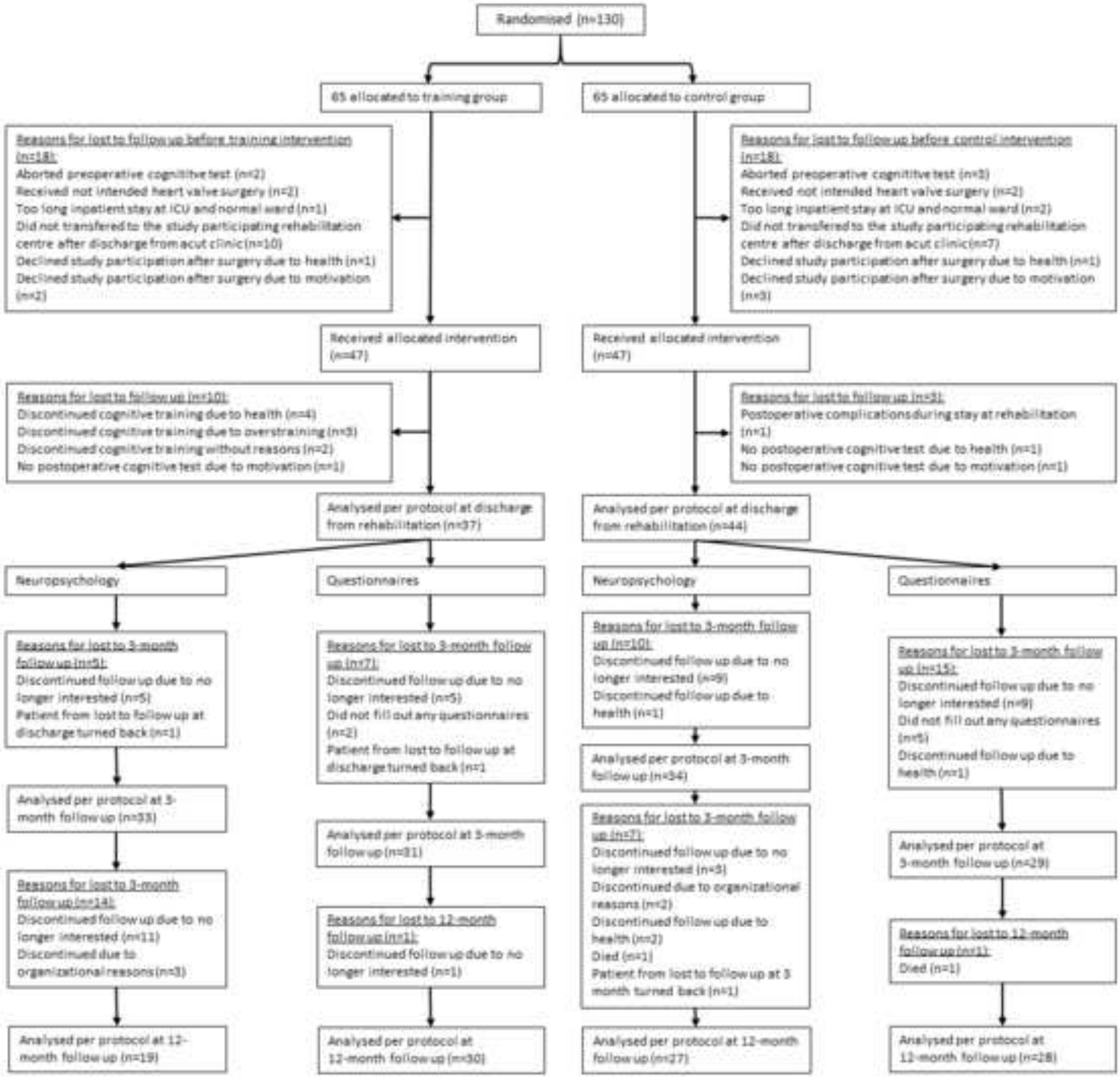

Figure 2

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